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Population Reference Values and Prevalence Rates following Universal Screening for Subclinical Hypothyroidism during Pregnancy of an Afro-Caribbean Cohort

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Subclinical hypothyroidism · Universal screening

Abstract
Background: Subclinical hypothyroidism (SCH) has been reported to be associated with adverse pregnancy outcomes, however universal screening and treatment is controversial. ***Objectives:*** Our objectives were to determine population-specific pregnancy reference values (R1) for serum thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) at 14 weeks' gestation, along with the prevalence of SCH and thyroid peroxidase antibody (TPOAb). ***Methods:*** This was a prospective hospital-based cohort study. 1,402 subjects were recruited. Blood samples were obtained from 769 singleton pregnancies due to default between recruitment and scheduled blood draw. The prevalence of SCH was determined using R1, the laboratory non-pregnant reference values (R2) and previously recommended pregnancy reference values (R3). ***Results:*** R1 for TSH and FT_4 was 0.03–3.17 mU/l (mean ± SD, 1.1 ± 0.76) and 8.85–17.02 pmol/l (mean ± SD, 11.96 ± 2.06), respectively. The prevalence of SCH using reference values R1, R2 and R3 was 1.4% (11/769), 0.5% (4/769) and 1.9% (15/769). Prevalence was significantly greater using R3 when compared to R2 ($p = 0.011$). TPOAb prevalence was 2.6%. A significantly greater prevalence of TPOAb was found in subclinical hypothyroid subjects using all three reference values than in euthyroid subjects (~25 vs. 2%, $p < 0.05$). ***Conclusions:*** These reference values are the first to be reported for an Afro-Caribbean population. Our findings support the use of pregnancy-specific reference values in our population.

Introduction

Hypothyroidism is the most common disorder of thyroid function in pregnancy [1]. Subclinical hypothyroidism (SCH) is defined as serum thyroid-stimulating hormone (TSH) >97.5% and normal free thyroxine (FT_4), with or without thyroid antibodies [2]. Frequency in pregnancy varies, being 0.19% in Japan [3], 2.2% in Belgium [4] and 2.5% in the United States [5]. Thyroid peroxidase antibody (TPOAb) is found in 10% of pregnancies [6]. SCH is associated with miscarriage, anaemia, gestational hypertension, placental abruption, premature delivery, postpartum haemorrhage, and neonatal intensive care ad-

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mission [4]. L-Thyroxine therapy to normalize thyroid function is reported to reduce these complications [7].

Thyroid function is important in early gestation, as the fetus derives maternal thyroid hormone for brain development [8]. SCH during pregnancy was reportedly associated with reduced childhood cognitive function [9, 10]. Normalization of serum TSH with L-thyroxine therapy was associated with reduced adverse neurodevelopmental outcome [9, 10]. A recent large trial, however, yielded contradictory results. Obstetric outcomes were not reported but prenatal screening and maternal treatment did not improve cognitive function [11]. Other authors have suggested that limitations in trial design and methodology may raise the possibility of flawed results [12, 13].

Routine prenatal universal screening is controversial. The American Thyroid Association (ATA) [14] does not endorse this. Instead, an aggressive case-finding approach was recommended in high-risk groups by measurement of serum TSH [15], but this approach was reported to miss 30% of women with overt or subclinical hypothyroidism [16]. Endocrine Society 2012 guidelines reflect this controversy with a majority opinion recommending selective and a minority universal screening [17].

The ideal screening test is debated. Serum TSH measurement using trimester-specific normal values is most advocated [18], with TPOAb added due to associated adverse pregnancy events. Reduced cognitive function in children of women with isolated low FT_4 has been reported [10, 19], and would not be identified if only TSH is measured. Laboratory commercial kit references were established in non-pregnant women and do not reflect pregnancy physiological changes, thus more pregnancy-specific data is needed for TSH and FT_4. It is recommended that laboratories establish pregnancy-specific references [20].

Routine prenatal screening is currently not practiced in Jamaica. Prevalence rates and normative reference values during pregnancy in this population have not been investigated or published. The prevalence of SCH amongst Afro-Americans is one third that of Caucasians [21]. This lower prevalence of thyroid antibodies and lower TSH concentrations was thought to require more research to correlate these findings to clinical status [21].

This was a prospective cohort study to universally screen pregnant subjects at the University Hospital of the West Indies at 14 weeks' gestation. The objectives were to establish pregnancy-specific reference values for TSH and FT_4, and to the determine prevalence of SCH and TPOAb.

Materials and Methods

A prospective cohort hospital-based study was conducted between September 2009 and June 2012. Ethical approval was obtained from the Ethics Committee, University of the West Indies. A standardized questionnaire was administered by an interviewer after informed consent. Of the study recruits presenting to the hospital's antenatal clinic, ~70% were self-referred low-risk patients from the surrounding communities. Demographic data along with reproductive history, personal and family histories of thyroid disease were collected. Subjects with a previous history of thyroid disease were excluded. Gestational age was determined from the last menstrual period and confirmed with ultrasound when menstrual dates were unsure. Data was anonymized for patient confidentiality.

The sera obtained were measured for TSH, FT_4 and TPOAb concentrations by the Chemical Pathology and Immunology Laboratories. TSH and FT_4 were determined by a chemiluminescent method on an Immulite 1000 analyzer (Diagnostics Products Corp.). Intra-assay precision of TSH was 4.5–13.8%, inter-assay precision was 8.0–17.5%, and functional sensitivity was 0.005 mIU/l. The intra-assay precision of FT_4 was 3.5–6.8%, inter-assay precision was 6.7–7.0%, and functional sensitivity was 3.86 pmol/l. TPOAb was considered positive at a titre of 1:100 measured by haemaglutination kit for semiquantitative measurement (Thymune-M, Murex).

The National Academy of Clinical Biochemistry (NACB) guidelines recommend TSH and FT_4 reference intervals are established from the 95% confidence limits of the log-transformed values of at least 120 rigorously screened euthyroid subjects [22]. log transformation did not normalize our data, thus pregnancy-specific reference values (R1) were calculated using the 2.5–97.5th centile values of serum TSH and FT_4 from 150 women with singleton pregnancies at 14 weeks' gestation who met NACB clinical requirements.

Adequacy of dietary iodine was confirmed as per World Health Organization guidelines, by determination of urinary iodine excretion on random urinary samples of 30 subjects using the ion-selective electrode method on a Thermo-Orion Model 720A Instrument [23]. The inter- and intra-assay CVs were <10%. During pregnancy, median urinary iodine concentrations of between 150 and 249 μg/l define a population without iodine deficiency [24].

Three reference values for TSH and FT_4 were used to diagnose and determine frequency of thyroid hormone deficiency: the pregnancy-specific reference values (R1), the laboratory reference values for the non-pregnant population (R2), and previously proposed pregnancy-specific reference values for screening and management of SCH (R3) [17, 25–27]. R2 values were serum TSH 0.4–4.0 mU/l and FT_4 10.29–24.45 pmol/l (Diagnostic Products Corp., Los Angeles, Calif., USA). R3 values were serum TSH <2.5 or 2.5–3 mU/l with negative TPOAb and FT_4 10.29–24.45 pmol/l. Subjects diagnosed with SCH were referred to the endocrinologist.

Data analysis was performed using Stata Statistical Software, Release 12 (StataCorp LP, College Station, Tex., USA). Values were expressed as counts (frequency) or means with standard deviation. Differences in group mean values were tested by independent t test. Associations between categorical variables were tested with the χ^2 statistic or Fisher's exact test as appropriate.

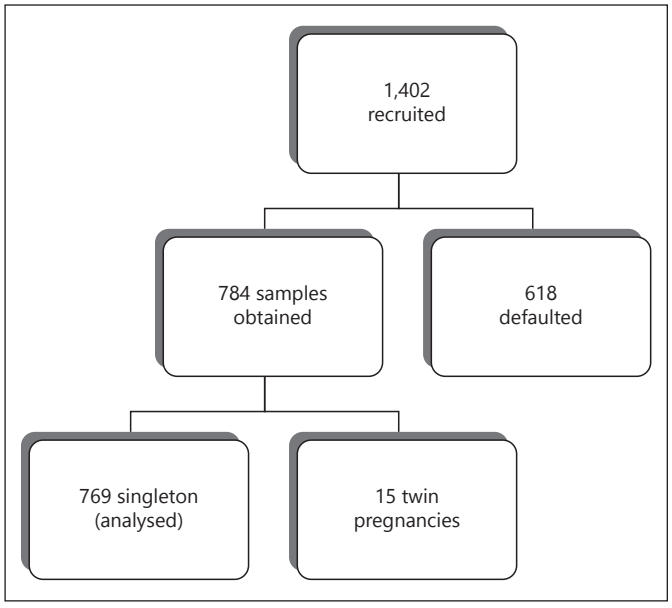

Fig. 1. Flow diagram showing subjects recruited and tested.

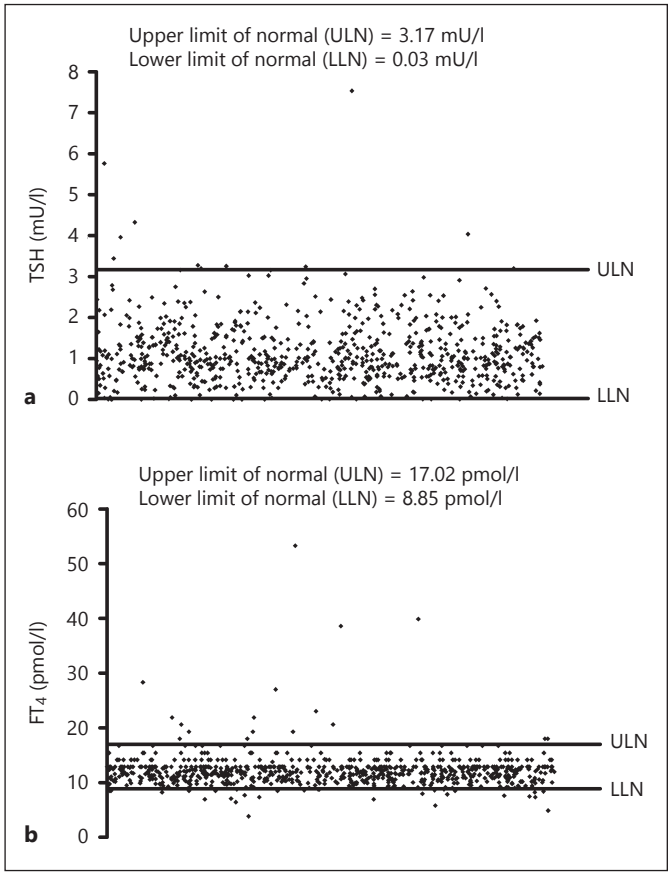

Fig. 2. Distribution of TSH (**a**) and FT_4 (**b**) concentrations in pregnant women.

Results

1,402 subjects were recruited at booking. 784 samples, consisting of 769 singletons and 15 twin pregnancies, were obtained due to patient default between recruitment and scheduled blood draw at 14 weeks. Analysis was confined to singletons (fig. 1). Mean gestational age at recruitment was 11 weeks (range 6–19); 744 (96%) were screened at 14 weeks. Mean TSH was 1.1 mU/l (0.0–7.5) and mean FT_4 was 11.58 pmol/l (3.86–52.77). The prevalence of TPOAb was 2.6% (20/769). Mean urinary iodine excretion was 158.7 μg/l.

Reference values (R1) for TSH and FT_4 were 0.03–3.17 mU/l (mean ± SD, 1.1 ± 0.76) and 8.85–17.02 pmol/l (mean ± SD, 11.96 ± 2.06), respectively. Figure 2 shows the distribution of TSH and FT_4 values of all subjects.

Table 1 shows the prevalence of thyroid hormone deficiency using all three reference values. Overt hypothyroidism defined as low FT_4 with increased TSH was only detected using R3 (0.6%). The prevalence of SCH using reference values R1, R2 and R3 was 1.4% (11/769), 0.5% (4/769) and 1.9% (15/769), respectively. The prevalence was significantly greater using R3 compared to R2 ($p = 0.011$). No significant difference in prevalence was found using R1 compared to R2 or R3. For TPOAb-negative subjects, the prevalence of SCH using reference values R1, R2 and R3 was 1% (8/749), 0.4% (3/749) and 1.4% (11/749), respectively. The prevalence was significantly greater using R3 compared to R2 ($p = 0.03$) but no difference was found using R1 compared to R2 or R3. For TPOAb-positive subjects' rates, reference values R1, R2 and R3 were 15% (3/20), 5% (1/20) and 20% (4/20), respectively.

Rates of positive TPOAb in euthyroid subjects using reference values R1, R2 and R3 were 2% (15/733), 2.2% (14/634) and 1.8% (11/614), respectively, while in subclinical hypothyroid subjects they were 27% (3/11), 25% (1/4) and 26.6% (4/15), respectively. Using all three reference values, there was a significantly greater prevalence of TPOAb seen in subjects with SCH than in euthyroid subjects ($p < 0.05$).

Hypothyroxinaemia defined as normal TSH values with low FT_4 was seen in 3.2, 17 and 17.5% of the cohort using values R1, R2 and R3, respectively. This was significantly greater using both R2 and R3 compared to R1 ($p < 0.05$). For R1, FT_4 <2.5th centile of the pregnancy-specific values was defined as abnormal and for R2 and R3 the lower limit of the laboratory non-pregnant values was utilized. Compared with all screened subjects, a sig-

Table 1. Prevalence of thyroid hormone deficiency using three reference ranges

Reference intervals TSH, mU/l	n	Euthyroidism	Subclinical hypothyroidism	Isolated hypothyroxinaemia	Overt hypothyroidism
0.03–3.17 (R1)	769	733 (95)	11 (1.4)	25 (3.2)[d]	0
TPOAb-pos	20	15 (75)[c]	3 (15)[c]	2 (10)	
TPOAb-neg	749	718 (95)	8 (1)	23 (3.1)	
0.4–4.0 (R2)	769	634 (82.5)	4 (0.5)[a]	131 (17)[d]	0
TPOAb-pos	20	14 (70)[c]	1 (5)[c]	4 (20)	
TPOAb-neg	749	619 (82.6)	3 (0.4)[b]	127 (17)	
<2.5/2.5–3					
TPOAb-neg (R3)	769	614 (79.8)	15 (1.9)[a]	135 (17.5)[d]	5 (0.6)
TPOAb-pos	20	11 (55)[c]	4 (20)[c]	4 (20)	1 (5)
TPOAb-neg	749	603 (80.5)	11 (1.5)[b]	131 (17.5)	4 (0.5)

Values are n (%). [a] Comparison of R3 vs. R2, $p < 0.011$. [b] Comparison of R3 vs. R2, $p = 0.03$. [c] Comparison of positive TPOAb in SCH subjects vs. subjects without diminished function, $p < 0.05$. [d] Comparison R2 vs. R1 and R3 vs. R1, $p < 0.05$.

nificantly higher incidence of a history of preterm labour and preterm premature rupture of the membranes (PPROM) was seen in groups R1, R2 and R3. No other significant differences were seen in demographics or past medical history.

Compared with TPOAb-negative subjects, TPOAb-positive subjects had a significantly greater incidence of family history of thyroid disease (25 vs. 5.2%, $p < 0.001$). No other significant difference in clinical characteristics was seen. κ analysis showed moderate agreement between classification schemes (κ 0.59, $p < 0.001$).

Discussion

This study seeks to determine pregnancy-specific reference values for TSH and FT_4, the prevalence of SCH and TPOAb, in an Afro-Caribbean population. Pregnancy physiological changes lead to altered levels of thyroid hormones. Previous studies have reported that when non-pregnant normative values are used for screening, SCH is undetected or misclassified as normal ranging from 3–6% [28] to 28% [18]. The ATA has recommended reference values be determined for each geographical region and trimester of pregnancy [27]. Fourteen weeks was chosen in order to screen and diagnose women early in gestation, allowing for possible intervention in the critical stages of fetal development, while avoiding first-trimester TSH suppression by high human chorionic gonadotropin levels. A recent report suggested initiation of treatment beyond 10 weeks may be too late to benefit neuropsychological development [11] but obstetric outcomes may benefit [13].

Using R1, the prevalence of SCH was 1.4 versus 0.5% using non-pregnant values (R2). Our misclassification of SCH was ~1%. This was less than previously reported, i.e. 3–6% [28] to 28% [18]. Prevalence was similar to that detected using R3 (pregnancy-specific values [17, 25–27]) and not significantly lower than reported in Caucasians, i.e. 2.2% [4] and 2.5% [5].

R1 for TSH using the 2.5–97.5th centile was 0.03–3.17 mU/l. The 2.5th centile is similar to previous reports which range from 0.02 to 0.05 mU/l, however the 95th centile was above that previously reported, i.e. 2.15–2.3 mU/l [13]. Concern was raised that a cut-off TSH value of >2.5 mU/l would result in 26.3% of pregnancies classified as hypothyroid [29]. Our study suggests that in our population the upper limit of normal for TSH may be closer to 3 mU/l and differs from a previous study which reported women of African descent have TSH values on average 0.4 mU/l lower than Caucasians [30]. Less of the population is considered abnormal if a higher TSH cut-off is used.

Persons of African descent are reported to have the lowest prevalence of thyroid autoantibodies (<5%), among all ethnic groups [31]. Prevalence in our study was 2.6% which concurred with previous findings. Prevalence was similar in euthyroid women using all three reference values. As expected, subjects with SCH (using all reference values) had a significantly greater prevalence of TPOAb than euthyroid subjects, ~25 versus 2%. The genetic predisposition associated with autoimmunity pos-

sibly accounts for the greater incidence of thyroid disease family history seen in TPOAb-positive subjects.

SCH is noted in women with no detectable thyroid antibodies and may be related to pregnancy immunotolerance [32]. Among TPOAb-negative women, the prevalence of SCH was low in all groups ranging from 0.4 to 1.4%. The highest prevalence was found using reference value R3, which was significantly higher than that detected using non-pregnant R2 values.

Age was not found to be a risk factor for elevated TSH amongst people of African descent [31], but other ethnic groups show an increased risk with age >30 years [33]. In our study the mean age of subjects diagnosed with SCH was ~25 years, which lends support to the concept of universal screening regardless of age. Prevalence and non-detection of potential cases at age <30 years should not be disregarded [13].

A significantly higher prevalence of a history of preterm labour and PPROM was seen in subjects diagnosed using R1, R2 and R3 values compared to all screened subjects ($p < 0.05$). SCH is associated with prematurity [34]. Unrecognized SCH in past pregnancies may have been a contributing factor to this finding of more preterm deliveries in this group.

Hypothyroxinaemia was seen in 3.8% of subjects using R1 but 17% of subjects using the non-pregnant value of FT_4. It is usually secondary to an underactive thyroid caused by iodine deficiency. Normal urinary iodine results confirmed adequacy of dietary iodine intake. Universal salt iodization is practised. FT_4 normal values may thus be lower in pregnant subjects. Reduced intellectual function in offspring of women with an isolated low FT_4 has been reported [35, 36], but a recent report has contradicted these findings [37]. These reports have defined hypothyroxinaemia as normal TSH with FT_4 <10th centile. Given the conflicting reports about the clinical importance of hypothyroxinaemia, utilizing the more stringent pregnancy value may identify those subjects with a significantly low FT_4 who may exhibit neuropsychological benefit from L-thyroxine replacement. Treatment of isolated hypothyroxinaemia is currently not recommended [13, 27], but the need for more studies to define relevance and need for treatment is recognized [19].

Our results provide new data for an Afro-Caribbean population which may help resolve this clinical controversy. The hospital is a tertiary centre, managing high- and low-risk cases. Results are likely generalizable. Targeted screening was not done, thus estimates of prevalence are likely robust but may be limited by small group numbers. Data on FT_4 should be interpreted with caution due to intrinsic technical weaknesses of virtually all commercialized kits for measuring FT_4 in pregnant women. Our findings support use of pregnancy-specific values in our population.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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