The prevalence of maternal hypothyroidism in first trimester screening from 11 to 14 weeks of gestation

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Aim. The aim of this study was to determine the prevalence of maternal hypothyroidism in the first trimester from 11 to 14 weeks of gestation according to the American Thyroid Association (ATA) guidelines from 2017 and to compare the rates for singleton and twin pregnancies.

Methods. A total of 4965 consecutive Caucasian singleton pregnancies and 109 Caucasian twin pregnancies were included in the investigation. Patients with a history of thyroid gland disorder were excluded. Subclinical maternal hypothyroidism was defined as a thyroid stimulating hormone (TSH) concentration above the 97.5th percentile and free thyroxine (fT4) within the range of a reference population of women at 11–14 weeks of gestation. Overt maternal hypothyroidism was defined as a TSH concentration above the 97.5th percentile and an fT4 below the 2.5th percentile of the reference population.TSH, fT4, and anti thyroid peroxidase antibody (TPOAb) were measured by immunochemiluminescent assays on an 16200 Abbott Architect analyzer.

Results. The prevalence of hypothyroidism for twin pregnancies was no higher than that for singleton pregnancies; 6.42% (7/109) vs. 5.32% (264/4965), respectively; *P*=0.61. All twin pregnancies were subclinical. Singleton hypothyroid pregnancies included 4.91% (244 cases) of subclinical and 0.41% (20 cases) of overt hypothyroidism. The prevalence of TPOAb positive hypothyroid women for twin pregnancies and singleton pregnancies was 71% (5/7) vs. 52% (137/264 cases), respectively but the differences were not statistically significant; *P*=0.31.

Conclusion. Each first trimester screening center should establish its TSH and fT4 reference ranges. Our center had higher upper reference limits of TSH than that of the universally fixed limit of 2.5 mU/L, which led to a lower measured prevalence of maternal hypothyroidism. A large number of hypothyroid women were TPOAb positive.

Key words: hypothyroidism, pregnancy, thyroid disease, immunoassay, gestation

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INTRODUCTION

Optimal maternal thyroid function is essential for fetal growth and development as the fetal thyroid gland only reaches maturity by week 11–12, close to the end of the first trimester, and begins to secrete thyroid hormones by about week 16 (ref.[1]).

Maternal thyroid dysfunction is associated with increased risk of various adverse maternal and child outcomes, including miscarriage, intrauterine growth retardation, hypertensive disorders, preterm delivery, and a decreased child IQ (ref.[2]).

Hypothyroidism in pregnant women can adversely affect their children's subsequent performance on neuropsychological tests[3].

The physiological regulation of thyroid hormone secretion is changed in pregnancy. Human chorionic gonadotropin (HCG) produced by the placenta directly stimulates the production of thyroxine (T4) and triiodothyronine (T3) by the maternal thyroid gland. Negative feedback regulation by free thyroid hormones decreases the production of TSH by the anterior pituitary gland in pregnancy to values lower than those in the general population[4].

Increased iodine supply is required for the adequate synthesis of T3 and T4 in pregnancy. Universal salt iodization is the first-line strategy for the elimination of severe iodine deficiency and iodine supplementation may be further recommended for pregnant women[5].

Maternal hypothyroidism is a major public health problem and meets the general criteria for screening. Universal or selected screening programs may be discussed[6].

The definition of overt and subclinical hypothyroidism is based on TSH and fT4 laboratory test results. Interpretation of any laboratory test depends on cut-off

values or reference ranges. Current guidelines define reference ranges as 2.5th and 97.5th percentiles of TSH and fT4 concentrations of a reference population in serum. For decision making in pregnancy, percentile-based reference ranges are preferred over the universally fixed limit of 2.5 mU/L. Subclinical maternal hypothyroidism is defined as TSH plasma concentration above 97.5th percentile of a reference population with or without positivity of TPOAb and fT4 within reference ranges. Overt hypothyroidism is a combination of TSH above the 97.5th percentile and fT4 below 2.5th percentile of the reference population[7].

The cut off point determines how many subjects will be considered as having the disease. The prevalence of maternal hypothyroidism is not well established. This motivated us to determine the prevalence of maternal hypothyroidism and compare the rates for singleton and twin pregnancies in our fetal medicine center using current ATA guidelines.

MATERIALS AND METHODS

Subjects

A retrospective observational study design was used. Data were analyzed from January 2010 to November 2017. A total of 4965 singleton and 109 twin consecutive Caucasian pregnant women who underwent simultaneously both prenatal first trimester Down's syndrome and thyroid function screening with results for TSH, fT4 and TPOAb included in the study. Women with a medical history of thyroid disease were excluded from the screening. Those positive for TPOAb were excluded for the determination of the reference limits of fT4 (678 singleton and 12 twin pregnancies).

The median, interquartile range (IQR) of age for singleton pregnancies was 30 years (26–33) and 31 years (27–34) for twin pregnancies.

Adequate iodine supplementation was assumed because of the universal availability of iodized salt in Czech Republic from 1947 (ref.[8]).

The study was approved by the Tomas Bata hospital Ethics committee in Zlín, Czech Republic and performed according to Declaration of Helsinki.

Methods

TSH, fT4, and TPOAb were measured by immunochemiluminescent assays on ci 16200 Abbott Architect analyzer.

Institutional assay specific 2.5th and 97.5th percentiles of TSH and fT4 of reference population of women pregnant from 11 to 14 weeks of gestation were used for decision making. Women with history of thyroid disease and positivity of TPOAb were excluded for establishment of reference intervals. The positivity of TPOAb was defined as a concentration of 5.6 kU/L and higher according to manufacturer recommendation.

The reference ranges of TSH in singleton and twin pregnancies followed in our center were previously published[9].

Reference intervals of TSH and fT4 for both singleton and twin pregnancies are shown in Table 1.

Subclinical hypothyroidism was defined as concentration of TSH elevated above 97.5th percentile and concentration of fT4 within reference ranges of our reference population.

Overt hypothyroidism was defined as elevation of TSH concentration above 97.5th percentile and decline of fT4 below 2,5th percentile of our reference population.

Statistical analysis

MedCalc statistical software version 17.4 (MedCalc Software bvba, Ostend, Belgium) was used for data analysis. D'Agostino-Pearson test was employed for normal distribution testing. The normal distribution was rejected for all parameters. The nonparametric percentile method was used for calculation of 2.5th and 97.5th percentile of TSH and fT4. Mann-Whitney test for independent samples was used for comparison of medians of fT4.

Two sided chi-squared test was used for comparison of proportions.

RESULTS

The median (IQR) of gestational age for singleton pregnancies was 12 weeks + 5 days (12+2–13+0) and for twin pregnancies 12 weeks + 5 days (12+2–13+1).

The prevalence of hypothyroidism for twin pregnancies was no higher than that for singleton pregnancies; 6.42% (7 cases out of 109) vs. 5.32% (264 cases out of 4965), respectively; P=0.61. All twin pregnancies were subclinical. Singleton hypothyroid pregnancies included 4.91% (244 cases) of subclinical and 0.41% (20 cases) of overt cases.

The prevalence of TPOAb positive hypothyroid women for twin pregnancies and singleton pregnancies was

Table 1. Reference ranges of TSH and fT4 for singleton and twin pregnancies from 11 to 13+6 weeks of gestation.

	Lower Reference Limit	Upper reference limit
TSH Singleton pregnancy (n=10592)	0.16 mU/L	3.43 mU/L
TSH Twin pregnancy (n=201)	0.02 mU/L	2.95 mU/L
fT4 Singleton pregnancy (n=4287)	11.8 pmol/L	18.4 pmol/L
fT4 Twin pregnancy (n=97)	12.2 pmol/L	23.2 pmol/L

TSH: Thyroid stimulating hormone
fT4: free thyroxine

71% (5/7) vs. 52% (137/264 cases), respectively but the differences were not statistically significant; *P*=0.31.

The median fT4 concentrations for twin pregnancies was no higher than that for singleton pregnancies 14.6 pmol/L vs. 14.6 pmol/L, respectively; *P*=0.13.

DISCUSSION

The prevalence of maternal hypothyroidism in first trimester screening from 11 to 14 weeks of gestation was determined.

The ATA guidelines from 2011 also suggested in its recommendation number 2 as a universal cut-off limit for decision making: if trimester-specific reference ranges for TSH 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 (ref.[10]). Carty et al. reported that using a TSH cut-off of 2.5 mU/L in keeping with European and US guidelines means that over 12% of women in this cohort would be classified as having subclinical hypothyroidism[11]. The universal limit of 2.5 mU/L would lead to much higher prevalence of maternal hypothyroidism also in our cohort.

Medici et al. in a review found that 90% of all upper limits of TSH are higher than the recommended fixed TSH cutoff concentrations of 2.5 mU/L for first trimester[2]. It is consistent with our results.

Springer et al. established reference ranges for seven analytical platforms of measurement and all of them had their upper reference limit defined as 97.5th percentile higher than the fixed limit of 2.5 mU/L (ref.[12]). Abbott Architect platform was also included with similar results of upper reference limit, which would lead to similar subclinical hypothyroidism prevalence.

Castillo et al. also used the 97.5th percentile as the upper reference limit of TSH normal values and found their prevalence of subclinical hypothyroidism of 5 % (ref.[13]). It supports our results.

Casey et al. showed that the prevalence of maternal subclinical hypothyroidism exceeded 6% using 97.5th percentile of TSH upper limit of reference population[14].

Lin et al. reported an association between TSH and positivity for TPOAb in a cohort of pregnant women in early pregnancy[15]. It supports our finding of much higher prevalence of TPOAb positivity in hypothyroid women compared to euthyroid ones.

Ashoor et al. demonstrated the same serum concentrations of fT4 in both singleton and twin pregnancies[16]. Our results confirm this.

The limitation of this study is that we did not measure anti thyreoglobulin antibodies in serum or iodine in urine.

CONCLUSION

In summary, each screening center should establish its TSH and fT4 reference ranges. Our center has a higher upper reference limit of TSH than that of universally fixed limit of 2.5 mU/L, which led to a lower measured prevalence of maternal hypothyroidism. Both the prevalence of hypothyroidism and positivity of TPOAb were the same for both singleton and twin pregnancies.

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