“Thyroid stimulating hormone (TSH) ≥2.5mU/l in early pregnancy; prevalence and subsequent outcomes”

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Objective

There remains controversy over how women with abnormal thyroid function tests in pregnancy should be classified. In this study we assessed the proportion of women with thyroid stimulating hormone (TSH) ≥2.5mU/l in a large obstetric cohort, and examined how many have gone on to develop thyroid disease in the years since their pregnancy.

Study Design

4643 women were recruited and samples taken in early pregnancy between 2007 and 2010. Thyroid function tests were analysed in 2014; in women with raised TSH computerised health records and prescription databases were used to identify thyroid disease detected since pregnancy.

Results

58 women (1.5%) had a TSH over 5mU/l and 396 women (10.3%) had TSH between 2.5 and 5mU/l. Women with TSH>5mU/l delivered infants of lower birthweight than those with TSH<2.5mU/l; there were no other differences in obstetric outcomes between the groups. Of those who have had thyroid tests since their pregnancy, 78% of those with TSH>5mU/l and 19% of those with TSH between 2.5 and 5mU/l have gone on to be diagnosed with thyroid disease.

Conclusions

Using a TSH cut-off of 2.5mU/l in keeping with European and US guidelines means that over 12% of women in this cohort would be classified as having subclinical hypothyroidism. Treatment and monitoring of these women would have major implications for planning of obstetric services.

Key words: hypothyroidism, subclinical

TSH ≥ 2.5mU/l in early pregnancy; prevalence and subsequent outcomes

Introduction

Pregnancy has a significant impact on thyroid metabolism. A number of factors contribute, including increased thyroid binding globulin levels,[1] the interaction of human chorionic gonadotrophin (β-hCG) with thyroid stimulating hormone (TSH), [2] placental deiodinase activity, and altered urinary iodine excretion.[3] Although the foetus can concentrate iodine and synthesise thyroid hormone from 10-12 weeks,[4] it is mainly reliant upon the transfer of maternal thyroid hormone until approximately 20 weeks of gestation.[5]

As a result most women with hypothyroidism, particularly those with previous surgery or radioactive iodine therapy, will require an increase in thyroxine dose in pregnancy. Many laboratories have developed trimester-specific reference ranges for TSH, but where such reference ranges are not available, the American Thyroid Association and the Endocrine Society recommend an upper limit of 2.5 mU/l in the first trimester, 3 mU/l in the second trimester and 3.5 mU/l in the third trimester.[6,7]

Subclinical hypothyroidism (SCH) refers to those with a TSH above the reference range, but with normal fT_4 levels. How to define and whether to treat SCH in pregnancy has been an area of increasing debate in recent years. The American Thyroid Association guidelines (2011) define SCH in pregnancy as TSH >2.5mU/l with normal fT_4 levels, and recommend that women with SCH be treated if they have detectable thyroid peroxidase antibodies [7]. The Endocrine Society (2012) and the European Thyroid Association (2014) recommend treatment of pregnant women with TSH >2.5 mU/l regardless of their antibody status[6,8], while the American College of Obstetrics and Gynecology

(ACOG, 2015) do not recommend treatment of SCH in pregnancy. [9] Most of the reported benefits of treatment of SCH have been in the setting of assisted conception clinics [10] or in women who have detectable thyroid peroxidase antibodies. [11] In general obstetric populations, however, clear evidence of the benefits of treating SCH is lacking; two large studies in which women were screened and treated for SCH where identified, did not find any difference in the primary outcome, the IQ of the offspring. [12] [13]

The overall aim of this study was therefore to determine how many women have a TSH above 2.5mU/l in a large low-risk obstetric cohort; our hypothesis was that a significant proportion of women would fall into this category and according to guidelines would require treatment. We compared pregnancy outcomes in these women to women with TSH < 2.5mU/l. We also investigated whether women with elevated TSH in pregnancy have gone on to develop thyroid disease during 5 years of follow-up after pregnancy.

Material and Methods

The Proteomics In Pre-eclampsia (PIP) study was conducted between 2007 and 2010. The study aimed to develop a proteomic biomarker pattern for the prediction of pre-eclampsia in otherwise healthy pregnant women and has been described in detail elsewhere [14]; in brief 4643 low-risk pregnant women were recruited at their initial antenatal appointment in hospitals across the West of Scotland. The study originally was powered to recruit 100 pre-eclampsia cases; based on an

estimated prevalence of 2.5% it aimed to recruit at least 4000 women. Women with known chronic medical problems, including pre-existing diabetes, chronic hypertension, renal disease, epilepsy and hyperthyroidism, were mainly seen in specialist medical obstetric clinics, and were not recruited for the PIP study. Women were recruited at gestational week 12-14 and women were followed until delivery where information on pregnancy outcomes was obtained from hospital databases. Birthweight was corrected for maternal height, weight, ethnicity, gestation at delivery, infant sex and parity using customised centile charts (Perinatal Research Institute, http://www.gestation.net). Plasma samples were stored in -80°C freezers until defrosting for the current analysis.

For the analyses reported here, all available plasma samples from gestational week 12-14 in the PIP study were used. TSH and free thyroxine (fT_4) levels were analysed in 2014 using automated clinically validated platforms (e411, Roche, Burgess Hill, UK) using the manufacturer's calibrators and quality control material. For the purpose of this study, women were classified into three groups; those with TSH level of greater than 5mU/l with fT_4 levels either within or below the non-pregnant reference range (9-21pmol/l), those with a TSH level between 2.5 and 5 mU/l but with free thyroxine within the normal range, and those with TSH levels of less than 2.5 mU/l. These cut-offs were chosen since 5mU/l is the upper limit of the local (non-pregnant) reference range, and 2.5mU/l is the level at which many guidelines recommend treatment of SCH in pregnancy.

TFTs were analysed some years after pregnancy; women found to have had TSH ≥2.5mU/l in the index pregnancy were therefore mainly undiagnosed and untreated during the index pregnancy. We used the Community Health Index (CHI) number, a 10-digit unique patient identifier based upon date of birth (NHS Scotland) which facilitates the linkage of all electronic medical records to determine whether women with TSH greater than 2.5mU/l in pregnancy have gone on to develop thyroid disease in the years since their pregnancy. We accessed computerised health records and laboratory results (Clinical Portal, NHS Greater Glasgow and Clyde), GP referral letters and prescription

databases (NHS Scotland) in 2015 to identify whether women had been given a diagnosis of thyroid disease, had attended a GP or hospital clinic for treatment of thyroid disease, had received a medication for thyroid disease, or had thyroid tests in the years since their pregnancy.

Statistical analyses were undertaken using SPSS version 22 (SPSS, IBM, USA). Data are expressed as mean [lower and upper bounds of 95% confidence interval] for normally distributed data or as median [inter-quartile range] for non-normally distributed data. Normality of data was assessed using the Kolmogorov-Smirnov test and by manual inspection of Q-Q normality plots. Comparisons between groups were made using Student's T-tests for normally distributed data, and by non-parametric tests for non-normally distributed data. Categorical variables were compared using Chi-square tests with measurement of odds ratio.

All women gave written informed consent for both the study and for follow up of health records. The study was approved by the West Glasgow Research ethics committee (07/S0709/79) and the study adhered to the principles of the Declaration of Helsinki.

Results

An outline of the overall study design is shown in Figure 1. A total of 4643 women were recruited to the study at gestational week 12-14 at hospitals across Glasgow and Ayrshire. 88 women were known to have had a history of hypothyroidism and were analysed separately, while for 723 women there was no plasma remaining for thyroid function testing.

There were therefore thyroid tests available for 3832 women who were not known to have had thyroid disease. Median TSH level was 1.3 [inter-quartile range 1.06], mean fT_4 level was 14.399 ± standard deviation 2.26 (95% confidence interval 14.33, 14.47). Manufacturer quality control materials yielded low and high control coefficients of variation which were 2.9% and 3.1% for fT_4 and 5.5% and 6.1% for TSH respectively between runs.

58 women had TSH above 5mU/l (1.5%), 396 had TSH between 2.5 and 5mU/l (10.3%), and 3378 had TSH less than 2.5 mU/l (88%). Of the 3378, 6 women had isolated hypothyroxinaemia, with a free thyroxine below the non-pregnant reference range (< 9 pmol/l) but with normal TSH levels; these women were not included in the analysis.

Pregnancy outcomes are shown in Table 1. Delivery data was not available for 381 of the women. Women in whom delivery information was not available were younger than those in the remainder of the study cohort (28 years ± 7.8 vs 29 years ± 6.1, p=0.001). There were no other differences observed; characteristics of women for whom delivery information was not available are shown in Supplementary Table 2.

Women with TSH greater than 5mU/l delivered infants of lower birthweight than those with TSH below 2.5mU/l (mean corrected birthweight centile 37.1±30 vs 44.1±30, p=0.02). There were no differences in any other obstetric outcomes observed when comparing women with TSH>5mU/l, women with TSH 2.5-5mU/l and women with TSH<2.5mU/l (Table 1). There was no correlation between fT4 or TSH levels and uncorrected birthweight, corrected birthweight centile, or delivery at gestation.

Computerised health records were used in 2015 to examine what has happened to women with TSH≥2.5mU/l in the 4-6 years since the index pregnancy. 58 women were found to have TSH greater than 5mU/l at gestational week 12-14. Of these 1 woman developed typical symptoms and was diagnosed with hypothyroidism and treated with thyroxine during pregnancy, 13 have been diagnosed and treated for hypothyroidism since their pregnancies, 1 has been diagnosed with Graves' disease, 3 women have had raised TSH on repeat testing but do not appear to have been formally diagnosed or treated, while 5 have had normal thyroid function testing. The 35 remaining women have not, as far as we can ascertain, had thyroid function testing, or been started on any thyroid medications in the years since pregnancy.

396 women were found to have TSH between 2.5 and 5mU/l during their pregnancy. None were diagnosed with thyroid disease during their pregnancy, but 16 have been since diagnosed and treated for hypothyroidism. 21 have had raised TSH but do not appear to have had a formal diagnosis of (or treatment for) hypothyroidism, 4 had postpartum thyroiditis with subsequent normal thyroid function tests, 179 have had normal TFTs, 2 have developed Graves' disease, while the remainder do not appear to have had thyroid function testing performed in the years since their pregnancy.

88 women in the study were known to have had a history of hypothyroidism prior to the index pregnancy; these women were analysed separately. Of them, 23 (26%) had a TSH greater than 5mU/l at gestational week 12-14, 24 (27%) had a TSH of between 2.5mU/l and 5 mU/L, and 41 (47%) had a TSH of less than 2.5 mU/L. Pregnancy outcomes for these women are shown in Supplementary table 3. In women with identified and treated hypothyroidism before pregnancy,

pregnancy outcomes were similar in all groups regardless of measured TSH in early pregnancy, and birth weights were similar to women without diagnosed (or biochemically identified) hypothyroidism.

Discussion

The overall aim of this study was to determine how many women in a large healthy pregnant population had a TSH over 2.5mU/l, which would be defined according to guidelines as SCH. We then aimed to determine how many of these women have gone on to develop thyroid disease in the years since their pregnancy.

Thyroid function tests from gestational week 12-14 were retrospectively analysed. After excluding women with known thyroid disease we found that 1.5% of women had TSH greater than 5mU/l, and 10.3% of women had TSH between 2.5 and 5mU/l. Women with TSH > 5mU/l delivered infants of lower birthweight than those with TSH < 2.5mU/l but there were no other differences in obstetric outcomes.

Of the women found to have had TSH>5mU/l, 31% (78% of those who have been tested) have gone on to develop thyroid disease, or have had abnormal tests in the 5 years since their pregnancy. Of the women with TSH between 2.5 and 5mU/l, only 11% (19% of those who have been tested) have gone on in the subsequent 5 years to develop thyroid dysfunction.

Guidelines, both in Europe and the USA have proposed that women with TSH>2.5mU/l be defined as SCH and treated with thyroxine, but the evidence behind this is mixed, and many would argue against the "medicalisation" of such large numbers of women. Treatment of SCH also raises questions about whether the treatment should be continued after pregnancy, and how, when and by whom it should be reduced. Using an arbitrary cut-off of 2.5mU/l as recommended in current guidelines will mean that 12% of women in this cohort, and potentially higher proportions of patients in other populations will be defined as SCH,[15,16] with differences between ethnic groups.[17] Reflecting recent data indicating that the upper limit of normal first trimester ranges are higher than 2.5mU/l, [5,18] the forthcoming American Thyroid Association guidelines, first presented in April 2016, recommend that an upper limit of 4mU/l be used. [19]

Only 88 women with previously known thyroid disease were included in the study, and as such the study was not sufficiently powered to show a difference in obstetric outcomes in these women. Of them, more than half had a TSH of greater than 2.5mU/l at week 12-14, indicating (according to guideline recommendations) that they were under-replaced. Guidelines indicating that thyroxine dose should be increased by 30% in early pregnancy [6,7] have not always come into routine clinical practice, particularly in primary care where most hypothyroid women contemplating pregnancy are managed.

In this large study of otherwise healthy pregnant women we have shown that a significant proportion fall into the category where they would be diagnosed with subclinical hypothyroidism, reflecting other studies using the same diagnostic cut-offs. [15,18] Although maternal thyroid antibody status was not checked, making accurate interpretation of thyroid function less reliable, this situation reflects real-life practice where clinicians have to decide on treatment without such information. We found that the majority of women with TSH >2.5mU/l do not go on to have further

thyroid problems. Although this may be an underestimate (since the majority of women have not been tested,) our results reflect those of a previous study which reported that 75% of women with SCH in pregnancy have normal thyroid function at five years of follow-up. [20] The study has some limitations. Since the overall study was designed only to examine obstetric outcomes, there was no information regarding IQ or other long-term outcomes of the offspring. Thyroid function tests from pregnancy and analysis of pregnancy outcomes was not available in all women, although there was no demonstrable difference between these women and the rest of the cohort (Supplementary Table 1 & 2.)

The question of whether women should be screened for thyroid dysfunction continues. It is clear that there is a requirement for local trimester-specific and ethnicity-specific reference ranges. Classification of large numbers of women as having SCH would have major implications for the planning and costing of obstetric services, and given the mixed message from the guidelines, further evidence of the benefits of treating SCH is required before such treatment can come into routine clinical practice.

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