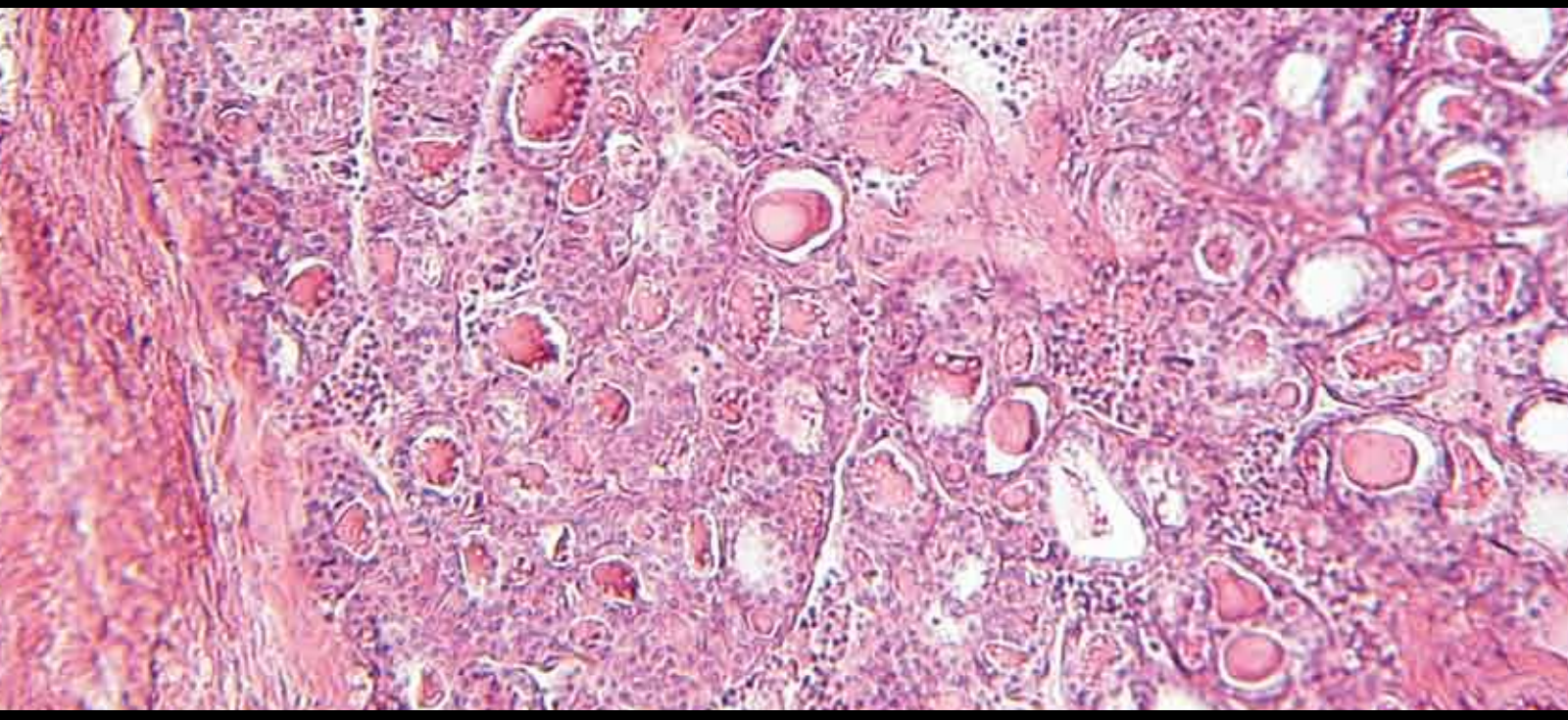
Journal of Thyroid Research

Thyroid and Pregnancy

Guest Editors: Bijay Vaidya, Roberto Negro, Kris Poppe, and Joanne Rovet



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Editorial Board

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 680328, 3 pages
doi:10.4061/2011/680328

Editorial
Thyroid and Pregnancy

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Received 31 October 2011; Accepted 31 October 2011

In the last two decades, there have been major advances in our understanding of the thyroid physiology during pregnancy, the role of thyroid hormones in fetal development, and the effects of thyroid dysfunction on pregnancy outcomes. The main objective of this special issue was to highlight how these advances have enhanced our knowledge and influenced the clinical practice in the field.

The emerging evidence for an association between thyroid autoimmunity and spontaneous miscarriages is one of such advances. As A. Stagnaro-Green reviews in this special issue, since the publication of the first report describing the association in 1990 [1], many subsequent studies have lent further evidence to support this association. However, despite the robust evidence for the association, the pathogenesis of miscarriages in pregnant women with thyroid autoimmunity remains uncertain, and whether levothyroxine treatment prevents the adverse outcome in these women is yet to be confirmed.

For many decades, it has been recognised that overt maternal hypothyroidism during pregnancy is associated with impaired neurological development of the offspring; however, several studies in the recent years have suggested that even mild maternal thyroid hormone deficiency (subclinical hypothyroidism and isolated maternal hypothyroxinaemia) during pregnancy can affect the offspring's neuropsychological development [2, 3]. However, this association has not been consistent in all studies [4], and J. Chevrier and colleagues in this special issue report a prospective study showing lack of association between maternal thyroid hormone levels at 27-week gestation and neuropsychological development of the offspring. Indeed, as M. Moleti and colleagues highlight in their review, there is also a great deal of controversy surrounding the diagnosis, adverse effects, and management of isolated maternal hypothyroxinaemia in pregnancy, and more studies are needed to resolve these controversies.

The last two decades have also witnessed significant advances in the diagnosis and management of hypothyroidism in pregnancy. The importance of trimester-specific reference ranges for thyroid function tests in pregnancy has been established [5, 6]; it has become clear that the upper reference limit of serum thyrotropin (TSH) in pregnancy is much lower than that in the general population. It has also been convincingly shown that most hypothyroid women need an increased dose of levothyroxine during pregnancy. However, there remains uncertainty at what level of TSH should the levothyroxine replacement be considered and whether women with isolated maternal hypothyroxinaemia or isolated positive thyroid peroxidase antibodies should be treated with levothyroxine. Furthermore, there is no consensus on whether all pregnant women should be screened for hypothyroidism. J. Klubo-Gwiezdzinska and colleagues review the issues surrounding indications, efficacy, and monitoring of levothyroxine replacement in pregnancy, and J. H. Lazarus appraises evidences for and against screening all pregnant women for thyroid dysfunction. The current guidelines from the Endocrine Society and the American Thyroid Association do not endorse universal screening of pregnant women for thyroid dysfunction but recommend case-finding approach in high-risk pregnant women [5, 6]. However, V. Nambiar and colleagues show, in the Asian-Indian population, that the case-finding approach misses a significant proportion of pregnant women with thyroid dysfunction, in line with findings of several studies from

the western countries. Their study also provides further evidence to support that both maternal thyroid autoimmunity and maternal mild hypothyroidism are associated with an increased risk of spontaneous miscarriages. And, although not as fiercely debated as screening pregnant women for hypothyroidism, there is also lack of consensus on screening for postpartum thyroiditis. M. A. Adlan and L. D. Premawardhana review the issues surrounding screening for postpartum thyroiditis and the utility of thyroid peroxidase antibodies testing as a screening tool for this condition.

In pregnancy, Graves' disease is the commonest cause of hyperthyroidism, and thionamide antithyroid drugs are the mainstay of treatment for this condition. However, in the recent years, reports of rare association of carbimazole (and its active metabolite, methimazole) use in early pregnancy with multiple congenital malformations in the foetus and association of propylthiouracil with severe liver injury have led to the controversy surrounding the choice of antithyroid drugs in pregnancy. For example, which antithyroid drug should be prescribed for a woman with Graves' disease planning pregnancy? If a pregnant woman is on propylthiouracil, should the drug be switched to carbimazole (or methimazole) after the first trimester? In this special issue, P. Bowman and B. Vaidya, by analysing all birth defects related to maternal treatment of carbimazole and propylthiouracil reported to the UK Pharmacovigilance authority over a 47-year period, provide further evidence to support an embryopathy associated with carbimazole exposure in utero. However, their study also raises a question whether the currently apparent lack of association of similar embryopathy with propylthiouracil is related to historically lower use of the drug as compared to carbimazole or methimazole. Furthermore, transient gestational hyperthyroidism—another common cause of hyperthyroidism in pregnancy—is often confused with Graves' disease, sometimes leading to inappropriate treatment. A. M. Goldman and J. H. Mestman review the aetiology, pathogenesis, diagnosis, and management of this intriguing condition.

The association between severe iodine deficiency and cretinism has been known for more than a century [7]. Furthermore, recent studies have shown that mild iodine deficiency is also associated with impaired cognitive and behaviour outcomes in the children, including attention deficit hyperactivity disorder. Despite these observations and all national and international efforts to optimise dietary iodine intake in the population, iodine deficiency during pregnancy continues to be a major preventable cause of mental retardation in many countries. In fact, recent studies suggest that iodine deficiency is on the rise in Europe, Australia, and the USA [8–10]. C. Yarrington and E. N. Pearce review the adverse effects of dietary iodine deficiency on maternal thyroid function and fetal neurological outcomes and discuss the recommendations for optimum dietary iodine intake during pregnancy.

As a byproduct of a modern life, humans are increasingly being exposed to environmental endocrine disrupting chemicals, with potential harmful health consequences. Recent studies suggest that some of these chemicals could interfere with normal thyroid hormone function. Therefore, there is a growing concern that an exposure to these chemicals during pregnancy may adversely affect maternal and fetal thyroid function impacting on the fetal development, as M.-L. Hartoft-Nielsen and colleagues discuss in their review.

Finally, although fortunately rare, thyroid cancer presents special challenges in the management during pregnancy. S. A. Imran and M. Rajaraman discuss various issues surrounding management of differentiated thyroid cancer in pregnancy and underline the importance of multidisciplinary approach in the management. However, much of the clinical decisions in the management of thyroid cancer in pregnancy are hampered by the lack of good quality evidence, as G. V. Alves and colleagues highlight in their systemic review.

We believe that the papers in this special issue illustrate the highlights of advances made in the diverse areas of thyroid and pregnancy over the last two decades. At the same time, they also underline many yet unanswered questions and areas for further studies. However, with the volume and the quality of ongoing research activities in the field, we are optimistic that we will not need to wait for a further two decades to have the answers for many of these questions.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 426427, 13 pages
doi:10.4061/2011/426427

Research Article

Maternal Thyroid Function during the Second Half of Pregnancy and Child Neurodevelopment at 6, 12, 24, and 60 Months of Age

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Received 23 March 2011; Revised 26 June 2011; Accepted 7 July 2011

Academic Editor: Joanne Rovet

Although evidence suggests that maternal hypothyroidism and mild hypothyroxinemia during the first half of pregnancy alters fetal neurodevelopment among euthyroid offspring, little data are available from later in gestation. In this study, we measured free T4 using direct equilibrium dialysis, as well as total T4 and TSH in 287 pregnant women at 27 weeks' gestation. We also assessed cognition, memory, language, motor functioning, and behavior in their children at 6, 12, 24, and 60 months of age. Increasing maternal TSH was related to better performance on tests of cognition and language at 12 months but not at later ages. At 60 months, there was inconsistent evidence that higher TSH was related to improved attention. We found no convincing evidence that maternal TH during the second half of pregnancy was related to impaired child neurodevelopment.

1. Introduction

The profound deleterious neurodevelopmental effect of maternal and fetal hypothyroidism caused by iodine deficiency has been recognized for more than a century [1]. More recent evidence from experimental and observational studies suggests that even among euthyroid offspring, maternal hypothyroidism and hypothyroxinemia (low thyroxine (T4) with normal thyroid-stimulating hormone (TSH) levels) during early pregnancy may be associated with impaired brain development. Man and colleagues, for instance, reported associations between maternal hypothyroxinemia in early pregnancy and lower scores on neurodevelopmental scales at 8 months, 4 years, and 7 years of age [2–4]. A more recent study by Haddow et al. found reduced scores on tests of intelligence, attention, and visual-motor performance at 8 years of age among children of 48 mothers with untreated clinical hypothyroidism (defined as TSH levels >99.7th percentile or TSH between the 98th and the 99.6th percentile and total T4 < 7.75 μg/dL) at the 17th week of gestation relative to 124 controls [5]. A Chinese study ($n = 1,268$) also found that children of 19 women with hypothyroxinemia (defined as total T4 below the reference range but normal TSH and free T4) and 18 women with subclinical hypothyroidism (high TSH and normal free and total T4) in the first half of pregnancy scored 7.6–10.0 point lower than controls on the mental (MDI) and psychomotor (PDI) development indices of the Bayley Scales of Infant Development [6].

Studies have reported reduced scores on cognitive, motor, and language scales even among children of mothers with mild hypothyroxinemia. For instance, in a large population-based cohort study conducted in The Netherlands ($n = 3,659$), Henrichs et al. found 80% increased odds of expressive language delays at 18 and 30 months of age among children whose mother had free T4 levels <10th percentile at 13 weeks' gestation [7]. Pop and colleagues also reported lower scores on the orientation cluster of the Neonatal Behavioral Assessment Scale three weeks after birth ($n = 204$) [8] and a 7.4 point decrease on the PDI at 10 months of age ($n = 220$) [9] in children of mothers with

lower free T4 at 12 weeks' gestation. They also found 8–10 point reductions on the MDI and the PDI at 12 and 24 months of age in children of 57 mothers with low-normal free T4 relative to 50 controls [10]. The one study to contradict the above findings did not measure free T4 [11]. Thus, the bulk of the literature points to an association between adverse neurodevelopmental outcomes in offspring and maternal hypothyroidism, hypothroxinemia, and low-normal free T4 levels during the first half of pregnancy.

Evidence suggests that TH of maternal origin may also play a role in fetal development later in pregnancy. This hypothesis was supported by early studies which demonstrated that transfer of radiolabeled T4 and T3 through the placenta continues to occur after the onset of fetal thyroid function [12]. Maternal T4 appears to reach the fetus in significant amounts up until birth, as evidenced by a study conducted by Vulsma et al. [13]. In that study, T4 was detected in the cord blood of 25 neonates with a complete iodide organification defect, a genetic condition that prevents the iodination of tyrosine and therefore inhibits T4 synthesis. T4 measured in cord blood reached concentrations equivalent to 30–60% of the mean values found in full-term fetuses without this condition [14]. Given that a substantial proportion of thyroid hormone reaching the fetus is of maternal origin in the latter part of gestation, it is conceivable that maternal thyroid hormone may continue to affect fetal neurodevelopment during this period. To date, only the studies by Pop and colleagues examined this question in humans and found no relationship between low-normal maternal free T4 (<10th percentile) measured at 24 and 32 weeks' gestation and child neurodevelopment [8–10]. To our knowledge, these results have not been replicated by other groups.

Most studies investigating the association of maternal thyroid function during pregnancy and child cognitive development have focused on hypothyroidism/hypothyroxinemia, perhaps because this condition is more common than hyperthyroidism. Maternal hyperthyroidism is nevertheless a significant condition that affects 0.05–0.2% of pregnancies in the form of Graves' disease; an additional 2-3% of pregnant women are also believed to experience gestational transient thyrotoxicosis [15]. In rats, fetal/neonatal hyperthyroidism causes decreased brain and cerebellar weight as well as abnormal brain development, including an acceleration of neuronal differentiation, a delay in glial cell differentiation and early termination of cell proliferation, resulting in a smaller number of granular and basket cells [16]. In humans, maternal hyperthyroidism during pregnancy has been linked to preeclampsia, fetal loss, premature births, growth restriction, and low birth weight [17–21]. Subclinical hyperthyroidism (defined as TSH values below the reference range with normal free T4 levels [22]), on the other hand, was not found to be associated with low birth weight, major malformations, or fetal, neonatal, or perinatal mortality in infants of 433 women with TSH levels ≤2.5th percentile and normal free T4 (≤1.75 ng/dL) relative to 23,124 women with normal TSH levels [23]. However, we are aware of no studies that investigated associations between high-normal T4 or subclinical hyperthyroidism and neurodevelopment.

The current study thus aims to examine whether maternal TH levels in the second half of pregnancy are associated with child neurodevelopment at 6, 12, 24, and 60 months of age. Prior studies used immunoassays to determine free T4 levels, but these measurements are influenced by T4-bound protein concentrations which increase during pregnancy [24]. In the present study, we used direct equilibrium dialysis to measure free T4 [25], a method that yields valid results in samples with normal or elevated T4-bound protein levels [26].

2. Methods

2.1. Participants. Pregnant women were recruited through the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a birth cohort study of primarily Latino children born in the Salinas Valley, California. Women were eligible for inclusion in the study if they were ≥18 years old, had completed <20 weeks' gestation, spoke English or Spanish, were Medi-Cal eligible (state-sponsored health care for low-income families), were planning to deliver at the Monterey county hospital (Natividad Medical Center), and received prenatal care in this hospital or at one of five clinics of Clinica de Salud del Valle de Salinas. Screening and enrollment occurred between October 1999 and October 2000. We obtained informed consent from the 601 women who agreed to participate. Out of the 526 singleton live births (there were 20 miscarriages, 3 stillbirths, 2 neonatal deaths, 5 twin births, and 45 women were lost to follow-up), we excluded children with conditions that may impact scores on neurodevelopmental tests such as hydrocephaly ($n = 1$), autism ($n = 1$), and a history of seizures ($n = 7$). Children whose neurodevelopment was never assessed ($n = 139$) or whose mother's banked serum volume was insufficient for TH analysis ($n = 91$) were also excluded, leaving a final sample of 287 mother-child pairs. A total of 271 children were included at 6 months, 258 at 12 months, 240 at 24 months, and 207 at 60 months of age.

Women who were excluded or who dropped out at one or more time-point were more likely to be employed, to have been born in the US, to be depressed, and had lived longer in the US compared to those who were included in analyses. Excluded children were more likely to be firstborns and to have had lower birth weights compared to those who were included in the analyses. This study was approved by the University of California, Berkeley Committee for the Protection of Human Subjects.

2.2. Interviews. Women were interviewed in English or Spanish by bilingual, bicultural staff during pregnancy (at 13 and 27 weeks' gestation on average), at delivery, and when their children were 6, 12, 24, and 60 months of age. We obtained information about sociodemographic and lifestyle characteristics at each interview, including smoking, alcohol consumption, drug use, and diet during pregnancy; and on childcare, breastfeeding, number of children in the home,

and housing density (number of people per room) after birth. The Peabody Picture Vocabulary Test (PPVT; at the 6 month visit) [27] and the Center for Epidemiologic Studies Depression Scale (CES-D; at the 12 month visits) [28] were also administered to mothers. In addition, the Infant-Toddler Home Observation for Measurement of the Environment (HOME) [29] was completed at 6 and 12 months; some subscales of the HOME were completed at 24 months. We also administered the Kotelchuck Adequacy of Prenatal Care Utilization Index [30], the Duke-UNC Functional Social Support Questionnaire [31], and the Diet Quality Index proposed by Bodnar and Siega-Riz [32] and modified by Harley and Eskenazi [33]. Mothers' (during pregnancy) and children's (up to age 24 months) medical records were abstracted by a registered nurse. We obtained data on delivery complications including vacuum extraction, placental abruption, amnionitis, and hemorrhage, or other bleeding; and on neonatal TSH levels (see below).

2.3. Neurodevelopmental Evaluations. Children were evaluated at the ages of 6, 12, 24, and 60 months. We selected for analyses those tests that assessed the same constructs examined in previous studies of maternal thyroid hormone and child neurodevelopment [2–7, 9–11]. Children were assessed at 6, 12, and 24 months of age on the Mental Development Index (MDI) and Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development-Second Edition [34], and at 6 and 12 months on the auditory and expressive comprehension subscales of the Preschool Language Scale (PLS). At 60 months of age, the Performance Intellectual Quotient (IQ) was evaluated using the Wechsler Preschool and Primary Scale of Intelligence 3rd edition (WPPSI-III) [35]. We also administered the Vocabulary subtest of the WPPSI-III. Motor and language development, memory, attention, and school readiness were assessed using the McCarthy Scales of Children's Abilities (Digit Span Forward and Backward, Words and Sentences, Draw-a-Child, and Gross Motor Leg and Arm) [36], the Woodcock-Johnson Test of Cognitive Ability (Letter-Word and Applied Problems) and its Spanish-validated version (the Woodcock-Muñoz Test [37, 38]), the Pegboard subtest of the Wide Range Assessment of Visual-Motor Abilities (WRAVMA) for both dominant and non-dominant hands [39], the Conner's Kiddie Continuous Performance Test (KCPT) [40], and the PPVT [27]. The mother was queried about her child's behavior using the Child Behavior Checklist (CBCL). The Bayley Scales, the WPPSI performance IQ, the WRAVMA, the Woodcock-Johnson/Muñoz test, and the PPVT are age-standardized to a mean of 100 and a standard deviation of 15. Standardized scores on the McCarthy Scales are only available for full subscales but not for individual subtests. Raw scores were thus used for gross motor subtests. Scores on other McCarthy subtests were determined by subtracting children's chronological age from their developmental age (in months), as determined using methods published by Kaufman and Kaufman [41]. Positive scores show accelerated development while negative scores represent a delay. Finally, raw scores were used for the CBCL following recommendations from the test manual [42].

Neurodevelopmental evaluations were conducted in Spanish and/or English by psychometricians blind to mothers' TH levels in the study office or in a recreational vehicle (RV) modified for this purpose. Psychometricians were trained and supervised by a child neuropsychologist (CJ) and were videotaped and evaluated on a regular basis to ensure consistency across psychometricians and over time. All tests were reviewed by graduate students trained by the child neuropsychologist to ensure accurate scoring.

2.4. Thyroid Hormone Measurements. We measured TSH, free T4 and total T4 in serum collected by venipuncture from pregnant women at the time of the second interview (Mean $\pm$ SD = 26.9 $\pm$ 3.4 weeks' gestation). Samples were processed immediately at Natividad Medical Center and stored at -80°C at the UC Berkeley School of Public Health Biorepository until shipment to Quest Diagnostic's Nichols Institute (San Juan Capistrano, CA) where they were analyzed on a Bayer ADVIA Centaur system (Siemens Healthcare Diagnostics, Deerfield, IL). A pilot experiment revealed that every freeze-thaw cycle was associated with a 0.1 ng/dL increase in free T4 levels ($P < 0.001$); this variable accounted for 33% of the variance (unpublished results). Samples were thus thawed only once for aliquoting, shipped refrigerated, and analyzed within 48 hours. TSH was measured by ultrasensitive third generation immunochemiluminometric assay (ICMA; functional sensitivity (FS): 0.01 mIU/L, intra-assay coefficients of variation (CV) = 2.3–6.0%); total T4 was determined by solid-phase ICMA (FS: 0.1 μg/dL, CV: 4.5–5.7%); free T4 was analyzed by direct equilibrium dialysis (ED) followed by radioimmunoassay (RIA; FS: 0.1 ng/dL, CV: 2.4–6.2%) [25]. Serum protein-bound T4 levels usually increase during pregnancy [15], which may bias results obtained by immunoassays not preceded by ED [24]. ED uses a semipermeable membrane to physically separate the bound hormone from the free portion, which is then measured using a highly sensitive RIA. This method measures free T4 accurately in samples with normal or elevated protein-bound T4 levels [26]. Previous studies used butanol-extractable iodine [2–4], which estimates T4 levels by measuring protein-bound iodine [43] or immunoassays [5–10]. Trimester-specific reference ranges for TH levels were provided by the analytical laboratory. Neonatal TSH was also measured in dried blood spots by the Genetics Disease Branch of the California Department of Health Services as part of the State's Newborn Screening Program. Hospital staff collected blood spots by heel stick on average 24.8 hours after birth (SD = 15.5); samples were analyzed by solid-phase, time-resolved sandwich fluoroimmunoassay (AutoDELPHIA; PerkinElmer, Wellesley, MA).

2.5. Statistical Analyses. Multiple linear regression models were used to evaluate associations between TH and neurodevelopmental outcomes. Models were first run with TH expressed continuously. We also ran models with TSH categorized as low ($n = 43$) versus normal based on trimester-specific reference ranges provided by the analytical laboratory. There were however not enough women with high

Table 1: Demographic characteristics of study participants (n = 287).

	No. (%)
Mothers	
Age (years)	
18–24	130 (45.3)
25–29	95 (33.1)
30–34	42 (14.6)
35–45	20 (7.0)
Race/Ethnicity	
White	5 (1.7)
Latino	278 (96.9)
Other	4 (1.4)
Education	
≤6th grade	121 (42.2)
7–12th grade	105 (36.6)
≥High School	61 (21.3)
Income (% poverty)	
<100	171 (59.6)
100–200	105 (36.6)
>200	11 (3.8)
Country of birth	
United States	32 (11.1)
Mexico	251 (87.5)
Other	4 (1.4)
Time in the USA (years)	
≤5	156 (54.4)
6–10	69 (24.0)
≥11	62 (21.6)
Parity	
0	91 (31.7)
≥1	196 (68.3)
Smoking during pregnancy	
No	271 (94.4)
Yes	16 (5.6)
Alcohol during pregnancy (≥one serving)	
No	282 (98.3)
Yes	5 (1.7)
Children	
Sex	
Boy	140 (48.8)
Girl	147 (51.2)
Birthweight (g)	
<2500 g	10 (3.5)
2500–3500 g	149 (51.9)
>3500 g	128 (44.6)
Gestational duration (weeks)	
<37	21 (7.3)
37–42	266 (92.7)
>42	0 (0.0)

TSH or with other TH measurements outside of the reference range to conduct such analyses. Therefore, to obtain sufficient sample size and to replicate methods used in prior studies [7–10], we dichotomized TH at the 10th and the 90th percentile based on distributions in our sample and at 0.8 ng/dL. Neurodevelopmental scores were expressed continuously. We used generalized additive models with a 3-degrees-of-freedom cubic spline function to evaluate the shape of the relationship between continuously expressed TH and scores on neurodevelopmental assessments and to test for linearity [44]. Since altered neurodevelopment was hypothesized to occur at both ends of the distribution of TH values (i.e., following an inverse U-shaped association), scores with P values for digression from linearity <0.10 were fit using a quadratic term while scores with a P value ≥0.10 were fit linearly in multiple regression models. Conclusions were similar when using quadratic or linear terms. We therefore only present results using linear terms.

We removed outliers as identified by the Generalized Extreme Studentized Deviates Many-Outlier procedure at an $\alpha = 0.01$ [45]. Covariates considered for inclusion in models were identified based on prior reports suggesting that they influenced neurodevelopment (see Appendix A for a complete list). They included (categorized as shown in Table 1 or as indicated below): maternal age at enrollment (continuously), race, education, income, parity (continuously), depression (yes versus no), maternal PPVT score (continuously), Diet Quality Index (continuously), Kotelchuck Adequacy of Prenatal Care Utilization Index (adequate plus, adequate, inadequate), Composite Social Support Index (continuously), employment status at the time of and prior to assessments (yes versus no), smoking (yes versus no), alcohol (yes versus no) and illegal drug (yes versus no) consumption during pregnancy, delivery type (natural versus cesarean section), pregnancy complications (any versus none), infant sex, premature birth (yes versus no), months of breastfeeding (continuously), HOME score at the time of and prior to assessments, and psychometrician administering assessments.

To ensure that neurodevelopment was not affected by neonatal hypothyroidism, we also considered neonatal TSH levels as a covariate. In addition, we considered the potential confounding effect of some known neurotoxicants. Lead was measured in maternal and cord blood samples using graphite furnace atomic absorption spectrophotometry. As exposure to organophosphate insecticides has been associated with altered neurodevelopment in this cohort of farmworker families [46, 47], this variable was also considered. Organophosphate insecticide exposure was assessed by measuring dialkyl phosphate metabolites in maternal urine collected at approximately 13 and 26 weeks' gestation by high-resolution gas chromatography-tandem mass spectrometry (HRGC/MS-MS) with isotope dilution quantification [48]. Measurements at the two time points were averaged and log10-transformed. For each time point, covariates were included in final models if they were associated with any of the TH measurements at $P < 0.10$ based on analysis of variance (ANOVA) or Pearson's correlations.

In order to control for potential selection bias due to exclusion from analyses and/or loss to followup, we ran all models with and without weights determined as the inverse

Table 2: Mean scores on neurodevelopmental scales at 6, 12, and 24 months of age.

	6 Months		12 Months		24 Months	
	N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)
Bayley						
Mental development index	271	95.0 (7.9)	258	101.3 (9.1)	240	86.4 (11.7)
Psychomotor development index	271	96.2 (11.1)	257	107.0 (12.8)	240	98.2 (10.4)
Preschool language scale						
Auditory comprehension	270	104.6 (12.9)	257	99.1 (12.9)		
Expressive comprehension	270	91.1 (13.5)	257	94.5 (13.8)		
Total score	270	97.7 (11.3)	257	96.6 (13.5)		

Table 3: Mean scores on neurodevelopmental scales at 5 years of age.

	N	Mean (SD)
Intelligence		
WPPSI[1]		
Performance IQ	207	94.7 (14.7)
Motor		
WRAVMA[2]		
Pegboard-Dominant	205	110.7 (17.4)
Pegboard-Nondominant	204	110.3 (17.2)
McCarthy		
Draw-a-Child	206	3.9 (16.1)
Gross Motor-Leg	194	11.0 (2.2)
Gross Motor-Arm	202	4.1 (2.4)
Language Development		
WPPSI[1] Vocabulary	207	8.8 (2.6)
PPVT[3]	205	94.8 (17.5)
Memory		
McCarthy		
Words and Sentences	205	−4.5 (16.6)
Digit Span Forward	204	−15.2 (13.0)
Digit Span Backward	199	−15.3 (10.6)
School Readiness		
Woodcock-Johnson/Muñoz		
Letter-Word	199	92.4 (12.1)
Applied Problems	206	87.0 (15.8)
Attention		
CBCL[4]		
ADHD[5]	200	4.7 (2.8)
KCPT[6]		
ADHD Confidence Index[5]	188	45.7 (17.5)

[1]Weschler Preschool and Primary Scale of Intelligence.
[2]Wide Range Assessment of Visual Motor Ability.
[3]Peabody Picture Vocabulary Test.
[4]Child Behavior Checklist.
[5]Attention Deficit Hyperactivity Disorder.
[6]Kiddie Continuous Performance Test.
Note: We report differences between chronological and developmental ages for the McCarthy Draw-a-Child, Words and Sentences, and Digit Span Forward and Backward subtests (in months). Raw scores are reported for the gross motor tasks of the McCarthy scales (no developmental ages are available for these subtests) and for the CBCL as recommended by the test manual [42]. Standardized scores are used for other tests.

probability of inclusion in our samples at each time-point [49]. Probability of inclusion was determined based on multiple logistic regression models using covariates listed in the Statistical Analyses section as potential predictors. Model selection was performed using a Deletion-Substitution-Addition (DSA) algorithm, which finds the combination of variables (including interactions and polynomials) that minimizes cross-validated risk [50]. Results were similar with and without this adjustment; we present results without the adjustment. Missing covariates were imputed. In addition, two free T4 and two TSH values below the limit of detection (LOD) (0.1 ng/dL and 0.01 mIU/L, resp.) were imputed as half the LOD. Statistical significance was defined as $P < 0.05$ on two-tailed tests. TSH values were $\log_2$-transformed for all statistical analyses. Analyses were performed using Intercooled STATA, version 10.0 (StataCorp, College Station, TX) and R, version 2.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Mothers were mostly low-income, Mexican-born, Spanish-speaking Latinas with a low level of education, and many were recent immigrants to the United States (Table 1). A large proportion of women (73.7%) lived in farmworker families. During pregnancy, smoking was rare in this population (5.2%), and only 2.6% of women had ≥1 serving of alcohol per week. Mothers' mean PPVT score was 88.0 (SD = 21.2).

Mean free and total T4 levels were 0.8 ng/dL (SD = 0.2) and 10.5 μg/dL (SD = 1.5), respectively; the geometric mean for TSH was 1.2 mIU/L (GSD = 1.7). Nine (2.7%) women had low free T4 (<0.5 ng/dL) and 13 (3.9%) had low total T4 (<8.0 μg/dL) levels. None of the women were hypothyroidic based on the reference range for TSH provided by the analytical laboratory (TSH > 5.2 mIU/L), but 16 were hypothyroidic using the criteria proposed by the National Academy of Clinical Biochemistry (TSH > 2.5 mIU/L) [51, 52]. Five women had high free T4 (>1.6 ng/dL), none had elevated total T4 (>17.8 and >20.1 μg/dL in the second and third trimesters, resp.), and 43 had low TSH (<0.5 and <0.8 mIU/L in the second and third trimesters, resp.). All children had normal TSH levels at birth (<25 mIU/L).

Scores on neurodevelopmental scales when children were aged 6, 12, 24, and 60 months are shown in Tables 2 and 3. Except for a low MDI score at 24 months (mean = 86.1; SD = 12.0), Bayley and PLS scores were close to the expected mean (i.e., 100) at all time points. At 60 months of age, children performed well on fine motor tests but scored relatively low

Table 4: Associations between maternal thyroid hormone levels during pregnancy (27 weeks' gestation) and child neurodevelopment at 6, 12 and 24 months of age.

			Bayley scales		Preschool language scale		
			Mental development index	Psychomotor development index	Auditory comprehension	Expressive comprehension	Total score
6 Months[1]	Free T4	β	−3.14	−3.27	−2.03	1.65	−0.10
		(95% CI)	(−7.65, 1.36)	(−9.36, 2.82)	(−9.80, 5.75)	(−5.48, 8.79)	(−6.45, 6.25)
	Total T4	β	0.03	−0.06	−0.24	0.58	0.19
		(95% CI)	(−0.57, 0.62)	(−0.86, 0.74)	(−1.28, 0.80)	(−0.37, 1.53)	(−0.66, 1.05)
	TSH	β	0.85	1.46	1.51	0.24	1.06
		(95% CI)	(−0.49, 2.18)	(−0.33, 3.26)	(−0.81, 3.84)	(−1.91, 2.38)	(−0.87, 2.98)
12 Months[2]	Free T4	β	−0.48	−6.40	4.39	1.26	3.45
		(95% CI)	(−6.22, 5.26)	(−13.89, 1.08)	(−3.56, 12.34)	(−7.20, 9.72)	(−4.76, 11.67)
	Total T4	β	−0.12	−0.45	0.33	−0.15	0.12
		(95% CI)	(−0.92, 0.68)	(−1.53, 0.63)	(−0.79, 1.46)	(−1.34, 1.04)	(−1.05, 1.28)
	TSH	β	1.71	0.10	2.92	0.46	1.91
		(95% CI)	(0.05, 3.37)*	(−2.16, 2.35)	(0.59, 5.25)*	(−2.04, 2.95)	(−0.51, 4.33)
24 Months[3]	Free T4	β	−4.29	−2.67			
		(95% CI)	(−11.60, 3.02)	(−8.95, 3.62)			
	Total T4	β	−0.17	0.43			
		(95% CI)	(−1.20, 0.85)	(−0.43, 1.30)			
	TSH	β	0.33	−1.31			
		(95% CI)	(−1.97, 2.63)	(−3.25, 0.63)			

*$P < 0.05$.

[1]Models adjusted for maternal age, employment status at enrollment and at the 6-months visit, country of birth, time lived in the US, Diet Quality Index, blood lead levels and delivery complications; child hospitalization before 6 months, season of assessment and psychometrician.

[2]Models adjusted for maternal age, employment status at enrollment and at the 6 months visit, country of birth, time lived in the US, Diet Quality Index, Kotelchuck Adequacy of Prenatal Care Utilization Index, blood lead levels, delivery complications and PPVT score; child age, preterm birth, hospitalization at 6 months and 1 year, family structure at 1 year; season, and language spoken at the time of assessment.

[3]Models adjusted for maternal age, income, employment status at enrollment, 6 months and 1 year, country of birth, Diet Quality Index, Kotelchuck Adequacy of Prenatal Care Utilization Index, blood lead levels, delivery complications, PPVT score; child hospitalization at 1 year; number of children in the home at 6 months, home density at 2 years, family structure at 1 year; season, psychometrician and language of assessment.

[4]Since TSH was expressed on a $\log_2$ basis, β are equal to the change in neurodevelopmental outcomes for a doubling in TSH levels.

on cognitive (verbal and nonverbal), language, and memory tests.

Table 4 shows associations between maternal thyroid hormone levels and child scores on the Bayley and Preschool Language scales at 6, 12, and 24 months of age. Associations between maternal free T4 and scores on the Bayley scales were consistently negative but none were statistically significant either in unadjusted (results not shown) or adjusted models. Associations between Bayley scores and total T4 were also generally negative but not statistically significant. Increasing maternal TSH was related to better performance on the Bayley MDI and on the auditory comprehension subscale of the PLS at 12 months but maternal thyroid hormone was not related to these constructs at later points. Maternal free and total T4 levels were not significantly associated with scores on the PLS.

Maternal free T4, total T4, and TSH were not associated with performance on any tests of neurodevelopment in 60-month-old children (Table 5) with one exception: every doubling in TSH levels was associated with a 0.65 point decrease (95%CI $= -1.26, -0.04$) on the Attention Deficit Hyperactivity Disorder (ADHD) subscale of the CBCL, although there was no significant association between maternal TH levels and CBCL Attention Problems and Pervasive Developmental Problems scales nor on child's performance on the KCPT (results not shown). Categorizing each measure of TH at the 10th or 90th percentiles yielded no significant association; subclinical hyperthyroidism was also not related with outcomes.

4. Discussion

We found little evidence that TH levels measured around the 27th week of gestation in mothers of euthyroid infants living in an iodine-sufficient area [53] were associated with child neurodevelopment. Although increasing maternal TSH levels were associated with better performance on the Bayley MDI at 12 months, these results did not persist at 24 months. Similarly, a reduction in ADHD symptoms, as reported by mothers in 60-month-old children, was not supported by other measures of hyperactivity and/or inattention at this age (i.e., maternal report on the Attention Problems scale of the CBCL or child performance on the KCPT). Better Auditory

Table 5: Associations between maternal thyroid hormone levels during pregnancy (27 weeks' gestation) and child neurodevelopment at 5 years of age.[1]

	Free T4		Total T4		TSH[2]	
	β	(95% CI)	β	(95% CI)	β	(95% CI)
Performance IQ						
WPPSI[3]	−4.12	(−13.73, 5.49)	0.03	(−1.35, 1.41)	−2.26	(−5.27, 0.74)
Motor Development						
WRAVMA[4]						
Pegboard-Dominant	−3.76	(−15.45, 7.93)	−0.97	(−2.64, 0.70)	0.51	(−3.12, 4.15)
Pegboard-Nondominant	−4.21	(−16.03, 7.61)	−1.55	(−3.23, 0.13)	0.02	(−3.65, 3.68)
McCarthy						
Draw-a-Child	−5.98	(−16.74, 4.77)	0.10	(−1.44, 1.63)	0.06	(−3.27, 3.39)
Gross Motor-Leg	−0.14	(−1.60, 1.32)	0.00	(−0.22, 0.22)	0.16	(−0.31, 0.63)
Gross Motor-Arm	0.08	(−1.51, 1.66)	−0.04	(−0.27, 0.19)	0.04	(−0.45, 0.53)
Language Development						
WPPSI[3] Vocabulary	−0.21	(−1.98, 1.57)	−0.22	(−0.47, 0.03)	−0.37	(−0.92, 0.19)
PPVT[5]	−2.71	(−14.18, 8.77)	−0.89	(−2.54, 0.76)	−1.05	(−4.66, 2.57)
Memory						
McCarthy						
Words and Sentences	0.10	(−11.32, 11.52)	−0.55	(−2.17, 1.07)	−1.44	(−4.97, 2.09)
Digit Span Forward	4.06	(−4.72, 12.83)	0.77	(−0.46, 2.00)	−1.83	(−4.51, 0.86)
Digit Span Backward	4.43	(−2.55, 11.42)	−0.10	(−1.13, 0.94)	−0.38	(−2.63, 1.87)
School Readiness						
Woodcock-Johnson/Muñoz						
Letter-Word	−1.86	(−9.33, 5.60)	0.21	(−0.88, 1.31)	1.43	(−0.94, 3.80)
Applied Problems	−3.82	(−14.06, 6.42)	−0.51	(−2.01, 1.00)	−1.48	(−4.74, 1.78)
Attention						
CBCL[6]						
ADHD[7]	−0.10	(−2.03, 1.82)	0.00	(−0.28, 0.27)	−0.65	(−1.26, −0.04)*
KCPT[8]						
ADHD[7] Confidence Index	7.52	(−4.86, 19.91)	0.09	(−1.70, 1.87)	−0.75	(−4.61, 3.12)

*$P < 0.05$.

[1]Models adjusted for maternal age, income, employment status at 6 months, country of birth, Diet Quality Index, delivery complications, PPVT score; child 5-minute APGAR, hospitalization at 1 year; number of children in home at 1 and 2 years, home density at 2 years, family structure at 1 year; season of assessment.

[2]Since TSH was expressed on a $\log_2$ basis, β are equal to the change in neurodevelopmental outcomes for a doubling in TSH levels.

[3]Weschler Preschool and Primary Scale of Intelligence.

[4]Wide Range Assessment of Visual Motor Ability.

[5]Peabody Picture Vocabulary Test.

[6]Child Behavior Checklist.

[7]Attention Deficit Hyperactivity Disorder.

[8]Kiddie Continuous Performance Test.

Comprehension also was noted at 12 months but not on other tests of language (WPPSI Vocabulary and PPVT) at 60 months.

Our results are in agreement with those reported by Pop and colleagues, the only other group that examined associations between maternal TH levels during the second half of gestation and child neurodevelopment [8–10]. In these studies, authors reported no associations between free T4 levels measured at 24 and 32 weeks' gestation and infant and toddler development, but did find relations with maternal thyroid hormone measured earlier in pregnancy. Other studies that measured TH during the first half of pregnancy have also reported associations with child neurodevelopment [2–10] with a notable exception in the study by Oken et al., which found no association between maternal TSH and total T4 at 10 weeks' gestation and child cognition at 6 months and 3 years of age in a large study of 500 mothers and children dyads [11]. TH of maternal origin may thus be of particular importance to brain development before the onset of fetal thyroid function, which occurs around midgestation [54]. Evidence for the potential role of maternal TH before the onset of fetal thyroid function includes the detection of T4 in coelomic fluid as early as 6 weeks' gestation [55], the fact that nuclear T3 receptors were identified in the brain of 10 week old fetuses [56], and that T3 binding to these receptors was detected between 9 and 13 weeks' gestation [57].

This study has some limitations. Women who were excluded from analyses were more likely to be depressed and to give birth to children of lower birth weight. This may have introduced bias since these variables are related to both thyroid hormone levels and neurodevelopment. However, our results were not substantially altered after applying inverse probability of inclusion weights, suggesting that this potential bias may not explain our null finding. In addition, in our study, as well as in those of Pop and colleagues [8–10], most women were euthyroid. Hence, our findings do not preclude the possibility that more extreme maternal thyroid hormone levels in the latter half of pregnancy may influence fetal neurodevelopment.

This study has a number of strengths. We examined a wide range of domains of behavior and neurodevelopment at multiple ages and examined maternal thyroid hormone using direct equilibrium dialysis, which is currently considered the gold standard method to measure free T4. Prior studies exclusively used immunoassays, which, according to the National Academy of Clinical Biochemistry, may only be considered as free T4 "estimates" [52]. Another strength of the present study is that we were able to consider, and control for, a large number of potential confounders, including exposure to neurotoxicants such as lead, cigarette smoke, and organophosphate insecticides [58]. In addition, our population is demographically homogenous, further reducing the potential for confounding. Finally, Zoeller and Rovet proposed that maternal hypothyroxinemia and hypothyroidism at the beginning of the third trimester (when we determined thyroid function in CHAMACOS women) primarily affects gross and fine motor skills, memory, and visuospatial skills [59]. In this study, we evaluated these constructs using well-validated and widely used instruments and yet found no clear evidence of a relationship between maternal thyroid hormone levels and child neurodevelopment.

In summary, this is the first study of maternal thyroid hormone and child neurodevelopment to use direct equilibrium dialysis to measure free T4. Although prior studies did report associations between maternal clinical hypothyroidism and mild hypothyroxinemia during the first half of pregnancy and cognitive impairments in children, we find no convincing evidence that TH measured during later gestation is associated with neurodevelopment in euthyroid children living in an iodine-sufficient area.

Appendices

A. Maternal Covariates

Baseline visit	
Age at enrollment (years), No. (%)	
18–24	130 (45.3)
25–29	95 (33.1)
30–34	42 (14.6)
34–45	20 (7.0)
Age at enrollment (years), Mean (SD)	25.8 (5.0)
Race, No. (%)	
White	5 (1.7)
Latino	278 (96.9)
Other	4 (1.4)
Education, No. (%)	
≤6th grade	121 (42.2)
7–12th grade	105 (36.6)
≥High School	61 (21.3)
Income (% poverty), No. (%)	
<100	171 (59.6)
100–200	105 (36.6)
>200	11 (3.8)
Average income per person per month ($), Mean (SD)	413.8 (255.7)
Employment status, No. (%)	
No	209 (72.8)
Yes	78 (27.2)
Country of birth, No. (%)	
United States	32 (11.1)
Mexico	251 (87.5)
Other	4 (1.4)
Time in the USA (years), No. (%)	
≤5	156 (54.4)
6 to 10	69 (24.0)
≥11	62 (21.6)
Parity, Mean (SD)	1.3 (1.2)
Smoking during pregnancy, No. (%)	
No	271 (94.4)
Yes	16 (5.6)
Smokers in household during pregnancy, No. (%)	
No	258 (89.9)
Yes	29 (10.1)
Any second-hand smoke exposure during pregnancy, No. (%)	
No	179 (62.4)
Yes	108 (37.6)
More than one alcoholic drink per week during pregnancy, No. (%)	
No	282 (98.3)
Yes	5 (1.7)
Any drug consumption during pregnancy, No. (%)	
No	282 (98.3)
Yes	5 (1.7)
Kotelchuck Adequacy of Prenatal Care Utilization Index, No. (%)	
Inadequate	62 (21.6)
Adequate	93 (32.4)
Adequate Plus	132 (46.0)
Diet Quality Index during pregnancy, Mean (SD)	45.3 (9.7)
Composite Social Support Index, Mean (SD)	3.7 (0.9)
Urinary DAP[1] metabolites during pregnancy (nmol/L), Mean (SD)	2.1 (0.4)

Lead levels during pregnancy (ug/dL), Mean (SD)	1.5 (2.1)
6-Month Visit	
Income (% poverty), No. (%)	
<100	199 (69.3)
100–200	86 (30.0)
>200	2 (0.7)
Employment status, No. (%)	
No	199 (69.3)
Yes	88 (30.7)
PPVT[2] score, Mean (SD)	88.2 (21.1)
WAIS[3] score, Mean (SD)	6.3 (2.6)
12-Month Visit	
Income (% poverty), No. (%)	
<100	179 (62.4)
100–200	99 (34.5)
>200	9 (3.1)
Employment status, No. (%)	
No	198 (69.0)
Yes	89 (31.0)
Composite Social Support Index, Mean (SD)	3.8 (1.0)
Depression, No. (%)	
No	140 (48.8)
Yes	147 (51.2)
24-Month Visit	
Income (% poverty), No. (%)	
<100	167 (58.2)
100–200	107 (37.3)
>200	13 (4.5)
Employment status, No. (%)	
No	174 (60.6)
Yes	113 (39.4)
Composite Social Support Index, Mean (SD)	3.9 (1.0)
Three-Year Visit	
Income (% poverty), No. (%)	
<100	178 (62.0)
100–200	103 (35.9)
>200	6 (2.1)
Employment status, No. (%)	
No	175 (61.0)
Yes	112 (39.0)
Depression, No. (%)	
No	161 (56.1)
Yes	126 (43.9)
60-Month visit	
Income (% poverty), No. (%)	
<100	182 (63.4)
100–200	93 (32.4)
>200	12 (4.2)
Employment status, No. (%)	
No	158 (55.1)
Yes	129 (44.9)
Composite Social Support Index, Mean (SD)	3.9 (1.0)

[1]Dialkyl phosphates (DAPs) measured in maternal urine (organophosphate pesticide metabolites).
[2]Peabody Picture Vocabulary Test (PPVT).
[3]Wechsler Adult Intelligence Scale (WAIS).

B. Child Covariates

Baseline visit	
Sex, No. (%)	
Boy	140 (48.8)
Girl	147 (51.2)
Birthweight (g), Mean (%)	
<2500	10 (3.5)
2500–3500	149 (51.9)
>3500	128 (44.6)
Gestational duration (weeks), No. (%)	
≥37	266 (92.7)
<37	21 (7.3)
Cesarean section, No. (%)	
No	220 (76.7)
Yes	67 (23.3)
Pregnancy complications, No. (%)	
No	284 (99.0)
Yes	3 (1.0)
5-minute APGAR score, Mean (SD)	8.9 (0.4)
Months child breastfed, Mean (SD)	8.6 (8.2)
Neonatal TSH (mIU/L), Mean (SD)	6.5 (3.5)
6-Month Visit	
Number of children in household, Mean (SD)	2.1 (0.4)
Housing density (people per room), No. (%)	
≤0.5	4 (1.4)
0.51–1.00	52 (18.1)
1.01–1.50	93 (32.4)
≥1.51	138 (48.1)
Lived with father, No. (%)	
All the time	242 (84.3)
Most of the time	11 (3.8)
Some of the time	14 (4.9)
Not at all	20 (7.0)
HOME[1] score, Mean (SD)	32.0 (4.1)
Hospitalized overnight, No. (%)	
No	253 (88.2)
Yes	34 (11.8)
Age at assessment (months), Mean (SD)	6.6 (1.1)
Medication/herbal intake within 24 hours of assessment, No. (%)	
No	279 (97.2)
Yes	8 (2.8)

Location assessment performed, No. (%)	
Office	187 (65.2)
Other	100 (34.8)
Season assessment performed, No. (%)	
January–March	68 (23.7)
April–June	71 (24.7)
July–September	77 (26.8)
October–December	71 (24.7)
Psychometrician at assessment, No. (%)	
01	117 (40.8)
07	32 (11.1)
13	42 (14.6)
16	4 (1.4)
23	92 (32.1)
12-Month Visit	
Number of children in household, Mean (SD)	2.0 (1.7)
Housing density (people per room), No. (%)	
≤0.5	1 (0.3)
0.51–1.00	55 (19.2)
1.01–1.50	105 (36.6)
≥1.51	126 (43.9)
Lived with father, No. (%)	
All the time	239 (83.3)
Most of the time	11 (3.8)
Some of the time	13 (4.5)
Not at all	24 (8.4)
HOME[1] score, Mean (SD)	35.9 (3.1)
Hospitalized overnight, No. (%)	
No	276 (96.2)
Yes	11 (3.8)
Age at assessment (months), Mean (SD)	12.7 (1.3)
Medication/herbal intake within 24 hours of assessment, No. (%)	
No	255 (88.9)
Yes	32 (11.1)
Location assessment performed, No. (%)	
Office	190 (66.2)
Other	97 (33.8)
Season assessment performed, No. (%)	
January–March	73 (25.4)
April–June	67 (23.3)
July–September	74 (25.8)
October–December	73 (25.4)
Psychometrician at assessment, No. (%)	
01	109 (38.0)
07	83 (28.9)
23	95 (33.1)
24-Month visit	
Number of children in household, Mean (SD)	1.8 (1.5)
Housing density (people per room), No. (%)	
≤0.5	2 (0.7)
0.51–1.00	51 (17.8)
1.01–1.50	94 (32.8)
≥1.51	140 (48.8)
Lived with father, No. (%)	
All the time	236 (82.2)
Most of the time	23 (8.0)
Some of the time	5 (1.7)
Not at all	23 (8.0)
HOME[1] score, Mean (SD)	26.1 (2.5)
Hospitalized overnight, No. (%)	
No	275 (95.8)
Yes	12 (4.2)
Age at assessment (months), Mean (SD)	24.7 (1.2)
Medication/herbal intake within 24 hours of assessment, No. (%)	
No	205 (71.4)
Yes	82 (28.6)
Location assessment performed, No. (%)	
Office	194 (67.6)
Other	93 (32.4)
Season assessment performed, No. (%)	
January–March	73 (25.4)
April–June	85 (29.6)
July–September	71 (24.7)
October–December	58 (20.2)
Psychometrician at assessment, No. (%)	
01	122 (42.5)
07	31 (10.8)
23	134 (46.7)
60-Month visit	
Number of children in household, Mean (SD)	1.9 (1.3)
Housing density (people per room), No. (%)	
≤0.5	1 (0.3)
0.51–1.00	87 (30.3)
1.01–1.50	126 (43.9)
≥1.51	73 (25.4)
Lived with father, No. (%)	
All the time	221 (77.0)
Most of the time	16 (5.6)
Some of the time	11 (3.8)
Not at all	39 (13.6)
Hospitalized overnight, No. (%)	
No	279 (97.2)
Yes	8 (2.8)

Attended preschool, No. (%)	
No	124 (43.2)
Yes	163 (56.8)
Attended kindergarten, No. (%)	
No	68 (23.7)
Yes	219 (76.3)
Age at assessment (months), Mean (SD)	60.7 (2.2)
Medication/herbal intake within 24 hours of assessment, No. (%)	
No	240 (83.6)
Yes	47 (16.4)
Location assessment performed, No. (%)	
Office	245 (85.4)
Other	42 (14.6)
Season assessment performed, No. (%)	
January–March	76 (26.5)
April–June	72 (25.1)
July–September	86 (30.0)
October–December	53 (18.5)
Psychometrician at assessment, No. (%)	
01	117 (40.8)
21	23 (8.0)
23	32 (11.1)
43	115 (40.1)

[1]Home Observation for Measurement of the Environment (H.O.M.E).

Acknowledgments

This publication was supported by grant numbers: RD 83171001 from the US Environmental Protection Agency and P01 ES009605 from the National Institute for Environmental Health Sciences. Additional funding was provided by the University of California Institute for Mexico and the United States (UC MEXUS), the Fonds de la Recherche en Santé du Québec and the Canadian Institutes for Health Research. The contents of this publication are solely the responsibility of the authors and do not necessarily represent funders' official views. The authors gratefully acknowledge study participants as well as Jon Nakamoto, MD, Ph.D., Michelle Vedar, MPH and Kristin M. Tyler, BA, for their invaluable contributions. Authors declare that they have no competing financial interests.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 235130, 5 pages
doi:10.4061/2011/235130

Research Article

Suspected Spontaneous Reports of Birth Defects in the UK Associated with the Use of Carbimazole and Propylthiouracil in Pregnancy

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Received 19 April 2011; Revised 19 June 2011; Accepted 19 June 2011

Academic Editor: Kris Gustave Poppe

The concept of a carbimazole embryopathy underlies current Endocrine Society advice to avoid this drug in early pregnancy, favouring propylthiouracil as an alternative for the treatment of maternal hyperthyroidism. We aimed to establish whether suspected spontaneous reporting of adverse drug reactions in the UK via the Yellow Card Scheme supports a carbimazole embryopathy and the lack of association between propylthiouracil and congenital anomalies. All birth defects related to maternal treatment with carbimazole or propylthiouracil reported over a 47-year period via the Yellow Card Scheme were analysed. 57 cases with 97 anomalies were reported following in utero exposure to carbimazole. These anomalies included aplasia cutis, choanal atresia, tracheo-oesophageal fistula, and patent vitellointestinal duct, which have previously been reported in association with carbimazole/methimazole exposure in utero. Only 6 cases with 11 anomalies were reported for propylthiouracil, all within the last 15 years. Therefore, these findings may support a carbimazole embryopathy. There are few birth defects associated with propylthiouracil, but this should be interpreted in the context of higher historical prescription rates for carbimazole.

1. Introduction

Hyperthyroidism, primarily caused by Graves' disease, affects about 1 in 500 pregnancies. Although not common, it is important to recognise and treat maternal hyperthyroidism, because failing to do so can have detrimental effects. In the mother, untreated hyperthyroidism can cause spontaneous miscarriage, pregnancy induced hypertension, preterm labour, congestive cardiac failure, and thyroid storm; for the fetus this could mean still birth, intrauterine growth restriction, or low birth-weight [1]. Further, hyperthyroid states in the mother have been associated with congenital anomalies including oesophageal atresia, tracheo-oesophageal fistula, and biliary tree atresia [2, 3].

There is also an association between the antithyroid drugs used to treat maternal hyperthyroidism and congenital anomalies. This association is most widely reported for carbimazole and its active metabolite, methimazole, such that the concept of a carbimazole embryopathy is being increasingly acknowledged amongst prescribing clinicians [4–9]. There has been no convincing link between the alternative thionamide drug propylthiouracil and birth defects [10] despite the rate of placental transfer of the drug being the same as that of carbimazole [11]. Both drugs are equally efficacious at controlling maternal hyperthyroidism [12]. This has led to the Endocrine Society's current advice to use propylthiouracil as a first-line drug during pregnancy, if available, especially during first trimester organogenesis [13]. Carbimazole or methimazole should be used only if propylthiouracil is not available or if the patient cannot tolerate or has an adverse response to it [13].

Recognition of serious adverse effects of anti-thyroid drugs in pregnancy is dependent upon reporting of such effects by prescribing clinicians. Since 1964, the Yellow Card

Scheme has allowed healthcare professionals involved in prescribing in the UK to report suspected serious adverse drug reactions (ADRs) to the Commission on Human Medicines (CHM)/Medicines and Healthcare Products Regulatory Agency (MHRA). The professional reporting the suspected ADR submits a Yellow Card found at the back of the British National Formulary, or electronically via the MHRA website, giving brief clinical details supporting their suspicions that the drug is responsible for the adverse outcome(s) seen. In addition, pharmaceutical companies are legally required to report suspected serious ADRs of their products. Since October 2005, patients have also been able to report suspected ADRs through the Yellow Card Scheme.

In this paper, we aimed to establish whether spontaneous reporting via the Yellow Card Scheme in the UK lends support to an association between congenital anomalies and the use of carbimazole or propylthiouracil in pregnancy.

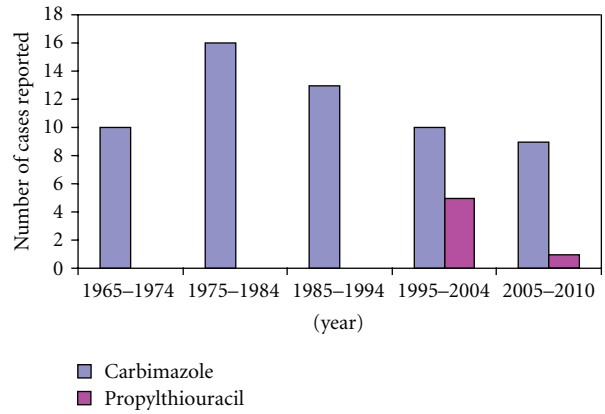

Figure 1: Bar graph showing number of cases with congenital malformations reported following exposure to carbimazole or propylthiouracil by decade from 1965 until 2010.

2. Methods

Data on all birth defects reported via the Yellow Card Scheme in association with treatment with carbimazole or propylthiouracil between July 1963 and September 2010 was obtained in "Drug Analysis Prints" from the MHRA [14]. Drug Analysis Prints give a complete listing of all UK spontaneous suspected ADRs reported through the Yellow Card Scheme by healthcare professionals, patients, and the pharmaceutical industry to the MHRA and CHM. They do not present a complete overview of the risks associated with specific medicines, and conclusions on the safety and risks of medicines cannot be made on the information contained in Drug Analysis Prints alone.

3. Results

The Drug Analysis Print from the MHRA included 64 reports of birth defects following exposure to antithyroid drugs, reported between 1963 and 2010. Of these, 54 reports came from healthcare professionals, 9 from pharmaceutical companies, and one from a patient. On review, one of the reports was found not to comprise birth defect and was excluded from further analysis.

Figure 1 shows the total numbers of birth defects reported following exposure to carbimazole and propylthiouracil by decade. For carbimazole, there have been 57 cases with a total of 97 congenital anomalies. Three (5%) of these cases (with tracheo-oesophageal fistula, anencephaly, and unspecified congenital heart disease, respectively) have been reported as fatal. For propylthiouracil, only 6 cases with 11 congenital anomalies have been reported, but these have all been within the last 15 years. None of the six cases has been reported as fatal.

Table 1 describes the type of birth defects reported for carbimazole and propylthiouracil exposure in utero and the number of defects seen in conjunction with other anomalies in the same individual. Two-thirds of the cases with birth defects associated with both carbimazole and propylthiouracil exposure had multiple anomalies in the same individuals. Birth defects associated with carbimazole exposure included aplasia cutis, choanal atresia, tracheo-oesophageal fistula, patent vitellointestinal duct, and dysmorphic facies, which have been previously reported as components of carbimazole embryopathy [9]. The doses of carbimazole used were known for 34 out of 57 cases (60%), and ranged between 5 mg and 60 mg daily (median 15 mg). Similarly, the dose of propylthiouracil, known for 5 out of 6 cases (83%), ranged widely from 50 mg to 350 mg daily (median 50 mg).

4. Discussion

Our results support an association between exposure to carbimazole in utero and birth defects. There have been far fewer reports via the Yellow Card Scheme of birth defects related to propylthiouracil exposure, but all the reports related to this drug have been within the last 15 years; this may reflect the fact that historically carbimazole has been the more widely prescribed drug in the UK [15], rather than it its rate of teratogenicity being significantly higher. There has been a 3.5-fold increase in PTU prescription relative to carbimazole since 1981 in the UK [15], which may have unmasked adverse effects that had previously gone unnoticed. Changes in prescribing trends are also reflected by data from the USA, where between 2002 and 2008, propylthiouracil use increased in women of childbearing age [16].

The teratogenicity of anti-thyroid drugs remains a source of controversy [17]. Two previous studies comparing carbimazole with propylthiouracil showed no difference in the number of major congenital anomalies seen in babies exposed to these drugs in utero [12, 18]. However, both studies were relatively small. A study from Sweden found 4 reports between 1995–2000 of infants born with oesophageal atresia and omphalocele or choanal atresia, 3 of whom had been exposed to methimazole in the first trimester; there was no association between these anomalies and propylthiouracil [19]. A recent larger case control study which included over 18,000 cases with congenital malformations, 127 of whom were exposed to antithyroid drugs in the first trimester, showed a significant association between exposure to carbimazole/methimazole and choanal atresia or omphalocele [20]. For

Table 1: Suspected adverse drug reactions of congenital anomalies associated with carbimazole and propylthiouracil received via the UK Yellow Card Scheme.

System	Congenital anomalies*	Carbimazole			Propylthiouracil		
		Number of anomalies (total)	Number with single anomaly	Number with other anomalies	Number of anomalies (total)	Number with single anomaly	Number with other anomalies
Skin	Aplasia cutis	6	2	4	0	0	0
	Other (skin disorder, ulcer)	2	0	2	0	0	0
Respiratory	Choanal atresia	5	2	3	0	0	0
	Tracheo-oesophageal fistula	2	2	0	0	0	0
	Other (neonatal respiratory distress syndrome, respiratory disorder)	2	0	2	0	0	0
Gastrointestinal	Cleft palate	5	3	2	1	1	0
	Omphalocele/umbilical abnormalities	4	2	2	2	0	2
	Patent vitellointestinal duct	1	0	1	0	0	0
	Duodenal atresia	1	1	0	0	0	0
	Anal atresia	1	0	1	0	0	0
	Other (neonatal jaundice and abnormal liver function tests)	2	0	2	0	0	0
	Not specified	3	2	1	0	0	0
Cardiovascular	Septal defects	3	1	2	0	0	0
	Other (Fallot's tetralogy and coarctation of aorta)	2	2	0	0	0	0
	Not specified	1	0	1	0	0	0
Musculoskeletal	Limb/hand/foot malformation	4	1	3	3	1	2
	Not specified	4	3	1	0	0	0
Neurological	Spina bifida	3	1	2	0	0	0
	Hydrocephalus	5	1	4	0	0	0
	Anencephaly	4	4	0	1	0	1
	Hypotonia	2	0	2	0	0	0
	Other (spine malformation and holoprosencephaly)	1	0	1	1	0	1
Renal/urinary tract	Renal aplasia	1	0	1	0	0	0
	Other (urinary tract malformation, epispadias)	1	0	1	1	1	0
Endocrine	Thyroid disorder	1	0	1	0	0	0
	Hypogonadism	1	0	1	0	0	0
Craniofacial	Dysmorphic facies	2	0	2	1	0	1
	Skull malformation	4	1	3	0	0	0
	Ear malformation	3	1	2	0	0	0
	Deafness	4	2	2	0	0	0
	Eye malformation	4	1	3	0	0	0
	Other (nose malformation and teeth malformation)	2	0	2	0	0	0
Others	Nipple/breast anomalies (athelia and hypoplastic nipples)	2	0	2	0	0	0
	Developmental delay	2	0	2	0	0	0
	Autism	0	0	0	1	0	1
	Not specified	7	1	6	0	0	0
Total		**97**	33	64	**11**	3	8

*One Yellow Card report may contain more than one reaction term. Therefore, the total number of reactions is greater than the total number of reports.

propylthiouracil, there was a tentative suggestion of an association with situs inversus, renal agenesis, or dysgenesis and cardiac outflow tract malformations although these were not as strong as the associations reported for carbimazole [20]. Consistent with these observations, we found five cases of choanal atresia and four cases of umbilical anomalies associated with carbimazole exposure in our study (Table 1). There were no reports of situs inversus, renal agenesis, or cardiac malformations associated with propylthiouracil exposure (Table 1).

The nature of congenital malformations seen in our cases is wide ranging, keeping with previous reports of birth defects related to these drugs (Table 1). Several of the congenital malformations associated with carbimazole exposure observed in this study, including aplasia cutis, choanal atresia, tracheo-oesophageal fistula, omphalocele, patent vitellointestinal duct, nipple abnormalities, and dysmorphic facies, have previously been reported in association with carbimazole/methimazole exposure in utero [9]. Furthermore, two-thirds of the anomalies associated with carbimazole exposure occurred with other defects in the same cases, lending further support to an embryopathy as opposed to a single malformation which might have occurred spontaneously irrespective of exposure to teratogens or not. It should be noted that most of the anomalies seen following propylthiouracil exposure also did not occur in isolation, but given the small numbers for propylthiouracil, this should be interpreted with caution.

We acknowledge that there are several limitations to our study. Firstly, true prevalence of birth defects related to carbimazole and propylthiouracil cannot be calculated from the information we have collated. We do not know the total number of births to mothers with Graves' disease over the study period, and we do not have data relating to the types of anti-thyroid drugs prescribed to pregnant women over the study period. In addition, Yellow Card data cannot be used as a reliable indicator of the frequency of suspected ADRs to medicines. The number of reports received via the Yellow Card Scheme does not directly equate to the number of people who suffer adverse reactions to drugs. It is recognised that this scheme is associated with an unknown and variable level of underreporting. The level of ADR reporting may fluctuate between given years due to a variety of reasons, for example, a medicine being new, stimulated interest/publicity, and variations in exposure to the medicine. In this case, there is potential for bias in that prescribers may be more likely to make an association between a congenital anomaly and carbimazole given previous reports of an embryopathy related to the drug which is not the case for propylthiouracil. Similarly, carbimazole and propylthiouracil were introduced to the market at different times, and therefore, reporting bias means that they should not be directly compared.

Secondly, causality cannot be proven. It is important to note that a report of an ADR does not necessarily mean that it was caused by the drug. Many factors have to be taken into account in assessing causal relationships including temporal association, the possible contribution of concomitant medication, and the underlying disease. We do not have information on maternal thyroid function for our cases; this is important, because maternal hyperthyroidism itself is associated with congenital anomalies [2, 3]. Furthermore, in a cohort study of infants of mothers with Graves' disease, the incidence of congenital malformations was significantly higher in infants whose mothers were hyperthyroid in the first trimester compared to those who were euthyroid, with a reported prevalence of 6% and 0.3% in the two groups, respectively [21].

Thirdly, we do not have a complete data on the doses and durations of the carbimazole or propylthiouracil exposure in our cases. We only know doses used for 60% of patients treated with carbimazole and 83% of patients treated with propylthiouracil.

Nevertheless, the multiple characteristic congenital anomalies we have reported in this study lend support to the teratogenicity of thionamide drugs, in particular carbimazole. This has important clinical implications, and prescribing physicians should be aware of the potential association with congenital anomalies whilst balancing this risk with that of uncontrolled maternal hyperthyroidism in pregnancy.

5. Conclusion

The evidence we have described in this study may support a carbimazole embryopathy. There are few birth defects associated with propylthiouracil, but this should be interpreted in the context of higher historical prescription rates for carbimazole.

Conflict of Interests

The authors declare that there is no conflict of interest.

Acknowledgments

The authors are grateful to staff at the Medicines and Healthcare Products Regulatory Agency (MHRA), UK, for extracting the data from the Yellow Cards, and providing helpful comments on our manuscript. Work of BV was partly supported by the National Institute for Health Research (NIHR). The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health, United Kingdom.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 342189, 14 pages
doi:10.4061/2011/342189

Review Article

Do Thyroid Disrupting Chemicals Influence Foetal Development during Pregnancy?

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Received 15 March 2011; Revised 13 May 2011; Accepted 2 June 2011

Academic Editor: Bijay Vaidya

Maternal euthyroidism during pregnancy is crucial for normal development and, in particular, neurodevelopment of the foetus. Up to 3.5 percent of pregnant women suffer from hypothyroidism. Industrial use of various chemicals—endocrine disrupting chemicals (EDCs)—has been shown to cause almost constant exposure of humans with possible harmful influence on health and hormone regulation. EDCs may affect thyroid hormone homeostasis by different mechanisms, and though the effect of each chemical seems scarce, the added effects may cause inappropriate consequences on, for example, foetal neurodevelopment. This paper focuses on thyroid hormone influence on foetal development in relation to the chemicals suspected of thyroid disrupting properties with possible interactions with maternal thyroid homeostasis. Knowledge of the effects is expected to impact the general debate on the use of these chemicals. However, more studies are needed to elucidate the issue, since human studies are scarce.

1. Introduction

Maintaining maternal euthyroidism during pregnancy is important for growth and development, in particular neurodevelopment of the foetus. Even subtle changes in thyroid function of the pregnant woman can cause detrimental effects for the foetus [1–5]. In the first trimester, the foetus relies solely on the thyroid hormones thyroxine (T4) and triiodothyronine (T3) and iodine from the mother. Later in pregnancy and during lactation, maternal thyroid hormones still contribute significantly to foetal thyroid homeostasis [6–8]. Worldwide, both overt and subclinical hypothyroidism are frequent among fertile women [9–14]. Prior maternal thyroid diseases as well as iodine and selenium deficiencies are known risk factors for hypothyroidism.

Abundant industrial and household use of various chemicals—called endocrine disrupting chemicals (EDCs)—expose humans with potential harmful influences on health and hormone regulation. As recently reviewed, several of these EDCs have been found to have thyroid disrupting properties as well [15–17]. Probably each chemical has limited thyroid disruptive effects at environmental exposure doses. However, the combined influence of several chemicals through different pathways of thyroid hormone synthesis and action may have significant impact on both maternal and foetal thyroid function [18, 19] and, thus, a potential to compromise foetal development and maturation.

This paper will focus on the influence of thyroid hormones on foetal development in relation to the chemicals suspected to have thyroid disrupting properties. Knowledge on these effects is expected to impact international debate on the general use of these chemicals.

2. Maternal and Foetal Thyroid Status during Pregnancy

The main task of the thyroid gland is to generate the necessary quantity of thyroid hormone to meet the demands of the organism. The mechanisms involved in thyroid homeostasis are shown in Figure 1. Each step of thyroid hormone metabolism is crucial for normal function. Maternal thyroid

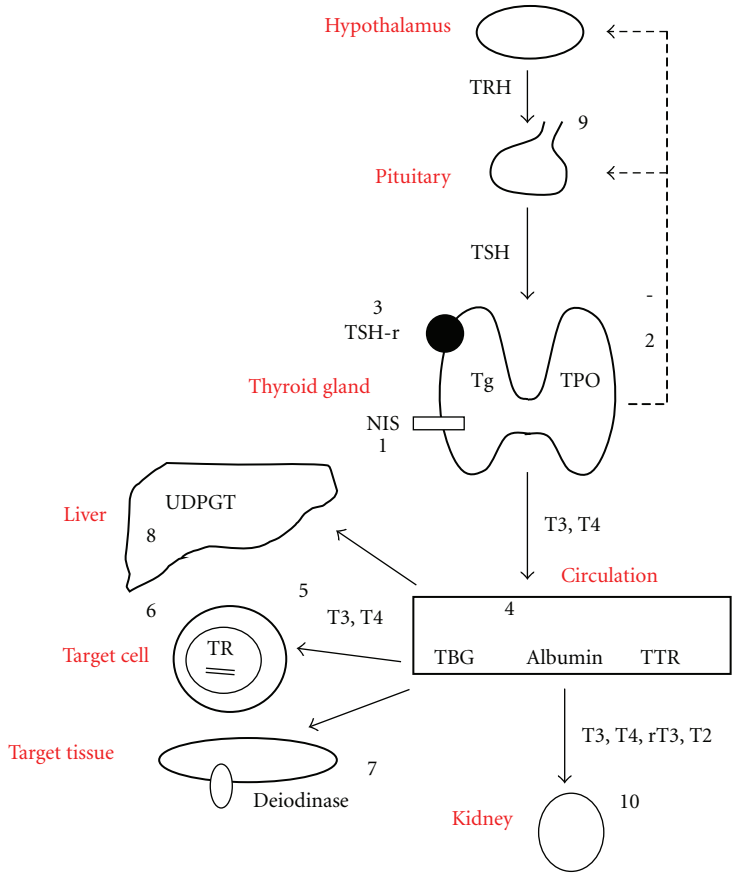

Figure 1: The complex mechanisms of regulation of thyroid hormone homeostasis and the possible mechanism of action of the thyroid disrupting chemicals. The thyroid and the thyroid hormones, tri-iodothyronine (T3) and thyroxine (T4), participate with the hypothalamus, secreting thyrotropin releasing hormone (TRH), and pituitary, secreting thyrotropin (TSH) in a classical feedback controlled loop. Iodide is transported into the cell by the sodium-iodine symporter (NIS) and oxidized by thyroid peroxidase (TPO). TPO also catalyzes the iodination of thyrosine residues on thyroglobulin (Tg). All processes in the cell are stimulated by binding of TSH to the TSH receptor (TSH-R). In the circulation, thyroid hormones are bound to thyroxine-binding globulin (TBG), albumin and prealbumin, and in some cases transthyretin (TTR). T4 is deiodinated by deiodinases in the liver and target tissues. In the target cells, T3 binds to nuclear thyroid hormone receptor (TR), and with the retinoid X receptor, it binds at specific sequences at the DNA string, forming the thyroid hormone response elements (TRE). In the liver, thyroid hormones are metabolized by UDP-glucuronyl transferase (UDPGT), and finally, the metabolites are excreted in the urine. (1) Inhibition of iodine uptake in the cells by inhibition of NIS: perchlorate, thiocyanate, nitrate, and phthalates. (2) TPO inhibition: NP and isoflavones. (3) Inhibition of TSH-R: DDT and PCB. (4) Binding to transport proteins: PCB, phthalates, phenol, flame retardants, and HCB. (5) Cellular uptake of thyroid hormones: phthalates and chlordanes. (6) Binding to thyroid hormone receptor and affecting gene expression: PCB, phenols, flame retardants, BPA and HCB. (7) Inhibition of deiodinases: Styrenes and UV-filters, (8) Activation of hepatic UDPGT: dioxins and pesticides, (9) Inhibition of the hypothalamo-pituitary-thyroid axis: lead. (10) Excretion/clearance of thyroid hormones: PCB, dioxin, phenols, flame retardants, HCB, and BPA.

status is subject to substantial pregnancy-related physiological changes. Importantly, maternal thyroid hormone is metabolized by or crosses the placenta to reach the foetus [20]. In the placenta, the inner ring placental deiodinase inactivates most of the maternal T4 to reverse T3 (rT3), securing a minimal but highly significant supply of thyroid hormones to the foetus [20, 21], which further demands an increased thyroid hormone production by the mother.

The foetal thyroid function is established in the 11th week after conception [6]. However, the production and secretion of foetal thyroid hormones do not reach notable levels until midgestation [6]. Even at term, up to 30% of the foetal thyroid hormones are of maternal origin [22], and during the remaining part of pregnancy and lactation, the foetus and neonate are strongly dependent on the maternal thyroid gland.

3. Influence of Maternal Thyroid Disease on Foetal Development

The estimated prevalence of overt and subclinical hypothyroidism in pregnancy is 0.5% and 3%, respectively. Thyroid autoantibodies are found in 5%–15% of women of childbearing age [9–14]. The estimated high prevalence of thyroid disease in pregnant women has spurred a debate of whether screening of all pregnant women, instead of only targeted

case-finding, should be advised. In recent studies, 50% to 80% of the pregnant women with possible hypothyroidism would be missed if only high-risk cases were examined [23, 24], but screening of all pregnant women is not yet agreed upon in international scientific associations [25].

At least 50% of the offspring of women with free T4 (fT4) levels below the normal 10th percentile had delayed neurobehavioral development [2, 3, 26]. Even mild-to-moderate iodine deficiency during first trimester caused an intelligence quotient (IQ) 10–15 points below the normal mean and 11 of 16 children born to mothers with low iodine intake presented attention deficit hyperactivity disorders [27]. Iodine deficiency is the most frequent cause of maternal hypothyroxinaemia and a potentially preventable cause of mental retardation in children.

4. Endocrine Disrupting Chemicals and the Thyroid Gland

In recent years, numerous chemicals have been shown to interfere at different levels of thyroid hormone regulation and function (Figure 1). Most chemicals have not yet been sufficiently evaluated in humans. Yet, a number of detrimental effects on human thyroid function are suspected from a variety of chemicals, and a review of available evidence on this issue will be focused upon in the following.

4.1. Perchlorate. Perchlorate is a persistent ubiquitous chemical used worldwide in nitrate fertilizers, fireworks, road flare, matches, airbag inflation systems, and as oxidizers in solid propellants for rockets and missiles. Perchlorate appears in drinking water, milk, wine, beer, and lettuce, but also a natural perchlorate background of atmospheric origin exists [28]. Perchlorate has previously been used in the treatment of hyperthyroidism [29] due to its potent competitive inhibition of thyroid iodine uptake through the sodium-iodine symporter (NIS) [30]. However, the thyroid disrupting effect of perchlorate is dose dependent. Thus, occupational or environmental exposures of perchlorate have been associated with a reduction in thyroid iodine uptake [31–33] but without direct effects on thyroid function or volume except in a study of women with urinary iodine excretion below 100 μg/L in whom TSH was increased and TT4 was found reduced [34], and these findings are further supported by findings of an interaction of perchlorate and thiocyanate on thyroid status in smoking women with low iodine intake [35] (Table 1). A study of euthyroid and hypothyroid pregnant women from Cardiff in Wales and Turin in Italy found perchlorate in all urine samples and low iodine excretion from all the pregnant women, but no correlation was found between perchlorate levels and thyroid function parameters [36]. Likewise, in pregnant women and their neonates, perchlorate in drinking water did not influence thyroid hormone levels [37, 38], and no correlations were found between urinary perchlorate concentrations and fT4 or thyroid stimulating hormone (TSH), respectively, during first trimester in mildly hypothyroid women. Iodine is secreted into breast milk through NIS, and one study found that the highest concentrations of perchlorate in breast milk were associated with lower iodine concentrations [39], while others found no obvious correlations [40].

4.2. Thiocyanate and Nitrate. Thiocyanate and nitrate are less potent inhibitors of NIS than perchlorate [30] but, nitrate may decrease iodine absorption from the intestine [47].

Thiocyanate is present in a number of vegetables such as cabbage, broccoli, Brussels sprouts, rapeseed and mustard seed, cassava, radishes, spinach and tomatoes but also in milk. In many tropical countries, cassava as staple food is a major ingredient in the daily food supply. In iodine-deficient regions, food with high concentrations of thiocyanate contributes significantly to goitre development [48, 49]. However, in industrialized societies, the main source of thiocyanate is cigarette smoke [48]. Although this has well-known detrimental effects on the thyroid function of neonates and breastfed babies, it is beyond the scope of this paper.

Nitrate is found in several food items either occurring naturally, as in green leafy vegetables, or added as a preservative in cubed meats and other food and is also generated from the decomposition of organic materials. Inorganic nitrates are used as fertilizers, which may contaminate drinking water supplies, groundwater, and soil. Finally, the intestinal flora causes an endogenous formation of nitrate. Population studies on nitrate exposure through drinking water have found increased thyroid volume and slightly reduced thyroid function [50], but the isolated effect of nitrate has been difficult to assess due to concomitant iodine deficiency [51, 52]. But low levels of nitrate intake did not influence thyroid volume in adults despite of previous iodine deficiency [53].

4.3. Polychlorinated Biphenyls (PCBs). PCBs are still in use though several of them have been banned for decades in many countries. PCBs and their hydroxylated metabolites are biologically active, highly persistent compounds accumulating in lipid tissues, and structurally very close to T4 [54]. Many studies have been performed on the thyroid disturbing effects of PCBs, but results are conflicting (Table 2). PCBs may interfere with thyroid hormone homeostasis in several ways (Figure 1): by binding to transthyretin (TTR) [55], by affecting the expression of thyroid hormone-responsive genes, and by antagonizing the complexes from the thyroid hormone responsive elements (TRE) [56, 57]. Perinatal exposure may be most important in humans. Negative correlations have been demonstrated between PCBs in maternal blood during pregnancy and maternal thyroid hormones, and positive correlations have been described between PCBs and TSH [58]. As thyroid hormones in humans are mainly bound to thyroid hormone-binding globulin (TBG), the reduction in total T4 (TT4) and total T3 (TT3) could be explained by a reduced TBG level, whereas this would not necessarily affect free hormone levels [59]. In cord blood, a positive correlation of PCB and TSH of the child and a negative correlation with maternal TT3 and TT4 were found [60]. PCBs in cord blood have generally not demonstrated associations to T3 and T4 levels of the child [58, 61–65],

Table 1: Thyroid-disrupting properties of perchlorate in human studies on pregnant women, neonates, infants, adolescents, and adults and the effect of perchlorate on iodine contents in breast milk.

Year	Author	*N*	Subjects	Effect	Reference
2005	Tellez et al.	185	Early pregnant women	No effect	[38]
		135	Late pregnant women	No effect	
		162	Newborns	No effect	
2010	Pearce et al.	1641	Pregnant women	No effect	[36]
2000	Brechner et al.	1542	Newborns	↑TSH	[41]
2000	Li et al.	23000	Newborns	No effect	[42]
2007	Amitai et al.	1156	Newborns	No effect	[37]
2000	Crump et al.	9784	Newborns	↓TSH otherwise no effect	[43]
		162	Schoolchildren	No effect	
2006	Blount et al.	350	Iodine deficient women	↓ TT4 ↑TSH	[34]
		697	Iodine sufficient women	↑TSH	
			Men	No effect	
2000	Lawrence et al.	9	Healthy volunteers	No effect	[33]
				↓ thyroid radioiodine up-take	
2002	Greer et al.	8	Healthy volunteers	↓ thyroid radioiodine up-take	[32]
2006	Braverman et al.	13	Healthy volunteers	No effect	[44]
1998	Gibbs et al.	119	Occupationally exposed	No effect	[45]
1999	Lamm et al.	58	Occupationally exposed	No effect	[46]
2005	Braverman et al.	29	Occupationally exposed	↓ thyroid radioiodine up-take	[31]
2005	Kirk et al.	36	Lactating women	↓ Iodine in breast milk	[39]
2007	Pearce et al.	57	Lactating women	No effect on iodine in breast milk	[40]

N: number, TSH: thyrotropin, TT3: total tri-iodothyronine, TT4: total thyroxine, fT3: free Tri-iodothyronine, fT4: free thyroxine, and TBG: thyroid hormone-binding globulin.

except in a recent study finding higher TSH and lower T4 in infants of mothers with high levels of PCB in breast milk [66, 67]. Yet, not all studies found associations between infant thyroid hormone levels and PCB exposure [63–65, 68], and in a study of a prenatal boys exposed to high PCB levels, the thyroid function was comparable to that of the control group [69].

In several studies of humans of all ages from high PCB-exposed areas, blood PCB concentrations correlated negatively to circulating thyroid hormone levels [76, 79, 80, 83] and positively to TSH [74], while others could not find such associations [78, 81]. Increased thyroid volume has also been found more often in a PCB-polluted area with the largest volumes among subjects with the highest levels of PCB [82].

4.4. Dioxin. Dioxins are highly toxic, lipophilic, widely used, and persistent environmental pollutants from industrial burning processes or production of herbicides, detectable in samples from humans and wildlife populations though banned for years in many countries. The most toxic prototype is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and the toxic equivalent of all other dioxins is measured against this. In particular, the metabolites show a high degree of structural similarity to T4 and are the most biologically active. Dioxins have been found to decrease the level of circulating thyroid hormones in rats [85–87], and mixtures of dioxin-like compounds were even found to reduce levels of T4 in an additive manner [88]. Given to pregnant rats, a single dose of TCDD was transferred to the pups via placenta and during lactation [89] and resulted in a dose-dependent decrease of T4 and fT4 with a concomitant increase in TSH [86, 87]. High exposure with TCDD of US war veterans of the Vietnam war resulted in significantly increased TSH [90]. In children, no associations between placental dioxins and thyroid hormones were found at the age of 2 years, but after 5 years, T3 was significantly higher in the highly exposed individuals in utero [91]. But as recently reviewed, so far, no clear and significant correlation between background exposure to dioxins and thyroid function during development has been found [92].

4.5. Phthalates. Phthalates are widely used chemicals mainly to improve the flexibility of materials such as plastic and have been widely used in medical products, food handling and storage products, electrical devices, toys, and in non-polyvinylchloride applications such as paints, lacquers, and cosmetics. Phthalates can leach, migrate, or evaporate into indoor air and atmosphere, foods, and liquids and have become ubiquitous. Consequently, humans are constantly exposed by oral, inhalation, and dermal routes [93]. Unfortunately, certain vulnerable groups may be massively exposed to phthalates, such as hospitalized neonates in whom urinary excretion of phthalates was shown to correlate with exposure

Table 2: Thyroid-disrupting properties of polychlorinated biphenyls in human studies on pregnant women, neonates, infants, adolescents, and adults.

Year	Author	*N*	Subjects	Effect	Reference
1994	Koopman-Esseboom et al.	105	Pregnant women	↓ TT3 ↓ TT4	[62]
		105	Infants	↑TSH at 2 weeks and 3 months	
2005	Takser et al.	101	Pregnant women	↓ TT3 ↑TSH	[58]
		92	Cord blood	No effect	
2008	Wilhelm et al.	165	Pregnant women	No effect	[65]
		127	Cord blood	No effect	
2009	Alvarez-Pedrerol et al.	1090	Pregnant women	↓TT3↑fT4	[70]
2009	Dallaire et al.	120	Pregnant women	↑T3	[71]
		95	Cord blood	↓TBG↓ fT4	
		130	Infants, 7 months old	No effect	
2000	Longnecker et al.	160	Cord blood	No effect	[63]
2005	Wang et al.	118	Cord blood	↓T3↓T4	[72]
2008	Dallaire et al.	670	Cord blood	↓TBG	[68]
2008	Herbstman et al.	289	Cord blood,	↓TT4↓fT4	[67]
		265	Neonatal blood spot**	↓TT4	
2007	Chevrier et al.	285	Newborns	↑TSH	[66]
2001	Matsuura et al.	337	Breastfed infants*	No effect	[64]
2003	Ribas-Fito et al.	98	Infants	Trend toward ↑TSH	[61]
2010	Darnerud et al.	150	Infants	↓ TT3	[73]
1999	Osius et al.	320	Children	↓ fT3 ↑TSH	[74]
2000	Steuerwald et al.	182	Children	No effect	[60]
2008	Alvarez-Pedrerol.	259	Children	↓TT3↓fT4	[75]
2005	Hsu et al.	60	Boys	No effect	[69]
2008	Schell et al.	232	Adolescents	↓ fT4↑TSH	[76]
2001	Sala et al.	192	Adults	Trend toward ↑TSH	[77]
2001	Hagmar et al.	110	Adult men	No effect	[78]
2001	Hagmar et al.	182	Adult women	↓ TT3	[79]
2001	Persky et al.	229	Adults	Female: ↓T4,FTI. Men ↓T3-uptake	[80]
2003	Bloom et al.	66	Adults	No effect	[81]
2003	Langer et al.	101	Adults	↑thyroid volume	[82]
2004	Schell et al.	115	Adults	↓ fT4↓ T4 ↑TSH	
2007	Tyruk et al.	2445	Adults	↓TT4, in older persons↑TSH	[83]
2008	Abdelouahab et al.	211	Adults	Female ↓T3; men ↓T4 ↑TSH	[84]
2009	Dallaire et al.	623	Adults	↓ TT3, ↓TBG	[59]

PCBs were measured in blood unless otherwise stated. *PCBs measured in breast milk. **neonatal blood spot at day 18 postpartum. *N*: number, TSH: thyrotropin, TT3: total tri-iodothyronine, TT4: total thyroxine, fT3 free Tri-iodothyronine, fT4: free thyroxine, FTI: free T4 index, and TBG: thyroid hormone-binding globulin.

to medical devices [94]. However, a followup of adolescents exposed to high concentrations of phthalates in the neonatal period showed normal thyroid hormones [95]. On the other hand, men recruited from a fertility clinic [96] and pregnant women [97] demonstrated a negative association between phthalates and fT4 and T3, respectively.

We studied 845 children aged 4–9 years with determination of urinary concentrations of 12 phthalate metabolites and serum levels of TSH, thyroid hormones, and insulin-like growth factor-I (IGF-I) [98]. Our study showed a negative association between urinary phthalate concentrations and thyroid hormones, IGF-I and growth of the children, respectively. Although our study was not designed to reveal the mechanism of action, the overall coherent negative associations may suggest causative negative roles of phthalate exposures for child health.

4.6. Triclosan and Bisphenol A. The exact thyroid disturbing mechanisms of these chemicals are not known, but triclosan, and bisphenol A (BPA) share structural similarities with thyroid hormones and may bind to and interact with the thyroid hormone receptor (TR). Phenols bind competitively to TTR, [99, 100] and act as a T3 antagonist [101, 102].

BPA is used to manufacture polycarbonate and several hard plastic products such as compact discs, food can linings, adhesives, powder paints, dental sealants, and clear plastic

bottles which means that humans are ubiquitously exposed to BPA [103, 104]. BPA is rapidly glucuronidated in humans and rodents.

Phenols were found to bind competitively to TTR, possibly with a very strong binding affinity [99, 100], but a recent study found that the concentrations of BPA usually found in humans is probably not high enough to interfere with T4 transport [105]. Finally, T3-mediated gene activation through TRα1 and TRβ was dose-dependently suppressed by, BPA and the expression of T3- suppressed genes was up-regulated by BPA [101, 102]. In pregnant rats, BPA was associated with a significant increase of TT4 in the pups 15 days postpartum [106].

Triclosan in an antibacterial and antifungal agent used in products for personal hygiene and household cleaning agents but also in plastics and fabrics. Though found in human urine [107] and breast milk [108], so far, no epidemiological studies have been published on the influence of triclosan on thyroid hormone homeostasis. A small intervention study [109] could not demonstrate changes in CYP3A4-activity or peripheral thyroid hormone levels after triclosan exposure through toothpaste. However, in vitro studies suggest that higher exposure levels may activate human pregnane x receptor, which upregulates the activity of CYP3A4 [110]. In rats, gestational exposure to triclosan lowered T4 in the pregnant animal and transitorily in the pups at postnatal day 4 [111, 112].

4.7. Isoflavones. Isoflavones, naturally occurring phytoestrogens, are mainly found in soy and grain products [113]. Isoflavones inhibit thyroid peroxidase (TPO) function and thereby thyroid hormone production [114]. Iodine insufficient children fed on soy products risk development of goitre and hypothyroidism [115]. As reviewed by Messina and Redmond several studies have been performed in humans to explore the thyroid disrupting effect of isoflavones, but only one study from Japan of healthy volunteers fed for 1–3 months with soy beans reported increased TSH though within the normal reference interval and increased thyroid volume. But other studies could not reveal such relationships [116].

4.8. Brominated Flame Retardants. Flame retardants constitute a group of chemicals such as tetrabromobisphenol A (TBBPA), a halogenated derivative of BPA and polybrominated biphenyls. These chemicals are found in different products such as plastic paints and synthetic textiles and are often used in electrical devices such as televisions, computers, copying machines, video displays, and laser printers. These chemicals are structurally more similar to T4 than PCBs and bind competitively to TTR [99]. In general, flame retardants are found to reduce thyroid hormone levels. A recently published study of pregnant women showed a negative association between serum levels of brominated flame retardants and TSH [117]. A newer study of recreational fish consumers reported a negative association between concentrations of some congeners in serum and serum levels of T3 and TSH and a positive relationship with T4 [118]. This was confirmed by others [78] but not all [119], and in a smaller study of 12 mother-infant pairs, maternal brominated flame retardants levels were not significantly correlated to thyroid hormone levels in cord blood [120].

4.9. Pesticides. Pesticides constitute a large and very inhomogeneous group of chemicals, which differ significantly in their chemical and physical properties and, thus, their ability to be either detoxified in vivo or to bioaccumulate in lipid-rich tissue. It is beyond the scope of the paper to give a comprehensive overview about potential thyroid disrupting effects. Many of the organochlorine pesticides are persistent with long environmental half-lives, and therefore, humans are continuously exposed though many pesticides have been banned for years in many countries while still in use in others. Dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), and nonylphenol (NP) are among the most examined. Metabolites of HCB are used as a biocide and wood preservative in the timber industry and as antifungal agent in the leather industry. NP is an industrial additive used in detergents, plastics, and pesticides. In humans, an enlarged thyroid was found after accidental exposure to HCB [121], and studies have found negative associations between HCB and T4 [77, 81] or T3 [58] but not TSH or free thyroid hormone levels [77]. In newborns, pentachlorphenol (PCP) in cord blood but not HCB [58] was negatively correlated to T3, fT4 and TBG [122], and thus may potentially impair neurodevelopment. Also, other pesticides seem to posses thyroid disrupting properties [123–127].

4.10. Others. Ultraviolet (UV) filters also called sunscreens, that is, benzophenone, 4-methylbenzylidene camphor and 3-benzylidene camphor, comprise a group of chemicals used to absorb and dissipate UV irradiation in cosmetic products, not only sun lotions, to enhance product longevity and quality. So far, only animal and in vitro studies have indicated that UV filters may disrupt thyroid hormone homeostasis.

Parabens are commonly used as preservatives in food, cosmetics and pharmaceutical products. In vitro methylparaben dose-dependently inhibited iodine organification and thus seemed to have a weak intrinsic antithyroid effect [128], but human studies are lacking.

The industrial use of perfluorinated chemicals (PFC) is increasing in products such as stain- and oil-resistant coatings for example, food packaging for fast food, as well as in floor polishes and insecticide formulations. PFCs are extremely persistent in the environment. Women with high levels of PFCs were treated more often for thyroid disease than controls [129], and in employees from a PFC factory, PFCs displayed a negative association to fT4 [130].

Styrene is an industrial chemical widely used in the production of plastics, resins, and polyesters. Humans are exposed by low-level contamination in food items, but the exposure is most abundant through inhalation of tobacco smoke, automobile exhaust, and vapors from building materials [131]. Occupational styrene exposure resulted in thyroid disrupting effects: there was a positive correlation

between exposure time and thyroid volume and a positive correlation between urinary concentrations of styrene metabolites and f T4 or fT4/fT3 ratios without a correlation to TSH. This indicated an inhibition of the conversion of T4 to T3 [132].

Exposure to lead is typically from cigarette smoke or gasoline, but also workers in the mining, smelting, refining, battery manufacturing, soldering, electrical wiring, and ceramic glazing industries are at risk of occupational exposure. Lead may cause a toxic effect on the central part of the hypothalamic-pituitary-thyroid axis [133, 134], but the mechanism is not yet known and effects on the selenium metabolism is also possible. In lead-exposed children, an impaired release of TSH has been reported [135], but another study found unchanged T4 levels after lead exposure [136].

Studies in occupational lead exposed workers indicates induction of secondary hypothyroidism; one study found low T4 and fT4 and inappropriately normal TSH [137] and in auto repair workers, a negative correlation between blood lead levels and fT4 was found, but TSH, T3, and thyroid volume were comparable to unexposed controls [133]. In another group of petrol pump workers or mechanics, TSH was increased compared to the unexposed controls, and T3 declined by longer exposure, but T4 levels were unchanged [134]. These findings are in contrast to the evaluation of subacute and cumulative effects in lead smelter workers, where no thyroidal effects were shown [138].

Lithium is widely used in the treatment of bipolar mental disorders and has known influences on thyroid function [139], and lithium is used in the manufacturing of button and rechargeable batteries, ceramics, and glass. Recently, lithium has been found in ground and drinking water in Argentina, where the urine lithium concentration corresponded to a daily lithium intake of 2–30 mg [140]. Exposure to lithium in drinking water and other sources seem to suppress thyroid function as urinary lithium was found to correlate negatively with T4 and positively with TSH [141].

5. Discussion

As discussed above, several groups of EDCs may have thyroid disrupting potential, but only perchlorate and PCBs have been studied in more detail in humans. Perchlorate reduced expectedly thyroid iodine uptake, but so far, no significant effects on circulating thyroid hormones have been found after exposure to environmental levels of either perchlorate, thiocyanate, or nitrite. Most of the other chemicals have still only been studied in animal models, sporadically, in high doses in volunteers or after occupational or accidental exposure, and results are conflicting. However, all the mentioned chemicals can theoretically have thyroid disrupting properties and consequently further studies are needed to clarify the mechanisms and the general consequences of constant environmental exposure to lower doses. Although thyroid disrupting properties were not documented for all chemicals, especially vulnerable groups like pregnant women, foetuses and children of all ages may be more sensitive because of pregnancy- and growth-related added stress on the thyroid gland, in particular for people living in iodine insufficient areas. Most human studies are performed in groups like healthy volunteers, occupationally exposed individuals, or persons living in certain areas and do not include all thyroid relevant factors as life style, preexisting thyroid disease, age groups, or exposure to other EDCs. However, exposure during the foetal and neonatal period is of much concern, as it is a very vulnerable point in central nervous system development, especially in preterm children. Only few studies of the chemicals in question have addressed the issue of health effects on the offspring of exposed subjects. Yet, many of the potential thyroid disrupting chemicals accumulate both in nature and in exposed individuals and may have a negative influence on maternal thyroid function during pregnancy with consequent risk of impaired neurodevelopment of the foetus. While significant exposure to all these chemicals are suspected to affect human thyroid homeostasis, the effects of environmental exposure still remain to be confirmed in humans and, in particular, in vulnerable groups.

Epidemiological studies have reported that pre- and perinatal exposure to PCBs is associated with poorer neurodevelopment in neonates, toddlers and school-age children [142–147]. The influence of PCBs on thyroid function has been suggested as a reasonable explanation for the results although this was not evaluated in detail. PCB correlated negatively to fT4 in pregnant women [148], and therefore, even exposure at background levels could possible disturb foetal development.

The subjects in human epidemiological studies have always been exposed to many different compounds through different time periods, and it is, therefore, difficult to isolate specific effects of chemicals and their metabolites on functions of the human organism, which is an obvious caveat in concluding from such studies [59].

Some studies have been performed in people more intensively exposed due to either occupation, residency in/near contaminated areas [74, 90, 149, 150], accidents [151], or fish consumption [78, 79, 152, 153], but other studies have focused on general population exposures [58, 83, 96]. There may, thus, be several reasons for the divergence in findings. One explanation could be current low exposure after reduction of allowed limits and, therefore, current unmeasurable levels of a chemical that once was present and exerted an effect. Conflicting results may also reflect that findings depend on the choice of biomarkers, detection methods of the examined EDCs, and sample material, for example, in maternal blood, breast milk, cord blood, or child blood. Furthermore the sex of the foetus, comorbidities, and medication as well as a possible influence from combined effects of other EDCs may influence study outcomes [72]. Even in adult populations, there are probably both age and gender differences in responses in an adult population [83].

Given that most of the mentioned chemicals have subtle influences on the thyroid axis, in many cases within the normal reference interval, the question is whether or not such subtle changes in, for example, maternal thyroid function can eventually compromise foetal neurological development. The relationship between T4 and TSH is very unique to each

human [154], and the variations within each person are much smaller than the variation within a population [155, 156], which is also the case during pregnancy [157, 158]. Comparison with more or less well-defined population-based reference ranges is probably quite irrelevant considering the discrepancy between these large ranges compared to the much narrower intraindividual variations in thyroid hormone levels [155, 156]. In addition, no first-trimester-specific reference ranges for fT4 analog assays currently exist, available commercial analog fT4 assays are unreliable in pregnant women, and fT4 levels are often over- or underestimated. In these cases, TT4 and free thyroid hormones indexes are more reliable [159]. Consequently, minor, yet real, changes in thyroid hormone levels due to EDC exposure in small human studies may easily be camouflaged by the broad interindividual variation. As human exposure is lifelong, starting during pregnancy and cumulative for persistent chemicals, it is not possible to design human studies evaluating thyroid function within an individual before and after exposure. Even small intervention studies, like the study with triclosan [109], are performed on a preexisting background of chemical exposure to many other compounds simultaneously.

Despite this individuality of the thyroid function variables, the levels of TSH and thyroid hormones vary greatly during the early stages of life. TSH increases dramatically immediately after birth peaking at 30 minutes, followed by an increase in T4 and T3, where after all hormone levels decrease. Thyroid hormones measured in newborns may be affected by intrapartum stress [67] and even by use of iodine containing antiseptics [160]. Thus, estimation of any influence of thyroid disrupting chemicals on TSH and thyroid hormones during pregnancy, neonatal period, or early childhood should, therefore, allow for exact age as a critical confounder.

A possible influence of thyroid hormone-induced metabolism and elimination processes of EDCs, such as detoxification in the liver and kidneys, has not been extensively investigated, and further studies should be performed. Other confounding factors in interpretation of the many results include population-specific level of selenium and iodine, since deficiency of these two substances may render the thyroid system more prone to be affected by EDCs. In addition, exposure to EDCs may cause only transient changes in thyroid hormone levels, which cannot be traced afterwards but, nevertheless, may leave permanent effects on the central nervous system if occurring during a developmentally critical phase. Furthermore, measurement of peripheral thyroid hormone concentrations may not reflect a chemical effect on the full thyroid homeostasis (Figure 1). As outlined in this paper, various chemicals may have different and antagonistic or synergistic effects on the thyroid axis. Such effects have also been found in studies of chemicals disrupting reproduction [18, 19].

Finally, it is not possible in association studies to distinguish whether EDCs could act by direct toxic effects or by indirect mechanisms via disrupting the thyroid function. More mechanistic studies are, therefore, warranted in the future.

6. Conclusions

The influence of environmental thyroid disrupting chemicals on maternal thyroid function and consequently on foetal development in humans is still difficult to estimate for several reasons. However, for some of the chemicals, in particular perchlorate and PCBs, evidence is emerging that thyroid function is indeed affected by their exposure, and they therefore potentially possess a damaging effect on foetal development. However, many individual factors including the narrow individual set point for thyroid function, interactions with other environmental factors such as exposure to several EDCs, and deficiency of iodine and/or selenium may interfere with study results and thereby complicate conclusions. Furthermore, it is still not clear which specific cognitive functions in childhood, and consequently which methods of testing, would be the most representative when evaluating permanent effects of thyroid dysfunction during development. Further research in this particular field is necessary to ensure optimal health, growth and development of the foetus, but also for subsequent general thyroid health in children and adults. So, while most available evidence indicates detrimental effects of many EDCs on human thyroid function, thereby potentially affecting pregnant women and consequently foetal development, astonishingly few studies can substantiate this suspicion. Since this may appear to be extremely important for foetal neurodevelopment, researchers in the field should be strongly encouraged to continue the efforts to elucidate the mechanisms in order to be able to prevent damage. This may be so much more important since both populations in iodine deficient areas but also in iodine sufficient areas, with high prevalence of autoimmune hypothyroidism in women of the childbearing age, have an increased susceptibility to the thyroid disrupting properties of EDCs. The complexity of the field and the scarcity of current publications should spur researchers to perform large-scale studies including all relevant confounders, thus hopefully allowing for evidence-based regulations and recommendations.

Abbreviations

BPA: Bisphenol A
DDT: Dichlorodiphenyltrichlorethane
EDC Endocrine disrupting chemical
FT3: Free T3
FT4: Free T4
HCB: Hexachlorobenzene
HCG: Human chorionic gonadotropin
IGF-I: Insulin-like growth factor-I
IQ: Intelligence quotient
NIS: Sodium-iodide symporter
NP: Nonylphenol
PCB: Polychlorinated biphenyl
PFC: Perfluorinated chemical
PCP: Pentachlorophenol
RT3: Reverse T3
TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin
TBBPA: Tetrabromobisphenol A

TBG: Thyroxine-binding globulin
TPO: Thyroid peroxidase
Tg: Thyroglobulin
TR: Thyroid hormone receptor
TRE: Thyroid hormone response element
TRH: Thyrotropin-releasing hormone
TSH: Thyrotropin
TSH-R: Thyrotropin receptor
TT3: Total T3
TT4: Total T4
TTR: Transthyretin
T3: Tri-iodo-thyronine
T4: Thyroxine
UDPGT: Uridinediphosphate-glucuronyl transferase
UV: Ultraviolet.

Conflicts of Interest

The authors have no conflicts of interest.

Acknowledgments

M. Boas was supported by the University of Copenhagen, Denmark, and the European Commission (QLK4-2002-0063). U. F. Rasmueeen has received a grant from Arvid Nilsson's Foundation. K. Mair was supported by a grant from the Novo Nordisk Foundation and the Danish Agency of Science, Technology, and Innovation.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 843591, 12 pages
doi:10.4061/2011/843591

Review Article

Levothyroxine Treatment in Pregnancy: Indications, Efficacy, and Therapeutic Regimen

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Received 1 March 2011; Revised 30 May 2011; Accepted 30 May 2011

Academic Editor: Roberto Negro

The prevalence of overt and subclinical hypothyroidism during pregnancy is estimated to be 0.3–0.5% and 2–3%, respectively. Thyroid autoantibodies are found in 5–18% of women in the childbearing age. The aim of this review is to underscore the clinical significance of these findings on the health of both the mother and her offspring. Methods of evaluation of thyroid function tests (TFTs) during pregnancy are described as are the threshold values for the diagnosis of overt and subclinical hypothyroidism or hypothyroxinemia. Anticipated differences in TFTs in iodine-sufficient and iodine-deficient areas are discussed and data are provided on potential complications of hypothyroidism/hypothyroxinemia and autoimmune thyroid disease during pregnancy and adverse effects for the offspring. The beneficial effects of levothyroxine therapy on pregnancy outcomes and offspring development are discussed with a proposed treatment regimen and follow up strategy.

1. Introduction

During normal gestation, thyroid hormone production is augmented in order to meet the increased physiologic demands of the growing fetal placental unit. Alterations in thyroid function with pregnancy are derived via several mechanisms. Notably, there is an increase in serum estrogen levels during the first half of gestation up to 500–1000 pg/mL, resulting in upregulation by two- or threefold of hepatic production of thyroxine binding globulin (TBG) [1, 2]. The increased TBG levels alter the equilibrium between bound and free thyroxine (FT4) causing a temporary reduction in FT4 that in turn leads to increased thyrotropin (TSH) stimulation of the thyroid gland and physiologic restoration of FT4 at the cost of higher serum total T4 (TT4) levels. A second factor is the increased placental production of human chorionic gonadotropin (hCG), reaching a peak of approximately 50,000–75,000 IU/L at 8–11 weeks. This is significant because of the direct stimulatory effect of hCG on thyrocytes that is mediated through binding to the TSH receptor. Yet a third issue is related to the increased need for iodine in pregnancy that is required to fuel the increases in thyroid hormone synthesis and compounded by the loss of iodine due to enhanced renal clearance [3, 4]. Therefore, the recommended average iodine intake during the pregnancy is between 250 and 500 ug/d [5, 6]. A final factor is the presence of placental iodothyronine deiodinase type III which alters the metabolism, distribution, and availability of T4 for both mother and fetus [4].

The prevalence of hypothyroidism during pregnancy is estimated to be 0.3–0.5% for overt hypothyroidism (OH) and 2-3% for subclinical hypothyroidism (SH). Thyroid autoantibodies are found in 5–18% of women in the child-bearing age, and chronic autoimmune thyroiditis (AITD) is the main cause of hypothyroidism during pregnancy in iodide sufficient areas [7–9]. However, on a worldwide basis the most important cause of thyroid insufficiency remains iodine deficiency [10].

In view of the frequency of either OH or SH during pregnancy and the associated altered physiology, several questions face clinicians managing subjects with suspected thyroid dysfunction during pregnancy including (1) what

are the threshold values for the diagnosis of overt hypothyroidism (OH), subclinical hypothyroidism (SH), or hypothyroxinemia during the pregnancy? (2) Is the interpretation of thyroid function tests different in iodine-sufficient than in iodine-deficient areas? (3) What are the complications of hypothyroidism/hypothyroxinemia and autoimmune thyroid disease during the pregnancy? (4) Is levothyroxine therapy beneficial and effective in regard to improved outcomes and reduced complications associated with pregnancy and delivery? (5) How to select the patients for whom the treatment may be beneficial? (6) What is the appropriate treatment regimen and what are target thyroid function test values and how often should they be monitored? The aim of this paper is to address all of the above mentioned questions.

2. Methods

We have searched PubMed database from January 1970 to January 2011 for the articles written in English using the following keywords: "pregnancy and thyroid function", "pregnancy and hypothyroidism", "pregnancy and subclinical hypothyroidism", "pregnancy and hypothyroxinemia", "pregnancy and levothyroxine treatment", "pregnancy and iodine deficiency", "offspring complications and hypothyroidism", "offspring complications and hypothyroxinemia" and "offspring complications and iodine deficiency". We have included retrospective and prospective observational studies, clinical trials, meta-analyses, review papers, and guidelines published in the indexed journals.

2.1. What are the Threshold Values for the Diagnosis of Overt Hypothyroidism (OH), Subclinical Hypothyroidism (SH), or Hypothyroxinemia during the Pregnancy?

Establishment of reference ranges for thyroid function tests during pregnancy has been problematic due to variables based upon age, smoking status, ethnicity, BMI, iodine nutritional status, and the presence of latent or overt autoimmune thyroid disease [8, 11].

Interpretation of any given value for FT4 or TSH should take into account the possible differences between population based reference ranges of thyroid function tests and a given patient's narrower individual reference range. Based on data from 877 pregnant women, Shields et al. suggested that an individual's level of TSH is associated with variation in the PDE8B gene with AA genotypic women being more likely to have elevated TSH concentrations (>4.21 mIU/L) compared to women with AG or GG genotypes (9.6 versus 3.5%, $P < 0.0004$). This observation was independent of the presence or absence of autoimmune thyroid disease (AITD) [12].

2.1.1. Normal Absolute Values and Optimal Methods for Assessment of Thyroid Function during Pregnancy

TSH. TSH is the single best indicator of insufficient thyroid hormone due to primary hypothyroidism [6]. However, there is a necessity for the trimester-specific reference range for TSH in each laboratory or at least each country/region in order to properly interpret the thyroid function tests.

Guidelines for diagnosis developed by the Endocrine Society and endorsed by the American Thyroid Association in 2007 recommend that TSH values should be <2.5 mIU/L in the first trimester and <3 mIU/L in the second and third trimester [6]. Data supporting this recommendation were derived from observations of the consistency in TSH ranges for first-trimester thyroperoxidase antibody-negative women, with a consensus centering around a lower limit of normal of 0.04 and upper range of normal of 2.5 mIU/L. It is worthwhile to underscore that this reference range was not significantly different between various populations. In a prospective study of 343 Chinese women, Panesar et al. [13] noted a normative range for first-trimester TSH levels of 0.03–2.3 mIU/L, which did not differ significantly from the range of 0.02–2.15 mIU/L established by Gilbert et al. [14] in 1817 Australian women between 9 and 13 weeks of gestation. A somewhat wider range and higher upper limit was seen by Pearce et al. [15] of 0.04–3.6 mIU/L in 585 thyroid antibody-negative women before 14 wks gestation, and by Stricker et al. [16] after screening 783 thyroid antibody-negative women in Switzerland (TSH 0.08–2.83 mIU/L). Männistö et al. based on a large ($n = 9362$) prospective population-based cohort from Northern Finland without AITD and with sufficient iodine intake reported a TSH reference range of 0.07 to 3.1 in the first trimester and up to 3.5 mIU/L in the second trimester. Moreover, they also observed that thyroid hormone levels are affected by BMI with higher TSH and FT3 and lower FT4 concentrations observed in obese women [11].

FT4, FT3. Although equilibrium dialysis and mass spectrometry/gas chromatography are the gold standards and are the most reliable methods of measurement of both FT4 and FT3 concentrations, these methods are too technically complex and expensive for routine use. Consequently, most FT4 testing in clinical laboratories is based on two-step or labeled antibody methodology, which is sensitive to abnormal TBG levels and liable to error [17, 18]. There is a need for a method-specific, trimester-specific, and possibly population-specific FT4 reference range. Männistö et al. addressed this question for the anti-TPO negative and iodine sufficient Caucasian population, documenting that FT4 measured with chemiluminescent immunoassay increases slightly during early pregnancy and then decreases with the reference ranging being between 11 and 22 pmol/L. Reference intervals for FT3 in the same study were stable during the pregnancy and ranged from 3.4 to 7 pmol/L [11]. However, Lee et al. documented that FT4 measured by two different immunometric assays diverges so significantly during the second and third trimesters that the vast majority of women would be diagnosed incorrectly as hypothyroxinemic by laboratory criteria alone. Each specific immunoassay needs to have normals and abnormals determined for the pregnant state, or immunoassays may underestimate FT4 [19].

TT4. The TT4 increase in pregnancy is more predictable than alterations in FT4, being generally 1.5 times

nonpregnant levels which is primarily related to increases in serum TBG as described above. Many studies have shown remarkably consistent ranges for T4 throughout pregnancy—approximately 143–158% of nonpregnant values. Adjusting the TT4 in pregnancy by a factor of 1.5 compared with nonpregnant reference ranges is a good reflection of FT4 [19]. Therefore, some authors advocate the use of TT4 in preference to FT4 for the evaluation and management of pregnant patients [20]. The Endocrine Society Guidelines as well as Laboratory Medicine Practice Guidelines advocate a TT4 cutoff of 100 nmol/L as appropriate for detecting a low FT4 state in pregnancy [6, 20].

FT4 Index. The free thyroxine index (FT4I) is measured as total T4 mathematically corrected for thyroxine binding globulin (TBG). FT4I is calculated by dividing TT4 by the thyroid hormone-binding ratio—the estimate of TBG. Changes in FT4I are consistent with the expected effects of TBG and hCG during pregnancy with a physiologic increase in the first trimester with normalization to nonpregnant levels in the second and third trimesters. This pattern of change during pregnancy corresponds to that described using the gold standard FT4 methods of equilibrium dialysis and tandem mass spectrometry [19].

To summarize, the FT4I index or the TT4 adjusted for pregnancy are reliable methods of estimating free thyroxine status in pregnancy.

2.2. Is the Interpretation of Thyroid Function Tests Different in Iodine-Sufficient than in Iodine-Deficient Areas?

Approximately 1.9 billion individuals, including 285 million school-aged children, are estimated to have inadequate iodine nutrition. Severe iodine deficiency in pregnancy can cause hypothyroidism, poor pregnancy outcome, cretinism, and irreversible mental retardation. Mild-to-moderate iodine deficiency *in utero* and in childhood may result in less severe learning disability, poor growth, and diffuse goiter [21]. It has been also suggested that even mild iodine deficiency may be associated with attention deficit and hyperactivity disorders in offspring [22].

The prevalence of iodine deficiency is lowest in the Americas (10.1%) and highest in Europe (59.9%) [23]. The thyroid gland responds to iodine deficiency through regulatory mechanisms that include decreased synthesis and secretion of T4 in favor of T3. In the case of mild to moderate iodine deficiency during the pregnancy, the circulating T3 levels remain normal or even increase slightly and circulating TSH levels do not increase. So the thyroid function tests may misleadingly indicate euthyroidism, while the amount of T4 available for the fetus might be insufficient [24, 25]. Another commonly seen diagnostic marker of iodine deficiency is an elevated serum thyroglobulin level [26]. Serum Tg is well correlated with the severity of iodine deficiency as measured by UI [27]. Intervention studies examining the potential of Tg as an indicator of response to iodine supplementation revealed that Tg falls rapidly with iodine repletion and that Tg is a more sensitive indicator of iodine repletion than TSH or T4 [28, 29].

Iodine repletion in severely iodine-deficient pregnant women or infants may reduce the infant mortality rate by at least 50% [21]. A blinded, placebo-controlled clinical trial conducted in the 1960s in Papua, New Guinea, demonstrated that preconception supplementation of severely iodine-deficient women with iodinated oil eliminated the risk for cretinism and improved offspring cognitive function and survival [30]. These findings have subsequently been replicated in many regions of the world, indicating that iodine supplementation in severely iodine-deficient regions may increase the average child IQ by 12.5 points [31, 32].

Iodine supplementation of moderately deficient pregnant women appears to consistently decrease maternal and neonatal thyroid volumes and Tg levels [31]. Effects on maternal thyroid function have been variable, with significant maternal TSH decreases seen only in four of eight published studies and with increases in maternal T4 or FT4 noted in two studies [31]. The observed differences in the response to iodine supplementation may be related to the onset of intervention. In a prospective observational study, Moleti et al. studied 433 euthyroid anti-TPO antibody-negative women and observed TSH increases during gestation in 26.1% women taking 150 ug iodine supplementation during the pregnancy compared to 15.6% of women with a history of iodinated salt intake several months before the pregnancy ($P < 0.05$). However both methods of iodine supplementation were sufficient to reduce the proportion of pregnant women with hypothyroxinemia, which was observed in 8.3% of women taking 150 ug iodine supplements, 9.5% of women with a history of iodine salt use, and 20% of women without any iodine supplementation [33]. These observations were confirmed in other studies [34, 35]. Neurodevelopmental outcomes were improved in children whose mothers received iodine supplementation early in pregnancy and were lost if supplementation was started after the 10th week of pregnancy [36, 37].

These results suggest that women from mildly and moderately iodine-deficient areas, which include several European countries, should be advised to start iodine supplementation several months prior to conception in order to saturate intrathyroidal iodine stores. Ideally, women should have adequate intrathyroidal iodine stores (10–20 mg) before conception. Unfortunately, well-conducted randomized maternal iodine-supplementation studies with long-term follow-up data on psychomotor and mental development of children are lacking.

2.3. What are the Complications of Hypothyroidism/ Hypothyroxinemia and Autoimmune Thyroid Disease during the Pregnancy?

2.3.1. Hypothyroidism

Pregnancy Complications. There is a known association between hypothyroidism and decreased fertility, as well as increased risk for early and late obstetrical complications, such as increased prevalence of abortion, anemia, gestational hypertension, placental abruption, and postpartum hemorrhages. As would be expected, these complications are more

frequent with OH than with SH [38–43]. In one study of 216 women with early miscarriage, SH and AITD were independently associated with miscarriage with SH being specifically associated with very early embryo loss at 6.5 weeks [44]. In contrast, a prospective study of 10,990 women in US and Ireland with biochemical evidence of SH did not reveal excessive adverse pregnancy outcomes [45]. Recent studies from The Netherlands documented an association between TSH levels exceeding >2.4 mIU/mL between the 35th and 38th week of gestation are associated with the approximately 2-fold increased risk for breech presentation [46, 47]. Elevated TSH levels earlier during the pregnancy were not associated with risk of breech presentation. Interestingly, higher levels of TSH at end term were independently associated with the lack of successful outcome of external cephalic version [48].

Adverse Outcomes for the Neonate/Offspring. Untreated maternal OH is associated with adverse neonatal outcomes including premature birth, low birth weight, and neonatal respiratory distress. Although less frequent than with OH, complications have also been described in newborns from mothers with SH, including a doubling of the rate of preterm delivery [49] in pregnant women before 20 wk gestation. Stagnaro-Green et al. [50] compared the thyroid status of women with preterm delivery to matched controls who delivered at term and found a 3-fold increase in the incidence of SH in the women with very early preterm deliveries (before 32 wks).

Four decades ago Man et al. [51, 52] observed that children born to mothers with inadequately treated hypothyroidism had significantly reduced intelligence quotients (IQs). The first large-scale prospective study on the outcome of children born to mothers with SH during pregnancy was reported by Haddow et al. in 1999 [53]. In this study, extensive neuropsychological testing of the school-age children revealed that children born to women with untreated SH had on average an IQ score that was 7 points below the mean IQ of children born to healthy women and thyroxine-treated women. Furthermore, there were three times as many children with IQs that were 2 SD scores below the mean IQ of controls in the children born to untreated women with SH.

Of note, there is a specific type of combined maternal and fetal hypothyroidism during gestation associated with the presence of TSH receptor blocking antibodies in women with AITD. This entity is associated with more severe cognitive delay in the offspring than seen with either fetal or maternal hypothyroidism alone, probably because maternal T4 is unavailable to compensate for the fetal hypothyroidism. This disorder should be suspected if unusually high doses of levothyroxine (LT4) are required to normalize maternal thyroid function during gestation [54]. Additional studies will be required to elucidate the effect of SH on the long-term neuropsychological development of offspring.

2.3.2. Isolated Hypothyroxinemia

Pregnancy Complications. Cleary-Goldman et al. showed that isolated hypothyroxinemia,which was observed in 232 of 10,990 pregnant women, is not associated with adverse pregnancy outcomes [45]. Similar observations were noted by Casey et al. who observed hypothyroxinemia among 233 of 17,298 pregnant women. This was not associated with any increased risk for adverse pregnancy outcomes in this subpopulation [55].

Adverse Outcomes in Offspring. Despite the limitations of FT4 assays, multiple studies have demonstrated that low-normal FT4 concentrations are associated with adverse outcomes in the offspring. Pop et al. investigated the developmental outcome in children born to women with isolated low T4 levels in the first trimester of pregnancy, defined as values within the lowest 10th decile of "normal" pregnant T4 values [56]. Results suggested that isolated hypothyroxinemia is associated with a lower developmental index in the children at approximately 10 months of age. This observation was confirmed later by the same group based on a larger cohort and more refined motor and mental evaluations in infants aged 1 and 2 yrs [57]. They documented that children born to mothers with prolonged levels of low T4 (until wk 24 or later) showed an 8- to 10-point deficit for motor and mental development compared to infants of women whose serum FT4 levels recovered spontaneously to normal later in gestation.

These results were confirmed by Vermiglio et al. [22], who compared the neuropsychological development of children of mothers from a moderately iodine-deficient area to that of children of mothers from a marginally iodine-sufficient area. The offspring of the mothers with lower FT4 values during gestation were found to have an increased incidence of attention deficit and hyperactivity disorder as well as a reduced IQ, compared with controls. Similarly, Kooistra et al. observed that newborns from hypothyroxinemic mothers (FT4 below the 10th percentile at 12th week of pregnancy), and evaluated 3 weeks after delivery with the Neonatal Behavioural Assessment Scale, had significantly lower orientation index scores compared to children whose mothers had FT4 levels between the 50th and 90th percentiles [58]. Similar observation was found in Chinese population, indicating that children of women with either SH, hypothyroxinemia, or elevated TPO Ab titres at 16–20 weeks gestation had mean intelligence and motor scores significantly lower than controls [59]. Finally, a recent population-based cohort study from The Netherlands involving 3659 children and their mothers documented that both mild (below the 10th percentile) and severe (below 5 percentile) maternal hypothyroxinemias were associated with a higher risk of expressive language delay at 18 and 30 months. Severe maternal hypothyroxinemia also predicted a higher risk of nonverbal cognitive delay [60].

2.3.3. Euthyroid Autoimmune Thyroid Disease

Pregnancy Complications. Experimental studies on pregnant mice have shown an increased rate of miscarriage after immunization with Tg [61, 62]. Several studies have also indicated an association in women between the presence of AITD and an increased miscarriage rate and preterm

delivery [63–65]. Three hypotheses have been proposed to explain this association: (1) thyroid antibodies may represent a marker of a generalized autoimmune imbalance that increases risk of miscarriage; (2) preexisting subtle thyroid dysfunction due to AITD may worsen during pregnancy; (3) because women with AITD have a higher prevalence of infertility, they may be older than those without AITD and thus be more prone to fetal loss. Women with AITD are also more likely to suffer from postpartum thyroiditis and postpartum depression [66–69].

Side Effects in the Offspring. As far as we could determine, other than the one study cited above [59], there is no other evidence that high maternal TPO Ab titers are associated with a delayed neurologic development of the offspring.

2.3.4. Euthyroid TPO Ab Negative Women with TSH between 2.5 and 5 mIU/L

Pregnancy Complications. A higher rate of spontaneous pregnancy loss was observed in a study of 642 women with serum TSH ranging between 2.5 and 5 mIU/L in the first trimester than in 3481 women with TSH below 2.5 (6.1% versus 3.6%, $P = 0.006$, resp.) [70].

2.4. Is Levothyroxine Therapy Beneficial and Effective in regard to Improved Outcomes and Reduced Complications Associated with Pregnancy and Delivery?

Based upon data in the study by Abalovich et al. [38] focused on 150 pregnancy outcomes in 114 women who had either OH ($n = 52$) or SH ($n = 62$) (Table 1), Stagnaro-Green analyzed the preterm delivery rate of women who were either adequately treated at conception ($n = 99$) or during pregnancy ($n = 27$) versus women who were inadequately treated during pregnancy ($n = 24$). The analysis revealed a significantly lower preterm delivery rate of 1.6% after adequate treatment with L-T4 compared to a rate of 12.5% in the group of inadequately treated women with TSH > 4 mIU/L during pregnancy ($P < 0.05$) [74]. There is also evidence that LT4 treatment can improve implantation rate and live birth rate in infertile women with subclinical hypothyroidism undergoing in vitro fertilization [75].

Rovet [76] investigated children up to the age of 5 born to women who, although having been treated for hypothyroidism during pregnancy, received suboptimal LT4 dosage as indicated by mean TSH levels between 5 and 7 mIU/liter. The children at preschool age were found to have a mild reduction in global intelligence that was inversely correlated with maternal TSH level during the third trimester. No negative impact was noted on language, visual spatial ability, fine motor performance, or preschool ability.

Preliminary results of the "Controlled Antenatal Thyroid Screening Study" (CATS) were presented in September 2010 during International Thyroid Congress [73]. The CATS trial was a prospective randomized study that screened 22,000 women within the 16th week of gestation for thyroid status with TSH and FT4 measurements. Women with FT4 values lower than the 2.5th percentile and/or TSH values above the 97.5th percentile were randomly assigned into an intervention group treated with LT4 or a control group without intervention. Neuropsychological development assessed by Wechsler Preschool and Primary Scale of Intelligence (WPPS III) was performed in the offspring of both groups at 3 years of age. Primary outcomes consisted of the mean WPPS III score and the percentage of offspring with IQ of <85 points. A primary analysis that included an intention to treat analysis revealed no significant differences. The secondary analysis which excluded women who had been noncompliant with LT4 treatment also revealed no difference in relative risk of full-scale IQ being below 85 in the screened group compared to the control group.

A second study is presently in progress under the auspices of the NIH. Pregnancy screening was initiated in October 2006, and study completion is anticipated in 2015. That study will eventually comprise a total of 120,000 pregnant women, recruited from an obstetrical US network of 14 institutions. Women with SH or isolated hypothyroxinemia will be randomized to placebo versus LT4 treatment to normalize serum TSH in women with SH or to normalize serum FT4 in women with isolated hypothyroxinemia [77]. The primary outcome of the study will be intellectual function of children at 5 years of age as measured by the WPPSI-III. The WPPSI-III scores of progeny of treated women will be compared to the children of untreated women. Secondary outcomes of the study include assessment of fetal growth, rates of preterm delivery, preeclampsia, placental abruption, stillbirth, and development of postpartum thyroid dysfunction.

2.4.1. Euthyroid Women with AITD. Negro et al. published the first study focused on the possible benefit of LT4 treatment of anti-TPO positive euthyroid women defined as having serum TSH within a range 0.27–4.2 mIU/L [72]. Among 984 patients who completed the study, there were 155 anti-TPO positive women randomized into an intervention group ($n = 57$) treated with LT4 at their first prenatal visit performed at a median 10 weeks of gestation and a no intervention group ($n = 58$). TPO Ab negative women ($n = 869$) served as a normal control group. This study importantly demonstrated salutary effects of LT4 administration to both correct maternal thyroid dysfunction and also decrease the rate of adverse obstetrical events such as miscarriage and premature delivery, bringing their prevalence down to those of the control population (Table 1). No study has yet demonstrated whether similar benefit might be gained with LT4 therapy of TPO Ab negative women.

2.5. How to Select the Patients for Whom the Treatment May Be Beneficial?

2.5.1. Screening for Thyroid Dysfunction during Pregnancy. In view of the growing evidence that abnormal thyroid function during pregnancy is associated with less optimal outcomes that can be improved with LT4 treatment, the question arises as to whether to screen in early pregnancy for thyroid dysfunction. The 2007 Endocrine Society Guidelines

Table 1: Intervention studies describing the efficacy of LT4 treatment during pregnancy.

Study	Design	Material	Intervention	Target TSH	Pregnancy complications	Offspring complications
Abalovich et al. [38]	Retrospective study of pregnant women with OH TSH > 5 mIU/L, T4 < 4.5 ug/dL and SH TSH > 5 mIU/L, T4 normal	114 women OH $n = 52$ SH $n = 62$ 99 pregnancies conceived under euthyroidism, 51 under OH or SH	Treatment with LT4 before or during pregnancy as soon as OH or SH was diagnosed	Optimal treatment TSH < 4 mIU/mL Inadequate treatment TSH > 4 mIU/L	Among pregnancies conceived under OH or SH miscarriage rate inadequate versus adequate treated 60% versus 0% in OH and 71.4% versus 0% in SH	Among pregnancies conceived under OH or SH preterm deliveries rate inadequate versus adequate treated 20% versus 0% in OH and 7.2% versus 9.5% in SH
Hallengren et al. [71]	Prospective observational	63 pregnant women with OH treated with LT4	Adjustment of the LT4 dose	<2 mIU/L	Fetal loss 6% (2/32) of optimally treated patients versus 29% (9/31) of women treated inadequately	Not examined
Negro et al. [72]	Prospective randomized trial	984 euthyroid women with TSH levels <4.2 mIU/L	group A, $n = 57$ TPO Ab (+) women treated with LT4 initiated at median 10 weeks of gestation versus group B, $n = 58$ no treatment for TPO Ab (+) women versus groups C $n = 869$ control TPO Ab (−)	Dose of LT4 stable during pregnancy 0.5 ug/kg/d for TSH < 1.0 mIU/L 0.75 ug/kg/d TSH 1.0-2.0 mIU/L, 1 ug/kg/d TSH > 2.0 mIU/L or anti-TPO > 1500 kIU/L	The rate of miscarriage lower in intervention group A compared to group B (3.5% versus 13.8%, $P < 0.05$) and similar to controls (3.5% versus 2.4%, $P = ns$)	Not examined
CATS study Lazarus [73]	Prospective randomized trial	22,000 women within the 16th week of gestation	In the intervention group LT4 was initiated during pregnancy in women with FT4 values lower than the 2.5th percentile and/or TSH values above the 97.5th percentile. The control group received no intervention.	<2.5 mIU/L I trimester <3 mIU/L II and III trimester	No data	The primary outcome was the mean WPPS-III score and the percentage of offspring with IQ < 85 points. The primary intention to treat analysis revealed no significant differences. A secondary analysis excluded women noncompliant with LT4 and also revealed no difference in relative risk of full scale IQ being below 85 in the screen group compared to the control group.

[6] recommend case finding by measurement of TSH in women in any of the following categories:

(1) personal history of abnormal thyroid function,

(2) family history of thyroid disease,

(3) goiter,

(4) positive thyroid antibodies,

(5) symptoms or clinical signs suggestive of thyroid dysfunction,

(6) type 1 diabetes,

(7) other autoimmune disorders,

(8) infertility,

(9) history of therapeutic head or neck irradiation,

(10) history of miscarriage or preterm delivery.

However, it has been suggested that we might fail to detect 30% of hypothyroid and 69% of hyperthyroid women if only high-risk pregnant women are screened [78]. This argument is supported by demonstrating that screening a low-risk group identified both hypothyroidism and hyperthyroidism and allowed early therapy that resulted in a lower rate of adverse obstetrical and fetal outcomes [79]. While a major argument against screening is the associated cost of TSH measurements, it has been demonstrated that screening pregnant women with TSH in the first trimester of pregnancy is cost-saving compared with no screening and screening by measurement of anti-TPO antibodies is also an economically favorable screening strategy [80].

2.6. What is the Appropriate Treatment Regimen; What are Target Thyroid Function Test Values, and How Often Should They Be Monitored?

Once a diagnosis of either OH or SH is made during pregnancy, the Guidelines of the Endocrine Society clearly recommend initiation of treatment with LT4 [6].

> *"LT4 dose often needs to be incremented by 4–6 wk gestation and may require a 30–50% increment in dosage. If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible. The target threshold TSH should be less than 2.5 mIU/L in the first trimester and less than 3 mIU/L in second and third trimesters or to trimester-specific normal TSH ranges. Thyroid function tests should be remeasured within 30–40 d. After delivery, most hypothyroid women need to decrease the thyroxine dosage they received during pregnancy."[6]*

Notwithstanding the data extant demonstrating efficacy of LT4 therapy in preventing adverse pregnancy and offspring outcomes and the availability of published guidelines addressing the treatment strategy, there is evidence that 24–49% of women treated with LT4 before conception still have elevated TSH levels at their first prenatal visit [71, 81, 82]. The reasons for this are not clear but could include failure to appreciate and recognize that dosage requirements for LT4 may change with pregnancy as well as perhaps failure to remeasure TSH at sufficiently frequent intervals. In women already taking LT4, the magnitude of increase in LT4 requirements with pregnancy is approximately 40–50% of the prepregnancy dosage in athyreotic patients and about 20–30% for patients with underlying Hashimoto's thyroiditis [6, 83–89]. The difference is due to the fact that the latter patients typically will have some residual functioning mass of thyroid tissue capable of releasing T4 that complements the daily exogenous LT4 dose.

Because of the potential for clinicians to fail to identify the demand for an increased LT4 dosage in pregnancy, several studies have aimed to identify a practical therapeutic approach to address this issue [90]. Rotondi et al. [91] pointed out that the intervention should be made preconception. They prospectively examined 25 women with compensated hypothyroidism of different etiology anticipating pregnancy and assigned them to two groups: 14 patients had their LT4 dose increased to a partially suppressive dose, while 11 patients continued the same therapeutic regimen. Their results indicated that a preconception dosage of LT4 targeted at TSH in the lower quartile of the reference range may result in adequate maternal thyroid function up to the first postconception evaluation. This observation is in agreement with a retrospective study by Abalovich et al. of 53 women with compensated hypothyroidism defined as a TSH <2.5 mIU/L six months prior to conception. When the preconception TSH was below 1.2 mIU/mL, only 17.2% of women required incremental LT4 adjustment during the pregnancy compared to 50% of women having a preconception TSH between 1.2 and 2.4 mIU/mL ($P < 0.02$) [92].

These data support the logic of the premise that women will need varying degrees of adjustment of their prepregnancy LT4 dosage based upon the underlying cause of their thyroid dysfunction. The best example of this was demonstrated by Loh et al. [93] who observed that patients with a history of thyroid cancer on doses of LT4 sufficient to suppress preconception TSH required smaller and less frequent incremental adjustments of LT4 during the pregnancy in order to keep TSH within the normal range than did patients suffering from other causes of hypothyroidism. Some investigators have proposed a simple and practical formula to address this issue, suggesting that hypothyroid women on LT4 should be advised that once pregnant they should increase their LT4 dose by about 25% by taking two extra doses per week of their usual daily dose of LT4 [94]. Other than the consideration of the cost of additional TSH measurements throughout pregnancy, we would propose that assurance of euthyroidism during pregnancy is best obtained by an individualized approach to LT4 dosage adjustment based on a TSH measurement done every 2 weeks during the first trimester and then less frequently thereafter as suggested by Burman [95].

The very recent THERAPY trial (Thyroid Hormone Early Adjustment in Pregnancy) proposed another approach [96]. Sixty women with treated hypothyroidism were prospectively randomized before their anticipated pregnancy to one of two groups who received an increased LT4 dose of either 2 or 3 tablets per week once pregnancy was confirmed. Enrollment took place at a median 5.5 weeks of pregnancy, and patients were followed with the measurements of TSH, TT4, and thyroid hormone binding ratio every 2 weeks through week 20 and then once again at 30 weeks. Interestingly, despite the early enrollment, nearly 30% of women were already hypothyroid. The authors documented that increasing LT4 by 2 tablets per week resulted in the achievement of TSH below 2.5 mIU/L during the first trimester in 85% of patients without a significantly increased risk of iatrogenic hyperthyroidism, which was observed in 2/25 patients compared with

the group receiving a 3-tablet per week increment, in which suppressed TSH was observed in 14/23 women. This study also assessed the optimal follow-up strategy throughout the remainder of pregnancy; documenting that 92% of abnormal TSH values would be detected by testing every 4 weeks.

Based upon this review of the literature, it appears clear that there is a necessity to both update and promulgate novel guidelines in regard to LT4 treatment during pregnancy. In addition to the endocrine community, the guidelines importantly should reach a target population of obstetricians and family care physicians who provide the majority of antenatal care. Indeed, according to one study of obstetricians and general practitioners in Wisconsin, there is currently a limited awareness of the 2007 Endocrine Society Guidelines in only 11.5% of the latter population of caregivers [97].

2.6.1. A Future Research Agenda That Could Illuminate Remaining Aspects of the Care of Pregnant Women with Thyroid Dysfunction Might Include the Following.

(1) Determination of which strategy is most appropriate, universal screening, or case finding, based on large prospective trials like CATS and NIH trial.

(2) Assessment of the best screening strategy (TSH versus anti-TPO Ab versus TSH + anti-TPO Ab) in different populations characterized by various iodine nutritional status.

(3) Examining the effects of LT4 treatment of SH and isolated hypothyroxinemia on the long-term intellectual development of offspring.

(4) A study of the efficacy of LT4 treatment of TPO Ab negative women with preconception TSH levels >2.5 mIU/L.

(5) Confirmation of whether the optimal preconception target TSH concentration is 1.2 mIU/L versus 1.2–2.5 mIU/L.

3. Addendum

After the acceptance of this review for the publication, the new Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum were released online [98].

The content of this review is concordant with ATA guidelines in the following recommendations.

(1) Trimester and population specific reference ranges for TSH should be applied. If they are not available in the laboratory, the following reference ranges are recommended: first trimester, 0.1–2.5 mIU/L; second trimester, 0.2–3.0 mIU/L; third trimester, 0.3–3.0 mIU/L.

(2) Method-specific and trimester-specific reference ranges of serum FT4 are required.

(3) All women with hypothyroidism and women with subclinical hypothyroidism who are positive for TPOAb should be treated with LT4; however due to the lack of randomized controlled trials there is insufficient evidence to recommend for or against universal LT4 treatment in TPO Ab negative pregnant women with subclinical hypothyroidism.

(4) The goal of LT4 treatment is to normalize maternal serum TSH values within the trimester-specific pregnancy reference range.

(5) LT4 dose should be increased by 25–30% upon a missed menstrual cycle or positive home pregnancy test. This adjustment can be accomplished by increasing LT4 by additional 2 tablets of LT4 per week. Further adjustments should be individualized as they are dependent on the etiology of maternal hypothyroidism, as well as the preconception level of TSH. Serum thyroid function tests should be monitored closely.

(6) Hypothyroid patients (receiving LT4) who are planning pregnancy should have their dose adjusted by their provider in order to optimize serum TSH values to <2.5 mIU/L preconception.

Some controversial problems pointed out in this review have been addressed by the guidelines in the following manner.

(1) Euthyroid women (not receiving LT4) who are TPOAb positive require monitoring for hypothyroidism during pregnancy.

(2) Serum TSH should be evaluated every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks gestation.

(3) Isolated hypothyroxinemia should not be treated in pregnancy, because of the lack of a documented effect of this intervention.

Some controversial problems included in this review that remain unsolved or not addressed.

(1) There is insufficient evidence to recommend for or against screening for TPO Ab in the first trimester of pregnancy, or treating TPO Ab positive euthyroid women with LT4.

(2) There is insufficient evidence to recommend for or against universal TSH screening at the first trimester visit.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 691719, 5 pages
doi:10.4061/2011/691719

Review Article

Prognosis of Thyroid Cancer Related to Pregnancy: A Systematic Review

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Received 16 March 2011; Accepted 27 May 2011

Academic Editor: Roberto Negro

Differentiated thyroid cancer (DTC) is the second most common cancer in pregnancy. Its management is a challenge for both doctors and patients, and the best timing for surgery is unclear. A systematic review evaluating the prognosis of DTC in pregnant patients was conducted. After reviewing 401 unique citations and 54 full texts, 4 studies that compared the prognosis of patients with DTC related to pregnancy (DTC diagnosed during pregnancy or within 12 months after childbirth) or not were included. In two studies the primary outcome was overall survival, in one study the primary outcomes were recurrent disease and death related to thyroid cancer, and in one study the primary outcome was recurrent or persistent disease. In the first two studies, there was no difference in overall survival in patients with pregnancy-related DTC, when compared with matched controls; in one study, there was no difference in death caused by DTC nor recurrence in DTC related to pregnancy. Nevertheless, in a recent retrospective study, a higher rate of recurrent or persistent DTC was observed in patients with DTC related to pregnancy. There are not many studies on which to base treatment decisions in pregnant patients with DTC.

1. Introduction

Thyroid cancer currently ranks tenth in incidence among solid organ malignancies. The majority of thyroid cancers are classified as papillary (88%) or follicular (9%); together these two histological types are grouped as differentiated thyroid cancers (DTC) [5]. While the annual rate of cancer incidence is decreasing, there has been a 2.4-fold increase in thyroid cancer from 1973 to 2002 [6].

DTC occurs more commonly in women of child-bearing age with an incidence of 14 per 100,000 live births and represents the second most frequent tumor diagnosed during pregnancy only behind breast cancer [7, 8]. As DTC is commonly found during pregnancy or in the early postpartum period [9], it is possible that physiological changes associated with it, as high levels of estrogen, human chorionic gonadotropin (hCG) and/or others, could create a favorable environment to tumor development and growth. Maternal thyroid gland secretes more thyroid hormone during early pregnancy in response to the thyrotropic activity of hCG that overrides the operation of the hypothalamic-pituitary-thyroid feedback system. This could partially explain an increase in the size of preexisting thyroid nodules as well as new thyroid nodule formation in pregnancy [10–15].

The best treatment option for thyroid cancer in pregnant women or in the early postpartum period should be based on evidence, so the aim of this paper was to evaluate whether the prognosis of DTC associated with pregnancy is similar or not to DTC in nonpregnant women.

2. Methods

2.1. Search Strategy. This literature search was conducted in the PubMed, Cochrane, and Scopus databases, combining the MESH terms: thyroid neoplasms and pregnancy. All studies in English until February 2011 were included.

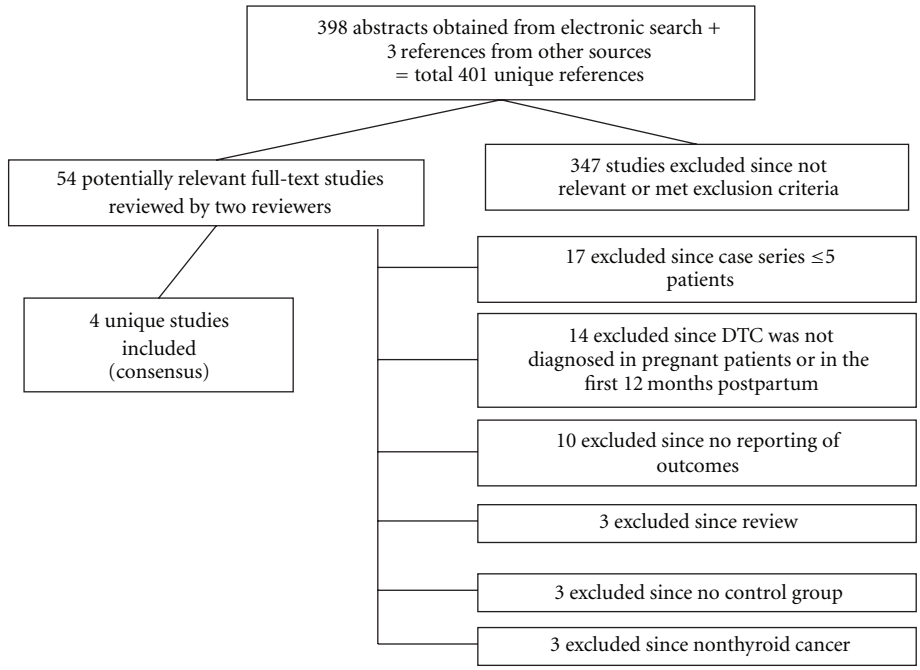

Figure 1: Process of study selection for the systematic review.

2.2. Inclusion and Exclusion Criteria for Studies. To be included in this review the original article should describe the comparison between the outcomes in patients diagnosed with DTC during pregnancy or in the first 12 months postpartum (DTC related to pregnancy), with a control group comprising women of child-bearing age, diagnosed with DTC when nonpregnant or at least 12 months after delivery.

Patients should have no prior exposure to radiation or previous malignancies.

2.3. Selection of Studies for Inclusion. All citations and abstracts identified by the electronic search were reviewed by two independent reviewers. Any abstract identified as relevant was analyzed as a full text. Other sources of obtaining papers were used, as cross-referencing texts reviewed.

3. Results and Discussion

After reviewing 398 abstracts from the electronic search and 3 summaries obtained by manual search, 54 articles were reviewed in full-text form. However, after analysis of these studies, several were excluded, for the following reasons: DTC did not occur during pregnancy, there was no control group, there was no reporting of outcomes, or they described small case series, so only four studies were included in this paper, as shown in Figure 1 [1–4]. The characteristics of the studies and the outcomes are described, respectively, in Tables 1 and 2.

There are only a few studies about outcomes of DTC related to pregnancy. As DTC has a good prognosis, the number of patients studied should be large, and the followup should be very long to detect any difference in survival or even recurrence. Most recurrences of DTC occur within the first five years after initial treatment, but recurrences may occur many years or even decades later, particularly in patients with papillary cancer [16, 17]. In addition to this, decisions about cancer treatment during pregnancy are associated with ethical conflicts between the best option for the mother and for the fetus [18, 19]. The management of pregnant women with cancer should consider the maternal-fetal risk related to treatment, as well as the possibility of tumor progression for postponing treatment or for the tumor being related to pregnancy. During this study we could observe that there is little published data comparing outcomes in patients with DTC related to pregnancy or not. No randomized controlled trial was available.

In the study of Moosa and Mazzaferri there was no impact from pregnancy in DTC-related death [3]; in the studies of Yasmeen et al. and Herzon et al. overall survival was not affected by DTC [2, 4]; when evaluating if the timing of surgical treatment, during pregnancy or after birth, affected the prognosis of patients with DTC detected during pregnancy, Moosa and Mazzaferri and Yasmeen et al. [2, 3] have not shown differences in recurrence rates and, respectively, in DTC-related death and overall survival. Such findings, however, are not in agreement with the study published by Vannucchi et al. They found a strong association of DTC in pregnant women with recurrence or persistence of cancer (60% in pregnant women (group 2) versus 4.2% in women with DTC diagnosed 1 year after delivery (group 1) versus 13.1% in nulliparous patients when diagnosed with DTC (group 3)). After a stepwise logistic regression analysis entering the following variables: extrathyroidal extension,

Table 1: Characteristics of the included studies.

Study	Study design	Study population	Control group description	Followup (median)
Vannucchi et al., 2010 [1]	Retrospective cohort in a single institution—1995–2006	14 women (one affected twice), age 32.2 ± 6.4 yr, DTC diagnosed during pregnancy (G2)	47 women, age 36.1 ± 3.6 yr, DTC diagnosed at least one year after delivery (G1), and 61 nulliparous women when diagnosed with DTC, age 34.1 ± 6.2 yr, (G3)	G1: 68.2 months G2: 60.1 months G3: 64.7 months
Yasmeen et al., 2005 [2]	Population-based case control study—California 1991–1999	595 pregnant women with DTC, 129 diagnosed during pregnancy and 466 diagnosed within 12 months postpartum	2270 age-matched nonpregnant women with DTC	Not reported
Moosa and Mazzaferri, 1997 [3]	Case control study—United States Air Force registry	61 pregnant women with DTC, age 26.0 ± 5.9 yr	528 age-matched nonpregnant women with DTC, age 26.3 ± 5.9 yr	22.4 yr in study population and 19.5 yr in control group
Herzon et al., 1994 [4]	Case control study—New Mexico Registry 1970–1991	22 pregnant women with DTC, age 18–46 yr	465 women with DTC in the same database, age 18–46 yr	6 months to 20 years reported for study population

Age (years) is expressed as mean + SD; DTC: differentiated thyroid cancer; G: group.

lymph-node metastases, radioiodine treatment, pregnant or not pregnant status at diagnosis, histotype, and tumor size ≤2 or >2 cm, pregnancy was found to be the most significant predictor for disease recurrence or persistence [1]. As the outcomes and the methodology employed in each study were different, it was not possible to compare their results and to combine the data in a meta-analysis. In the studies of Yasmeen et al. and Herzon et al., the overall survival was the main outcome [2, 4], while the study of Moosa and Mazzaferri had death related to DTC and recurrence, evaluated by biopsy or by ^{131}I uptake in distant sites, as primary outcomes [3], and the more recent study of Vannucchi et al. evaluated persistent/recurrent DTC through more sensible tests such as Tg basal levels and Tg response to rhTSH [1]. Such methods were not used in the study of Moosa and Mazzaferri [3], which could explain some of the discrepancies among them.

In the study of Vannucchi et al. more patients from the pregnant women with DTC had follicular histotype. However, this factor does not seem to explain the worse outcome which has been found on the group of patients with DTC associated to pregnancy, since two of three patients with follicular histology remained in remission [1].

Two studies reported differences among clinical presentation between pregnant and nonpregnant women [1, 3]. In the study of Moosa and Mazzaferri, fewer pregnant patients showed symptoms associated to thyroid nodules (74% versus 43%, $P < 0.01$) [3]. On the other hand, in the study of Vannucchi et al. DTC was less commonly an incidental finding in pregnant patients, probably indicating that these patients had more aggressive disease [1].

A very interesting molecular datum was described by Vannucchi et al. The expression of the estrogen receptor alfa through immunohistochemical analysis was higher in group 2 patients, as compared to groups 1 and 3 [1]. As estrogen probably increases proliferative activity of thyroid follicular cells [20], this hormone could be implicated in a more aggressive pattern of DTC diagnosed in pregnancy.

Other important factor found in this paper refers to the time of followup of the studies. The mean median followup ranged from four to twenty-three years. Considering that DTC is a disease with low lethality and the followup was not very long, it is possible that the full impact of DTC on the patients survival was not evident.

The treatment of choice for both pregnant and nonpregnant patients was thyroidectomy. The central lymphadenectomy (VI-VII levels) was performed on all patients in the cohort described by Vannucchi et al. [1], and, according to clinical judgment, in the other studies [2–4]. There seemed to be no difference on the outcome of DTC during pregnancy whether the surgery took place at the second trimester of pregnancy or after childbirth [2–4]. In contrast to these findings, Kuy et al. compared the risk of thyroid and parathyroid surgery complications in pregnant and nonpregnant women, paired by age, in a retrospective cross-sectional study. A total of 201 pregnant women and 31155 nonpregnant women were included; among the 201 pregnant women, 45.8% have undergone surgery due to thyroid cancer, the others had benign thyroid and parathyroid diseases. Thyroidectomy during pregnancy was associated with an increased surgical complication rate in both malignant (21% to 8%) and benign diseases (27% to 14%), as well as higher endocrine complication rates (15.9% to 8.2%) and treatment costs ($6873 versus $5963) [21].

In summary, there are few studies which give base to the policies about pregnant patients with DTC. Up to present time, data obtained through systematic review show conflicting results when it comes to observed outcomes in this population. There seem to be a higher disease recurrence and persistence rates in this population when current treatment

Table 2: Main outcomes in patients with differentiated thyroid cancer (DTC) diagnosed during pregnancy or within 12 months of childbirth.

Study	Timing of surgery (study group)	Outcomes	Main study results	Comments and others outcomes
Vannucchi et al., 2010 [1]	(i) 11 patients operated during pregnancy and (ii) 4 patients operated after delivery[d]	(i) Persistent or recurrent disease detected by highly sensitive Tg and rhTSH (ii) ERα tumor expression by IHC	(i) ↑Persistent/recurrent disease in G2 versus G1 and G3 (60% versus 4.2% and 13.1%)[a] (ii) ↑ERα tumor expression in G2 versus G1 and G3 (87.5% versus 31% and 0%)[b]	(i) PTC more frequent in G1 and G3 versus G2 (97.8% and 98.3% versus 80%)[c] (ii) DTC was an incidental finding more frequently in G1 and G3 (iii) More sensitive methods for detecting recurrence were used in this study when compared with others (iv) Conclusion: pregnancy has a negative impact on the outcome of DTC
Yasmeen et al., 2005 [2]	(i) 96 patients operated during pregnancy and (ii) 27 patients operated after delivery[e]	Overall survival	No difference in survival between pregnancy-associated thyroid cancer and aged-matched nonpregnant women with DTC	Persistent/recurrent disease was not evaluated
Moosa and Mazzaferri, 1997 [3]	(i) 14 patients operated during pregnancy and (ii) 47 patients operated after delivery	(i) Death (ii) Recurrence diagnosed by biopsy, or by 131I uptake in distant site	No difference in cancer recurrence and death in study and control groups	(i) Outcomes similar in patients operated after delivery and during pregnancy (ii) Fewer pregnant patients showed symptoms associated with thyroid nodules when compared with nonpregnant (74% versus 43%)[b]
Herzon et al., 1994 [4]	(i) 6 patients operated during pregnancy and (ii) 16 patients operated after delivery	Overall survival	No difference in survival between pregnancy-associated thyroid cancer and aged-matched nonpregnant women with DTC	

PTC: papillary histotype; Tg: serum thyroglobulin; rhTSH: recombinant human TSH; ERα: estrogen receptor alfa; G: group; G1: DTC diagnosed at least one year after pregnancy, G2: DTC diagnosed during pregnancy, G3: DTC diagnosed in nulliparous women or before pregnancy; [a]$P < 0.0001$; [b]$P = 0.01$; [c]$P < 0.0001$; [d]1 patient was considered twice: she had two tumors in two different pregnancies; [e]In patients with DTC diagnosed during pregnancy.

response evaluation methods are employed. However, the impact on overall survival in the long time appears to be unaltered. There is no evidence to support termination of pregnancy when the diagnosis of DTC is performed. The guidelines of the endocrine society for pregnancy-related DTC recommend thyroidectomy after delivery for patients with no evidence of advanced disease or without rapid progression, and thyroidectomy in the second trimester of pregnancy for the others (USPSTF recommendation level B). Radioactive iodine should only be given after delivery and the ending of breastfeeding [22].

Prospective studies should be done to compare the prognosis of DTC diagnosed during pregnancy or not, as well as the effects of postponing surgery after childbirth in DTC diagnosed during pregnancy.

Conflict of Interests

The authors declare that there is no conflict of interests.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 429097, 6 pages
doi:10.4061/2011/429097

Clinical Study

Prevalence and Impact of Thyroid Disorders on Maternal Outcome in Asian-Indian Pregnant Women

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Received 9 March 2011; Revised 24 May 2011; Accepted 18 June 2011

Academic Editor: Bijay Vaidya

Aims. To establish the prevalence and the effect of thyroid dysfunction on pregnancy outcomes in Asian-Indian population. *Subjects and Methods*. The study cohort comprised of 483 consecutive pregnant women in the first trimester attending the antenatal clinic of a tertiary center in Mumbai, India. Thyroid hormone levels and thyroid peroxidase antibody were estimated. Patients with thyroid dysfunction were assessed periodically or treated depending on the severity. Subjects were followed until delivery. *Results*. The prevalence of hypothyroidism, Graves' disease, gestational transient thyrotoxicosis, and thyroid autoimmunity (TAI) was 4.8% ($n = 24$), 0.6% ($n = 3$), 6.4 % ($n = 31$), and 12.4% ($n = 60$), respectively. Forty percent of the hypothyroid patients did not have any high-risk characteristics. Hypothyroidism and TAI were associated with miscarriage ($P = 0.02$ and $P = 0.001$, resp.). *Conclusions*. The prevalence of hypothyroidism (4.8%) and TAI (12.4%) is high. TAI and hypothyroidism were significantly associated with miscarriage.

1. Introduction

Pregnancy can be viewed as a state in which a combination of events concurs to modify the thyroidal economy. There is change in the level of thyroxine-binding globulin, total thyroid-hormone level and change in the level of thyroid stimulating hormone (TSH) during normal pregnancy [1]. Thyroid dysfunction (TD) may be overlooked in pregnancy because of the nonspecific symptoms and hypermetabolic state of normal pregnancy.

Thyroid dysfunction has varied impact on pregnancy outcome. The risk of miscarriage is increased in autoimmune thyroid disease. Severe maternal hypothyroidism can result in irreversible neurological deficit in the offspring. Graves' disease (GD) can lead to pregnancy loss as well as fetal thyroid dysfunction.

The prevalence of hypothyroidism in pregnancy is around 2.5% according to the Western literature [2]. The prevalence of GD is around 0.1–0.4% and that of thyroid autoimmunity (TAI) is around 5–10% [3]. Data on the prevalence of TD during pregnancy is lacking in Asian-Indian population. Hence, this study was planned to establish the prevalence of TD and to evaluate maternal outcome in patients with TD.

2. Material and Methods

Study cohort was selected prospectively from consecutive pregnant females in the first trimester of pregnancy who attended the antenatal clinic of a tertiary referral center, in Mumbai, India, between January and April 2007. The patients with documented history of hypothyroidism or thyrotoxicosis were excluded. The females were included irrespective of their gravida status (primigravida/multigravida), and multiple pregnancies were also included.

Institutional ethics committee permission was obtained, and subjects were recruited for the study after obtaining written informed consent. They were subjected to clinical evaluation with emphasis on the family history of thyroid disorder and the obstetric history.

Serum TSH and thyroid peroxidase antibody (TPOAb) were done as initial hormonal investigations, and the subjects were grouped based on the system proposed by Glinoer [4]. The division into different groups and their followup are shown in Figure 1. Subjects with TSH <2 μIU/mL and TPOAb negative (group 1) were considered as normal. Patients with TSH 2–4 μIU/mL, TPOAb positive (group 4) and TSH > 4 μIU/mL (group 5) were treated with thyroxine. The aim of the treatment was to maintain TSH in the range of 0.2–2 μIU/mL. Once treatment was initiated or changed, TSH was repeated at 6 weeks. Once TSH became normal, it was repeated 2 monthly. TPOAb titres were repeated every trimester in those with baseline positivity.

In patients with TSH <0.1 μIU/mL, TSH receptor antibody (TRAb) was estimated. If TRAb is elevated, diagnosis of GD (group 6) was made. If TRAb was negative and β-human chorionic gonadotropin (hCG) level is elevated, it was diagnosed as gestational transient thyrotoxicosis (GTT) (group 7). In GD, maternal thyroid functions were monitored by free T3 (FT3)/free T4 (FT4) at monthly intervals. The aim of the treatment was to maintain FT3/FT4 in the upper quartile of normal nonpregnant range. Fetal monitoring of the patient with GD was done using ultrasound monthly from the 5th month of gestation focusing on fetal heart rate, goiter, growth, and movements. For patients with GTT, FT3, FT4, and TSH were done at 4 weekly intervals. All subjects were followed till and attended to at the time of delivery.

TSH was estimated by the third generation chemiluminescent immunometric assay (CLIA) (Immulite, analytical sensitivity = 0.004 μIU/mL, reference range = 0.4–4). FT3 (analytical sensitivity = 0.15 pmol/L, reference range = 0.23–0.63) and FT4 (analytical sensitivity = 11.58 pmol/L, reference range = 10.3–24.45) were done by competitive analogue-based immunoassay (Immulite). TPOAb (reference range < 35 IU/mL, analytical sensitivity = 5 IU/mL) and β hCG were done by CLIA (Immulite) (reference ranges vary according to gestational age). TRAb was done by ELISA (Medizyme TRA, reference ranges: negative < 1 IU/L, grey zone = 1–1.5 IU/L, positive > 1.5 IU/L, analytical sensitivity = 0.5 IU/L).

Statistical analysis was done using SPSS Version 17 software. The statistical significance between means was calculated by Student's t-test or Mann-Whitney U test whenever appropriate. P value <0.05 was considered to be significant.

3. Results

Four hundred and eighty-three subjects were recruited for the study. The mean age of the subjects was 25.19 ($\pm$4.17) years. The mean gestational age at presentation was 10.03 ($\pm$1.87) weeks. The prevalence of hypothyroidism was 4.8% and that of GD was 0.6% (Figure 1). Goiter was present in 78 subjects (16.1%). Family history of thyroid disease was present in 12 subjects (2.5%), and TPOAb positivity was seen in 60 subjects (12.4%). Of the 483 subjects, follow-up data is available for 379 while the rest (21.5%) were lost to follow up. The groupwise followup is as follows.

Group 1 (TSH 0.1–2 μIU/mL, without TAI). The baseline characteristics and pregnancy outcome are as given in Tables 1 and 2, respectively. This group was taken as reference for comparison for other groups.

Group 2 (TSH 0.1–2 μIU/mL with TAI). The baseline characteristics were similar to group 1 except for the significant association with previous history of stillbirth ($P = 0.042$). Followup revealed a significant rise in TSH by 0.78 μIU/mL as pregnancy advanced. ($P = 0.002$). The titers of anti-TPO antibodies decreased progressively towards the last trimester by 85% (242 to 34 IU/mL) ($P = 0.043$). Miscarriage was 3 times more common (26.3% versus 7.35%) in this group of patients. There was no significant association with other pregnancy outcomes.

Group 3 (TSH 2–4 μIU/mL without TAI). There was significant increase (by 0.25 μIU/mL) in TSH ($P = 0.029$) and significant decrease in FT3/FT4 ($P = 0.025$ and 0.033, resp.) at 6 months of pregnancy. Two patients (5.1%) had TSH >4 μIU/mL at 6 month followup. One of these patients had stillbirth for which no specific cause was found.

Group 4 (TSH 2–4 μIU/mL with TAI). These patients were treated with thyroxine and followed up. There was no significant difference in baseline parameters or pregnancy outcome in these patients.

Group 5 (TSH > 4 μIU/mL). The women in this group were older as compared to other groups ($P = 0.02$). Forty percent of these women did not have the high risk characteristics required for targeted case finding as laid down by the Endocrine Society guidelines [5].

The rate of miscarriage was 3 times higher in patients with hypothyroidism ($P = 0.02$) (Table 2). Four patients with hypothyroidism had miscarriage. Three patients were overtly hypothyroid (TSH > 10 μIU/mL). One patient (with TSH 69 μIU/mL) had abortion at 12 weeks of gestation, and the other two proceeded to term without any significant complications. There was no significant difference in stillbirth or premature delivery.

Group 6 (GD). All patients ($n = 3$) with GD presented with classical features of thyrotoxicosis (palpitation, weight loss, sweating, and tremor). One patient had abortion soon after starting treatment, and another was lost to follow up. One patient regularly followed up and required Propylthiouracil throughout pregnancy in tapering doses. TRAb titres reduced at third trimester (27 IU/L to 14 IU/L). She had normal delivery. Thyroid hormonal evaluation of the baby was normal.

Group 7 (GTT). The prevalence of GTT was 6.4%. Thyroid functions normalized in majority of the patients (70%) by the first followup (average gestational age = 14.4 weeks). In the rest, it normalized by 18 weeks of gestation.

The comparison of baseline characteristics and pregnancy outcome between TPOAb-positive and -negative

Table 1: Baseline clinical characteristics in different groups and comparison to subjects with group 1*.

	Group 1 $N = 323$	Group 2 $N = 28$	Group 3 $N = 59$	Group 4 $N = 16$	Group 5 $N = 23$	Group 7 $N = 31$
Age in years (mean ± SD)	25.09 ± 4.21	25 ± 4.65	24.42 ± 3.4	25.57 ± 3.3	29.37 ± 3.7	26.41 ± 4.9
P		1.00	1.00	0.622	0.022	0.544
H/O miscarriage *N* (%)	65 (20.1)	6 (21.4)	13 (21.6.)	2 (12.5)	5 (21.4)	7 (22.5)
P		0.620	0.728	0.513	0.712	0.726
H/O stillbirth *N* (%)	15 (4.6)	4 (14.3)	6 (10)	0 (0)	1 (4.2)	0 (0)
P		0.042	0.087	0.551	0.823	0.231
Infertility treatment *N* (%)	8 (2.4)	1 (3.6)	1 (1.7)	0 (0)	1 (4.2)	0 (0)
P		0.582	0.793	0.592	0.761	0.548
Family history *N* (%)	6 (1.9)	0 (0)	1 (1.7)	0 (0)	2 (8.9)	1 (3.2)
P		0.631	0.704	0.791	0.324	0.435
Goiter *N* (%)	52 (16.1)	5 (17.9)	5 (8.3)	4 (25)	5 (21.4)	4 (12.9)
P		0.587	0.130	0.155	0.241	0.451

* Patients with GD (Group 6) not included as the number is small ($N = 3$).

Table 2: Pregnancy outcome in various groups*.

Group	Number	Miscarriage *n* (%)	Stillbirth *n* (%)	Premature delivery (<37 weeks) *n* (%)	Full-term delivery *n* (%)
Group 1	272	20 (7.35)	4 (1.47)	14 (5.14)	234 (86.02.)
Group 2	19	5 (26.31)	1 (5.3)	2 (10.6)	11 (57.9)
P		**0.001**	$NS	NS	**0.034**
Group 3	40	3 (7.5.)	2 (5.0)	4 (10.0)	31 (77.5)
P		NS	NS	NS	NS
Group 4	7	1 (14.3)	0 (0)	1 (14.3)	5 (71..4)
P		NS	NS	NS	NS
Group 5	17	4 (23.5)	0 (0)	1 (5.9)	12 (70. 6)
P		**0.02**	NS	NS	NS
Group 7	22	1 (4.5)	0 (0)	2 (9.1)	19 (86.36)
P		NS	NS	NS	NS

$ NS: nonsignificant.
* Patients with GD (Group 6) not included as the number is small ($N = 2$).

Table 3: Comparison between TPOAb-positive and -negative women#.

Variables	TPOAb + ($n = 33$)	TPOAb − ($n = 322$)	*P* value
Age (yrs)	25.77 ± 4.24	25.09 ± 2.54	0.372
Goiter (%)	23.8	15.2	0.301
Family history (%)	3.03	4.23	0.897
Past H/O miscarriages (%)	19.93	20.6	0.892
Infertility treatment (%)	2.56	2.46	0.580
TSH (μIU/mL)	3.88 ± 1.2	1.24 ± 1.2	**<0.001**
Mean TPO titers (IU/mL)	352.92 ± 335.6	14.71 ± 5.2	**<0.001**
Any complication* (%)	19.04	12.8	0.463
Miscarriage (%)	24.24	7.76	**0.005**
Preterm delivery (%)	9.09	5.9	0.730
Stillbirth (%)	3.03	1.42	0.124
Full term delivery (%)	66.7	84.16	**0.023**
Birth weight (kg)	2.7 ± 0.63	2.6 ± 0.52	0.590

* Complication includes miscarriages, preterm delivery, pregnancy-induced hypertension, gestational diabetes mellitus, and intrauterine death.
# Baseline data of patients who are lost to follow up is not shown. Patients in Group 6 and 7 are excluded.

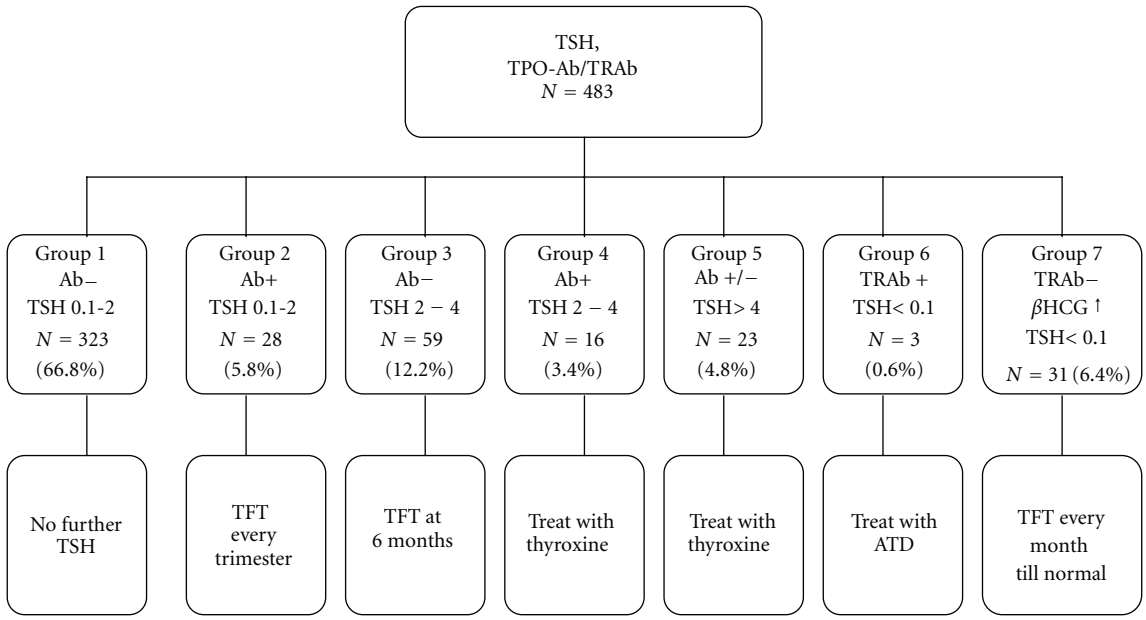

Figure 1: Classification into various groups based on TSH and antibody status. TSH: Thyroid stimulating hormone in μIU/mL, TPOAb: thyroid peroxidase antibody. TRAb: TSH receptor antibody, hCG: human chorionic gonadotropin. TFT: thyroid function tests (FT3, FT4, TSH, and TPO titres in those with positive TPOAb). ATD: antithyroid drugs.

women is given in Table 3. These women belong to groups 1, 2, 3, 4, and 5.

4. Discussion

The association between TD and adverse pregnancy outcomes has been studied earlier in western countries [6–9]. This has scarcely been studied in Indian population except two studies which looked at the prevalence of hypothyroidism in pregnant females [10, 11].

The mean age at presentation is lower (25.19 ± 4.17 years) compared to Western studies, namely, 27 ± 6 years [12], 29 ± 5 years [9] reflecting early marriage and early conception prevalent in India. The mean gestational age at presentation was 10.03 (±1.87) weeks indicating that most of the pregnant women in India do not visit the antenatal clinic during the first 8 weeks of gestation.

Our study demonstrates a higher incidence of hypothyroidism and TAI. The prevalence of hypothyroidism in this cohort is 4.8% which is higher than that in the western literature (2.5% [13], 2.6% [12]) and a previous Indian study (3.69% [11]). The higher prevalence in our study could be due to the higher prevalence of TAI in our cohort (12.4% versus 6.5% [13] and 8% [12]). Studies systematically assessing the prevalence of TAI during pregnancy, however, have not been reported from India. Iodine deficiency could be a contributory cause, but this information cannot be generated from our study as urinary iodine estimation was not done. The percentage of households consuming iodised salt in India as per the Iodine Network Global score card 2010 is 51% [14].

In the present study, the probable reason for higher miscarriage in patients with hypothyroidism was that they might have had undetected hypothyroidism at conception, and the treatment might have been insufficient to restore euthyroidism. The higher age (mean = 29 years) could also have contributed to miscarriage. Abalovich et al. [9] showed that untreated hypothyroidism, subclinical, or overt, at the time of conception is associated with miscarriage rate of 31.4% compared with 4% in euthyroid subjects at conception. The prevalence of stillbirth and premature delivery was not significantly higher than that in our hypothyroid patient population probably due to the adequate treatment given to the patients to maintain euthyroid state.

The miscarriage rate was 3 times more common in subjects with TAI (7.35 versus 26.5%) in our cohort (Table 3). The association has previously been established by various studies [6–8, 13]. TAI may be viewed as a marker of generalized immune imbalance that will explain the rejection of fetal graft [15]. Presence of TAI could be associated with a subtle thyroid hormone deficiency, due to the reduced functional reserve characteristic of chronic thyroiditis [15]. Women with thyroid antibodies tend to become pregnant at an average 3-4 years later and are, therefore, more prone to pregnancy loss. In our cohort, the relatively higher age in the patients with miscarriage might also have contributed to pregnancy loss.

In subjects with TSH <2 μIU/mL with TAI, history of stillbirth was significantly higher suggesting the association between thyroid autoimmunity and pregnancy loss. Some of the previous studies showed higher number of premature deliveries in women with TAI compared to normal women [9, 13]. Our study did not reveal such association.

Thyroid function in subjects with TSH 2–4 μIU/mL without TAI showed significant increase in TSH and decrease in FT3 and FT4 at 6 months compared to baseline. The

significant decline in thyroid functions for this subgroup at the latter half of pregnancy may justify thyroxine supplementation and regular monitoring (though presently not recommended) in this subgroup in the second half of gestation.

Patients with TSH 2–4 μIU/mL with TPOAb positivity were treated with thyroxine. The rationale for opting for treatment in these patients is the fact that despite the TSH downregulation in the first trimester by hCG, TSH level is in the upper half of normal, and there would be a tendency for progressive decline in thyroid function since they have TAI [16]. Though it is recommended to perform FT4 estimation before initiating treatment (in low-normal or low FT4) in this subset of individuals, the lack of trimester-specific normal values for FT4 and the inherent problems with FT4 assay made us focus on serum TSH as the marker for initiating and monitoring treatment. There was no significant difference in the pregnancy outcome in this group of patients compared to normal. This may be due to the smaller number of patients in this subset and the treatment given to these patients.

The prevalence of GTT in the cohort was 6.4%. In India, the prevalence of GTT has not been assessed previously. The prevalence of GTT varies from 2-3% in the Western literature [17]. The prevalence of GD in this cohort is 0.6%, higher than that published in the Western literature (0.2–0.4%) [18]. Further conclusions could not be derived since the sample size was small.

Our data gives a prevalence of thyroid dysfunction in subjects attending a tertiary care centre in Western India which can be generalized to population in the same setting in other parts of India. One limitation of our study was that 21% of subjects were lost to follow up. The Endocrine Society guidelines suggest that universal thyroid screening during pregnancy cannot be recommended, and aggressive case finding is recommended in specific subsets of subjects [5]. But recent studies have shown that targeted case finding will miss around 30–50% cases of hypothyroidism and/or TAI [12, 19]. This is similar to the present study in which 40% of the hypothyroid and 45% of TPOAb positive patients did not have high-risk characteristics. Approximately 60% of the hypothyroid or TPOAb positive pregnant women could have been missed by targeted case finding.

5. Conclusions

The prevalence of hypothyroidism (4.8%) and TAI (12.4%) was found to be high in the present study. TAI and hypothyroidism were found to be significantly associated with miscarriage.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 142413, 11 pages
doi:10.4061/2011/142413

Research Article

Transient Non-Autoimmune Hyperthyroidism of Early Pregnancy

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Received 22 March 2011; Revised 4 May 2011; Accepted 4 May 2011

Academic Editor: Roberto Negro

It is characterized by chemical and sometimes clinical hyperthyroidism, without evidence of thyroid autoimmunity that resolves spontaneously by 16 weeks gestation without significant obstetrical complications.

1. Introduction

Common Presentation. 26 y/o women, G1, P0, at 8 weeks gestation presents to the physician with a 3 weeks history of nausea and vomiting, weight loss of 2 kg., unable to tolerate solid foods, mild hands tremor, and palpitations with a pulse rate of 104 beats per minute. Serum TSH 0.02 mIU/L and FT4 2.8 ng/cl (0.9–1.8).

For the last few years, thyroid function tests have been frequently requested in early pregnancy because of physicians' awareness of potential obstetrical complications, both maternal and fetal, with an additional concern about the neuropsychological well-being of children born of mothers with thyroid dysfunction. Although universal screening is not recommended by some obstetric and endocrine societies, an aggressive detection program based on medical history and physical examination (presence of goiter) is encouraged. The interpretation of thyroid function tests in early pregnancy needs to be assessed in the context of the physiopathological changes taking place. Perhaps the most striking difference in normal pregnancies, from nonpregnancy thyroid test values, is the significant lowering of serum TSH, due to TSH-like activity of human chorionic gonadotropin (hCG). Serum TSH in the first trimester, particularly between 7 and 12 weeks gestation, fall to a nadir and present a mirror image with peak hCG values [1–3]. In a recent review, the lower normal TSH limit of approximately 0.03–0.08 mIU/L in the first trimester of pregnancy was derived from several studies using trimester-specific reference ranges [4]. Therefore, a "low serum TSH" in the first trimester of gestation should be considered "physiologic" in the presence of normal serum-free thyroxine (FT4) value. The exception could be a woman with T3 hyperthyroidism due to an autonomous or "hot" thyroid nodule. Thyroid tests in the hyperthyroid range may be seen in the first trimester of pregnancy in women without previous or present history of Graves' disease; they present to the consult with a clinical spectrum from no symptomatology, to morning sickness, to different degrees of vomiting sometimes severe as in the syndrome of hyperemesis gravidarum. Thyroid tests could be quite abnormal, presenting a challenge to the physician in the differential diagnosis and management of such individuals.

In this paper, we will discuss the following:

(i) definition,

(ii) causes or etiologies,

(iii) clinical and laboratory diagnosis,

(iv) management.

An emphasis will be placed on early series of women affected, on the difficulty in the differential diagnosis from Graves' hyperthyroidism and its management, and on the evolution of the role of hCG in its pathogenesis through the years.

We decided to use the term "transient nonimmune hyper-thyroidism of early pregnancy" because of its multiple

Table 1: Transient nonautoimmune hyperthyroidism in early pregnancy.

(i)	Normal pregnancy
(ii)	Mild nausea and vomiting
(iii)	*Hyperemesis gravidarum (transient hyperthyroidism of hyperemesis gravidarum)*
(iv)	Twin or multiple pregnancies
(v)	Mutation in the TSH Receptor
(vi)	Hyperplacentosis
(vii)	Hyperreactio luteinalis
(viii)	Hydatidiform mole
(ix)	Choriocarcinoma

etiologies although the etiology related to hyperemesis gravidarum is the most common. Different names have been suggested for this clinical entity. In 1992, Goodwin et al. used the term "transient thyrotoxicosis of hyperemesis gravidarum" [5, 6]; "gestational thyrotoxicosis" was proposed in 1993 as a new clinical entity by Kimura et al. [7]. Other nomenclatures were and are still employed when describing the syndrome, such as gestational hyperthyroidism (GH) and gestational transient thyrotoxicosis (GTT). In most of these reports, the common findings are vomiting of different intensity and thyroid tests in the hyperthyroid range without evidence of thyroid autoimmunity.

2. Definition

Hyperthyroidism diagnosed for the first time in early pregnancy, transient, without evidence of thyroid autoimmunity, lack of physical findings consisting with Graves' disease, resolving spontaneously by the end of the first or early second trimester of pregnancy.

3. Etiology

In the first trimester of pregnancy, several situations may present in which thyroid tests are consistent with hyperthyroidism in the absence of either autoimmune thyroid disease or an autonomous or functioning thyroid adenoma (Table 1).

3.1. Morning Sickness (Nausea and Vomiting) in Early Pregnancy. Mori et al. [8] reported in 1988 the relationship between morning sickness and thyroid function in pregnancies not affected by autoimmune thyroid disease. They studied 132 women in early pregnancy and compared them to 20 nonpregnant controls. Pregnant women were grouped in (a) no symptoms, (b) nausea only, and (c) nausea and vomiting. Serum-free T4 (FT4), hCG and serum thyrotropin stimulating hormone (TSH) with assay sensitivity of 0.1 μU/m were measured. The authors concluded that the increased serum concentration of free T4 and hCG and decreased serum TSH correlated with the severity of morning sickness. Unfortunately, the authors did not report the percent of patients in each group with values outside the normal range.

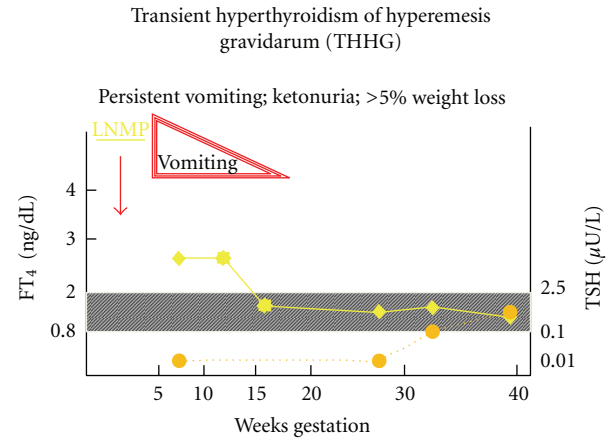

Figure 1: A representative example of transient hyperthyroidism of hyperemesis gravidarum. By week 6, vomiting begins and becomes severe by week 10. Serum-free thyroxine (T4) index is elevated and thyrotropin is suppressed. By weeks 16 to 18, vomiting subsides with marked improvement of the free T4 index value. During this period, the patient loses 3.6 kg. By week 18, the serum free T4 index returns to normal, but the serum thyrotropin remains suppressed until week 26. Patient regains and gains weight with a term delivery of a healthy infant. The gray band indicates reference range. LNMP: last normal menstrual period. Patil-Sisodia and Mestman [12].

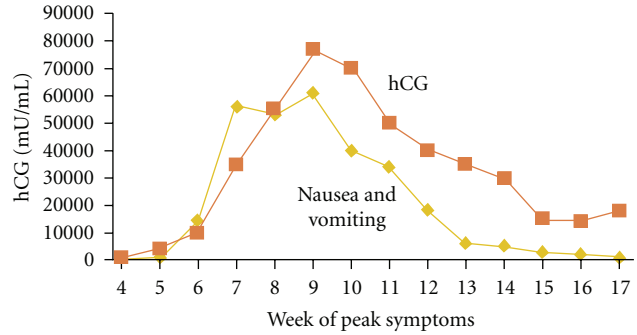

Figure 2: Relation between peak nausea and vomiting symptoms and human chorionic gonadotropin (hCG) levels. Niebyl [10].

3.2. Transient Hyperthyroidism of Hyperemesis Gravidarum (THHG). Hyperemesis gravidarum (HG) is reported to occur in 0.3% to 1.0% of pregnancies; it is defined as persistent nausea and vomiting resulting in greater than 5% weight loss, ketonuria, dehydration, and electrolytes (hypokalemia, metabolic alkalosis, hyponatremia, and hypochloremia), and liver abnormalities in severe cases [9, 10]. The onset of nausea is within 4 weeks after the last menstrual period, with worsening by 9 weeks gestation, resolution by the end of the first trimester in 60% of cases, and complete resolution by 20 weeks in the vast majority of women (Figure 1). Decreased risk of miscarriage has been reported in women with nausea and vomiting [11]. The clinical course of nausea and vomiting during pregnancy correlated closely with the level of hCG (Figure 2) [10]. The cause of nausea and vomiting is unclear although high levels of estrogen and/or Vitamin B deficiency have been implicated.

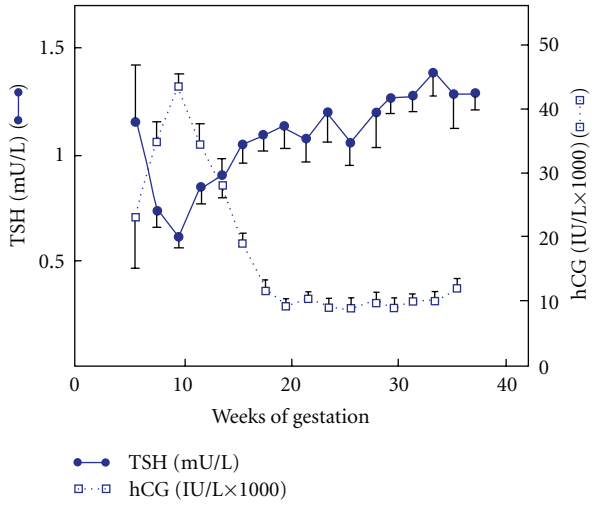

Figure 3: Serum hCG and TSH as a function of gestational age Glinoer et al. [1].

Ethnic variation in the incidence of HG has been suggested by several studies. For example, a birth registry in Norway from 1967 to 2005, revealed an overall prevalence of 0.9%; however, when broken down by ethnicity, it affected 2.2% of Pakistani women; 1.9% of Turkish women, and 0.5% of Norwegian women [14]; a California study suggested a lower incidence in Caucasian and Latina women as compared to nonwhites or non-Hispanics [15]. A familial aggregation was suggested by Zhang et al. [16] in a study in which women were recruited through advertising on the Hyperemesis Education and Research Foundation Web Site. In their study, sisters of women with HG have a significantly increased risk of having HG themselves (OR, 17.3; $P = 0.005$); mothers were also more affected than controls 33% versus 7.7% ($P < 0.001$). The authors suggested that the study provides strong evidence for a genetic component of HG. A report from the same group, described three women with a history of HG, developing severe nausea and vomiting during ovarian stimulation for gestational surrogacy [17].

In a high percent of women affected by HG, (30 to 73%), abnormal thyroid tests consistent with hyperthyroidism are detected; indeed, HG is the most common cause of THHG. The incidence of hyperthyroidism depends on the severity of symptoms, ethnic background, perhaps dietary iodine intake, interpretation of thyroid tests, and other unknown factors. The diagnosis of THHG is based on the presence of clinical and physical clues: the most common physical findings are tachycardia which is the result of dehydration and improved after fluid and electrolytes replacement, with average pulse rate of about 100 bpm after hydration in the vast majority of patients; fine tremor of fingers may be present as well as mild proximal weakness. In cases with significant elevations of thyroid hormones, particularly in those with high serum T3 values, other symptoms such as shortness of breath, heat intolerance, and palpitations may be present. Characteristically, no goiter or Graves' ophthalmopathy are detected. There is an elevation in serum FT4 or free thyroxine index (FT4I), a suppressed or undetectable serum TSH and no markers of thyroid autoimmunity. Serum TT3 is slightly elevated in less than 20% of affected women. Until a few years ago, a suppressed serum TSH was considered diagnostic of THHG in spite of a normal serum FT4. With the improvement in the sensitivity of immunoassay techniques, the serum TSH in normal first trimester of pregnancy could be as low as 0.03–0.08 mIU/L secondary to the thyrotropic activity of hCG; indeed, there is an inverse relationship between serum levels of hCG and TSH, and serum TSH exhibit a mirror image to the hCG peak (Figure 3).

The development of hyperthyroidism is most likely due to the thyrotropic action of hCG, its thyroid-stimulating activity as shown in bioassays in mice, rats, chicks, and men [18]. hCG stimulates iodine uptake and adenylate cyclase, and DNA synthesis in cultured rat thyroid cells. These studies demonstrated unequivocally that hCG activates the TSH receptor and is a weak thyrotropin. The thyrotropic activity of hCG is influenced by the metabolism of the hCG molecule, particularly by the number and structure of the oligosaccharide side chains. Deglycosylation and/or desialylation of hCG enhance its thyrotropic potency in rat (FRTL-5) thyroid cells. As discussed by Yoshimura et al. [19] the thyrotropic activity of hCG is regulated by two factors: the amount of desialylated hCG produced from trophoblast cells and its plasma half-life. hCG molecules that are less sialylated activate the TSH receptor to a greater extent, as has been reported in patients with the syndrome of THHG [20]. In bioassays, hCG is only about $1/10^4$ as potent as human TSH during normal pregnancy; it is likely that the thyrotropic activity of hCG during this peak secretion overrides the normal operation of the hypothalamic-pituitary feedback system [20].

Kauppila et al. [21], in 1979, reported on women with hyperemesis gravidarum, and how their serum hCG concentrations compared to those in a group of normal pregnant women. The 42 women with hyperemesis gravidarum were compared to 115 women with normal pregnancies during various periods in the first 20 weeks of pregnancy. In women with hyperemesis gravidarum, compared to normal pregnant women of matched gestational age, their mean HCG concentrations were higher at 7-8 weeks, 9–11 weeks, and 12–14 weeks, but there was no difference found between the mean serums concentrations when women were tested at 15–20 weeks. The authors suggested a causal relation between a high serum HCG concentration and HG.

Kennedy et al. [22] and Kimura [7] reported on patients with HG whose serum contained an activity, which stimulated cyclic AMP (cAMP) accumulation in cultured human thyroid cells and cultured FRTL-5 cells, but the authors were unable to identify the thyroid stimulator. The thyroid stimulating properties of the sera were immediately abolished by addition of anti-hCG antibody [7]. Several investigators suggested that Asialo-hCG with higher thyrotropic bioactivity was the cause of the syndrome, explaining the poor correlation between HCG serum concentrations and clinical symptoms reported in some studies [9, 23, 24]. Jordan et al. [25] suggested that more acidic isoforms of hCG with longer

half-life might result in more robust thyrotrophic effects in women with hyperemesis.

The first clinical description of an association between HG and hyperthyroidism was reported in 1978 by Bruun and Kristofferson [26]. The authors first considered the possibility of a related cause for the symptoms of hydatidiform mole and hyperemesis gravidarum and studied thyroid function tests. They found that in both conditions, there is an accompanying increase in serum hCG concentrations. Their findings that thyroid function abnormalities varied with hCG concentrations when compared to normal pregnancies, and opened the door to further clinical studies of hCG as a cause for the thyrotoxicosis that accompanies hyperemesis. They studied 35 women with HG, 14 with hydatidiform mole, and 57 normal pregnancies, as controls. They reported high values of protein binding iodine (PBI) in most patients with hydatidiform mole and in almost one third of HG women; in addition, they noticed lower serum cholesterol levels. They concluded "that there may be a common cause of the thyroid stimulation in patients with mole and hyperemesis." Soon thereafter, several reports of isolated or few cases of hyperthyroidism and HG were reported, showing the diagnostic challenges presented to physicians in the differential diagnosis from Graves' hyperthyroidism and the difficulties in management. In 1980, Valentine and Jones [27] demonstrated a case of a patient that began to establish the transient, self-limiting nature of hyperemesis gravidarum as well as the difficulty in establishing a definitive differential diagnosis from Graves' hyperthyroidism. The patient was treated with intravenous fluids to correct her severe dehydration. After developing pyrexia and tachycardia, her thyroid parameters were tested. She had an elevated FT4 index (FT4I) and long-acting thyroid stimulator (LATS), later recognized to be thyroid stimulating immunoglobulins (TSI), was negative; she was diagnosed with thyrotoxic crisis at 13 weeks' gestation and treated with carbimazole (CZ), propranolol, and Lugol's solution to normalize her thyroid function. The authors commented on several reports in the literature of patients with vomiting as the "cardinal symptom" of thyrotoxicosis [28]. Dozeman et al. [29] reported one patient during two pregnancies with severe HG (hypokalemia and abnormal liver tests), with similar clinical outcome, treated with ATD during the first but not during the second pregnancy, with normalization of thyroid tests at about the same gestational age; the authors diagnosis in the first pregnancy was Graves' hyperthyroidism and silent thyroiditis in the second pregnancy. Another case of two pregnancies in a patient with negative antibodies was reported with the same diagnostic dilemma as in previous cases [30].

By 1982, the first series specifically seeking to show the prevalence of hyperthyroxinemia accompanying HG (for purposes of this study, defined as irresistible vomiting for several weeks accompanied by a reduction in weight) was examined [31], showing that in 73% of 33 consecutive pregnancies complicated by hyperemesis gravidarum patients had some degree of hyperthyroxinemia, as determined by FT4I elevation. Important observations were pointed out by the authors: (a) serum FT3 was elevated in only 4 of 11 patients in whom FT3 was measured, (b) a blunted response to TRH test was seen in 5 hyperthyroxinemic women tested, (c) goiter, exophthalmos, or previous history of hyperthyroidism was absent in all patients, (d) a lower birth weight was observed in children born to hyperthyroxinemic mothers (3166 ± 501 gm, mean $\pm$ SD; $n = 19$) versus pregnancies not complicated by HG (3420 ± 501 gm; $n = 828$) ($P < 0.01$), findings not related to the use of ATD therapy, and (e) six mothers were treated with methimazole until normalization of thyroid tests, mean of 17 days with a range of 8 to 33 days, as compared to 19 days, range 6 to 46 days, in those women not receiving ATD therapy.

Juras et al. [32] reported an increased serum reverse Triiodothyronine (rT3) in women with HG, as compared to control women, suggesting an enhanced peripheral conversion of T4 to rT3, later confirmed by other studies [33, 34]. Elevation in serum nonesterified fatty acids (NEFA) and rT3 were postulated as protection against further weight loss and lipolysis [33].

A study of 10 HG patients in 1984 showed the great variability in thyroid parameters that accompany hyperemesis gravidarum [34]. Approximately half of the patients had both abnormally elevated serum FT4I and elevated reverse T3 (rT3) levels, or blunted TRH response, representing a THHG prevalence of approximately 50% among hyperemetic women. Peak TSH response to the thyrotropin releasing hormone (TRH) test inversely correlated to serum hCG concentrations, while no correlation was found between rT3 levels and TSH response. The lack of elevated FT3I in the patients could also be a result of the same T4 to T3 conversion blockade responsible for elevated rT3 levels due to reduced caloric intake. Though ATD therapy was not pursued, all women delivered normal term infants.

A series of 25 HG patients [35] in 1986 included ten patients, 40% of them, developing THHG, defined as elevated FT4 concentrations, all of whom also had blunted responses to TRH stimulation test and rT3 concentrations elevated above the reference range. A further six patients who had FT4 concentrations within the reference range also had blunted TSH response to TRH, including four with responses as blunted as in the thyrotoxicosis patients. No ATD treatment was given, and all thyrotoxic patients' thyroid parameters resolved spontaneously.

In 1987, a THHG prevalence of 43.6% was reported in a series of 39 patients with HG [36]. There was also evidence of abnormal liver function in some patients. There were similar pregnancy outcomes between the thyrotoxic and euthyroid HG patients, with a slightly elevated incidence of iron deficiency anemia among the thyrotoxic group. Two patients had persistent hyperthyroidism and were treated with ATD therapy.

In 1992, the largest series of HG women with hyperthyroidism was published [5]. Of the 67 HG patients 66% of them had biochemical hyperthyroidism, defined as either FT4I higher than the upper range of normal ($N = 39$), or a TSH less than 0.4 mU/L ($N = 60$), Twenty of the patients had undetectable TSH levels, <0.04 mU/L. Forty-two percent of women had abnormal liver function tests and 6% of them had an elevation in serum amylase titers. Abnormal

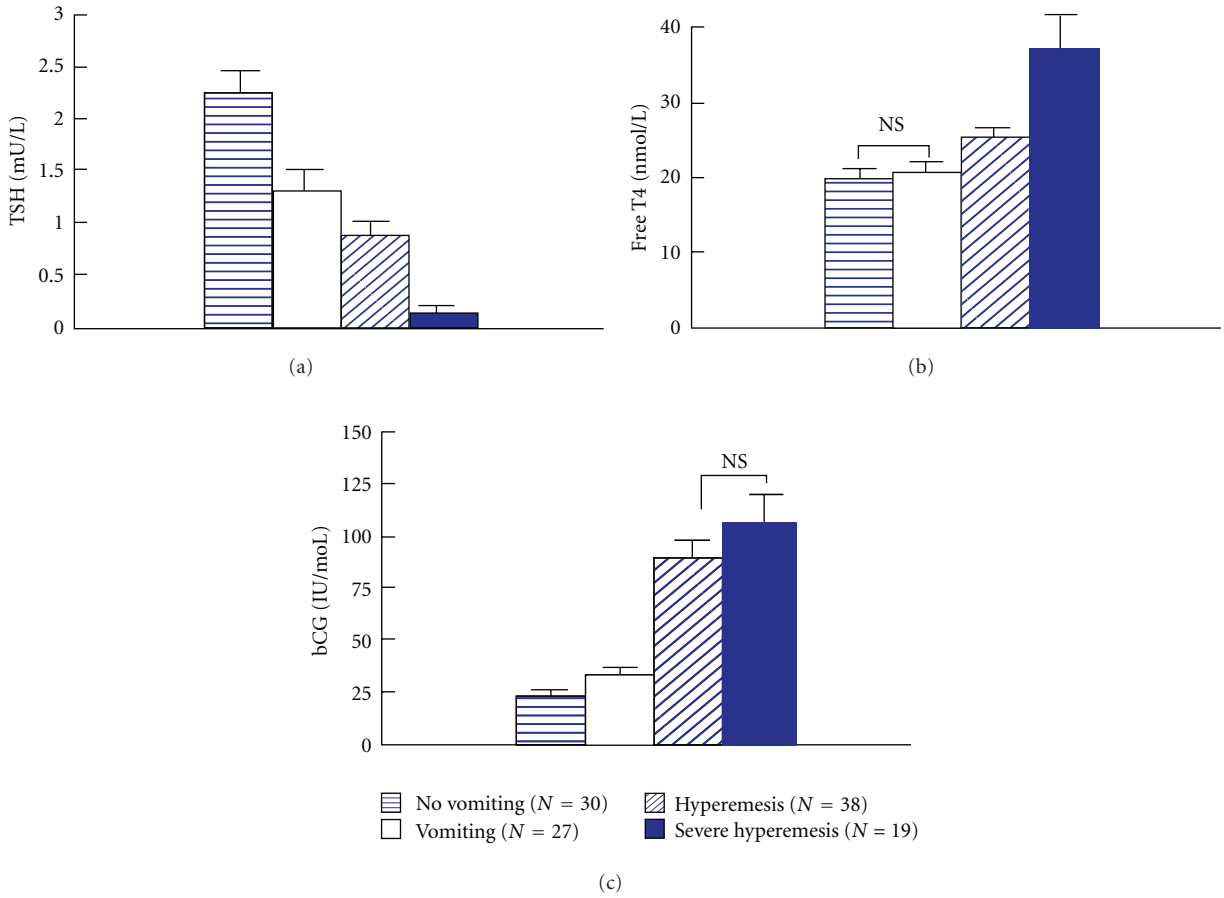

Figure 4: Relation between the severity of vomiting and serum concentrations of TSH, free T4, and hCG (mean ± SE). Hormone concentrations differed significantly between each group of patients except as indicated by NS Goodwin et al. [13].

electrolytes, hyponatremia, hypokalemia, and elevated bicarbonate levels were found in 28% of cases, mostly related to the degree of dehydration due to vomiting. FT3I elevation was detected in only 6 women related to severity of the reported vomiting. No patient received ATD therapy, and all had spontaneous resolution of vomiting in no more than 18 weeks gestation. In all cases, biochemical hyperthyroidism normalized by the time vomiting ceased; however, in seven cases, vomiting continued for two to fourteen weeks after normalization of thyroid function. From those same 67 patients, a series of 57 HG patients were selected and compared to 57 controls matched for gestational age and parity [13]. The authors divided the 57 women in four groups: no vomiting ($n = 30$), mild vomiting ($n = 27$), hyperemesis gravidarum ($n = 38$), and severe hyperemesis gravidarum ($n = 19$). Mean serum concentrations of hCG, FT4, estradiol, and prolactin (PRL) were all elevated in the HG groups. In Figure 4, the relationship between the severities of vomiting as indicated by clinical and biochemical parameters and the degree of thyroid dysfunction is shown. More severe vomiting was associated with a greater degree of thyroid stimulation and greater concentration of hCG. Serum from patients with HG was bioassayed for thyrotropic activity in thyroid cell culture, demonstrating a significant correlation between the serum concentration of hCG and the iodine uptake (Figure 5).

In 1993, Kimura et al. [7] studied 51 pregnant women divided into three groups based on the severity of their emesis symptoms, similar to the Goodwin et al. [13] protocol, their results confirmed previous findings of high serum FT4 and suppressed TSH, and high serum FT3 values in a few women. Interestingly, most of the patients in the emesis and hyperemesis group had undetectable serum TSH (<0.01 mIU/L). One difference in their study was that levels of hCG were not statistically different in the 3 groups. Two of the women in the hyperemesis group, who had both the highest FT4 concentration and thyroid-stimulating activity to hCG ratio, had clinical symptoms of thyrotoxicosis, which resolved as thyroid-stimulating activity and FT4 levels normalized. The authors suggested that a molecular variant of hCG with higher thyrotrophic activity was the cause of this syndrome.

Increased risk of THHG by ethnicity was evaluated by several investigators; among 294 South Asian women, from Pakistan, Bangladesh, or India, suppressed TSH concentrations < 0.35 mIU/L were found in 15.7%, compared to 4.8% of 292 age and parity-matched European women, suggesting that South Asian women may be at higher risk for gestational

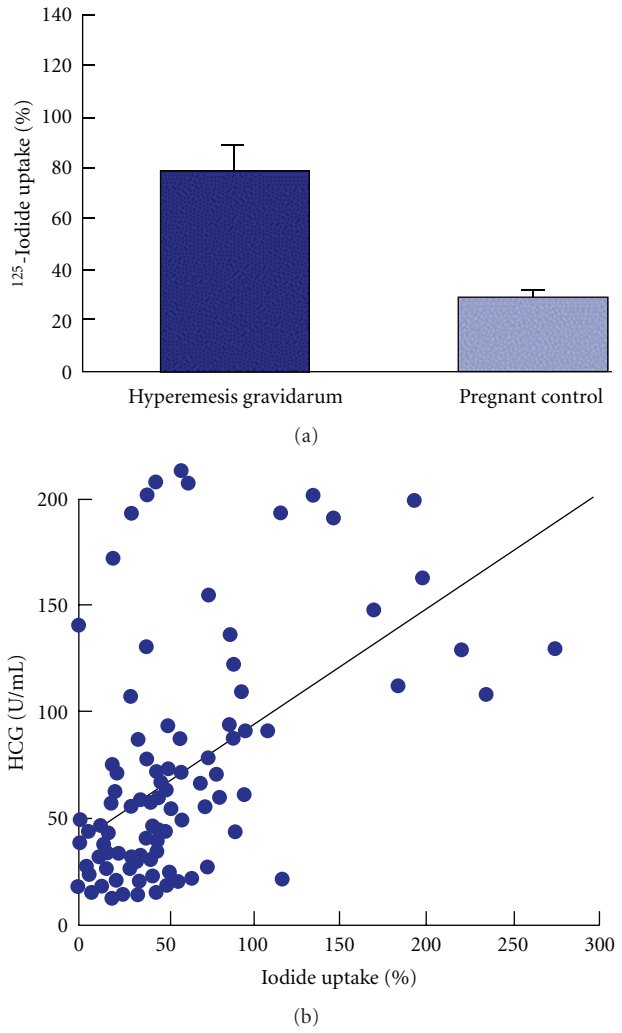

FIGURE 5: (a) Serum thyrotropic activity (measured as iodide uptake in cultured rat cells) in hyperemesis patients and pregnant controls, mean ± SE, $P < 0.001$) (b) correlation of serum hCG versus serum thyrotropic activity in hyperemesis and pregnant controls, $r = 0.50$, $P < 0.001$ Goodwin et al. [13].

thyrotoxicosis [37]. However, with the use of more sensitive assay for the determination of serum TSH, some of the patients with serum TSH < 0.35, considered "suppressed" by the authors could have had normal values. The higher prevalence by ethnicity was confirmed by other studies [38].

A review of previous series and a case report was undertaken in 2000, confirming that THHG generally resolves by 18 weeks' gestation without ATD treatment and without complicating the outcome of the pregnancy. The author suggested four clinical criteria for the diagnosis of HGGT: (1) abnormal thyroid function tests developing in the context of HG, (2) no evidence of prepregnancy hyperthyroidism, (3) absence of physical examination findings consistent with hyperthyroidism, and (4) negative thyroid autoantibodies titers [39].

A female predominance among the offspring of mothers with HG was reported by Deruelle et al. [40]. Of the 33 patients admitted with HG, 23 of them (66.7%) had THHG. The authors speculated about the involvement of hyperthyroidism and fetal sex in the pathogenesis of hyperemesis gravidarum.

Panesar et al. [41] attempted to determine the causal relationship between hCG and thyroid hormones in causing HG in Chinese women. A group of 58 HG women were compared to a gestational-age-matched group of 58 pregnant controls, and it was found that maternal age and all hormones were significantly different between the hyperemetic and control groups. Only FT4, sensitive TSH (sTSH), and maternal age were found to be significant independent variables.

In 2002, a study was done of 53 Asian women, from Singapore, who presented with HG and was later found to have accompanying hyperthyroidism [42]. Five had Graves' disease, and nine were excluded because of incomplete followup. In the remaining 39 women, none had clinically hyperthyroidism; there was a high incidence of abnormal electrolytes (60%) and abnormal liver function tests (56%). Without ATD therapy, FT4 levels normalized by 15 weeks' gestation, and TSH levels normalized by 19 weeks. There were no preterm deliveries, and a median birth weight of 2970 g, with a male-to-female ratio of 3 : 1. Birth weight was lower in mothers experiencing a weight loss of >5% of their prepregnancy weight, as compared to women who did not, however the difference was not significant ($P = 0.093$).

A case was reported in 1996 of a single patient with HG in three successful pregnancies, accompanied by THHG in at least the latter two, which resolved spontaneously by the second trimester. In this patient, symptoms of nausea and vomiting as well as thyroid function normalized by 16.5 weeks gestation [43].

3.3. Multiple Pregnancies. Grün et al. [44] described hyperthyroidism in women with twin pregnancy, due to a much higher and more sustained peak of hCG. They collected 30 euthyroid women, in whom conception had been assisted by *in vitro* fertilization techniques, which allowed for the precise determination of gestational age, with 17 single pregnancies and 13 twin pregnancies. The peak hCG concentration between 8–11 weeks was significantly higher and much more prolonged in twin compared to single pregnancy (mean ± SE 171,000 ± 12,500 versus 65,500 ± 7600 U/L; $P < 0.001$). Serum TSH values were lower and in 4 women serum FT4 were in the hyperthyroid range. None of the women complained of nausea or vomiting. Higuchi et al. [45] reported a triplet pregnancy, post-IVF treatment, developing hyperemesis at 6 weeks gestation, losing 14% of her original body weight at 9 weeks gestation. Hyperthyroidism was diagnosed at 12 weeks' gestation, without evidence of autoimmunity. hCG titers were 359,900 mIU/L (expected between 12–20 weeks, less than 192,766 mIU/L). Vomiting, palpitations and headache did not resolve and she was treated with daily oral Lugol's solution from 13 weeks gestation, with alleviation of symptoms and improvement of thyroid tests; it was discontinued at 19 week's gestation. Thyroid tests were within normal limits in the triplets at birth and at one year of life.

3.4. Hyperplacentosis. It is a condition of heightened trophoblastic activity characterized by increased placental weight and circulating hCG levels that are higher than those associated with normal pregnancy [46]. It may occur in association with diabetes, erythroblastosis, multiple pregnancies, and thalassemia. Clinically, it is characterized by tachycardia, heat intolerance, nausea, vomiting, and pruritus. The authors reported the first case in the literature of an association of hyperplacentosis and hyperthyroidism. When seen at 17 week's gestation, the patient had some nausea and vomiting but had gained weight normally throughout pregnancy. There were no signs of Graves' disease. Serum FT4 and FT3 were elevated and serum TSH was less than 0.3 mIU/L. Pregnancy was terminated one week later because of a nonviable fetus. The placenta weight was 219 g (normal for gestational age 140–150 g) with histological findings consistent with Hyperplacentosis. The patient received medical therapy for a few days before the termination of pregnancy, with worsening of hypermetabolic symptoms, suggestive of thyroid storm, a day before surgical procedure. Thyroid tests returned to normal within several days and β-hCG normalized in within two months.

3.5. Hyperreactio Luteinalis. A rare condition characterized by pregnancy-associated ovarian enlargement due to the presence of multiple theca-lutein cysts discovered incidentally at the time of ultrasound, cesarean section, or postoperative tubal ligation, with the vast majority of cases asymptomatic. Gherman et al. [47] reported a case of a woman with intractable hyperemesis gravidarum, when seen at 27 weeks' gestation; she had thyroid tests consistent with hyperthyroidism and negative markers of thyroid autoimmunity. Because of severe vomiting, a 15 kg weight loss and dehydration, total peripheral nutrition was started, but discontinued one week later because of hypotension due to sepsis. Thyroid and liver tests normalized 9 days after hyperalimentation was started. An additional finding was virilization with high androgens levels diagnosed after delivery.

3.6. Familial Gestational Hyperthyroidism Caused by a Mutant Thyrotropin Receptor Hypersensitive to Human Chorionic Gonadotropin. In 1998 [48], a case was reported of a woman and her mother with an inheritable mutation of the thyroid TSH receptor, enhancing the thyrotropic influence of hCG. As a result, while the women had normal hCG levels during pregnancy, she developed severe nausea and vomiting, weight loss, persistent tachycardia, sweating, and hands tremor. Serum FT4 was elevated and serum TSH was undetectable. No antibodies (TPO or TRAb) were detected in serum. She required PTU therapy until 38 weeks gestation. A second pregnancy resulted in similar symptoms and course of treatment. The mother had had a similar medical history in her only full-term pregnancy. Both mother and daughter were heterozygous for a missense mutation, the K183R, in the extracellular domain of the thyrotropin receptor, highly sensitive to hCG, explaining the clinical picture in both mother and daughter.

3.7. Trophoblastic Diseases: Hydatidiform Mole and Choriocarcinoma. Hyperthyroidism has been reported in patients with trophoblastic tumors, either mole or choriocarcinoma. The incidence of hydatidiform mole has been reported to be between 0.5 and 2.5 per one thousand pregnancies [49]. The clinical presentation is characterized as vaginal bleeding suggesting threatened abortion. No fetal tissue is present, but the uterus is enlarged, larger than gestational age. Hyperemesis has been described in 20% of women with a high incidence of preeclampsia or eclampsia, before the time of ultrasonography as a diagnostic tool. The diagnosis is made by ultrasonography, demonstrating a "snowstorm" appearance without a fetus. With the use of routine sonography early in pregnancy for gestational age confirmation, and earlier pregnancy diagnosis, many of the reported complications are avoided. In a series comparing mole diagnosis in the period between 1965 to 1975 and 1994 to 1997, evacuation of the mole was at 17.0 weeks versus 8.5 weeks, respectively, [50].

In 1955, Tisne et al. [51] reported the first cases of clinical and chemical hyperthyroidism in pregnant women with hydatidiform mole. The authors showed elevated radioactive iodine thyroid uptake in women with molar pregnancy as compared to normal pregnancy; one of their patients with a mole pregnancy had hyperthyroid symptoms. Soon thereafter, several investigators reported laboratory evidence of hyperthyroidism in women with molar pregnancy, with normalization of thyroid tests and reversal of hyperthyroid symptoms following evacuation of the mole. In 1963, Odell et al. [52] described a group of 93 patients with choriocarcinoma, seven of them with thyroid tests in the hyperthyroid range, but interestingly, none of them have symptoms or signs of hyperthyroidism. Thyroid tests returned to normal after evacuation of the mole. The authors found in the plasma of two of their patient's elevated thyrotropic activity by bioassay as well as in the extract of the tumor.

Hershman and Higgins [53] reported two cases of severe hyperthyroidism, one of them complicated by congestive heart failure, in patients with hydatidiform mole, and demonstrated for the first time thyrotropic activity in the molar tissue. This stimulator differed biologically and immunologically from the other three human stimulators: pituitary thyrotropin, chorionic thyrotropin found in normal pregnancies, and the long-acting thyroid stimulator (LATS) described by McKenzie in Graves' disease. The authors speculated that an excessive amount of the extracted molar stimulator was responsible for the hyperthyroidism in both patients that resolved following surgical extirpation of the moles. Galton et al. [54] reported the same year thyroid tests done in 11 patients, before and following the extraction of a molar pregnancy. They confirmed previous studies by Dowling et al. [55] that called attention of the striking abnormalities in several aspects of thyroid hormone economy in three patients with molar pregnancy. Consistent elevations in serum PBI, 24 hours 131 Iodine thyroid uptake, and serum total and free thyroxine were seen in the patients as compared to normal pregnant control patients. The prevalence of thyrotoxicosis in patients with trophoblastic tumors was reported to be close to 50% in some studies;

Table 2: Hyperthyroidism and pregnancy clinical clues in the differential diagnosis.

	Gestational	Graves'
Symptoms prepregnancy	−	++
Symptoms during pregnancy	−/+	+/+++
Nausea/vomiting	++++	−/+
Goiter/ophthalmopathy	−	+
Anti-TPO/TSHRAb	−	+
TT3/TT4 ratio	<20	>20

nowadays, with the ability of early detection of the disease, the incidence is much lower although still reported.

The diagnosis of trophoblastic disease is confirmed by ultrasonography and the presence of high levels of the β-subunit of hCG [3] that serves as a marker for the tumor. Therapy of hyperthyroidism is not indicated in the vast majority of cases, since evacuation of the mole or chemotherapy for management of choriocarcinoma removing high levels of hCG cures the hyperthyroidism. In those cases of severe symptoms, Lugol's solution, IV iodine, β-blocking agents and sometimes TD are indicated. A case of thyroid storm was reported [56].

3.8. Hyperemesis Gravidarum in Women with Graves' Disease. Women diagnosed with Graves' hyperthyroidism before pregnancy and in remission may have a flare up of the symptoms during the first trimester, secondary to the hCG and TRAb stimulating effect on the thyroid TSH receptor. The situation may be further complicated by the presence of severe vomiting in women with a previous diagnosis of Graves' hyperthyroidism. Tagami et al. [57] studied 39 pregnancies in 334 women with Graves' disease. Ten of the women (26%) had an episode of gestational hyperthyroidism; thyroid function tests, antibodies determination and measurement of hCG are of relative value in the differential diagnosis, because there is significant overlap between the two groups. A high T3/T4 ratio could be of diagnostic value, favoring Graves' hyperthyroidism when the ratio is >20.

4. Clinical and Laboratory Diagnosis

One of the most challenging situations in the presence of hyperthyroid thyroid tests early in pregnancy, is in the differential diagnosis between hCG induced hyperthyroidism and Graves' hyperthyroidism. Since the first recognition of the association between HG and hyperthyroidism, several small series (less than 100 patients each) have been reported. The most important tools in the evaluation of women with hyperthyroidism in the first trimester of pregnancy are a careful history and detailed and targeted physical examination. From all publications reviewed, a clear picture had developed both from the physiopathological and clinical point of view. These can be summarized as follows:

(1) a previous healthy woman presents by the 4–9th weeks' gestation with hyperemesis gravidarum, manifested by severe nausea, vomiting, and weight loss.

(2) depending on the severity of dehydration, hospitalization will be required in a significant number of patients.

(3) in up to 70% of patients, laboratory tests are consistent with hyperthyroidism, diagnosed by a suppressed or undetectable serum TSH with an elevation of serum FT4. Serum TT3 is rarely necessary to confirm the diagnosis. Very few patients have clinical hyperthyroid manifestations. Serum HCG concentrations are not helpful as a diagnostic tool, with few exceptions (hydatidiform mole and choriocarcinoma).

(4) the following features define the diagnosis in most patients and assist the physicians in the differential diagnosis from Graves' hyperthyroidism (Table 2):

   (a) medical history:
      (i) absence of hyperthyroid symptoms before conception,
      (ii) similar history of vomiting in previous pregnancies,
      (iii) family history of Hyperemesis Gravidarum,
      (iv) no previous history of thyroid disease,

   (b) physical examination:
      (i) no goiter,
      (ii) no Graves' ophthalmopathy,
      (iii) no other physical findings such as vitiligo and Plummer's nails,
      (iv) signs of dehydration,

   (c) laboratory tests:
      (i) FT4 or FT4I elevated,
      (ii) TSH suppressed or undetectable,
      (iii) negative thyroid antibodies: TPO and TRAb,
      (iv) determination of TT3 or FT3 indicated when strong suspicion of Graves' hyperthyroidism or presence of a dominant thyroid nodule,
      (v) the incidence of reported transient electrolytes abnormalities is about 60% and liver abnormalities about 50% of patients,
      (vi) abdominal ultrasound to rule out multiple pregnancies or the presence of a hydatidiform mole,
      (vii) thyroid ultrasonography: data not available in the literature,

(5) in the vast majority of situations, vomiting subsidies after 14–18 weeks gestation,

(6) serum FT4 returned to normal by the 15th week gestation or before,

(7) serum TSH may remained suppressed well into the end of the second trimester,

(8) obstetrical complications do not appear to be significant. The only consistent findings reported in several publications is a lower birth weight as compared to infants born to mothers not afflicted by the disease and same gestational age. Low birth weight is related to severity of vomiting and degree of weight loss and is not correlated to the transient maternal hyperthyroidism [58].

5. Management

Hyperemesis gravidarum management includes intravenous hydration, containing vitamin B complex, and nausea medications: for women with persistent vomiting, significant weight loss, and presence of ketones in urine, hospitalization is very frequently required. Parenteral nutrition or nasogastric feeding tube is required in a minority of affected women. One of the most devastating complications of HG, although extremely rare, is Wernicke encephalopathy [59]. ATD therapy is not recommended, and no prospective study is available comparing obstetrical outcome among women receiving treatment and control group. Very few patients from the published series were treated with ATD and showed no benefit from it. One of the clinical problems with ATD therapy is the poor tolerability by patients, because of the persistent vomiting and metal taste particularly of PTU. In one occasion, PTU suppository was employed; the hyperthyroidism resolved by 18 weeks but vomiting persisted and ceased at 27 weeks, 3 days after termination of pregnancy [60]. As mentioned above [45], one case of severe hyperthyroxinemia in a triplet pregnancy the symptoms improved with the combination of Lugol's solution and PTU.

6. Summary

Transient nonimmune hyperthyroidism of early pregnancy is defined as an episode of transient hyperthyroidism, without evidence of thyroid autoimmunity, lack of Graves' disease physical findings, resolving spontaneously by the end of the first or early second trimester of pregnancy. Of the several causes, hyperemesis gravidarum is the most common one. The challenge for the attending physician is the differential diagnosis from Graves' disease. High levels of hCG or a hCG molecule variant with high biological activity, stimulating the TSH receptor induces hyperthyroidism. Consistent laboratory findings are a suppressed of undetectable serum TSH, an elevation in serum FT4 and negative tests for autoimmunity (TPO and TRAb). Hyperthyroidism resolves with cessation of vomiting by 14–16 weeks gestation although serum TSH may remained suppressed for a few more weeks. Fetal ultrasound is indicated to rule out other causes of THHG, such as multiple pregnancies and trophoblastic disease. ATD therapy is rarely indicated; treatment is based on correction of hydration and electrolytes replacement. Obstetrical outcome is not affected, with the exception in some series of lower infant weight at birth.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 745135, 5 pages
doi:10.4061/2011/745135

Review Article

Thyroid Peroxidase Antibody and Screening for Postpartum Thyroid Dysfunction

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Received 14 March 2011; Accepted 10 May 2011

Academic Editor: Kris Gustave Poppe

Postpartum thyroid dysfunction (PPTD) is a common disorder which causes considerable morbidity in affected women. The availability of effective treatment for hypothyroid PPTD, the occurrence of the disease in subsequent pregnancies and the need to identify subjects who develop long term hypothyroidism, has prompted discussion about screening for this disorder. There is currently no consensus about screening as investigations hitherto have been variable in their design, definitions and assay frequency and methodology. There is also a lack of consensus about a suitable screening tool although thyroid peroxidase antibody (TPOAb) is a leading contender. We present data about the use of TPOAb in early pregnancy and its value as a screening tool. Although its positive predictive value is moderate, its sensitivity and specificity when used in early pregnancy are comparable or better compared to other times during pregnancy and the postpartum period. Recent studies have also confirmed this strategy to be cost effective and to compare favourably with other screening strategies. We also explore the advantages of universal screening.

1. Postpartum Thyroid Dysfunction Is Common

Postpartum thyroid dysfunction (PPTD) is a common disorder which causes considerable morbidity in some women [1]. The availability of effective treatment particularly for the symptomatic hypothyroid phase, and the awareness that hypothyroidism is a long-term consequence in a significant minority of these subjects, has prompted discussion about screening for PPTD [2, 3]. However, there is currently no consensus because of unresolved issues about an effective and sensitive prediction tool.

The current worldwide pooled prevalence for PPTD is estimated to be 8% (95% CI 7.8–8.2%), with regional variations—USA 5.7%, Asia 4.4%, Spain 9.3%, Sweden 7.3%, and The Netherlands 6.3% [4]. These differences may be due to (a) variable study design (timing and number of thyroid tests), (b) definition of PPTD, (c) prevalence of thyroid peroxidase antibody (TPOAb), (d) assay methods used (antimicrosomal versus TPOAb), and (e) population characteristics (including prevalence of type 1 diabetes mellitus (T1DM), PPTD in previous pregnancies, iodine intake and genetics) [5].

The early hyperthyroid phase of PPTD causes minimal symptoms and hardly ever requires specific treatment. However, the hypothyroid phase which occurs later often needs to be treated with thyroxine for up to 9 months [6]. A significant number of subjects who have hypothyroid PPTD remain so at the end of the first postpartum year and require long-term thyroxine replacement [7–10].

2. The Rationale for Screening for PPTD

There are strong proponents on both sides of the thyroid screening in pregnancy debate [3, 11, 12]. The Endocrine Society currently recommends selective screening of high-risk individuals only [13]. However, Vaidya et al. elegantly demonstrated that screening of high-risk individuals alone would miss 30% of hypothyroid and 69% of hyperthyroid pregnant women [14]. A recent randomised controlled trial

[15] and another study [16] confirmed this initial impression about selective screening.

Those who advocate screening for PPTD cite the following reasons in support of their argument:

(a) avoiding morbidity associated particularly with hypothyroid PPTD,

(b) predicting the need for long-term thyroxine treatment at the end of the first postpartum year,

(c) identifying subjects who might develop PPTD in subsequent pregnancies,

(d) identifying subjects for followup to detect long-term hypothyroidism several years from initial diagnosis [10, 17].

3. The Role of TPOAb in Pregnancy-Associated Morbidity

The prevalence of microsomal and TPOAb in pregnant women varies between 2.8 and 19.6% worldwide [18], and a recent pooled prevalence from published data was estimated to be 15.3–16% [4]. Although its role in causing PPTD remains speculative, the presence of TPOAb identifies a subset of pregnant women who have a higher risk of developing PPTD [4, 19]. In addition, TPOAb also identifies women who have a higher risk of long-term hypothyroidism after PPTD [10, 17, 20, 21].

The presence of TPOAb during pregnancy is also associated with miscarriage and preterm delivery [6], an IQ decrement in children of even euthyroid mothers [22], and postpartum psychiatric morbidity [23, 24]. The mechanisms for these remain unclear.

4. A Screening Tool for PPTD

The clinical utility of a screening tool depends on several factors. It needs to be sensitive with a high positive predictive value (to detect every subject with the condition if possible), easy to perform (using uncomplicated technology), cheap (so that widespread use is cost-beneficial), and harmless to the subject tested.

5. TPOAb as a Screening Tool

Some authorities recommend TPOAb as a suitable screening tool for PPTD [4, 25]. The relative high prevalence of TPOAb in early pregnancy, its easy measurement with current assays, and its role as a risk marker for PPTD and long-term hypothyroidism have been cited in its favour as discussed above. Although earlier assays measured microsomal antibodies, more recent assays measure antibodies to its specific antigen, thyroid peroxidase, that is, TPOAb. Sensitive assays for TPOAb which are relatively cheap to perform are now available commercially and are in use worldwide [26, 27].

5.1. TPOAb and PPTD

5.1.1. Noninterventional Studies. An extensive analysis of published data by Nicholson et al. examined the prevalence of TPOAb and the risk of developing PPTD in these subjects. They estimated a pooled prevalence of TPOAb of 16.2% and a risk ratio of 5.7 for the development of PPTD (Table 1) [4].

A closer examination of these data helps us understand why it is difficult to reach a consensus about the use of TPOAb for screening, despite favourable epidemiological and statistical evidence.

(i) Several of these studies measured antimicrosomal antibodies as this was acceptable practice at the time. However, following the identification of thyroid peroxidase (TPO) as the incriminating antigen, more recent studies have used a TPOAb assay.

(ii) Furthermore, these antibodies were tested at variable points during pregnancy and postpartum. We contend that, for a prediction tool to be useful, it needs to be used well in advance of the predicted event that is, early pregnancy in this instance. Although the risk ratios appear to be higher when postpartum testing is done, we feel an early antepartum test would be more pragmatic (Table 2). The immune modulation of pregnancy and its effect on TPOAb (significant decrease in levels as pregnancy advances and a rebound increase postpartum) need to be understood and taken into account.

(iii) The definitions of PPTD were variable in these studies.

(iv) There is also a significant variability of the populations studied. There may well have been a difference in factors known to increase the risk of PPTD which were not uniformly reported—iodine intake, genetic predisposition to thyroid disease, demographic and behavioural characteristics (age, parity, smoking, gender of offspring, etc.), prevalence of type 1 diabetes mellitus, a history of PPTD in previous pregnancies, and a family history of thyroid disease.

(v) There is no clear indication of the length of followup in these studies either—raising the possibility of missing some PPTD subjects.

Although extrapolating from these studies to a general population is not wise, we do not feel that the utility of TPOAb, when used appropriately as a screening tool, is significantly diminished.

Since then, other investigators have also studied this relationship. Diaz et al. found a 44% prevalence of TPOAb in 25 subjects (out of 157) who developed PPTD [28]. Only 4.5% had TPOAb in the group who did not develop PPTD ($P = .001$). Filippi et al. found a combined prevalence of TPOAb and antithyroglobulin antibodies (TgAb) of 9.3% and 28/43 (65.1%) had developed thyroid dysfunction at the end of the first year [29].

An earlier analysis of published data has shown that the sensitivity, specificity, and positive predictive value (PPV) of

Table 1: TPOAb prevalence and the risk of developing PPTD (adapted from [4] with permission).

Author (number of subjects in study)	Number/% prevalence of TPOAb (95% CI)	Number with PPTD	TPOAb +ve with PPTD	Risk ratio for PPTD in TPOAb +ve subjects (95% CI)
Shahbazian (1040)	248/24 (21–26)	119	73	5 (4–7)
Kent (718)	86/12 (10–14)	86	55	13 (9–19)
Furlanetto (284)	13/5 (3–8)	12	2	4 (0.9–15)
Lucas (579)	No information	45	30	—
Kuijpens (291)	31/14 (11–19)	15	10	17 (6–46)
Lervang (591)	38/6 (5–9)	23	20	97 (30–312)
Jansson (460)	44/10 (7–13)	30	23	31 (14–68)
Dahlberg (224)	11/4.9 (2.1–7.7)	12	11	58 (18.2–184.9)
Amino (507)	62/12 (10–15)	28	25	59 (18.6–192)
Totals (4914)	586	419	279	
Pooled estimate	16.2% (16–16.4)			5.7 (5.3–6.3)

Table 2: TPOAb and its utility for screening for PPTD: timing of screening and sensitivity, specificity, and PPV (adopted from [25] with permission).

Time of screening	Sensitivity	Specificity	PPV
Early pregnancy	0.67–1	0.62–0.93	0.31–0.55
3rd trimester	0.71	0.92	0.52
Delivery/early postpartum	0.45–0.89	0.91–0.97	0.4–0.73
Late postpartum	0.46–0.86	0.9–0.98	0.53–0.78

TPOAb as a prediction tool are widely variable and depend on the time of testing amongst other factors (Table 2) [25].

5.1.2. Interventional Studies. Several interventional studies also have strengthened our knowledge about the role of TPOAb in morbidity associated with pregnancy and PPT. In one study, the administration of thyroxine to euthyroid women with TPOAb significantly reduced the risk of miscarriage [30]. A more recent well designed, randomised placebo-controlled study elegantly showed that giving selenium to pregnant women significantly reduced postpartum TPOAb titres and the incidence of PPTD [31]. These effects of selenium may be mediated through selenoenzymes which are abundant in the thyroid gland [32]. Although these studies do not prove a causative role, they further clarify the relationship of TPOAb to pregnancy outcomes and PPTD.

5.2. TPOAb and Long-Term Thyroid Dysfunction after PPTD. The presence of TPOAb in pregnancy is also a marker for long-term thyroid dysfunction [5]. A recently published 12-year follow-up study comparing women who had PPTD with controls found odds ratios for the risk of hypothyroidism of 4.8 for PPTD, 9.7 for hypothyroid PPTD, and 51.4 for TPOAb in association with hypothyroid PPTD [10]. This increased risk is broadly in line with 2 previous studies in which TPOAb-positive women who had PPTD were followed up for a mean period of 60 and 78 months. These investigators found hypothyroidism in 26% [33] and 46% [17], respectively, which were significantly higher in comparison to TPOAb negative controls. The relationship of the hypothyroid phase of PPTD to the development of long-term hypothyroidism cannot be over-emphasized, and this is a consistent feature of studies published so far.

5.3. Timing of Screening. Although PPV remains only moderately high, early pregnancy (first trimester) screening seems to confer the highest sensitivity and specificity [25]. Early pregnancy screening would seem highly pragmatic in a screening programme too.

5.4. Cost Benefit. A recent study found screening pregnant women in the first trimester with TPOAb to be cost-effective and to compare favourably with other screening strategies currently in use [34]. These data supported previous evidence from other investigators [35].

However, there are two objections to using TPOAb as a screening tool based on the current data.

(a) No consensus can be achieved of its utility in screening because of the heterogeneity of the reported studies—opponents of screening often quote the difficulty in interpreting and extrapolating results of published studies because of a high degree of variability (see comments above).

(b) The occurrence of PPTD in antibody-negative subjects also detracts from its value as a screening tool—there are several studies where PPTD has been reported in TPOAb-(or microsomal antibody) negative subjects [10, 36, 37]. The reasons for this are speculative—insensitivity of assays used to detect TPOAb, the presence of TgAb only, sampling time during pregnancy, population characteristics, and so forth.

6. TPOAb Combined with Clinical Data

Some investigators have studied the utility of TPOAb combined with clinical features in predicting PPTD. Da Costa et al. recruited 98 unselected women at 9–12 weeks of pregnancy and followed them up for 1 year after delivery.

TPOAb was present in 10.2% (95% CI 4.1–16.3%) and PPTD developed in 10.2% (95% CI 4.1–16.3%). A goitre in early pregnancy and TPOAb were significantly associated with PPTD ($P = .01,\ .001$, resp.) [38]. The sensitivity (60%, 95% CI 31.3–83.2) and specificity (95.5%, 95% CI 88.9–98.2%) compared with data reported in earlier studies (Table 2). But the PPV increased from 60 to 82.4% when goitre and family history of thyroid disease were added to TPOAb as risk factors. Others have indicated the importance of ultrasound echogenicity in predicting long-term thyroid dysfunction following PPTD [17], and the importance of other antenatal indices needs to be confirmed and their clinical utility determined [39, 40].

7. Conclusions

The question of screening for PPTD is intimately linked with the broader issue of screening for thyroid dysfunction in pregnancy [41]. We have concentrated on the former for this review. Experts and expert societies take a variable stance on the question of screening in pregnancy, but there is broad consensus about its advantages. Most advocate targeted screening but numerous studies have indicated the futility of this approach as a significant number of affected women with thyroid dysfunction will fail to be identified [14–16].

PPTD is a common condition causing significant morbidity. Screening for PPTD is safe and has many benefits and few disadvantages (maternal anxiety is mentioned frequently in this regard). Its early detection may improve quality of life and reduce morbidity in subsequent pregnancies and in the long term. Cost benefit analyses have demonstrated definite cost advantages in screening.

TPOAb is a good screening tool and has been examined by many investigators for predicting PPTD. Although there are limited data of the benefits of intervention in TPOAb-positive women in early pregnancy [30, 31], such a paucity of data should not deter us from recommending a screening strategy using it. TPOAb in early pregnancy (first trimester) using a currently available sensitive assay seems to be the best available tool at present despite all its imperfections. What about women who are TPOAb negative but still develop PPTD? There is no clear explanation for PPTD in these women but this should not prevent clinicians from adopting a screening strategy using TPOAb where the majority who would develop PPTD would be identified.

The question about targeted or universal screening continues to be debated. Given the current evidence of the ineffectiveness of targeted screening in identifying all women with thyroid dysfunction during pregnancy and the lack of clarity of expert advice, we would advocate universal screening. We believe adopting such a stance could only be useful and its benefits could then be examined in future studies.

Acknowledgment

The authors thank Professor John Lazarus for his continuing inspiration and guidance.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 463029, 7 pages
doi:10.4061/2011/463029

Review Article

Doubts and Concerns about Isolated Maternal Hypothyroxinemia

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Received 23 February 2011; Accepted 10 April 2011

Academic Editor: Kris Gustave Poppe

There is evidence that isolated maternal hypothyroxinemia may have detrimental effects on both mother and foetus. Nonetheless, this condition is still far from being universally accepted as a separate thyroid disease, and a standard definition of this state of mild thyroid underfunction is still lacking. We will review the biochemical criteria used to define isolated maternal hypothyroxinemia, together with current methodological issues related to FT4 assays. We will also discuss its epidemiological impact in both iodine-deficient and-sufficient areas, and the effectiveness of iodine prophylaxis on maternal thyroid function and neuropsychomotor development in offspring.

1. Introduction

The literature of the last few decades provides evidence that any decrease in thyroid hormone levels during pregnancy may be harmful for both mother and foetus [1]. The vast majority of pertinent studies refer to well-defined clinical presentations of maternal thyroid underfunction, namely, overt hypothyroidism (OH) and subclinical hypothyroidism (SH), both these conditions being characterized by supra-normal serum TSH levels, with (OH) or without (SH) abnormally low FT4 concentrations. Besides these forms, a milder presentation of maternal thyroid underactivity, described as isolated maternal hypothyroxinemia, has been reported. This condition, characterized by low serum FT4 concentrations but normal serum TSH concentrations, is now recognized as possibly responsible for adverse maternal and foetal/neonatal outcomes [2, 3].

This paper aims to discuss some specific issues related to isolated hypothyroxinemia, including its epidemiological impact. In addition, the need to identify and treat early hypothyroxinemia will be briefly discussed.

2. Isolated Maternal Hypothyroxinemia: Which Is the Correct Definition?

Although almost 40 years have elapsed since Evelyn Man [4] first introduced the concept of hypothyroxinemia being associated with pregnancy, a precise definition of this condition is still lacking.

Analysis of published studies dealing with isolated hypothyroxinemia reveals that the biochemical criteria on the basis of which maternal hypothyroxinemia is currently diagnosed are quite variable (Table 1). In the studies carried out in the Netherlands by Pop and coworkers, maternal hypothyroxinemia was defined by FT4 levels below the 10th percentile and concomitant TSH values <2.0 mU/liter [5–7]. Similarly, Berbel et al. [8] classified as hypothyroxinemic those women who were found to have FT4 values below the 10th percentile. However, TSH concentrations were considered to be normal up to 4.8 mUI/liter, that is to say at values more than twice higher than that adopted in the Dutch studies. In a recent population-based cohort study in the Netherlands [9], women with TSH values <2.5 mU/liter were diagnosed as affected by mild and severe hypothyroxinemia

Table 1: Biochemical criteria used to define isolated maternal hypothyroxinemia and its epidemiological impact.

Author (reference number) (year) country	Lower FT4 percentile (pmol/liter)	Manufacturer's FT4 reference range (pmol/liter)	Upper TSH limit (mU/liter)	Manufacturer's TSH reference range (mU/liter)	Prevalence of isolated hypo-thyroxinemia (%)	Gestational age of hypo-thyroxinemia assessment
Pop et al. [5] (1999) The Netherlands	10th (1st tr. 10.4)	8.8–18.0[a]	2.0	0.15–2.0	NR	
Pop et al. [6] (2003) The Netherlands	10th (1st tr. 12.4)	8.7–19.6[a]	2.0	0.15–2.0	NR	
Kooistra et al. [7] (2006) The Netherlands	10th (NR)	8.7–19.6[a]	2.0	0.15–2.0	NR	
Casey et al. [10] (2007) USA	2.5th (GW 6-20 11.1)	11.2–24.7[b]	3.0	NR	**1.3**%	1st half of gestation
Vaidya et al. [11] (2007) UK	2.5th (1st tr. 10.6)	12.0–23.0[c]	3.0	0.27–4.2	**1.6**% (7.8%*)	1st trimester
Cleary-Goldman et al. [13] (2008) USA	2.5th (1st tr. 9.3; 2nd tr. 9.3)	10.3–24.4[b]	1st trim 4.28. 2nd trim. 3.93	NR	**2.1**% **2.3**%	1st trimester 2nd trimester
Moleti et al. [12] (2009) Italy	2.5th (1st tr. 11.9; 2nd tr. 10.4; 3rd tr. 10.3)	11.7–22.0[d]	1st tr. 2.3 2nd tr. 2.8 3rd tr. 3.0	0.4–4.0	**3.2**% **12.7**% **9.5**%	1st trimester 2nd trimester 3rd trimester
Berbel et al. [8] (2009) Spain	10th (10.5)	9.1–23.8[e]	4.8	0.38–4.8	**23.9**% **20.6**% **26.5**%	1st trimester 2nd trimester 3rd trimester
Shan et al. [14] (2009) China	2.5th (GW 4 14.1 GW 8 11.9 GW 12 11.4 GW 16 12.3 GW 20 11.6)	10.3–24.5[b]	GW 4 4.38 GW 8 3.8 GW 12 2.96 GW 16 3.29 GW 20 3.88	0.3–4.8	**2.2**% (0.4%*)	1st half of gestation
Henrichs et al. [9] (2010) The Netherlands	10th (11.76) 5th (10.96)	11.0–25.0[f]	2.5	NR	**8.5**% (<10th) **4.3**% (<5th)	GW 13 (median)

* According to manufacturer's FT4 reference range; GW: gestational week; NR: not reported.
[a]Enhanced chemiluminescence immunoassay, Amerlite-MAB (Kodak Clinical Diagnostics, *Amersham, UK*); [b]chemiluminescent immunoassay, Immulite 2000 Analyzer (Diagnostic Products Corporation, *Los Angeles, CA*); [c]electrochemiluminescent immunoassay, Modular E 170 Analyzer (Roche Diagnostics Ltd., *Lewes UK*); [d]electrochemiluminescence immunoassay, Modular E 170 Analyzer (Roche Diagnostics GmbH, *Mannheim, Germany);* [e]chemiluminiscence immunoassay, ADVIA Centaur-XP immunoassay system (Siemens Medical Solutions Diagnostics Ltd., *Llamberis, UK*); [f]enhanced chemiluminescent immunoassay, Vitros ECI Immunodiagnostic (ORTHO Clinical Diagnostics, *Rochester, NY*).

based on whether their FT4 concentrations were below the 10th or the 5th percentile, respectively. In the remaining five studies listed in Table 1, isolated hypothyroxinemia is defined by FT4 values below the 2.5th percentile, but by TSH values ≤3.0 mU/liter in two of them [10, 11], and by values that fall below the upper gestational specific limit in the remaining three [12–14]. In particular, Cleary-Goldman and coworkers identified an upper limit for TSH in the 97.5th percentile in a cohort of 10990 women at both 1st and 2nd trimester, corresponding to 4.28 mU/liter and 3.93 mU/liter, respectively [13]. Analogously, Shan et al. used TSH gestational age reference intervals, calculated from week 4 up to week 20 of gestation in 120–129 healthy women. The corresponding upper values ranged 2.96–4.38 mU/liter, depending on the week of gestation [14]. Finally, a study from our research group referred to TSH trimester-specific reference ranges derived from 495 healthy women at different stages of pregnancy. The normal upper limits were 2.3 mU/liter, 2.8 mU/liter, and 3.0 mU/liter, at 1st, 2nd, and 3rd trimesters, respectively [12].

From the above, it is clear that the criteria for defining normal levels of FT4 and TSH in pregnant women are far from homogeneous. This variance has obvious diagnostic and therapeutic implications. Indeed, depending on the FT4/TSH threshold considered to be normal, the same biochemical pattern may be variously defined as overt/subclinical hypothyroidism, which requires medical treatment, as isolated hypothyroxinemia, the treatment of which is advocated by some but not by others, or even as normal.

3. Are There Normative FT4 and TSH Values to Define Isolated Maternal Hypothyroxinemia?

Besides the definitions reported in these studies, Morreale De Escobar et al. [2] defined hypothyroxinemia to be any situation characterized by serum FT4 values lower than the 10th percentile value for normal pregnant women with a confirmed adequate iodine intake at comparable weeks of gestation, whether or not there is a concomitant increase in TSH values. Although this definition combines overt hypothyroidism and isolated hypothyroxinemia, it is of great interest as a basis for this discussion in that it emphasizes the need to refer to gestational-specific ranges calculated in properly iodine supplemented women. In the above-mentioned studies the reference ranges for FT4 and TSH are in some cases the same as those used for the general population, whereas in others they are specifically calculated using serum pools from normal pregnant women. The latter approach is currently regarded as the most appropriate [15] since pregnancy induces marked changes that invalidate the nonpregnant reference limits as a means of diagnosing thyroid dysfunctions in pregnant women. Indeed, during the 1st trimester, the stimulatory effect of hCG on thyrocytes induces a transient increase in FT4 levels, which is mirrored by a lowering of TSH concentrations. Following this period, serum FT4 concentrations decrease slightly (10–15% on average), and serum TSH values steadily return to normal [16]. In line with these variations, both FT4 and TSH reference intervals change throughout pregnancy, depending on gestational age. Thus, the utilization of nonpregnant reference intervals to interpret thyroid function tests in pregnant women carries the risk of misdiagnosis. In a cross-sectional study, Stricker et al. [17] in Switzerland established gestational age-specific reference ranges for free and total T3 and T4, and TSH using more than 1800 blood samples obtained from antibody-negative and iodine sufficient women at different stages of pregnancy. The main finding of this study was that there was a significant difference between the reference intervals of most thyroid parameters in the pregnant population and those reported by the assay manufacturer for nonpregnant subjects. The authors' conclusion was that the interpretation of thyroid function tests in pregnant women using nonpregnant reference intervals could potentially result in the misclassification of a significant percentage of results. It is worth noting that in that study the lower normal limits for FT4 in the pregnant population were *higher* than those reported by the manufacturer at each interval up to week 30 of gestation, and only began to decrease at late third trimester. Similarly, in a series of healthy, antibody-negative, and iodine sufficient women tested in the first half of pregnancy, Shan et al. [14] found FT4 lower limits to be consistently higher than those of the nonpregnant population. Accordingly, the prevalence of isolated hypothyroxinemia in their cohort of 4800 pregnant women decreased from 2.2% to less than 0.4% based on whether the gestational or general population reference ranges were used. Conversely, Vaidya and coworkers [11] found that the prevalence of hypothyroxinemia was 1.6% according to their own internal FT4 1st trimester-specific reference range, and as high as 7.8% when they used the manufacturer's general population reference range, the lower FT4 limit in the latter being higher than those found in the pregnant population (12.0 pmol/liter versus 10.6 pmol/liter). Can the different iodine intake account for these diverging results? Epidemiological data on nutritional iodine status from the regions where the three aforementioned studies were carried out would seem to support this hypothesis. In 2005, Zimmermann et al. [18] reported a median urinary iodine (UI) concentration of 249 μg/liter in a sample of 279 pregnant Swiss women, with almost 80% of them recording UI levels >140 μg/liter. Thus, although nutritional iodine status was not assessed by Stricker et al. [17], the women included in their study were reasonably iodine sufficient, as were those in the Chinese study [14], whose median UI concentration was 180.8 μg/liter. Conversely, the available data suggest that pregnant women in the UK, where the population is assumed to be iodine replete, might now be mildly iodine deficient. In particular, a study carried out in the north east of England has shown that 7% and 40% pregnant women had UI excretion of less than 50 μg/liter and 50–100 μg/liter, respectively [19]. More recent findings seem to confirm comparable data in the south of England, where median UI concentration in a population of pregnant women was 98 μg/liter [20]. Thus, given the possible underlying iodine deficiency in the population examined by Vaidya et al. [11], the resulting reference ranges may not actually reflect normal thyroid function, and the study may consequently have underestimated the prevalence of isolated hypothyroxinemia.

These considerations underline the importance of referring to specific gestational ranges when assessing pregnant women's thyroid function, provided that the women recruited to derive such ranges have an iodine intake that is known to be appropriate to the needs of pregnancy.

Another problem that deserves attention concerns the diagnostic accuracy of FT4 testing. Direct analogue FT4 immunoassays currently used to estimate FT4 concentrations are variously biased by either endogenous or in vitro factors. In particular, these assays are known to be influenced to variable degrees by the physiological changes in thyroxine-binding globulin (TBG) and albumin that occur during pregnancy [21, 22]. Because of these method-specific alterations, the same specimens analyzed by different immunoassay platforms may provide remarkably different results [23]. Conversely, methods of analysis based on the physical separation of the free from the protein-bound T4 fraction by equilibrium dialysis (ED) or ultrafiltration (UF), before direct quantification of the hormone content in the dialysate/ultrafiltrate, are generally regarded as reference methods [24, 25]. However, some theoretical and technical drawbacks seem to exist even with these methods, especially with regard to the separation step [26]. Recently, an International Federation of Clinical Chemistry (IFCC) working group proposed FT4 measurement by ED combined with isotope dilution-liquid chromatography/tandem mass spectrometry (ED ID-LC/tandem MS) as the reference measurement procedure (RMP) to measure serum FT4 [27]. In general, most of current routine immunoassays provide

lower FT4 values than the RMP, even if divergences seem to be greater for high values rather than for values in the low range [28, 29]. In a recent study, Anckaert et al. compared the FT4 results by three different immunoassays with those obtained by an ED ID-LC/tandem MS, with the objective of verifying the reliability of these assays for monitoring maternal thyroid function. Interestingly, although all the tested immunoassays were sensitive to alterations in T4-binding proteins, two of them gave a FT4 pattern during pregnancy which was similar to that obtained by ED ID-LC/tandem MS [30]. In our opinion, the results of this study are very important from a practical point of view, since currently the measurement of FT4 by LC/tandem MS is relatively expensive, technically demanding, and takes too long to be applied for routine clinical practice.

In summary, measurement of FT4 by isotope dilution tandem mass spectrometry provides accurate and reliable results during pregnancy, but these assays are not broadly available. In contrast, automated immunoassays are currently the most widely used systems for measuring FT4, but they are variously biased by several factors, which are responsible for significant method-dependent variations in FT4 measurement in pregnancy. Because of these methodological difficulties, establishing normative values of FT4 for pregnancy is challenging and, whatever the method, it is recommended that method- and gestation-specific reference ranges are used for interpreting results in pregnancy [15, 31].

4. How Common Is Maternal Isolated Hypothyroxinemia?

Defining the true incidence of isolated maternal hypothyroxinemia is rather difficult, especially, but not only, because of the aforementioned differences in diagnostic criteria used to define the condition. In addition, the epidemiological data presently available are somewhat sparse.

The issue of the epidemiological impact of isolated hypothyroxinemia was very recently reviewed by Krassas et al. [32], who estimated an overall incidence of approximately 2% in unselected pregnancies. However, it should be noted that wide differences exist among the quoted studies, apparently related mainly to iodine nutrition status in the areas where the studies were conducted. Indeed, in regions where iodine intake is sufficient, as is the case in the United States, the prevalence of isolated hypothyroxinemia ranges between 1.3% [10] and 2.3% [13]. It is worth noting that although the US population is generally iodine sufficient, approximately 15% of women of reproductive age have urinary iodine levels that fall below 50 μg/liter, clearly an indication of iodine deficiency [33]. In contrast, in mildly to moderately iodine deficient regions, isolated hypothyroxinemia affects a much higher percentage of women, reaching values up to 25–30% [8, 12]. Interestingly, in a very recent study by Henrichs et al. [9] carried out in The Netherlands on a cohort of 3659 women, the prevalence of mild hypothyroxinemia (FT4 < 10th percentile) was 8.5% and that of severe hypothyroxinemia (FT4 < 5th percentile) 4.3%. These figures are significantly higher than those reported in previous studies conducted in iodine sufficient regions [10, 13].

The question of when during gestation the diagnosis of maternal hypothyroxinemia is made is an important point that deserves attention when attempting an estimate of the prevalence of this condition. In 2009, we carried out a longitudinal study of 220 consecutive women from a mildly iodine-deficient area with the aim of evaluating the timing of maternal thyroid failure occurrence in conditions of mild iodine deficiency [13]. Although the overall prevalence of maternal isolated hypothyroxinemia over the course of gestation was about 25%, analysis of its frequency distribution revealed that at presentation (<week 12) a comparatively small number of women displayed FT4 values below the 2.5th percentile for gestational age, the vast majority dropping to this limit only later in gestation (12.5% versus 87.5%) (Figure 1). This finding indicates that this state of mild thyroid failure tends to become increasingly frequent as the pregnancy progresses, and our conclusion was that assessing the prevalence of isolated hypothyroxinemia on the basis of a single evaluation during early pregnancy only, has the potential to result in a substantial underestimation of its true prevalence. Notably, in our study only a small proportion (7%) of women who experienced isolated hypothyroxinemia were found to be antithyroid antibody positive, thus suggesting that features other than autoimmunity might play a major role in the occurrence of this condition. In particular, we speculated that isolated hypothyroxinemia might be the result of a failure of the maternal thyroid to keep up with sustained hormone demand due to a progressive depletion of iodine stores and an inadequate daily iodine supply.

5. Is Maternal Isolated Hypothyroxinemia an Iodine Deficiency Disorder?

Although the cause of isolated hypothyroxinemia is not fully understood, an iodine intake that fails to meet the requirements of pregnancy may well be responsible. Indeed, in conditions of mild-moderate iodine deficiency, thyroid stimulation by human chorionic gonadotropin leads to the preferential output of T3 over T4, the secretion of the latter becoming inappropriately low relative to the increasing TBG concentrations. This event leads to the progressive desaturation of TBG by T4, ultimately resulting in a decline in FT4 concentrations. Conversely, circulating T3 is normal (or even slightly over the upper limit) and triggers negative feedback on pituitary TSH secretion, the concentrations of which fall within the normal range. As a result, the women are clinically euthyroid even when biochemically hypothyroxinemic [2, 34].

The putative pathogenic role of iodine deficiency is now also suggested by clinical studies demonstrating that proper iodine supplementation during pregnancy reduces the risk of developing hypothyroxinemia. This point was addressed by our research group in a longitudinal study aimed at comparing thyroid function in pregnant women who had regularly used iodized salt for at least 2 years prior to becoming pregnant with that of women who began using iodized salt upon becoming pregnant [35]. The main finding

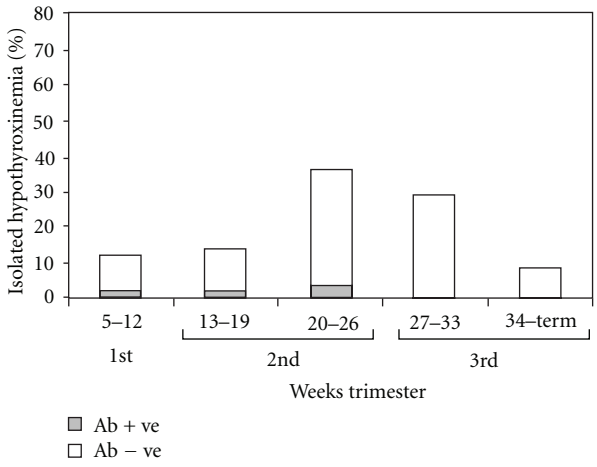

Figure 1: Frequency distribution of isolated hypothyroxinemia over the course of gestation in a series of 220 consecutive pregnant women from a mildly iodine-deficient area (from *European Journal of Endocrinology,* by *Bioscientifica* [12]).

of this study was that short-term iodine prophylaxis did not protect against the risk of isolated hypothyroxinemia, the prevalence of which was almost 5-fold higher in short-term than in long-term iodine supplemented women (36.8% versus 6.4%). Furthermore, in the long-term group isolated hypothyroxinemia could be detected almost exclusively late in gestation, thus suggesting that the greater replenishment of intrathyroidal iodine stores might guarantee an adequate thyroid hormone output for almost the entire period of gestation. In 2009, Berbel et al. [8] reported that iodine supplementation by means of 200 μg KI per day was effective in restoring euthyroidism (defined as FT4 concentrations above the 20th percentile) in those women who were found to be hypothyroxinemic at either weeks 4–6 or 14–16 of gestation, as well as in maintaining euthyroidism in the remaining women. Finally, we very recently examined the effect of different levels of nutritional iodine intake on maternal thyroid function throughout gestation in a cohort of healthy, antithyroid antibody negative women from a mildly iodine deficient area. The thyroid function of 168 women who had received prenatal preparations containing 150 μg of iodine from early pregnancy was compared with that of either 105 women who had regularly used (>2 yrs) iodized salt prior to becoming pregnant or 160 women who had neither taken iodine supplements nor used iodized salt. The regular use of iodine-containing supplements proved effective in reducing, though not in completely eliminating, the risk of inappropriately low FT4 levels during pregnancy, the overall prevalence of isolated hypothyroxinemia in the three study groups being 8.3%, 9.5%, and 20%, respectively [36].

Besides the importance of iodine supplementation in preventing/correcting maternal hypothyroxinemia, we would foreground that adequate iodine supply during pregnancy is essential to providing the foetus with enough substrate to draw on for its own thyroid hormone synthesis.

The importance of adequate supply of iodine and thyroid hormone to the developing foetus is emphasized by recent studies of intervention with iodine and L-thyroxine.

In 2009, Velasco et al. [37] compared the cognitive and psychomotor development of 133 infants (aged 3–18 months) born to mothers who had received 300 μg of iodine from the first trimester of pregnancy with that of 61 age-matched children whose mothers had not received iodine supplements. The most relevant result of this study is that the former had a more favourable psychomotor outcome than those born to mothers who were not treated. Similarly, Berbel et al. [8] showed that the mean developmental quotient in children born to mothers supplemented with a daily dose of 200 μg of potassium iodide from 4–6 weeks of gestation was significantly higher than the one recorded for babies born to mothers who had received iodine supplements later in gestation. The authors' conclusion was that a delay of 6–10 weeks in iodine supplementation in hypothyroxinemic mothers at the beginning of gestation increased the risk of neurodevelopmental delay in the progeny.

Finally, a large prospective randomized trial of L-T4 treatment in pregnant women with FT4 levels <2.5th centile and/or TSH >97th centile, the Controlled Antenatal Thyroid Screening Study (CATS), is presently ongoing. The main objectives of this study are to evaluate whether abnormal maternal thyroid function adversely affect neurocognitive function in offspring and to assess the benefits, if any, of maternal L-T4 treatment. Preliminary results from this study suggest that the mean IQ of children born from treated mothers is not different from that of controls. However, when the analysis was restricted to children whose mothers were considered to have been compliant with their L-T4 treatment, a significantly higher proportion of children with IQ < 85 was found in the untreated group [31, 38]. Once completed, this study will provide important evidence that should conclusively settle the question of whether or not L-T4 treatment of maternal isolated hypothyroxinemia is of benefit in preventing delayed neuropsychological development.

6. Concluding Remarks

There is growing evidence of the potential detrimental effects of maternal hypothyroxinemia on both mother and foetus. In particular, maternal hypothyroxinemia was reported to be associated with higher risk of placental abruption, preterm delivery, and increased frequency of Caesarian section [32]. Also, maternal hypothyroxinemia during early gestation may lead to irreversible brain damage in progeny ranging over a broad spectrum of neurological phenotypes, from mental retardation to neurobehavioral impairment, as well as Attention Deficit and Hyperactivity Disorder, among others [2, 5–9, 39]. Nevertheless, this condition is still far from being universally accepted as a separate thyroid disease. This is likely the main reason why a standard definition of this state of mild thyroid underfunction is still lacking. At present, the biochemical criteria used to determine whether or not a woman is affected with isolated hypothyroxinemia are in most cases arbitrarily established. Furthermore, normative

FT4 gestational ranges appropriately derived from iodine sufficient women are presently lacking [28]. Nor do we currently know the threshold below which the FT4 values should be considered potentially harmful to both gestational outcome and foetal development. Accordingly, there is no consensus on whether the treatment of women with isolated hypothyroxinemia with L-Thyroxine is deemed necessary. In the above mentioned paper by Morreale De Escobar et al., it is suggested that L-Thyroxine treatment should be prescribed in women whose free-T4 concentrations fall below the 10th percentile value, provided that they are also given adequate iodine supplements [2]. The results of currently ongoing studies should provide the evidence needed to conclusively determine whether or not the use of L-T4 in the treatment of isolated hypothyroxinemia is of benefit in preventing foetal brain damage [31, 32, 38]. In the meanwhile, we believe that women found to be hypothyroxinemic should be given substitutive L-thyroxine treatment in order to ensure FT4 levels that are similar to those observed in adequately iodine supplemented women at the same stage of pregnancy [40].

The incidence rates of isolated hypothyroxinemia vary widely among the studies, due to differences in either diagnostic criteria or in the timing of its evaluation, as well as in the iodine nutrition status of the population under examination. Overall, the results of more recent studies seem to indicate that the extent to which isolated hypothyroxinemia may occur is actually higher than previously estimated, and likely much higher than that of both subclinical and overt hypothyroidism. Even more significantly, a nonnegligible prevalence of the condition has been reported in geographical areas where iodine intake, at least for the general population, is assumed to be sufficient. In the absence of any evidence of other causes disrupting maternal thyroid function, the occurrence of isolated hypothyroxinemia in pregnant women from these areas may be interpreted as the result of a purely "gestational" iodine deficiency, that is to say an iodine supply that is inadequate to meet the increased demands of pregnancy.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 934104, 8 pages
doi:10.4061/2011/934104

Review Article

Iodine and Pregnancy

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Received 14 March 2011; Accepted 11 April 2011

Academic Editor: Roberto Negro

Iodine is a necessary element for the production of thyroid hormone. We will review the impact of dietary iodine status on thyroid function in pregnancy. We will discuss iodine metabolism, homeostasis, and nutritional recommendations for pregnancy. We will also discuss the possible effects of environmental contaminants on iodine utilization in pregnant women.

1. Iodine Homeostasis in Pregnancy

1.1. Iodine Absorption and Metabolism. Iodine, consumed in food, water, or supplements, is absorbed by the stomach and duodenum (97%) [1]. Its only known use in the human body is in the production of thyroid hormone. Uptake of iodine by the thyroid varies with intake. When iodine intake is sufficient, the proportion cleared from the blood by the thyroid ranges from 10% to 80% of absorbed iodine [1]. The active transport of iodine from the blood into the thyroid is regulated by thyroid-stimulating hormone (TSH) from the pituitary gland and by the concentration of iodine in the blood. This active transport is mediated by the sodium-iodine symporter (NIS), a protein present on the basolateral surface of the thyroid epithelial cell [1]. Iodine entering the thyroid is oxidized to form "active" iodine which then iodinates tyrosine to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). The coupling of MIT and DIT through an ether linkage generates the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), which are then cleaved from thyroglobulin, pass through the golgi, and are secreted into the peripheral circulation. All of the steps directed toward the generation of T4 and T3 are stimulated by thyroid peroxidase (TPO) (Figure 1). The half-lives of T4 and T3 in the circulation are approximately one day for T3 and seven days for T4. Peripheral deiodinases further metabolize thyroid hormone and add to circulating iodine (Figure 2). In particular, deiodinase 2 (D2) is responsible for the majority of extrathyroidal T3 production by cleaving iodide from the 5^1 position. The iodine that is cleaved from T4 and T3 re-enters the circulation where it is available for reutilization by the thyroid. Iodine that is not actively transported into the thyroid is primarily excreted in the urine (90%) with a very small amount present in the feces [1].

1.2. Physiologic Changes in Pregnancy. Pregnancy induces several major changes to thyroid physiology. The first is increased demand on the maternal thyroid gland. T4 production increases approximately 50% starting in early pregnancy. High levels of circulating estrogen during pregnancy decrease catabolism of the sialic acid-rich thyroxine-binding globulin (TBG) [2]. Consequently, circulating TBG levels increase 1.5-fold, increasing the levels of circulating total T3 and T4 and requiring an increase in thyroid hormone production to maintain normal unbound thyroid hormone levels. Additionally, in early gestation, the thyroid is stimulated not only by TSH but by the alpha subunit of human chorionic gonadotropin (hCG), which also binds to and stimulates the TSH receptor [3]. hCG is produced by the syncytiotrophoblasts of the developing pregnancy. Its production begins in the first days of pregnancy and peaks at 9–11 weeks of gestational age. Levels then decline until approximately 20 weeks of gestation and remain stable for the remainder of the pregnancy [3]. Finally, the placenta is

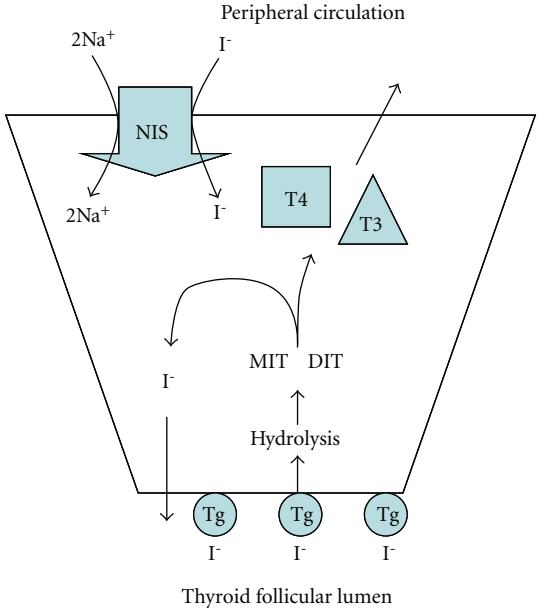

Figure 1: Thyroid hormone synthesis. NIS: Sodium-iodide symporter; T4: Thyroxine; T3: Triiodothyronine; MIT: Monoiodothyronine; DIT: Diiodothyronine; Tg: Thyroglobulin (I^-: iodinated).

an active site for the inner ring deiodination of T4 and T3, generating the inactive iodothyronines, reverse T3 and 3, 3^1-T2, respectively, presumably as a means of modulating the amount of active hormone that passes to the fetus [4]. (Figure 2) These processes all contribute to the increase in thyroid hormone requirement during pregnancy.

Increased thyroid hormone production in pregnancy requires adequate iodine availability. In iodine-replete regions, women typically begin pregnancy with 10–20 mg of iodine stored in the thyroid and, with continued sufficient iodine ingestion, are able to meet the increased demands of pregnancy. However, urinary iodine concentration (UIC), a reflection of iodine status, declines across pregnancy in women from iodine-deficient regions who may begin pregnancy with inadequate intrathyroidal iodine stores which are rapidly depleted [2]. If adequate iodine is not available, TSH rises and consequently goiter develops [2].

Another reason for increased iodine requirements in pregnancy is the increase in maternal glomerular filtration rate. Because iodine is passively excreted, increased renal glomerular filtration results in increased losses of ingested iodine [5].

The fetus and placenta also consume a proportion of maternal thyroid hormone and iodine. Fetal thyroidogenesis occurs by approximately the twelfth week of gestation. The fetal thyroid is capable of organifying iodine by approximately the 20th week of gestation. Before this time, maternal T4—the only form of thyroid hormone that can traverse the placenta in small amounts—must be adequate to meet the metabolic needs of the fetus. Fetal deiodinase converts maternal T4 to the bioactive T3 [6]. Once fetal thyroid gland function is established, fetal thyroidal turnover of iodine is much higher than adult [7]. Therefore, the fetal iodine store—supported exclusively by maternal intake—must be continuously refreshed.

Iodine homeostasis varies across the three trimesters as metabolic needs fluctuate. After parturition, maternal iodine continues to be the only source of iodine to the breast-fed neonate. NIS is present in breast tissue and is responsible for concentrating iodine in colostrum and breast milk [8].

2. Effects of Iodine Deficiency

2.1. Effects of Severe Iodine Deficiency. Severe dietary maternal iodine deficiency in pregnancy has the potential to cause both maternal and fetal hypothyroidism. Severe iodine deficiency is associated with poor obstetric outcomes including spontaneous abortion, prematurity, and stillbirth [9]. Thyroid hormone plays an essential role in neuronal migration, myelination, and synaptic transmission and plasticity [6, 10]. Animal models have demonstrated that even mild and transient maternal hypothyroxinemia during pregnancy can disrupt neuronal migration in the fetus, resulting in ectopic neurons in different cortical layers including the subcortical white matter and hippocampus [11]. Therefore, iodine deficiency is associated with adverse effects on the fetus including congenital anomalies, decreased intelligence, and neurological cretinism (which includes spasticity, deaf mutism, mental deficiency, and squint) [9]. Despite global public health efforts, iodine deficiency remains the leading preventable cause of mental retardation worldwide [12]. Severe iodine deficiency is also linked to intellectual development in early childhood in the absence of overt mental retardation. A 2005 meta-analysis of Chinese studies comparing intelligence quotient (IQ) of children living in naturally iodine-sufficient areas to children living in severely iodine deficient areas found that the IQ of iodine-sufficient children, on average, was 12.45 points higher [13].

2.2. Effects of Mild-to-Moderate Iodine Deficiency. The effects of mild-to-moderate iodine deficiency are less well understood than those of severe iodine deficiency. Hypotheses regarding the neurodevelopmental impact of mild-to-moderate maternal iodine deficiency are extrapolated from studies that examine the neonatal impact of mild maternal thyroid hypofunction on offspring. Pop et al. examined Bayley Scales of Infant Development scores among 10-month-old infants of women with fT4 levels below the tenth percentile in the first trimester of pregnancy compared to infants of women with higher fT4 levels at that gestational age [14]. The infants with lower maternal fT4 had significantly lower psychomotor scores. Henrich et al. studied expressive vocabulary at the age of 18 and 30 months in 3659 children of women with normal TSH but varying fT4 [15]. They found that lower maternal fT4 was associated with an increased risk of expressive language delay. Haddow et al. assessed the IQ of 7- to 9-year-old children of women with subclinical hypothyroidism in pregnancy, identified by elevated TSH in the second trimester, and found that IQ scores in these children averaged 7 points lower than children of matched women with normal thyroid function

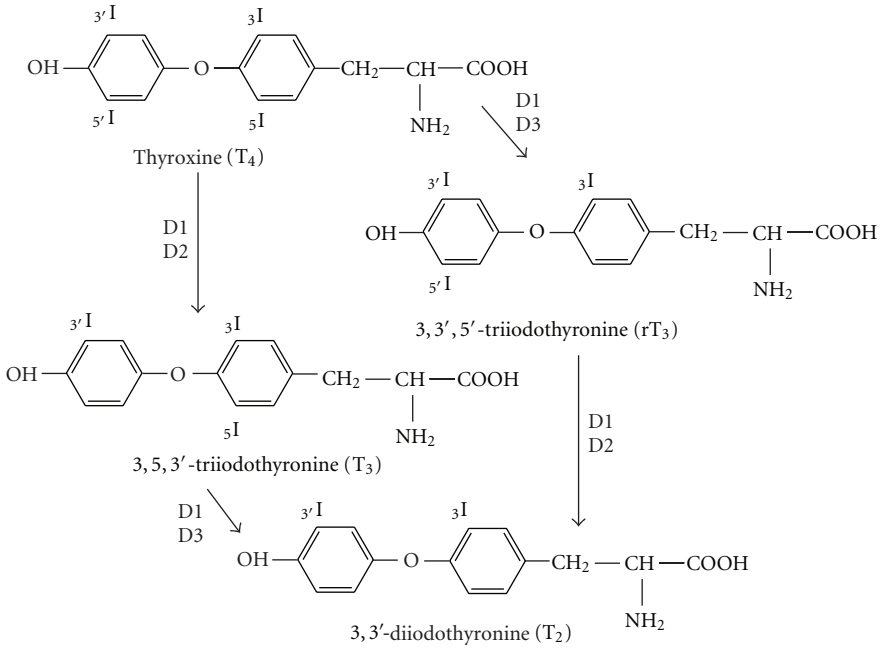

Figure 2: Thyroid hormone metabolism. D1: Type 1 deiodinase; D2: Type 2 deiodinase; D3: Type 3 deiodinase.

in the second trimester [16]. All of these studies underscore the impact of even mild thyroid hypofunction on fetal neurodevelopment. However, because they were conducted in iodine-sufficient areas, thus the thyroid hypofunction cannot be directly attributed to iodine deficiency.

A small study found a significantly greater prevalence of attention deficit hyperactivity disorder (ADHD) among the offspring of mothers from an area of mild-to-moderate iodine deficiency in comparison to those of mothers in a "marginally" iodine-sufficient area [17]. Vermiglio et al. followed these children over ten years, ultimately diagnosing 68.7% of the children from iodine-deficient areas with ADHD. In contrast, none of the children from the iodine-sufficient area were diagnosed with ADHD. 63.6% of the children diagnosed with ADHD were born to the mothers of the iodine-deficient area who were known to have been hypothyroxinemic early in gestation.

3. Assessment of Iodine Status

The World Health Organization (WHO)/International Council for the Control of Iodine Deficiency Disorders/United Nations Children's Fund (UNICEF) recommend median UIC as the primary tool for assessment of iodine status in pregnant populations [9]. This can be measured either over 24 hours or as a spot collection and can be expressed as mcg per liter or per gram creatinine. Because UIC is highly influenced by recent iodine intake, it can only be used to determine iodine status for populations, not for individuals [18]. Optimal median urinary iodine parameters are higher in pregnancy than the median values of 100–199 mcg/L consistent with iodine sufficiency in nonpregnant populations (Table 1).

Table 1: World Health Organization optimal median urinary iodine concentration values for populations [9].

Iodine sufficient population	Median UIC
Nonpregnant adult	100–199 mcg/L
Pregnant women	150–249 mcg/L
Lactating women	≥100 mcg/L

4. Iodine Nutrition in Pregnancy

4.1. Recommended Daily Intake. WHO recommends ingestion of approximately 250 mcg iodine daily for pregnant and lactating women [9]. The United States Institute of Medicine's recommended daily allowance for iodine is 220 mcg during pregnancy and 290 mcg during lactation [20]. The American Thyroid Association (ATA) strongly advocates adequate daily iodine intake in pregnancy, specifically recommending that women in North America take 150 mcg of iodine daily as a potassium iodide supplement during pregnancy and lactation in order to attain adequate levels [19] (Table 2).

4.2. Achieving Iodine Sufficiency. In many regions, the recommended iodine intake may be met by diet alone. Iodine enters the diet in multiple forms. In some regions, iodine is also present in drinking water. Worldwide, salt iodization is an ongoing effort springing from the recognition in the 20th century that inexpensive spraying of commercial salt with iodide can reverse iodine deficiency disorders [21]. In the USA women are exposed to iodine not only through iodized salt but also in other foods. Milk, yogurt, and other dairy products contain iodine as a result of the use of iodophor cleansers in the dairy industry and iodine supplementation

Table 2: World Health Organization (WHO) and Institute of Medicine (IOM) recommendations for dietary iodine intake [10, 19].

	WHO-recommended daily iodine intake	IOM-recommended daily iodineintake
Adequate intake for nonpregnant adult	150 mcg	150 mcg
Adequate intake in pregnant women	250 mcg	220 mcg
Adequate intake for lactating women	250 mcg	290 mcg

of cattle feed [22]. Some USA commercial breads contain high levels of iodine as well due to the use of iodate conditioners [23]. The most recent Total Diet Study by the U.S. Food and Drug Administration supports these two food groups as the main nonsalt sources for iodine in the U.S. [24]. In a market basket analysis, the average daily iodine intake among USA adults was calculated to be adequate at 138–353 mcg per person [24].

Despite ongoing availability of iodine in the diet and salt in the United States, National Health and Nutrition Examination Survey (NHANES) data demonstrates that the overall USA iodine intake has decreased over the past forty years from a median urinary iodine concentration of 320 mcg/L in 1970 to 160 mcg/L in 2003 [25]. The overall median UIC among pregnant women in the USA throughout from 2001 to 2006 was marginal at 153 mcg/L. NHANES 2005–2008 demonstrated that 35.3% of U.S. women of reproductive age had UIC < 100 mcg/L [25]. In the U.S., there is a higher prevalence of mild iodine deficiency in the pregnant population compared to the general population. The proportion of pregnant and reproductive aged nonpregnant women with UIC < 50 mcg/L has increased from 4% to 15% over the past 40 years, as documented by serial NHANES analyses [26]. These data suggest that in the U.S. an increasing proportion of this vulnerable population may be at risk for iodine deficiency. Worldwide, iodine deficiency remains an important public health problem, with an estimated 31% of the world's population still living in iodine-deficient regions [9].

4.3. Iodine Supplementation. If dietary iodine intake is insufficient, then supplementation is necessary. However, adequate supplementation is not currently easily achievable in the USA. A recent survey of all U.S. prescription and nonprescription prenatal vitamins revealed that only approximately 50% contained any iodine [27]. In prenatal multivitamins in which iodine was provided in the form of kelp, the amount of daily iodine was dramatically variable, making kelp an unreliable source for supplementation [27]. Among prenatal vitamins containing iodine in the form of potassium iodide, measured iodine levels were more reliable. However, when 150 mcg potassium iodide was listed as an ingredient, 23% of the mass was attributable to the potassium, thus providing only on average 119 mcg daily dose of iodide, lower than the 150 mcg daily dose recommended by the ATA. Worldwide, strategies to meet the iodine requirements set forth by WHO vary by region and local dietary intake [28].

4.4. Risks of Iodine Excess. There is controversy regarding the upper limit of acceptable iodine intake in pregnancy. When iodine is present in great excess, the iodination of thyroglobulin is acutely inhibited via the acute Wolff-Chaikoff effect [29]. The mechanism is not well understood but is believed to involve newly formed iodolipids or iodolactones temporarily inhibiting thyroid peroxidase synthesis. After a few days, the thyroid is able to "escape" from the acute Wolff-Chaikoff effect, in part by downregulating NIS on the basolateral membrane and thereby modulating the influx of iodine entering into the thyroid [30]. The fetal thyroid gland does not acquire the capacity to escape from the acute Wolff-Chaikoff effect until approximately 36 weeks gestation [31]. Therefore, a maternal iodine load could potentially cause fetal, but not maternal, hypothyroidism. The Institute of Medicine recommends an upper limit of 1,100 mcg dietary iodine daily in pregnancy, while WHO recommends an upper limit of 500 mcg per day [9, 20]. The benefits of correcting iodine deficiency far outweigh the risks of supplementation as long as supplementation is not excessive [32]. Studies have demonstrated increased umbilical cord and fetal TSH in study groups given iodine supplementation. None, however, have demonstrated poor outcome among these neonates, and in contrast, two studies have demonstrated improved neurocognitive outcomes in these groups [33, 34].

5. Impact of Iodine Supplementation in Deficient Populations

5.1. Impact on Maternal Thyroid Function. Studies assessing the impact of iodine supplementation in mildly to moderately iodine-deficient women have had variable results with regard to maternal thyroid function. However, supplementation of iodine in this population appears overall safe. Romano et al. found increased thyroid size in 17 pregnant women receiving daily iodine supplementation in the form of 120–180 mcg iodized salt compared to 18 women who were not supplemented [35]. Pedersen et al. randomly assigned 47 iodine-deficient pregnant women to start either 200 mcg daily potassium iodide or placebo at 17–18 weeks of gestation [36]. The untreated group not only had increased thyroid volume but also increased maternal and cord blood thyroglobulin and maternal TSH. No difference was found in maternal or cord blood thyroid hormone levels. In contrast, Antonangeli et al. found no significant differences in maternal TSH, thyroid hormone, thyroglobulin, or thyroid volume in 67 pregnant women randomly assigned to 50 mcg or 200 mcg iodide daily as compared to controls [37]. Liesenkötter et al. similarly found no difference in maternal thyroid volume in 38 pregnant women supplemented with 300 mcg of iodine daily compared to controls and no difference in thyroid function

testing of mother or neonate [38]. Nohr and Laurberg found increased cord blood TSH in neonates from 49 mothers supplemented with a daily multivitamin that contained 150 mcg iodine compared with controls [39]. However, fT4 was slightly higher in the neonates of treated versus control mothers. While the results regarding impact on maternal and fetal thyroid function are variable, none of these early studies addressed neurocognitive outcomes in the offspring.

5.2. Iodine Supplementation in Severe Deficiency: Effects on Offspring. The first study to demonstrate that iodine supplementation in severe iodine deficiency significantly decreases the risk of cretinism was performed in the 1970s [40]. Severely iodine-deficient women in Papua New Guinea, regardless of pregnancy status, were given iodine supplementation. The offspring from the treated group had no evidence of cretinism, while 6% of infants born to untreated mothers had cretinism. Subsequent studies were conducted in Zaire, China, Peru, and Ecuador, areas known to be severely iodine deficient. All four studies demonstrated varying but consistently improved cognitive scores for children whose mothers received iodine supplementation during pregnancy [41–44].

5.3. Iodine Supplementation in Mild to Moderate Iodine Deficiency: Effects on Offspring. Recently, two studies have identified improved neurologic outcomes in the infants of mildly to moderately iodine-deficient women who received iodine supplementation early in gestation. Velasco et al. supplemented 133 pregnant women with 300 mcg of iodine daily during the first trimester of pregnancy and examined psychological development of the offspring at the age of 3–18 months compared to offspring of a group of 61 control women [33]. Upon initiation of supplementation, the treatment groups had adequate mean UICs of 153 mcg/L and 213 mcg/L among women initiated at less than and more than 10 weeks of gestation, respectively, both adequate according to WHO criteria. However, by the third trimester, significant differences were seen in the UICs of the treatment versus control groups. Treated women had a mean UIC of 203 mcg/L, while the control group's mean value was 87 mcg/L, consistent with mild-to-moderate iodine deficiency. Psychomotor assessment at 3–18 months was significantly higher in the offspring of the treated group. Within this group, psychomotor scores were also noted to be higher in offspring of women whose serum fT4 measurement remained stable throughout pregnancy in comparison to those whose fT4 declined.

Berbel et al. examined the effects of a 200 mcg daily iodine supplement in mildly to moderately iodine-deficient Spanish pregnant women [34]. Women were divided into three groups, one of which started iodine supplementation at 4–6 weeks of gestation, the second at 12–14 weeks, and the third only in the postpartum period. Consistent with prior studies, neurocognitive scores were significantly higher in groups who received iodine supplementation during pregnancy when compared to women who did not start until postpartum. Importantly, neurocognitive scores were also significantly higher in the group who initiated iodine supplementation at 4–6 weeks of gestational age, during organogenesis, in comparison to those who began supplementation at 12–14 weeks of gestational age.

The effect of iodine supplementation on ADHD risk has not been studied.

6. Impact of Environmental Pollutants

Women with inadequate iodine nutrition in pregnancy may be particularly vulnerable to the effects of environmental thyroid disruptors. At pharmacologic doses, several environmental contaminants can affect iodine uptake at the thyroid and subsequent thyroid function. Exposures to low-dose perchlorate, thiocyanate, and nitrate are all ubiquitous in the United States. All three substances are competitive inhibitors of the sodium-iodine symporter (NIS) [45].

6.1. Perchlorate. Perchlorate is the most potent of the environmental NIS inhibitors, exhibiting roughly 30 times the affinity for NIS than iodine [46]. It is a byproduct of the manufacture of solid propellants used in rocket fuel. It has also been found in Chilean nitrate fertilizers used around the world. In the U.S., it is ingested in foods such as lettuce, wheat, and dairy and is detectable in low levels in groundwater in some regions [45]. Studies of perchlorate levels in infant formula found low levels in brands of U.S. formula tested [47, 48]. Perchlorate is remarkably stable not only in the environment but also in the human body, and thus exposure may be reliably assessed using urine concentrations. In vitro studies have demonstrated that at pharmacologic doses perchlorate decreases the active transport of iodine into tissue. There has been concern that low-level environmental exposure to NIS inhibitors could decrease iodine intake into the thyroid causing thyroid dysfunction and could also decrease NIS-mediated uptake of iodine into breast milk. The offspring of pregnant and lactating women would potentially be at highest risk for these effects [46].

The clinical impact of low-level environmental perchlorate on thyroid status in vulnerable populations remains unclear. An NHANES 2001-2002 analysis detected low levels of perchlorate in all urine samples ($n = 2820$) collected [49]. This large-scale study also demonstrated an inverse correlation between perchlorate and total T4 and a positive correlation with TSH in women but not men. This relationship was stronger among women with a UIC of < 100 mcg/L [50]. This effect on thyroid function has not been replicated in other studies. Several prospective studies administering increasing amounts of perchlorate to healthy human subjects have failed to demonstrate analogous changes in thyroid function other than a decrease in thyroidal iodine uptake at the highest doses [51–53]. Another cross-sectional study of environmental perchlorate exposure failed to find any association with first trimester thyroid function among 1600 iodine-deficient pregnant women [54]. While perchlorate has been identified in breast milk and colostrum in several small studies, there are no data yet to suggest that neonatal

consumption via breast feeding compromises the iodine status of the infant [47, 55].

6.2. Other NIS Inhibitors. Thiocyanate is a less potent competitive inhibitor of the NIS. It is a metabolite of cyanide produced from cigarette smoke and is found in various foods. Decreased T4, increased TSH, and thyroid enlargement have been reported among pregnant women who smoke [56]. Another study showed an association between cigarette smoking and decreased breast milk iodine concentration [57]. While compared to thiocyanate, perchlorate has 15 times the affinity for the NIS, the cumulative effects of one or both may still pose a risk to vulnerable populations.

Nitrate has a significantly lower affinity for NIS than either perchlorate or thiocyanate. However, it is omnipresent as a by-product of decomposition of organic materials. It is present in soil and groundwater and is found in virtually all crops, particularly root vegetables. Sodium nitrite is also used as a food preservative. The average daily adult intake of nitrate per day in the U.S. is 75–100 mg daily. Several recent studies from Bulgaria and Slovakia suggest an increased risk of goiter and subclinical hypothyroidism in iodine-sufficient areas with chronic exposure to very high nitrate concentrations. Small studies undertaken in the U.S. have failed to demonstrate the same association [45].

While the independent effect of these individual contaminants on iodine utilization and thyroid function may be small, it remains to be seen whether their cumulative exposure together with the national trend toward decreasing iodine intake among reproductive aged women in the U.S. may have adverse effects on thyroid function.

7. Conclusions

Women who are pregnant or lactating have increased dietary iodine requirements. Severe iodine deficiency leads to adverse maternal and fetal consequences. Even mild-to-moderate iodine deficiency in pregnancy has adverse effects on obstetric and neonatal outcomes. Recent data on the neonatal neurocognitive impact of early iodine supplementation suggests that adequate iodine intake should start as soon as the patient is aware she is pregnant, or, even better, should be incorporated as part of preconception planning. Research is needed on the impact of iodine supplementation in lactating women and their infants. Providers who care for pregnant women are encouraged to be aware of this essential micronutrient and counsel adequate iodine intake throughout preconception, pregnancy, and lactation.

Disclosure

All the authors have nothing to disclose.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 397012, 4 pages
doi:10.4061/2011/397012

Review Article

Screening for Thyroid Dysfunction in Pregnancy: Is It Worthwhile?

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Received 17 March 2011; Accepted 13 April 2011

Academic Editor: Bijay Vaidya

There is a high incidence of thyroid dysfunction during pregnancy resulting in adverse maternal (miscarriages, anaemia in pregnancy, preeclampsia, abruptio placenta and post-partum haemorrhage) and fetal effects (premature birth, low birth weight, increased neonatal respiratory distress) which may justify screening for thyroid function during early pregnancy with interventional levothyroxine therapy for thyroid hypofunction. There is a greater prevalence of subclinical hypothyroidism in women with delivery before 32 weeks and there is even an association between thyroid autoimmunity and adverse obstetric outcome, which is independent of thyroid function. Higher maternal TSH levels even within the normal reference range are associated with an increased risk of miscarriages, fetal and neonatal distress and preterm delivery. There are few prospective randomised trials to substantiate the benefit of screening and the recently reported CATS study did not show a benefit in child IQ at age 3 years. Nevertheless there seems to be a case for screening to prevent adverse obstetric outcomes. The clinical epidemiological evidence base does not justify universal screening at the present time. However, it is probable that more evidence will be produced which may alter this view in the future.

1. Introduction

Thyroid disorders are common. The prevalence of hyperthyroidism is around 5 per 1000 in women and overt hypothyroidism about 3 per 1000 in women. Subclinical hypothyroidism has a prevalence in child bearing age women in iodine sufficient areas of between 4 and 8%. As the conditions are generally much more common in the female it is to be expected that they will appear during pregnancy. During the last decade there has been an increasing appreciation of the incidence of thyroid dysfunction during pregnancy as well as the resultant adverse maternal and fetal effects [1–3]. In the hope that many of these adverse effects could be prevented or ameliorated by early detection and appropriate treatment the proposal to implement screening for thyroid function during pregnancy deserves consideration.

2. Screening for Disease

Medical screening is the systematic application of a test or inquiry to identify individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventive action [4]. The requirements for a justifiable screening test are shown in Table 1.

It will be apparent that screening a population must be considered very carefully in respect of the condition being screened for, the effectiveness (and safety) of any intervention, and the potential anxiety of the patient. If the effectiveness is not known with certainty then evidence should be sought, usually in the form of a randomised trial.

3. Does Thyroid Screening in Pregnancy Meet the Above Criteria for Screening?

The prevalence of Graves' disease is approximately 3.0/1000 with an incidence of about 0.5/1000/year. The prevalence and incidence in women during child bearing years is not known but thyrotoxicosis is said to occur in 2/1000 pregnancies and Graves' disease would be expected to account for at least 80% of these cases. While these figures are low, Graves' hyperthyroidism can have a dramatic effect on the mother

Table 1: Justification for screening test (adapted from Wald and Law 2010 [4]).

(1) Well-defined disorder with known incidence/prevalence.
(2) Medically important disorder.
(3) Screening test simple and safe with established cutoff values.
(4) Effective treatment available.
(5) Cost of test relative to benefit should be known.
(6) Adequate logistics for the testing and followup.
(7) Patient and management acceptability.

as well as the fetus. There are significant maternal complications including miscarriage, placenta abruptio, preterm delivery, and pre-eclampsia [5]. One to 5% of neonates of mothers with Graves' disease have hyperthyroidism due to the transplacental passage of maternal stimulating thyrotropin receptor antibodies (TRAbs) [6]. This may occur even though the mother may be euthyroid and has received previous treatment for Graves' disease. Neonatal hyperthyroidism may also be due to an activating mutation of the TSH receptor dominantly inherited from the mother. Transient neonatal central hypothyroidism is due to poorly controlled Graves' disease leading to suppression of the fetal pituitary thyroid axis due to placental transfer of T4 [7]. Subclinical hyperthyroidism (i.e., normal circulating concentrations of T4 and T3 but subnormal TSH levels) occurs in approximately 1.7% of pregnant women and is not associated with adverse pregnancy outcomes [8]. Screening for this condition is clearly not warranted, although if a low TSH is found the establishment of the cause will improve obstetric outcome in a number of women [9].

In contrast to hyperthyroidism, hypothyroidism is quite common in pregnancy [10]. The incidence of subclinical hypothyroidism (raised TSH and normal or low normal T4) is at least 2.5%, and these women have no clinical features and are often asymptomatic, but 50–60% will have evidence of autoimmune thyroid disease (positive TPOAbs and or thyroglobulin antibodies, TgAbs) in iodine-sufficient areas. It should be noted however that endemic iodine deficiency is the most common cause of hypothyroidism seen in pregnant women worldwide. Overt hypothyroidism occurs in only about 5% of all women who have a high TSH. During the last decade, it has become apparent that untreated maternal hypothyroidism and subclinical hypothyroidism in pregnancy is associated with adverse fetal and obstetric outcomes [11, 12]. These events include miscarriages, anaemia in pregnancy, preeclampsia, abruptio placenta, and postpartum haemorrhage while premature birth, low birth weight, increased neonatal respiratory distress, and more admissions to the neonatal intensive care unit have been described in babies born to mothers with hypothyroidism [13]. There is a greater prevalence of subclinical hypothyroidism in women with delivery before 32 weeks, and there is even an association between thyroid autoimmunity and adverse obstetric outcome, which is independent of thyroid function [14]. Higher maternal TSH levels even within the normal reference range are associated with an increased risk of miscarriages, fetal and neonatal distress [15] as well as preterm delivery [16]. In a prospective study, euthyroid TPOAb+ve women who received interventional L-thyroxine in early pregnancy had a reduced miscarriage rate and less preterm delivery [17]. Further prospective randomised trials are required to confirm these interesting data. Of equal or even greater importance than the above is the detrimental effect of hypothyroidism during pregnancy on fetal brain development. The availability of thyroxine to the developing fetal neurones is vital for their maturation and proper function [18]. Two studies [19, 20] have shown that low thyroid hormone concentrations in early gestation can be associated with significant decrements of IQ of the children when tested at 7 years and 10 months, respectively. Pop et al. [21] have also shown a significant decrement in IQ in children aged 5 years whose mothers were known to have circulating anti-TPO antibodies at 32-week gestation and were biochemically euthyroid. Moreover, as shown by Haddow et al. [22], the 7-year-old children of women known to be hypothyroid during gestation showed impaired psychological development compared to children of the same age from carefully matched control mothers whose thyroid function was known to be normal during pregnancy. In this paper it is interesting that a subgroup of children whose mothers had been receiving thyroxine for hypothyroidism during pregnancy (albeit at inadequate doses as evidenced by high TSH during pregnancy) also showed some impairment of psychological performance although not as great as the other children. The neurodevelopmental impairment is similar to that seen in iodine-deficient areas and implies that iodine status should be normalised in regions of deficiency. However, much of the USA and parts of Europe are not iodine deficient which raises the question of routine screening of thyroid function during early pregnancy or even at preconception. It is now appreciated that similar decrements in mentation can be seen in iodine-deficient areas as well as iodine-sufficient ones thus providing further evidence for the role of thyroid hormone in fetal neurodevelopment.

Isolated hypothyroxinaemia (low FT4 and normal TSH) either due to iodine deficiency or autoimmune thyroid disease has been shown to result in lower IQ in infants and young children in retrospective [22] and prospective [23] studies. Although it has been found not to be associated with adverse perinatal outcomes [24], it is associated with reduced motor and intelligence performance in neonates [25] and in children aged 25–30 months in a Chinese population [26]. While treatment of overt hypothyroidism has been shown to prevent the obstetric and neonatal complications the evidence for treatment of subclinical hypothyroidism in prevention is less secure. However, in a recent screening study where women were characterised as high risk or low risk in terms of the chance of adverse obstetric outcome there was a significant reduction in these outcomes even in low-risk women who were screened for subclinical hypothyroidism [27].

4. Evidence for Intervention in High-Risk Clinical Situations

The strength of evidence relating maternal hypothyroidism to low IQ in children suggests strongly that screening thyroid

function in early gestation with l-thyroxine intervention in appropriate women would be beneficial. In addition there is evidence that such a strategy would be cost-effective. A study by Thung et al. [28] compared the cost-effectiveness of no screening versus routine screening for subclinical hypothyroidism in pregnancy. The decision model demonstrated a saving of approximately $8.3 million per 100,000 women screened with an increment of 589.3 quality adjusted life years. Similar results were obtained by Dosiu et al. [29] using a different screening model.

Several organisations have issued guidelines on whether to adopt a screening strategy for thyroid function in early pregnancy [30–32]. The most recent published recommendations are from the Endocrine Society of America [33] which do not endorse universal screening. Instead, a targeted approach is suggested in which screening would be offered to women with a family history of thyroid or other autoimmune disease as well as to women with any risk factors for thyroid dysfunction (e.g., previous neck irradiation, previous thyroid surgery). Although this would seem a reasonable approach in relation to economic and logistic factors there has been accruing evidence that a substantial number of women with thyroid dysfunction would not be diagnosed in these circumstances. Vaidya [34] found that targeted testing of a previously defined high-risk group who had a personal history of thyroid or other autoimmune disorders or a family history of thyroid disease (413 women) failed to detect 28% of pregnant women with a TSH > 4.2 mIU/L. Li et al. [26] found that this strategy missed 36% of women with TSH > 4.0 mIU/L. In the study of Negro et al. [27], screening "low-risk women" identified 28% with thyroid dysfunction excluding those with just positive thyroid antibodies. The variability seen in these data may relate to different definitions of thyroid dysfunction and different ethnicity of the populations studied. Further work in this area is required. At the time of writing this paper the unpublished guidelines from The American Thyroid Association did not recommend screening while members from the as yet unpublished guidelines from The American Endocrine Society guidelines committee were divided 50/50 as to their recommendations.

At present there are no published prospective controlled trials of a screening strategy assessing child IQ. Preliminary results from a prospective randomized trial of L-T4 treatment in women screened prior to 16-week gestation (compared with control women not screened and therefore not treated with L-T4), the CATS study, are now available. The mean IQ of the two groups of children (screen and control) was not different. However, an on-treatment analysis showed that the number of children with IQ > 85 born to women with subclinical hypothyroidism who were considered to have been compliant with their T4 treatment was significantly less (9%) than that in the control group (15%).

5. Conclusion

The screening criteria for subclinical hypothyroidism in pregnancy are largely met. The condition is not rare, and several retrospective studies imply adverse obstetric and child neurodevelopmental outcomes. However there are few prospective randomised trials to substantiate the benefit of screening, and the recently reported CATS study did not show a benefit in child IQ at age of 3 years. Nevertheless there seems to be a case for screening to prevent adverse obstetric outcomes. From the child cognitive function aspect there should be further studies where intervention is initiated early in the first trimester during the course of brain development. Results of such a study being conducted by the National Institutes of Health are awaited.

From the forgoing discussion this author believes that the clinical epidemiological evidence base does not justify universal screening at the present time. However, it is probable that more evidence will be produced which may alter this view in the future.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 549609, 5 pages
doi:10.4061/2011/549609

Review Article

Management of Differentiated Thyroid Cancer in Pregnancy

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Received 23 March 2011; Accepted 31 March 2011

Academic Editor: Bijay Vaidya

In young women, differentiated thyroid cancer is the second most common malignancy diagnosed around the time of pregnancy. Management of thyroid cancer during pregnancy poses distinct challenges due to concerns regarding maternal and fetal well-being. In most cases surgery can be safely delayed until after delivery and with adequate management and outcome of pregnancy in women with thyroid cancer is excellent. Ideally these patients should be managed by a multidisciplinary team, and management plan should be determined by a consensus between the patient and the healthcare team.

1. Introduction

With the rising incidence of differentiated thyroid cancer (DTC), particularly in younger women, DTC is the second most common cancer diagnosed around the time of pregnancy with a prevalence of 14 per 100,000 [1]. Normal physiological changes occurring during pregnancy and concerns regarding fetal well-being pose distinct challenges to all aspects of DTC management. This paper reviews various facets of DTC management during pregnancy based on the published evidence and extensive clinical experience of the authors.

2. Is Pregnancy a Risk Factor for Thyroid Cancer?

Since DTC has a threefold higher incidence in women of reproductive age [2], an association between estrogen, human chorionic gonadotropin (HCG), and DTC has long been speculated. Several studies have suggested an association between the risk of DTC and high parity [3, 4], and there is also evidence that use of fertility agent, clomiphene, in parous women is associated with a higher risk of DTC [5]. The data regarding an association between estrogen and DTC, however, are inconsistent, with some studies reporting a pro-proliferative effect of estrogen on thyroid cancer cell lines [6], while others showing a stimulatory effect of estrogen on normal and adenomatous thyroid only, but not on thyroid cancer [7]. The clinical data are also conflicting; one study reported a higher risk of DTC in women exposed to estrogen-containing oral contraceptive and postmenopausal hormone replacement therapy [8], while another study reported no association between the use of exogenous estrogens and DTC [9]. Similar discordance exists in data regarding the outcome of DTC diagnosed during pregnancy; for instance, one study suggests that DTC diagnosed during pregnancy is associated with poorer prognosis and is more likely to have positive ERα expression as compared to tumours diagnosed in nongravidic period [10], while another retrospective study comparing the outcome of DTC diagnosed in pregnant women with age-matched controls showed no significant difference in cancer recurrence or cancer-related death [11]. The data regarding the effect of HCG on DTC are also nonconfirmatory. Although rising HCG during pregnancy has a stimulatory effect on thyroid hormone production, there is no evidence to date linking HCG with DTC. In a large cohort of women treated with fertility drugs, the use of HCG was not associated with a higher risk of DTC [5]. In summary, therefore, epidemiologic data suggest an

association between high parity and risk of DTC; but there is lingering unclarity regarding the outcome of DTC that is diagnosed during pregnancy.

3. Management of Thyroid Cancer during Pregnancy

The management of DTC during pregnancy generally falls into two clinical scenarios. One includes those women who are diagnosed de novo with DTC during pregnancy, while the other includes women with previous history of DTC who have either become pregnant or are planning pregnancy. Both groups present distinct therapeutic challenges requiring specific clinical approach based on disease stage, patient preference, and stage of pregnancy.

3.1. Thyroid Surgery during Pregnancy. For most women with newly diagnosed DTC or those with resectable macroscopic recurrence, a decision about whether or not to perform surgery during pregnancy has to be made. This question is perhaps the biggest source of vexation for patients and physicians alike. So far there has been no prospective study comparing the outcome of DTC in women undergoing surgery during pregnancy versus those where surgery was delayed until after delivery. A retrospective, cross-sectional study comparing 201 pregnant women undergoing thyroid and parathyroid surgery with age-matched nonpregnant controls reported that pregnant women had significantly longer hospital stay, higher hospital costs, and higher rates of general and endocrine complications [12]. Another large survey of almost thirteen thousand pregnant women reported a significantly higher risk of spontaneous abortion in women who underwent surgery during gestation compared with those who did not have surgery [13]. However, the risk of surgery during pregnancy must be balanced against patients' anxiety and perceived concern of tumour growth in case surgery is delayed for several months. This question was addressed through a retrospective study [11] that compared outcomes of DTC in 61 pregnant women with 528 age-matched nonpregnant controls. Of pregnant women with DTC, one underwent surgery in the first trimester, twelve in the second, and one in the third trimester, while most of the patients underwent surgery after delivery. After a median followup of 22.4 years, no significant differences in recurrence were observed between women who underwent surgery during or after pregnancy.

Currently there is no consensus about the optimum timing of surgery for DTC in pregnancy [14], and individualized decisions are generally based on patients' wishes and other risk factors, though most would agree that, in the absence of aggressive disease, it is reasonable to delay surgery until after delivery [15]. On the other hand, if surgery is to be considered, for example, in case of large tumour, compressive symptoms, aggressive pathological or clinical features, rapid enlargement of tumor, or patients' concern, it should be performed in the second trimester before 24-week gestation [14] primarily due to an increased risk of spontaneous abortion when surgery is performed in the first trimester [13].

In our interdisciplinary clinic setting (attended by an endocrinologist, surgeon, and a radiation oncologist), we stratify individual patient-risk based on several factors such as cytological features (in case of newly identified DTC), pathological aggressiveness and previous tumor behavior (in case of recurrence), rapidity of growth, compressive symptoms, and ultrasound features while also taking into account patient's wishes and concerns and the obstetrician's opinion before reaching a consensus. In the absence of any high-risk features, we would normally prefer to delay surgery until after delivery but we closely monitor patients throughout pregnancy by performing neck ultrasound scans during each trimester.

3.2. Radioiodine Therapy and Pregnancy. Radioiodine (^{131}I) administration during pregnancy is contraindicated due to the sequelae of exposing the embryo or fetus to high doses of radiation which include fetal hypothyroidism, attention deficit disorders, memory impairment, mental retardation, malformations, growth changes, induction of malignancies including leukemia, and lethal changes [16]. Women scheduled to have radioiodine therapy should exclude pregnancy with appropriate testing beforehand [14].

^{131}I should not be given to nursing women [14] due to the significant accumulation of ^{131}I in the lactating breast and its excretion in breast milk [16]. As most thyroid cancers are slow growing, delaying ^{131}I therapy to allow breastfeeding for a short duration may be considered through discussions between the patient and the treating physician. Postpartum ^{131}I therapy should be deferred for at least 6–8 weeks after lactating women have stopped breastfeeding [14]. There is a paucity of reliable data on the kinetics of ^{131}I excretion in breast milk. Therefore, after ^{131}I therapy, it is recommended that breastfeeding should only be resumed with the birth of another child [17, 18]. In order to avoid stagnation of ^{131}I in the lactating breast and minimize the risk of breast radiation exposure, suppression of lactation through dopaminergic agents has been utilized but this should only be used very cautiously [14] after discussion with the patient. Although one large study suggested a possible increase in miscarriage rate if conception occurred within 6 months of ^{131}I therapy [19], subsequent studies failed to confirm adverse outcomes for pregnancies or offspring related to previous ^{131}I therapy [20]. A conservative recommendation is that women receiving radioiodine therapy should avoid pregnancy for 6–12 months [14] to prevent any increase in risk of infertility, miscarriage, or fetal malformation [21].

3.3. Thyroid Hormone Replacement during Pregnancy. Most women undergoing subtotal or total thyroidectomy for DTC require thyroid hormone replacement. Adequate thyroid hormone levels are crucial for maternal and fetal well-being, and several studies have reported that even mild hypothyroidism during pregnancy is associated with both adverse maternal and fetal outcomes. For instance, one study showed that children of women with undiagnosed

hypothyroidism during pregnancy had lower IQ score than their age-matched controls [22]. In another study of women without overt thyroid dysfunction, the risk of miscarriage, fetal or neonatal death increased by 60% with every doubling in TSH concentration [23]. However, the data regarding low TSH in pregnancy is relatively reassuring, and, in a large survey of 25,765 women of which 433 had subclinical hyperthyroidism, low TSH was not associated with adverse outcomes [24].

The two major challenges in assessing and replacing thyroid hormones during pregnancy are emulating various physiological changes occurring in the thyroid gland during pregnancy and limitations of the commonly utilized laboratory tests for testing thyroid function. The thyroid gland undergoes remarkable changes during pregnancy. A rising HCG in early pregnancy, due to its similarity to thyroid-stimulating hormone (TSH), promotes the release of thyroid hormones which consequently leads to a transient drop in serum TSH values. At the same time, an increasing estrogen level causes two- to threefold rise in thyroid-binding globulin which alters the measured levels of total thyroxine (T4) and triiodothyronine (T3) and to some extent free thyroid hormones as well [25], thus limiting the usefulness of thyroid hormone measurement. This is further complicated by the fact that there can be a wide interassay variability in measured thyroid hormones during pregnancy [26]. Several other factors such as gestational age and singleton versus multiple-birth pregnancy can also alter thyroid hormone levels, in particular serum TSH values [27, 28]. A large survey of over thirteen thousand pregnant women reported a much tighter reference range for TSH especially in early pregnancy (2.5th and 95th percentiles of 0.1 mIU/L and 2.5 mIU/L, resp.), as compared with general population [27]. Based on these physiological variations, it is ideal to use gestational age-specific reference ranges expressed as multiples of the median, instead of reference values based on general population; however, most commercial assays do not quote pregnancy-specific reference values. Recently more elaborate techniques such as liquid chromatography-tandem mass spectrometry and equilibrium dialysis have been utilized to assess serum T4 in pregnancy [29, 30], but, apart from being much more expensive and time consuming, the correlation between free T4 measured through these techniques and serum TSH in pregnancy remains poor [29]. Furthermore, the requirement for thyroid hormone replacement increases by as much as 20–40% during pregnancy starting as early as the first few weeks of gestation [31, 32]. Due to its long half-life, T4 administration can take as much as 4–6 weeks before reaching a steady state in plasma.

With these multiple factors, pursuing a narrow therapeutic TSH target during pregnancy can be quite challenging. One study looked at the effect of empirically increasing the dose of thyroxin replacement immediately upon confirmation of pregnancy and concluded that giving an extra two tablets of thyroxin each week significantly reduces the risk of maternal hypothyroidism during the first trimester and mimics the normal physiology [33]. One caveat with this study was that patients who were athyreotic, those requiring a prepregnancy thyroxin dose of at least 100 μg/d, and those with prepregnancy serum TSH concentrations below 1.5 mIU/liter had the highest risk for developing TSH suppression and required subsequent dose modifications after the initial intervention.

In our centre, whenever possible, we typically begin the management of these patients with proper prepregnancy counseling by informing our patients about the rationale for more frequent TSH testing and the need for dose adjustment. In addition, we make patients aware of the possibility of reduced thyroxin absorption with commonly used prepregnancy supplements such as iron and calcium and advise to take them separately from their thyroxin. Those who are already taking suppressive TSH therapy and are planning to get pregnant are typically advised to reduce the dose of thyroxin aiming for a TSH in the range of 0.5–2.5 mIU/L. Upon confirmation of pregnancy, the dose is increased by an additional two tablets each week if TSH is $\geq$1.5 mIU/L and by one tablet if TSH is <1.5 mIU/L. Serum TSH levels are checked every 4–6 weeks and the dose adjusted to achieve and maintain TSH in the range of 0.5–2.5 mIU/L during pregnancy.

3.4. Followup of Thyroid Cancer during Pregnancy. Most pregnant women with low-risk DTC require little more than routine TSH monitoring and periodic clinical examination during pregnancy. Radioactive iodine scan or stimulated thyroglobulin (Tg) estimation through either thyroid hormone withdrawal or recombinant TSH (Thyrogen) is not justifiable in pregnancy. Several studies have reported that although serum Tg levels can vary significantly during each trimester, the overall values remain well within the normal nonpregnant range [34–36].

In our centre, we devise our followup strategy for such patients based on their risk factors. Pregnant women with low-risk DTC who were regarded free of disease prior to pregnancy, aside from their thyroxin dose adjustment, are followed on a three monthly (once in each trimester) basis with an unstimulated Tg, and a thorough neck examination is conducted at each visit. Those women who have high-risk DTC or had documented recurrence of DTC prior to pregnancy are followed more rigorously on a three monthly basis with unstimulated Tg and neck ultrasonography. Normal reference ranges for serum Tg are irrelevant for followup of such patients, and decision regarding cancer progress is based on their prepregnancy Tg levels as well as ultrasonography findings.

4. The Role of Multidisciplinary Team in Management of Thyroid Cancer

Outside specialist centers, DTC patients have traditionally been managed by a variety of specialties which leads to an inconsistent and fragmented care, borne out by several studies from various centers [37–39]. Patient surveys have also confirmed poor and inconsistent coordination of thyroid cancer care among different caregivers [40]. Over the past decade, several centers of excellence have developed models of multidisciplinary teams comprising

surgeons, radiologists, pathologists, endocrinologists, and allied specialists to deliver coordinated care within hospitals which ensures that each individual patient gets appropriate treatment decision made by a team of experts [41]. In our centre, all DTC patients (including pregnant females) are assessed and followed by a team of specialists including a surgeon, an endocrinologist, a radiation oncologist, a dietitian, specialist nurses and, in case of pregnant women, the team works closely with an obstetrician and gynecologist. In our opinion, pregnant women with DTC should ideally be referred to a specialist centre but, in the absence of such facility, management decisions should be made through close cooperation of all caregivers and the patient.

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SAGE-Hindawi Access to Research
Journal of Thyroid Research
Volume 2011, Article ID 841949, 7 pages
doi:10.4061/2011/841949

Review Article

Thyroid Antibodies and Miscarriage: Where Are We at a Generation Later?

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Received 4 February 2011; Accepted 10 March 2011

Academic Editor: Bijay Vaidya

In 1990, an association between thyroid antibody positivity and spontaneous miscarriage was first reported. A generation has passed since the initial observation. Over that time a robust literature has developed which has confirmed the initial finding and expanded upon it. The present paper reviews the literature that has been generated over the last twenty years on the following topics: (1) thyroid antibodies and spontaneous miscarriage, (2) thyroid antibodies and recurrent abortion, (3) etiology of pregnancy loss in thyroid antibody positive women, and (4) discussion of future research directions.

1. Introduction

It has been twenty years since the first paper reporting an association between thyroid antibodies and spontaneous miscarriage in euthyroid women was published [1]. The finding was serendipitous as the study was designed to evaluate the prevalence and etiology of postpartum thyroiditis. Five hundred and fifty-two women in the New York metropolitan area were screened in the first trimester of pregnancy for thyroid function and thyroid antibody status. A cohort of antibody positive and antibody negative women were selected and followed prospectively throughout pregnancy and into the postpartum period. As the study progressed, a high incidence of spontaneous miscarriage was observed in the cohort. In particular, it appeared that the miscarriage rate was disproportionately higher in women who were thyroid antibody positive. Following much discussion within the research team, as there was no known association between thyroid autoimmunity and miscarriage, nor was there a plausible mechanism, it was decided to examine the pregnancy outcome in the 552 women who were initially screened. A doubling of the miscarriage rate was found (17% versus 8.4%, $P = .011$) and reported in the Journal of the American Medical Association. It was unclear at the time if the finding was a statistical fluke or in fact represented an important association.

A generation has passed since the initial observation. Over that time a robust literature has developed which has not only confirmed the initial observation but expanded upon it. The present paper will summarize the data that has been published over the ensuing 20 years and speculate upon future directions. In particular, the areas of focus will be (1) thyroid antibodies and spontaneous miscarriage, (2) thyroid antibodies and recurrent abortion, (3) etiology of pregnancy loss, and (4) future directions. A comprehensive meta-analysis was published last year on the relationship between thyroid antibodies and in vitro fertilization (IVF) demonstrating that thyroid autoimmunity in women undergoing IVF is associated with an increased rate of pregnancy loss [2]. Consequently, the present discussion will not include a review of the IVF and thyroid antibody literature on spontaneous miscarriage.

2. Thyroid Antibodies and Pregnancy Loss

As noted above, Stagnaro-Green et al. reported a statistically significant doubling in the miscarriage rate in American euthyroid women in the first trimester of pregnancy who

were thyroid antibody positive. Of the 552 women initially screened, 57 were unavailable for followup. One hundred women were thyroid antibody positive (with a miscarriage rate of 17/100 or 17%), and 392 women were antibody negative (with a miscarriage rate of 33/392 or 8.4%). Prior to the 1990 paper the only antibody shown to be associated with spontaneous miscarriage was anticardiolipin antibody. Analysis of the sera of the 50 women who miscarried revealed no difference in percentage of women who were cardiolipin antibody positive between women who were thyroid antibody positive and miscarried versus women who were thyroid antibody negative and miscarried. There were also no demographic differences between the groups. The TSH level was slightly, but not significantly, higher in the thyroid antibody positive women as compared to thyroid antibody negative controls (TSH-2.35 mIU/L versus 1.60 mIU/L, resp., $P = .12$). Finally, no difference in thyroid antibody titers were noted in antibody positive women who miscarried as compared to antibody women who carried to term.

Glinoer and colleagues in 1991 [3] reported findings of a prospective study of 120 Belgian euthyroid women with mild thyroid abnormalities (nodules, goiter or thyroid antibody positivity) and 630 euthyroid controls. The goal of the study was to evaluate the progression of thyroid function tests throughout pregnancy and assess for adverse obstetrical and/or neonatal outcomes. Women with thyroid autoimmunity ($n = 45$) were found to have a dramatic increase in spontaneous miscarriage when contrasted to controls (13.3% versus 3.3%, $P < .001$). As found in the study by Stagnaro-Green et al. there was no association with anticardiolipin antibody or thyroid antibody titer. Further analysis of the study was published by Lejeune et al. in 1993 [4]. Specifically, analysis of first trimester pregnancy loss revealed a spontaneous miscarriage rate of 24% in thyroid antibody positive women when compared to 5% in controls ($P < .005$).

In 1997, Iijima and colleagues evaluated 1179 healthy pregnant Japanese women between 6-14 weeks gestation for the presence of seven autoantibodies [5]. A doubling of the miscarriage rate was reported in antithyroid microsomal antibody positive women as contrasted to women who were negative for all seven autoantibodies (10.4% versus 5.5%, resp., $P < .05$). Furthermore, the rate of small for gestational age births (SGA) was increased in microsomal antibody women when compared to controls (7.1% versus 3.4%). The thyroid antibody titer was related to neither the rate of spontaneous miscarriage nor the rate of SGA.

Bagis and colleagues published a study of 876 Turkish women initially screened at 12 weeks gestation [6]. All women had thyroid function tests and thyroid autoantibodies performed at 12 weeks gestation, revealing an antibody positive rate in the entire cohort of 12.3% ($P < .0001$). Fifty percent of the antibody-positive group had a history of a prior miscarriage as contrasted to only 14.1% in the antibody negative group ($P < .0001$). TSH levels were significantly higher in antibody-positive women with a history of miscarriage as compared to antibody women who had carried to term (1.90 μU/mL versus 1.2 μU/mL, $P < .006$). Free T4 values were also lower in the antibody positive women with a history of miscarriage (11.0 pmol/L versus 12.7 pmol/L, $P < .05$).

In 2006, Ghafoor et al. evaluated 1500 Pakistani women for thyroid peroxidase antibodies and thyroid function tests during pregnancy. Women were followed throughout gestation to determine pregnancy outcome [7]. Thyroid antibody positive women, which comprised 11.2% of the cohort, had a spontaneous miscarriage rate of 36.3% as compared to 1.8% in antibody negative women ($P < .01$). A significantly higher rate of prematurity was also reported (26.8% versus 8.0, $P < .01$) in antibody positive women. All 1500 women in the study were euthyroid.

In 2006, Negro et al. reported the findings of a prospective intervention trial. Nine hundred and eighty-four women from southern Italy in the first trimester of pregnancy were evaluated for thyroid function and thyroid peroxidase [8]. Women who were antibody positive ($n = 115$) were divided into two groups. Half of the antibody positive women were given levothyroxine during pregnancy ($n = 57$), the dose of which was determined by their initial TSH level and thyroid antibody titer. The remaining antibody positive women ($n = 58$), along with 869 antibody negative controls, did not receive levothyroxine intervention. The rate of spontaneous miscarriage was 13.8% in untreated thyroid antibody positive women and 2.4% in the 890 controls ($P < .05$). Thyroid antibody positive women who received levothyroxine had a spontaneous miscarriage rate of 3.5% which was similar to controls (2.4%), and statistically lower then the miscarriage rate in the untreated thyroid antibody positive group (13.8%) ($P < .05$). Thyroid antibody positive women who were not treated with levothyroxine had higher TSH levels at 20 weeks, 30 weeks, and three days postdelivery when compared to controls or thyroid antibody-positive women who were given levothyroxine. The largest difference was seen postdelivery (TSH-1.9 mIU/L in levothyroxine treated antibody positive women, TSH-3.5 mIU/L in untreated antibody positive women, TSH-2.1 mIU/L in controls, $P < .01$). Free T4 values were also lower in the untreated group at 30 weeks and postdelivery when compared to treated antibody positive women or controls (postdelivery values were 10.2 ng/liter, 14.3 ng/liter, and 14.6 ng/liter, resp., $P < .01$)

In summary, a total of seven studies (see Table 1) in six different countries have reported an association between thyroid antibody positivity in unselected women in the first trimester of pregnancy and spontaneous miscarriage (see Figure 1). It can therefore be concluded that there is a clear and consistent association between thyroid antibody positivity and pregnancy loss. Studies have excluded cardiolipin antibody as a potential explanation for the pregnancy loss.

3. Recurrent Abortion

Shortly after the initial publication demonstrating an association between thyroid antibody positivity and spontaneous miscarriage, researchers began evaluating women with recurrent abortion. Recurrent abortion occurs in 0.5–1%

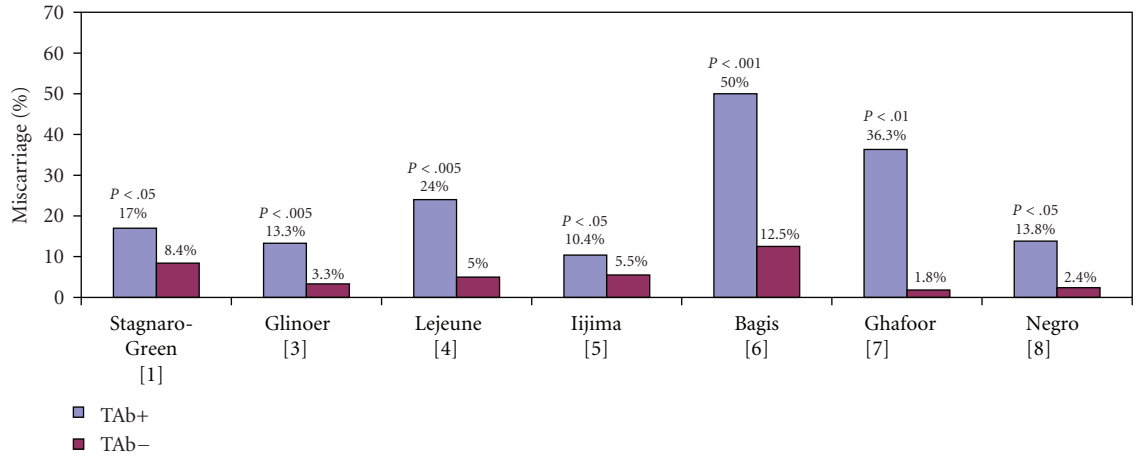

Figure 1: Percentage of spontaneous miscarriage in unselected pregnancies in women who were thyroid antibody positive (TAb+) and thyroid antibody negative (TAB−).

Table 1: Country of origin and number of women in each study of Figure 1.

Author	Country	TAb+	TAb−
Stagnaro-Green et al. [1]	USA	100	392
Glinoer et al. [3]	Belgium	45	360
Lejeune et al. [4]	Belgium	23	340
Iijima et al. [5]	Japan	24	52
Bagis et al. [6]	Turkey	108	768
Ghafoor et al. [7]	Pakistan	212	1288
Negro et al. [8]	Italy	115	869

of all women and is defined as three or more spontaneous miscarriages. The etiology is multifactorial, and includes uterine anomalies, endocrine disorders, genetic defects, and the anticardiolipin antibody. Nevertheless, despite comprehensive workups, approximately 50% of women with recurrent abortion will have no identified etiology. It is therefore not surprising that multiple research groups have studied the relationship between thyroid antibody positivity in women with recurrent abortion.

The first two studies investigating women with recurrent abortion were published in 1993 and performed by Pratt and colleagues in Chicago. The first study examined 45 women with recurrent abortion for four polynucleotides, five histones, six phospholipids, and thyroid antibodies [20]. Thirty-one percent of the recurrent aborters were thyroid antibody positive as compared to 19% in a control group of 100 normal blood donors (P = ns). The study was limited by the composition of the controls which included 46 men, and the small size of the group of women with recurrent abortion. Pratt and colleagues then performed a prospective study evaluating the outcome of a subsequent pregnancy in 42 women with recurrent abortion [9]. Thirty-one percent of the 42 women were thyroid antibody positive (n = 13) with 12 of the 42 women experienced a recurrent abortion in the subsequent pregnancy. Of the twelve women who miscarried, eight were thyroid antibody positive (8/12 = 67%). In comparison, only five of the thirty who went to term were thyroid antibody positive (17%) (P = .003). The authors concluded that in women with recurrent abortion the presence of thyroid antibody positivity was associated with an increased rate of pregnancy loss in a subsequent pregnancy.

Bussen and Steck also published two papers on the topic of thyroid antibodies and recurrent abortion. The first study was published in 1995 and evaluated 66 German women for thyroid antibody positivity. Three groups were studied, including 22 euthyroid nonpregnant women with recurrent abortion, 22 multigravida women without endocrine disorders, and 22 nulligravida women [10]. The recurrent abortion group had a significantly higher rate of antibody positivity (36%) then either the euthyroid nonpregnant controls (5%) (36% versus 5%, $P < .01$), or the nulligravida controls (9%) (36% versus 9%, $P < .01$). In their 1997 paper, Bussen and Steck evaluated 28 euthyroid nonpregnant women with recurrent abortion for thyroid antibodies and nonorgan specific antibodies [12]. Secondary causes of recurrent abortion were excluded in all 28 women. Thirty-nine percent (n = 11/28) of the women with recurrent abortion were positive for thyroid antibodies versus 7% (n = 2/28) of multigravida controls ($P < .01$). No correlation was found between the presence of phospholipid antibodies and thyroid antibody positivity.

In a small study performed by Roberts et al. in Scotland in 1996, thyroid antibody positivity rate was evaluated in 11 women with recurrent abortion, 11 healthy pregnant women, 10 nonpregnant women, 11 women with a spontaneous miscarriage, and 10 women who had an elective termination of pregnancy [11]. Thirty-six percent (4/11) of the women with a history of recurrent abortion were thyroid antibody positive as opposed to five percent (2/41) of the women in the other four groups ($P < .01$). Roussev et al. also performed a small study consisting of 45 women with recurrent abortion and 15 healthy controls [21]. No difference was found in the thyroid antibody positivity rate between the two groups (9% versus 0%, P = ns).

Interpretation of the results of both studies are limited by their small sample size.

In 1998, Esplin et al. published a study performed in Salt Lake City, Utah comparing the incidence of thyroid antibody positivity in 74 nonpregnant women with recurrent abortion with 75 healthy nonpregnant controls of similar gravidity [13]. Women included in the recurrent abortion group had all tested negative for secondary causes of pregnancy loss. Although the thyroid antibody positivity rate in the recurrent abortion group was elevated at 29% the control group had an unusually high rate of thyroid antibody positivity of 37% (P = ns). It is unclear if geographic differences in rates of thyroid antibody positivity was a confound in this study.

In the largest study performed to date, Kutteh and colleagues in 1999 compared the rate of thyroid antibody positivity in 700 women with a minimum of two spontaneous miscarriages and in whom secondary causes of pregnancy loss were excluded, to 200 healthy controls [14]. All sera were obtained at least three months following a spontaneous miscarriage or birth. Thyroid antibody positive rate was significantly higher in the recurrent abortion group when compared to the controls (22.5% versus 14.5%, P = .01). There was no difference between the groups in regards to percentage of women with abnormally elevated TSH values; however women with a history of recurrent abortion were older then controls (33.3 years versus 30.8 years, P < .01).

Four more studies with either limited numbers of participants, or lack of a control group, were published in 1999 and 2000. Rushworth et al. evaluated the pregnancy outcome of 24 antibody-positive euthyroid British women with a history of recurrent abortion through a subsequent pregnancy. Eighty-one thyroid antibody negative women with recurrent abortion served as controls [22]. The live birth rate of the two groups was identical at 58%. Although the authors concluded that thyroid antibody positivity in women with recurrent abortion does not portend a worse outcome when compared to women who are thyroid antibody negative, interpretation of the results are limited by the small number of thyroid antibody positive women evaluated (n = 24). Reznikoff-Etievant et al. evaluated 678 French women with recurrent abortion and found a prevalence rate of thyroid antibody positivity of 2.9%. The study did not include a control group and did not address the unusually low rate of thyroid anitbody positivity [23]. Dendrinos et al. reported a thyroid antibody positivity rate of 37% in 30 Greek women with recurrent abortion as compared to 13% of 15 age-matched controls (P < .05) [15]. Finally, Mecacci reported that 37.9% (11/29) of women with recurrent abortion were antithyroid antibody positive as compared to 14.5% (10/69) of controls (P < .02) [16].

In 2002, Abdel Aziz et al. [24] performed a prospective study that was similar in design to the second investigation performed by Pratt et al. in 1993 [9]. Fifty Egyptian women with a history of recurrent abortion were tested for thyroid antibodies and followed until the 20th week of pregnancy. Eighteen (36%) of the women had the presence of thyroid antibodies. Twelve of the eighteen women (67%) went on to have another spontaneous miscarriage as compared to 15.6% (5/32) of the thyroid antibody negative women (P < .001). These results are almost identical to the findings reported by Pratt and colleagues [9]. Antibody-positive women were older (33.1 years versus 29.0 years, P < .01), had a larger thyroid volume (23.9 mL versus 19.3 mL, P < .001) and reported a higher number of prior abortions (5.1 versus 3.9, P < .05) as compared to antibody-negative women.

A large scale study prospective trial comparing successful pregnancy in three groups of women with recurrent abortion was performed by De Carolis et al. in 2004 [25]. Group 1 consisted of women who were thyroid antibody positive but antiphospholipid syndrome (APS) negative (n = 162), group 2 women were APS positive but antithyroid antibody negative (n = 149), and group 3 women were both APS and thyroid antibody positive (n = 54). The group with the highest percentage of successful pregnancy outcome was Group 2 (92%), whereas the two groups of women who were thyroid antibody positive had significantly lower rates of successful pregnancies (Group 1–57%, Group 3–60%, P = .0003).

Another study published in 2004 was conducted by Marai et al. who evaluated 58 Israeli women [17]. Thirty-eight of the women had a history of recurrent abortion and 20 women had a history of infertility but no pregnancy losses. Thyroid antibody positivity rate was significantly higher in the women with recurrent abortion (21%) when compared to the thyroid antibody positive rate in women with a history of infertility (0%) (P = .001).

Shoenfeld and colleagues evaluated 109 women with recurrent pregnancy loss and compared the rate of thyroid antibody positivity to 120 healthy controls. Results on the presence of thyroid peroxidase or antithyroglobulin antibodies were only presented for 24 of the women with recurrent abortion. Thirty-three percent of the 24 women (8/24) were positive for thyroid antibodies as compared to only 11.2% (14/120) of the healthy controls (OR-3.79 {CI-1.2–11.7}) [18].

The most recent papers on thyroid antibodies and recurrent abortion were published in 2008. The first was a case control study performed by Iravani et al. [19] in Iran which included 641 women with three or more consecutive pregnancy losses and 269 age-matched controls. Women in the recurrent abortion group had a rate of thyroid antibody positivity almost twice that of the control group (24.5% versus 12.6%, P < .001). Mean TSH levels were higher in the recurrent abortion group when compared to controls (TSH-1.93 mIU/L versus 1.3 mIU/L, P < .001) and was independently associated with both pregnancy loss and autoimmunity. In a much smaller study, Bellver et al. found no difference in thyroid antibody positivity between 30 Spanish women with recurrent abortion and 32 controls (3.6% versus 15.6%) [26].

In conclusion, there have been 17 studies performed to date comparing thyroid antibody positivity rate in women with recurrent abortion as compared to control groups. The studies vary markedly in regards to the size of the population studied and have taken place in five different countries. Thirteen of the seventeen studies performed demonstrated a significant increase in the thyroid antibody positivity rate in women with recurrent abortion (Table 2, Figure 2). Of

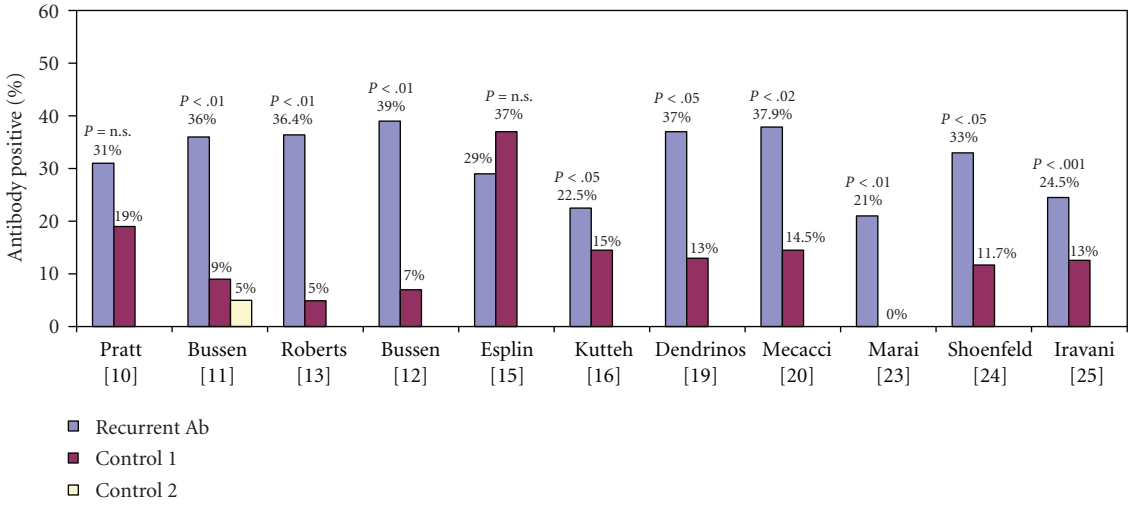

Figure 2: Percentage of thyroid antibody positivity in women with recurrent abortion (Recurrent Ab) and controls.

interest, the three negative studies were all performed in the United States.

4. Etiology of Pregnancy Loss

The etiology of pregnancy loss in thyroid antibody-positive women remains to be elucidated. Two meta-analyses have reported a difference in the mean age and mean TSH level between thyroid antibody-positive and thyroid antibody-negative women who miscarry [27, 28]. In the most recent meta-analysis, the mean TSH difference between groups was 0.61 mIU/L (1.7 mIU/L versus 1.1 mIU/L, $P < .00001$) [28]. Although the TSH levels are well within the normal range, a 2009 study by Benhadi et al. reported a statistically significant increase in child loss (defined as miscarriage, fetal, or neonatal death) with increasing levels of TSH between 0.34–5.60 mIU/L [29]. Similarly, Negro et al. found a 69% increase in the rate of miscarriage in thyroid antibody negative women with TSH values between 2.5–5.0 mIU/L as compared to thyroid antibody negative women with TSH values below 2.5 mIU/L (6.1% versus 3.6%, $P = .006$) [30]. Consequently, it is feasible that a component of the increased risk of pregnancy loss in thyroid antibody positive women could be attributable to increased TSH levels. On the other hand, the age difference reported in the meta-analysis of 1.3 years ($P < .003$) [28] appears to be limited to explain the marked difference in pregnancy loss between thyroid antibody positive and negative women. In support of this contention, Nybo Anderson et al. evaluated pregnancy outcome in 634,272 women and found only a minimal increase in the miscarriage rate between maternal ages 20 to 30 and approximately a 1.5%–2.0% increase in the miscarriage rate for each year between the maternal age of 30 to 40 [31].

Three research groups have evaluated the role of thyroid antibodies in pregnancy loss in an animal model. In 2001,

Table 2: Country of origin and number of women in each study of Figure 2.

Author	Country	TAb+	TAb−
Pratt et al. [9]	USA	45	100
Bussen et al. [10]	Germany	22	22
Roberts et al. [11]	Scotland	11	41
Bussen et al. [12]	Germany	28	28
Esplin et al. [13]	USA	74	75
Kutteh et al. [14]	USA	700	200
Dendrinos et al. [15]	Greece	30	15
Mecacci et al. [16]	Italy	29	69
Marai et al. [17]	Israel	38	20
Shoenfeld et al. [18]	Italy	33	120
Iravani et al. [19]	Iran	64	269

Imaizumi and colleagues evaluated the effect of experimental autoimmune thyroiditis on pregnancy outcome in a murine model of thyroglobulin immunized female mice [32]. Autoimmune thyroiditis and pregnancy loss were enhanced, but only when specific strains of mice were mated. Class II MHC antigens were found on placental cells from thyroglobulin induced mice but not on controls. The authors concluded that the pregnancy loss detected in the murine model of autoimmune thyroiditis was related to paternal antigens.

Matalon et al. in 2003 immunized and mated BALB/c mice with either human thyroglobulin or complete Freund's adjuvant (the control group) [33]. No difference in thyroid function tests were found between the two groups of mice. Animals immunized with human thyroglobulin developed high titers of antithyroglobulin antibodies and antibodies to thyroglobulin on the placenta. The rate of resorbed fetuses was higher in the immunized animals. Immunized animals also had lower placental and fetal weights. Interestingly, Mannisto et al. reported higher placental weights in thyroid

peroxidase antibody mothers, but not in thyroglobulin antibody women [34]. In 2009, Lee et al. reported similar findings to Matalon et al. in a study that immunized female C57bl/6 mice with recombinant mouse thyroid peroxidase [35]. Compared to controls, immunized mice had a significantly higher rate of resorped fetuses and a reduced liter size. The authors concluded that antithyroid peroxidase antibody may impact embryo development postimplantation.

To date, the only prospective randomized controlled treatment in thyroid antibody-positive euthyroid women was performed by Negro et al. in 2006 [8]. The rate of miscarriage was compared between 57 thyroid peroxidase antibody women who were given levothyroxine beginning in the first trimester of pregnancy with 58 euthyroid thyroid antibody positive women who were not given levothyroxine (the control group). As noted earlier, the dose of levothyroxine administered was based on a combination of initial TSH level and titer of thyroid antibody. A statistically significant decrease in spontaneous miscarriage was seen in the group of treated women as compared to the controls (3.5% versus 13.8%, $P < .05$).

5. Future Directions

Summarizing the studies which have been published over the last generation, the following can be concluded: (1) thyroid antibody positivity is associated with pregnancy loss in unselected pregnancies, (2) thyroid antibody positivity is associated with pregnancy loss in women with recurrent miscarriage, (3) murine data have demonstrated a direct impact of immunization of female mice, with either thyroglobulin or thyroid peroxidase, and the development of thyroid antibodies along with decreased litter size, fetal resorption, and diminished placental weight, and (4) the results of the study by Negro et al. demonstrating a decreased rate of pregnancy loss in euthyroid thyroid antibody-positive women are exciting initial data but need to be replicated. Future directions should include the following: (1) an expansion of the murine model in order to further elucidate potential pathophysiological etiologies, (2) studies of immune markers in thyroid antibody-positive pregnant women, (3) studies of placentas of thyroid antibody positive pregnant women who miscarry, (4) studies further separating the impact of thyroid antibodies and TSH differences (within the reported normal range for pregnancy) on miscarriage, and (5) replication of the study by Negro et al. Many answers should be forthcoming in the generation ahead.

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