J. Fetal Med. (September 2019) 6:123–126
https://doi.org/10.1007/s40556-019-00218-6

ORIGINAL ARTICLE

Women with Positive First Trimester Thyroid Disease Screening Results

Ishraq Dhaifalah[1,2,3] · Jana Havalova[1] · Dagmar Langova[4] · Zdenek Adamik[1] · Howard Cuckle[5]

Received: 25 July 2019 / Accepted: 9 September 2019 / Published online: 19 September 2019

Abstract The objective of this study was to follow up women with positive results on routine antenatal screening for maternal thyroid disease. Between November 2009 and September 2015, women having a first trimester Down's syndrome screening test were simultaneously screened for thyroid disease; those symptomatic or being investigated for thyroid problems were excluded. A blood sample was tested for anti-thyroid peroxidase antibodies and serum thyroid stimulating hormone, and in the first half of the study also for free thyroxine. Women with at least one analyte outside the range were classified as positive and referred to an endocrinologist for counselling. Among 10,052 women that were screened, 1190 (11.8%) were positive. Follow-up information was sought and this was available on 818 referrals. No further action was recommended in 440 (54%) and after repeat testing in 108 (13%) a total of 204 (25%) were recommended to take thyroxine, one was referred for surgery and propylthiouracil was recommended for five. Screening in the Czech Republic identifies an estimated 3.1% of pregnant women with subclinical thyroid disease.

✉ Ishraq Dhaifalah
ishraq.dhaifalah@gmail.com

[1] Department of Obstetrics and Gynecology, Regional Hospital, Zlin, Czech Republic

[2] FETMED (Fetmed Fetal Medicine Center and Genetics), Horni lan 13, 77900 Olomouc, Ostrava, Czech Republic

[3] Department of Biomedical Sciences, Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic

[4] Department of Internal Medicine Clinic, Regional Hospital, Zlin, Czech Republic

[5] Department of Obstetrics and Gynaecology, Columbia University Medical Centre, New York, USA

Keywords Thyroid disease · Screening · Antenatal · Endocrinologist · Follow-up

Introduction

Subclinical thyroid dysfunction is common in pregnancy with about 2–3% women having hypothyroidism [1]. Both overt disease and subclinical dysfunction are associated with pregnancy complications such as fetal death [2] and preterm birth [3] and adverse outcomes such as intellectual impairment of the infant [4].

These considerations prompted the Fetal Medicine Centre in the Department of Obstetrics and Gynaecologists, Zlin, Czech Republic—an iodine sufficient country—to promote routine antenatal screening using thyroid antibodies and hormones [5]. Between November 2009 and September 2015, women having a first trimester Down's syndrome screening test were simultaneously screened for thyroid disease. A blood sample was tested for anti-thyroid peroxidase (TPO) antibodies and serum thyroid stimulating hormone (TSH), and until March 2013 also for free thyroxine (fT4). Testing for the second hormone was stopped because of financial rather than scientific reasons. Women with at least one analyte outside the normal range were classified as positive and referred to an endocrinologist for counselling. 10,052 women were screened and 1190 (12%) had positive results; the screen-positive rate was 13% in the period when all three markers were used and 10% thereafter.

Our aim was to follow-up a sample of referrals in order to estimate the predictive value of the screening protocol in the diagnosis of thyroid dysfunction in our hospital.

Methods

Screening

Women screened between November 2009 and February 2013 were tested for each of the three markers, TPO, TSH and fT4; from March 2013 until September 2015 only TPO and TSH were tested. Testing was carried out using a high speed chemiluminiscent immunoassay analyzer immunoassay processor (Architect i2000SR, Abbott Diagnostics). Those who were symptomatic or being investigated for thyroid problems were excluded from the current study. The normal range for each marker was: TPO less than 5.6 kU/l; TSH 0.35–4.94 mU/l; and FT4 9.0–19.1 pmol/l. A result was regarded as positive if at least one of these markers was out of range.

Information was collected at the time of screening on maternal age, parity, use of assisted reproduction technologies (ART), ethnicity, smoking status and number of fetuses. The ultrasound crown-rump length was measured as part of the combined test and used to estimate gestational age using a published formula [6].

Follow-Up

Hospital records were examined in all those with positive results to determine the recommendation of the endocrinologist and the consequent sequence of events. Specifically, each record was categorised according to whether the endocrinologist recommended no further action, repeat testing, treatment and if so the type, drug dose, frequency and duration. Pregnancy outcome was sought in all such cases.

Results

Complete or partial follow-up information was available on 818 referrals. This included 38 twin pregnancies and 47 singletons where the test result was positive in more than two pregnancies.

The endocrinologist recommended no further action in 440 (54%) pregnancies and repeat testing was recommended in 108 (13%). Subsequently, a total of 278 (34%) received some form of treatment during pregnancy; one patient was referred for surgery, a lobectomy, and the rest for drugs. The recommended drug was thyroxine in 204 cases, propylthiouracil in 5 cases and iodine in 69 cases.

Of those recommended to take thyroxine, information on dose was available for 179. The range was 25–200 μg but for most it was 50 μg (121, 68%) or 75 μg (43, 24%). Each of the three patients recommended propylthiouracil with dose information had 50 mg. There was only information on dosage for 39 of those recommended iodine and this was in the range 100–150 μg with nearly all at 100 μg.

There was little information in the medical records on the recommended duration of treatment; apart from those recommended to take iodine, only one record specified this. Among 38 taking iodine, the recommendation in 30 (79%) was to take this during both pregnancy and lactation whereas only pregnancy was specified in six. In two cases, long term iodine treatment was recommended and in one of them it was noted that both the patient's mother and grandmother had multi-nodal disease.

Among the 47 women with positive screening result in two pregnancies, four were recommended thyroxine treatment in the first pregnancy but no such treatment in the second. The interval between pregnancies was 2–3 years. Another woman was not recommended treatment in the first pregnancy but a year later, in the second pregnancy, the recommendation was thyroxine. Two women were recommended thyroxine in both pregnancies, with intervals of 1 and 6 years.

Of the 210 women treated with either thyroxine or propylthiouracil or surgery, information on outcome of pregnancy was available for 143. There was a livebirth in 138 (96%), missed abortion in one, intrauterine fetal death in one and two pregnancies were terminated. There was one pregnancy with HELP syndrome but no other hypertensive disorders. In five pregnancies, gestational diabetes was diagnosed: at 25, 26, 27 (two cases) and 33 weeks gestation. Premature rupture of membrane was reported in 13 singletons and in two sets of twins. Gestation at delivery was available for 140 live born foetuses and was preterm in 17 (13%) of singletons and 8 (89%) twins. Birth weight was available for 136 of them and was below 2.5 kg in 12 (9.4%) singletons and 8 (89%) twins. Some outcomes of pregnancy were not substantially different from other women with screen-positive results: among the 303 with complete outcome information, there was a livebirth in 295 (97%); preeclampsia in 3; and gestational diabetes in 8. However, the prematurity and growth restriction was relatively high since in the other women with screen-positive results, there was only premature rupture of membrane in 16 (5.7%) singletons and 3 (19%) twins; and in 303 foetuses with known birth weight, this was below 2.5 kg in 16 (5.9%) singletons and 8 (73%) twins.

The predictive value of screening was higher during the period when screening used three markers in comparison with the later period when only two were used. The no further action rates were 47% (194/416) and 61% (246/402) respectively, with treatment rates of 35% (146/416) and 25% (100/402), respectively. Considering each marker individually, the treatment rates were: 53% (191/363) for

TPO less than 5.6 kU/l; 21% (102/495) for TSH 0.35–4.94 mU/l; and 12% (6/51) for FT4 9.0–19.1 pmol/l.

Discussion

We have previously shown that in the Czech Republic, a single relatively large hospital can readily incorporated maternal screening for thyroid disease into a routine first trimester Down's syndrome screening program. About 12% of women were found to have positive test results, indicating follow-up by an endocrinologist. The current study shows that of those referred about one-quarter were recommended to have thyroxine or propylthiouracil drug treatment or surgery.

The largest category was those women who were diagnosed with hypothyroidism and treated using thyroxine, mostly at a dose of 50 or 75 μg. They comprised 25% of referrals (204/818). In contrast those diagnosed with Graves–Basedow disease and treated with propylthiouracil comprised less than 1% of referrals (5/818). A further woman diagnosis with Graves–Basedow disease following referral was monitored throughout pregnancy and not treated with propylthiouracil until after pregnancy.

An intermediate sized group were those women treated with iodine, following ultrasound diagnosis of cystic nodules in the thyroid. Comprising 5% of referrals (39/818), the aim of treatment, at a dose of 100 μg, is to reduce the number and size of nodules. The Czech Republic is considered an iodine sufficient country and iodine treatment is not specifically recommended in pregnancy although some multivitamin preparations recommended in the first trimester do contain iodine.

The woman who had a lobectomy during pregnancy following referral had enlarged toxic cysts. Two other referred women had surgery following pregnancy. One woman diagnosed with Graves–Basedow disease and treated with propylthiouracil during pregnancy, subsequently had surgery as the disease had progressed. One woman diagnosed with hypothyroidism and treated with thyroxine during pregnancy, had thyrotoxicosis following pregnancy and had a total thyroidectomy.

In total, 212 referred women were diagnosed with subclinical thyroid disease. Assuming that the 818 referrals with complete or partial follow-up information are typical of the 1190 with positive screening results in our original study, it can be concluded that screening identified 3.1% of pregnant women with subclinical disease. This is consistent with the findings in other studies carried out in iodine sufficient countries. For example, in a study of about 17,000 pregnant women in the USA screened before 20 weeks gestation subclinical hypothyroidism was diagnosed in 2.3% [1]. In the Czech Republic a study of 611 non-pregnant women estimated the incidence of sub-clinical hypothyroidism to be 8.0% with a twofold relative risk in women aged over 55 compared with younger women [7]. This is consistent with the rate we found in pregnant women.

Recently, the normal range for TSH used for prenatal screening in the Czech Republic changed from 0.35–4.94 to 0.16–3.43 mU/l. Had this been used in our original study, the proportion of women referred would have reduced slightly from 11.8 to 11.6%. The impact of this change on the diagnosis of subclinical thyroid disease is unknown.

This study was restricted to assessing the predictive value of routine screening in early pregnancy for subclinical thyroid dysfunction. It did not aim to determine the screening detection rate. This would have required systematic follow-up of all pregnancies with negative screening results over an extended period and resources were not available to carry out such a study.

In conclusion, of the 12% of women in our centre referred to an endocrinologist following positive maternal screening test for thyroid disease, about one-quarter were recommended to have thyroxine or propylthiouracil drug treatment or surgery. Screening in the Czech Republic identifies an estimated 3.1% of pregnant women with subclinical thyroid disease.

Acknowledgements We thank Mr. Dvoracek and technicians of the Clinical Biochemistry and Pharmacology Department for providing the results promptly and for being available for discussion. We thank the nursing staff of the Centre of Fetal Medicine and the Department of Endocrinology for their help in gathering outcome information. We thank all gynaecologists who referred their patients to our centre.

Funding None.

Compliance with Ethical Standards

Conflict of interest HC is a consultant to PerkinElmer Inc. Other authors have no financial interests.

Ethical Statement This is an audit of a clinical service therefore no ethical approval was required.

References

1. Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol. 2005;105:239–45.
2. Andersen SL, Olsen J, Wu CS, et al. Spontaneous abortion, stillbirth and hyperthyroidism: a Danish population-based study. Eur Thyroid J. 2014;3(3):164–72.
3. Sheehan PM, Nankervis A, Araujo Júnior E, et al. Maternal thyroid disease and preterm birth: systematic review and meta-analysis. J Clin Endocrinol Metab. 2015;100(11):4325–31.
4. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 1999;34:549–55.

5. Dhaifalah I, Salek T, Langova D, et al. Routine first trimester screening for maternal thyroid disease. J Fetal Med. 2017;4(1):19–23.
6. Loughna P, Chitty L, Evans T, et al. Fetal size and dating: charts recommended for clinical obstetric practice. Ultrasound. 2009;17(3):161–7.
7. Mayer O Jr, Simon J, Hrbková J, Pikner R, Topolcan O. Epidemiological study of hypothyroidism as cardiovascular risk in population. Cas Lek Cesk. 2005;144(7):459–64.