Management of thyroid disease in pregnancy – Room for improvement in the first trimester

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Abstract

Background: First-trimester care of maternal thyroid dysfunction has previously been shown to be poor. This study evaluates early management of thyroid dysfunction in pregnancy in Australia.

Methods: Patients reviewed by the Obstetric Medicine team for thyroid dysfunction from 1 January 2012 to 30 June 2013 were included. Data were collected on gestation at referral from the patient's general practitioner to the antenatal clinic, information provided in the referral letter, thyroid function tests and thyroid medications.

Results: Eighty-five women were included in the study. At the time of general practitioner referral to antenatal services, 19% of women with preexisting thyroid disease had no thyroid function tested. Forty-three percent had an abnormal thyroid-stimulating hormone defined as being outside the laboratory-specific pregnancy reference range if available, or outside the level of 0.1–2.5 mIU/L in the first trimester, 0.2–3.0 mIU/L in the second trimester and 0.3–3.0 mIU/L in the third trimester. Only 21% of women increased their thyroxine dose prior to their first antenatal clinic review.

Conclusion: This study highlights that a significant proportion of women with known thyroid disease either have untested thyroid function in the first trimester or a thyroid-stimulating hormone outside of levels recommended by guidelines.

Keywords

Thyroid, pregnancy, first trimester, triage, general practitioner

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Introduction

Thyroid physiology is profoundly altered in pregnancy. Women have lower thyroid-stimulating hormone (TSH) levels in pregnancy than in the non-pregnant state and international bodies now recommend that trimester-specific reference ranges be used in pregnancy.^{1–3} If trimester-specific reference ranges are not available in the laboratory, then international bodies recommend a TSH level of 0.1–2.5 mIU/L in the first trimester, 0.2–3.0 mIU/L in the second trimester and 0.3–3.0 mIU/L in the third trimester.¹ A recent study using these ranges reported that 12.3% of women had either overt or subclinical hypothyroidism and 2.6% had a low TSH suggesting hyperthyroidism.⁴

Both overt and subclinical hypothyroidism are associated with adverse pregnancy outcomes in some studies.¹ Although there are no randomized controlled trials evaluating the benefit of treating overt hypothyroidism, the available data indicate that treatment provides benefit.¹ There is no such consensus with regard to treatment of pregnant women with subclinical hypothyroidism.¹ Overt hyperthyroidism is also associated with adverse pregnancy outcomes, mostly related to the control of hyperthyroidism.^{5,6} Subclinical hyperthyroidism on the other hand has not been not associated with adverse outcomes.⁷

Due to the changes in thyroid physiology, some pregnant women taking thyroxine need increased doses of thyroxine from as early as the fifth week of gestation.⁸ Several international guidelines recommend that pregnant women with hypothyroidism increase their thyroxine dose by 30% on confirmation of pregnancy.^{1,2}

As the fetal thyroid gland does not synthesise or secrete thyroid hormones until 16–18 weeks' gestation, the fetus is reliant on maternal thyroxine in the first trimester.⁹ Altered maternal thyroid hormone levels in the first trimester may therefore have deleterious effects on the fetus. For this reason, it is important that management of pregnant women with thyroid disease is optimised early in pregnancy. Several reports suggest that the first-trimester care of women with preexisting

thyroid disease in pregnancy may not be optimal. In one Scottish study, 65% of women taking thyroxine pre-pregnancy had at least one elevated TSH in pregnancy with 55% of these occurring in the first trimester.¹⁰ In addition, only 34% of women on thyroxine prior to pregnancy increased their dose in the first trimester. Similarly in a Swedish study, 49% of women had a TSH outside the reference range of 0.4–4.0 mIU/L at their first thyroid function test (TFT), with 83% of these tests being performed in the first trimester.¹¹ Fetal loss was noted to be greater in these women.

To our knowledge, there have been no studies evaluating the early management of thyroid disease in pregnancy in Australia. The aim of this study was to document management of maternal thyroid disorder prior to referral for specialist care.

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Methods

The study was conducted at Ipswich Hospital, Queensland. All women seen by the obstetric medicine team for thyroid disorder between 1 January 2012 and 30 June 2013 were included in the study. Women whose initial antenatal care had taken place at another hospital were excluded. All women wanting to deliver in the public health system and living within the Ipswich hospital catchment area are usually referred to the Ipswich hospital antenatal clinic by their general practitioner (GP). Referrals are then reviewed and triaged by an obstetric registrar (obstetrician in training). The decision to refer to obstetric medicine for thyroid disorder is made at triage or at an obstetric antenatal clinic review.

We collected information on patient demographics, gestational age when TFTs were performed, results of TFTs, gestational age at referral to specialist services, gestational age at first specialist review, documentation of preexisting thyroid disease on the referral letter and changes made to thyroid medications prior to the first antenatal specialist clinic.

Trimester-specific reference ranges for TFTs were used. Two of the four pathology providers in Queensland, Australia have trimester-specific reference ranges for TFTs. If the women's TFTs were performed at either of these providers then these reference ranges were used. If the TFTs were performed at one of the other two providers, a TSH was considered normal if it was between 0.1–2.5 mIU/L in the first trimester, 0.2–3.0 mIU/L in the second trimester and 0.3–3.0 mIU/L in the third trimester. Overt hypothyroidism was diagnosed if the TSH was elevated in addition to low free T4 (fT4) and/or free T3 (fT3). Overt hyperthyroidism was diagnosed if the TSH was suppressed and the fT4 and/or fT3 were elevated. Isolated hypothyroxinemia was diagnosed if the TSH was normal and the fT4 was low. Subclinical hypothyroidism was diagnosed if the TSH was elevated but the fT4 and fT3 were normal. Subclinical hyperthyroidism was diagnosed if the TSH was suppressed and the fT4 and fT3 were normal.

Data were analysed using the statistical program R, version 3.1.2. The relationship between categorical and continuous variables was assessed using two-sample t-tests. A threshold of $p < 0.05$ was considered statistically significant. Ethics approval was granted from the West Moreton hospital and health service human research and governance committee.

Results

A total of 87 women met the inclusion criteria. Two women were excluded as they received their initial antenatal care at another hospital, leaving 85 women in the study. Women's demographics are shown in Table 1. The majority of women were aged between 25 and 35 years, had a parity of 1 or 2 and a BMI between 18.5 and 25 kg/m².

Indication for referral

The most common indication for referral was for preexisting overt primary hypothyroidism (Table 2). Ten patients were referred for preexisting hyperthyroidism, of these 8 had a diagnosis of Grave's disease. Eighteen patients were referred for abnormal TFTs found on routine screening blood tests of which 12 were done for reasons outside of the American Thyroid Association recommended guidelines.¹ These 18 women had either normal TFTs for pregnancy (11%), subclinical hyperthyroidism (39%), or subclinical hypothyroidism (50%). No patients had isolated hypothyroxinemia.

Gestational age at referral

The median length of gestation at referral was nine weeks (interquartile range (IQR) 7–13 weeks), and the median gestation at the first

Table 1. Patient demographics.

Metric	Number (%)
Number	85
Age <25 years	14 (16)
Age 25–34.9 years	60 (71)
Age ≥35 years	11 (13)
Median gravida	2 (IQR 2–3)
Parity 0	28 (33)
Parity 1–2	42 (49)
Parity ≥3	15 (18)
Current smoker	14 (16)
BMI <18.5 kg/m ²	3 (4)
BMI 18.5–24.9 kg/m ²	40 (47)
BMI 25–29.9 kg/m ²	16 (19)
BMI 30–34.9 kg/m ²	14 (16)
BMI 35 kg/m ² and above	12 (14)

BMI: body mass index.

Table 2. Indication for referral to the antenatal clinic.

Reason for referral	Number 85 (%)
Pre-existing overt primary hypothyroidism	50 (59)
Pre-existing subclinical primary hypothyroidism	1 (1)
Graves disease (including currently and not currently active)	8 (9)
Pre-existing hyperthyroidism unspecified	2 (2)
Previous total thyroidectomy	3 (4)
Previous partial thyroidectomy	1 (1)
Goitre	2 (2)
Abnormal screening test result (done for age >30)	6 (7)
Abnormal screening test result (outside of current guidelines)	12 (14)

antenatal clinic review was 17 weeks (IQR 14–21 weeks). The median time between referral and first clinic review was 42 days (IQR 21–69 days). Sixty-four women (75%) were referred to antenatal clinic prior to 14 weeks' gestation and of these 19 (30%) were reviewed in the antenatal clinic prior to 14 weeks' gestation; 6% within two weeks and 29% within four weeks.

Women with preexisting thyroid disease

At the time of referral to the antenatal clinic, 13 women (19%) with preexisting thyroid disease had not had their thyroid function tested. The median gestational age at referral for these 13 women was nine weeks with a range of 6–29 weeks. Of those women who had had their thyroid function tested, 29 (43%) had a TSH outside the pregnancy-specific reference ranges at the time of referral, with a median gestational age at referral of nine weeks (range 4–18 weeks). TSH levels for these 29 patients ranged from <0.05 to 60. At the time of first antenatal clinic review, 27 women (40%) with preexisting thyroid disease had a TSH outside of pregnancy-specific reference ranges with a median gestational age of 16 weeks (range 6–36 weeks). TSH levels for these 27 women ranged from <0.01 to 60. Four women with preexisting thyroid disease had not had thyroid function tested at the time of the first antenatal clinic review.

Table 3. Correlation between variables documented in the GP referral letter and time between referral and first clinic review.

Variable	Presence of variable in the GP letter	Mean time between referral and clinic review (days)	Standard deviation	t-test statistic
Abnormal TFTs	Y	38.6	26.3	$t = 2.5, df = 83$
	N	55.7	36.6	$p = 0.01$
Diagnosis	Y	45.0	32.0	$t = 1.2, df = 73$
	N	53.9	35.8	$p = 0.23$
Thyroid medications	Y	45.9	31.9	$t = 0.7, df = 81$
	N	51.1	35.3	$p = 0.48$
Any variable	Y	43.6	30.9	$t = 2.4, df = 27$
	N	66.1	37.8	$p = 0.02$

GP: general practitioner; TFTs: thyroid function tests.

Women taking thyroid medication prior to pregnancy

Forty-seven women were taking thyroxine prior to pregnancy. The thyroxine dose was increased in 10 women (21%) prior to their first antenatal clinic appointment. Two women ceased their thyroxine on finding they were pregnant. Ten women had not had their TSH assessed at the time of referral to the antenatal clinic with a median gestational age at referral of 13 weeks (range 7–29 weeks). Of the 37 women taking thyroxine who did have their thyroid function tested prior to the antenatal clinic appointment, 19 had an elevated TSH (median 6 mIU/L, range 3.1–60 mIU/L). Of these 19 women, only nine (47%) had their thyroxine dose increased prior to their first antenatal clinic review.

Eight women had a prior history of Grave's disease with three taking propylthiouracil prior to pregnancy. None were taking carbimazole at the time of conception. Of the three women taking propylthiouracil, one ceased it on finding she was pregnant (TSH <0.01 mIU/L, T4 18 at five weeks' gestation), one had a dose reduction prior to TFTs being done and one stayed on her pre-pregnancy dose (TSH 3.8 mIU/L, T4 15 at five weeks' gestation.) Two women with a prior history of Grave's disease did not have a TSH level at the time of referral to antenatal clinic (six and eight weeks' gestation).

Analysis of GP referral letter

Women whose referral letter listed abnormal TFT results were seen significantly more quickly in the antenatal clinic than those without; mean time to review 38.6 vs. 55.7 days, respectively ($p = 0.01$.) There was no significant relationship between whether the GP letter listed a diagnosis of thyroid disease or thyroid medication and the time between referral and first clinic review. These results are shown in Table 3.

Discussion

This study shows that the first-trimester management of pregnant women with known thyroid disease is not optimal according to international guidelines. The majority of women with preexisting thyroid disease had either no TSH at the time of referral to antenatal clinic or a TSH outside pregnancy-specific reference ranges. In addition, only a minority of women taking thyroxine prior to pregnancy increased their thyroxine dose on finding they were pregnant. While our findings are concerning, they are not out of keeping with previous studies suggesting this is a global problem.^{10–12} Exactly why this problem exists is not clear; however, it is likely that many GPs are not aware of current recommendations with regards to the management of thyroid disease in pregnancy.

For women taking thyroxine prior to pregnancy who had a TSH tested at the time of referral to antenatal services, 51% had a TSH level outside of pregnancy reference ranges. Abalovich et al.¹² found that in women with hypothyroidism with a TSH of 1.2 mIU/L or less six months prior to pregnancy, only 17% needed an increase in their thyroxine dose during pregnancy.¹² If a TSH of 1.2 mIU/L or less became the target for hypothyroid women of child bearing age, then potentially there would be significantly fewer patients with inadequately (according to current guidelines) treated thyroid disease in the first trimester. However, a target of 1.2 mIU/L would have to be evaluated for efficacy and safety before it could become recommended practice.

Two of the four pathology services in Queensland provide trimester-specific pregnancy reference ranges with their results. The other two services provide non-pregnant reference ranges only. Only 14 women had their initial TFTs with one of the services with trimester-specific pregnancy reference ranges. This may explain why when some women had TSH levels outside of pregnancy-specific reference ranges their thyroid medication doses were not adjusted. If GPs were using the non-pregnancy reference ranges given by the pathology providers then the results could have appeared falsely normal. Trimester-specific reference ranges presented with TFT results would be extremely valuable to clinicians.

Fourteen percent of women in this study were referred as a result of abnormal results performed for reasons outside of the recommended guidelines.^{1,13} It would appear therefore that some GPs perform universal screening. Universal screening for thyroid disorders in pregnancy is currently not recommended in Australia. All of these patients had either normal TFTs, subclinical hyperthyroidism or hypothyroidism. If more GPs screen for thyroid dysfunction as part of routine antenatal screening the number of referrals to obstetric services for subclinical thyroid disease will likely increase.

The median length of time for women to be seen in the antenatal clinic was six weeks from the time of the GP referral letter. The only factor that led to patients being seen more quickly was documentation of abnormal TFTs in the referral letter. It is not clear why it was specifically the abnormal TFTs that led to an earlier clinic review. A delay of six weeks until first antenatal review is potentially too long for a woman with inadequately treated thyroid disease. Constraints on service provision may make it difficult to shorten this length of time. One option is to send GPs a proforma letter outlining the general management of thyroid disease in pregnancy in response to referrals for abnormal thyroid function. This could be done in addition to reviewing these patients in antenatal clinic.

Limitations of this study include that it was retrospective and only included patients referred to obstetric medicine. Patients with thyroid disease seen solely by the obstetrics team were not included in the study. The study also only assessed patients referred to Ipswich hospital for the management of their thyroid disorder during the pregnancy. It did not include patients within the same catchment area, managed by a service other than Ipswich hospital, such as a private endocrinologist. It is not known whether GPs knew how long the wait times were to be seen at the clinic. It is possible that GPs expected the wait time to be significantly shortly, and thus deferred making decisions about thyroid management themselves.

Conclusion

This study highlights that a significant proportion of women with known thyroid disease either have inadequately (according to current guidelines) treated thyroid disease or untested thyroid function in the first trimester.

Declaration of conflicting interests

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Ethical approval

Ethics approval was granted from the West Moreton Hospital and Health Service Human Research and Governance Committee. Patient consent is not applicable.

Guarantor

HR.

Contributorship

HR designed the study, collected and analysed the data and wrote the manuscript. PR analysed the data and revised the article critically for important intellectual content. MD'E revised the article critically for important intellectual content. KM designed the study and revised the article critically for important intellectual content.

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