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Abstract

Background: Women requiring thyroid hormone replacement after definitive therapy (surgery or radioiodine) for Graves' disease who later conceive require an early increase in levothyroxine dose and monitoring of thyroid hormone levels throughout pregnancy. In addition, as TSH receptor antibodies (TRAb) can cross the placenta and affect the fetus, measurement of these antibodies during pregnancy is recommended.

Aim: To review the management of pregnancies following definitive treatment for Graves' disease in order to assess the rates of maternal hypothyroidism and TRAb measurement.

Materials and Methods: Retrospective chart review of patients who had undergone definitive treatment for Graves' disease at a tertiary hospital and subsequently had one or more pregnancies.

Results: 29 women were identified who each had at least one pregnancy since receiving definitive treatment for Graves' disease. There were a total of 49 pregnancies (22 in the surgical group and 27 in the radioiodine group). Both groups had high rates of hypothyroidism documented during pregnancy (47% and 50%, respectively). The surgical group were more likely to be euthyroid around the time of conception. Less than half of the patients were referred to an endocrinologist or had TRAb measured during pregnancy. Neonatal thyroid function was measured in one-third of live births. One case of neonatal thyrotoxicosis was identified.

Conclusions: Adherence to the current American Thyroid Association guidelines is poor. Further education of both patients and clinicians is important to ensure that treatment of women during pregnancy after definitive treatment follows the currently available guidelines.

Introduction

Graves' disease, a common cause of thyrotoxicosis, is caused by the presence of antibodies which stimulate the TSH receptor (TRAb)[1]. Patients with Graves' disease are managed with either medical therapy (for example, 12-18 months of carbimazole or propylthiouracil) after which approximately 50% of patients achieve remission[2] or alternatively undergo definitive therapy either by surgery (thyroidectomy) or radioiodine ablation. The choice of treatment is determined by clinical and social factors, patient preference, and available resources.

Graves' disease commonly affects women of reproductive age and pregnancy needs to be considered in managing these patients. Definitive therapy in the form of a total, or near-total, thyroidectomy is expected to result in hypothyroidism in all cases[3] and radioiodine leads to hypothyroidism in 24% at 12 months and 59% at 10 years[4]. Patients with primary hypothyroidism who become pregnant require an early increase in the dose of thyroxine for fetal welfare[5]. This requirement for an increased dose of thyroxine in pregnancy is irrespective of the cause of the hypothyroidism. Overt hypothyroidism in pregnancy has been demonstrated to be associated with adverse pregnancy outcomes such as increased rates of premature birth, low birth weight and fetal loss[6]. Both subclinical hypothyroidism (i.e. normal serum free thyroxine level [FT4] but raised TSH)[7] and maternal hypothyroxinaemia (i.e. FT4 below the 10th centile with normal TSH)[8] may be deleterious to the fetus. The current American Thyroid Association (ATA) guidelines for women with primary hypothyroidism on levothyroxine replacement are to increase the thyroxine dose by approximately 25-30% as soon as the pregnancy is diagnosed and for the TSH to be measured 4-weekly during the first half of the pregnancy to keep the TSH within the pregnancy-specific

reference ranges (0.1-2.5mU/L for the first trimester, 0.2-3mU/L for the second trimester and 0.3-3mU/L for the third trimester)[9].

TRAb levels in patients with Graves' disease may be elevated for months to years following definitive therapy, particularly in patients who have received radioiodine therapy[10]. These antibodies can cross the placenta and may cause fetal thyrotoxicosis[11]. Current ATA guidelines recommend that women who have received radioiodine therapy for Graves' disease avoid pregnancy for 4-6 months following treatment in order to ensure TSH stability[12]. TRAb levels are recommended to be measured in the first trimester and if positive to be measured again at the end of the second trimester[12]. If the TRAb antibodies are positive these women should be referred for monitoring for fetal thyrotoxicosis and fetal goitre[12]. Women are probably only at increased risk however if the TRAb are at least 3-fold the upper limit of the reference range[9].

Our local recommendation has been for women to avoid pregnancy for the first year after radioiodine therapy due to concerns about increased TRAb levels following radioiodine[10], to allow time for further treatment of persistent thyrotoxicosis and to ensure that early hypothyroidism is adequately treated. We advise an early increase in thyroid hormone replacement as soon as the pregnancy is confirmed and four-weekly monitoring of levels as recommended by the ATA guidelines. However, we do not know if these recommendations are being followed or whether additional education in this area is required.

The aims of this study were:

1. To determine pregnancy rates following definitive treatment for Graves' disease
2. To assess gestational thyroid status and determine whether this varies according to treatment modality (surgery versus radioiodine)
3. To determine the frequency of TRAb measurement

Methods

A retrospective chart review of female patients was performed to identify women who had received definitive treatment for Graves' disease at Waikato Hospital, a 600-bed tertiary New Zealand hospital during the time period 1 December 2001 to 30 November 2012 and who were aged less than 45 years at the time of treatment. These patients were then cross-matched against the regional maternity database, hospital clinic letters, as well as hospital and community laboratory results to identify those who had a confirmed pregnancy following treatment. We determined an upper limit cut off of TSH for hypothyroidism during pregnancy of 4mU/L. TRAb were measured using the second generation BRAHMS TRAK human radioimmunoassay (Hennigsdorg, Germany). The reference range for the TRAK assay is: negative <1U/L, 1-1.5 indeterminate; >1.5U/L positive. The study was performed in accordance with the Northern Y regional ethics committee guidelines. Statistical analysis was performed using Chi-square tests or independent t-tests conducted to detect any differences between groups as appropriate, due to the categorical or continuous nature of the variables. All analyses were carried out using SPSS version 21 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY:IBM Corp). A P-value of <0.05 was considered significant.

Results (summarised in Table 1)

A total of 29 women were identified each of whom had at least one pregnancy since receiving definitive treatment for Graves' disease (12 post-thyroidectomy and 17 following radioiodine). There were a total of 49 pregnancies (22 in the surgical group and 27 in the radioiodine group).

The median age at surgery was 28 years (range 21-38 years) and for radioiodine 31 years (range 21-40 years).

TRAb levels were available in all but one patient at diagnosis of Graves' disease and ranged from undetectable to >40U/L pre-treatment (median 24U/L in surgical group and 7.4U/L in radioiodine group).

Surgery group

Sixty-six women of child-bearing age underwent thyroidectomy for Graves' disease during the time period specified. From these, 12 women had 22 pregnancies (6 women had a single pregnancy, 4 women had 2 pregnancies, and 2 women had 4 pregnancies). Seven patients were European, 2 Māori, 1 Pacific Islander and 2 Asian. In nine cases surgery was performed because of failed medical therapy, one due to intolerance of anti-thyroid drugs, one for compressive symptoms (performed during the second trimester), and one for severe thyroid eye disease. There were no cases of permanent hypoparathyroidism or recurrent laryngeal nerve injury.

One patient underwent a subtotal thyroidectomy and was euthyroid throughout on no levothyroxine replacement; the remainder had either a near-total (n=2), or total thyroidectomy (n=9), and all were on levothyroxine replacement. The median time from surgery to diagnosis of pregnancy was 19.6 months but ranged from -3 to 113.1 months. In five pregnancies conception occurred within 12 months following surgery. The median TRAb level at diagnosis of GD was 24U/L (range 2.7->40U/L). In three patients TRAb was >40U/L at diagnosis. In three pregnancies the woman was referred for endocrine assessment. The obstetrics service assessed patients in 10 pregnancies. TRAb levels were measured in 6/22 pregnancies (2/2 for one woman). These ranged from <1U/L (5 pregnancies) to 32U/L. Women with paired TRAb data available from diagnosis and during pregnancy are shown in Table 2.

Rates of euthyroidism in pregnancy

In two pregnancies there were no thyroid function tests performed. After excluding the patient who underwent thyroidectomy during pregnancy, 13/19 (68%) were euthyroid (TSH 0.3-4mU/L) at the time the pregnancy was diagnosed. The median TSH in the surgical group was 2.1mU/L (range <0.1-38.8mU/L). Documented hypothyroidism, at any stage of pregnancy, occurred in 9/19 (47%) pregnancies with the TSH ranging from 4.33-61mU/L. Maternal hypothyroxinaemia (FT4 <10th centile) during the first 20 weeks gestation occurred in 5/18 (28%) of pregnancies.

Pregnancy outcomes

There were 14 live births with a median gestation of 39.4 weeks (range 36.4-41.4 weeks) and a median birthweight of 3115g (range 2465-4410g, birth weight was unavailable in two cases). Two pregnancies ended in miscarriage, there were four

terminations, and in one case the outcome was unknown as the patient moved out of area prior to delivery. In 5/14 live births neonatal thyroid function was tested. There was one case of neonatal thyrotoxicosis (in the patient with known elevated TRAb levels) in which anti-thyroid drug treatment of the neonate was required.

Radioiodine group

One hundred and sixty-five women aged <45years underwent treatment with radioiodine during the time period studied. There were 27 pregnancies from 17 women (10 women had a single pregnancy, 4 had 2 pregnancies, 3 had 3 pregnancies). Seven women were European, 8 Māori, 1 Cook Island Māori, and 1 Indian. TRAb levels were available in 18/19 at diagnosis of GD, median 7.4U/L, (range undetectable to >40U/L).

Around the time of conception the women were on levothyroxine in 15 of the 27 pregnancies, anti-thyroid drugs in 5, and in 7 pregnancies the women were on no thyroid medication.

The median time to pregnancy from radioiodine was 32 months (range 0.5-96.2 months). Six pregnancies were diagnosed within 12 months of radioiodine administration (4 of which were within 6 months of treatment).

Endocrine assessments were performed in 12 pregnancies (but in 4 of these the patients were still under the care of an endocrinologist at the time of pregnancy) and referral to a hospital obstetric service occurred in 18 pregnancies.

TRAb was measured in 11 pregnancies. These ranged from <1 to >40U/L with a median of 3.2U/L. Five patients had TRAb levels greater than 3-fold the upper limit of the reference range (ranging from 14 to >40U/L). Women with paired TRAb data available from diagnosis and pregnancy are shown in Table 2.

Rates of euthyroidism in pregnancy

The median TSH at diagnosis of pregnancy was 4.5mU/L (range <0.01-59.8mU/L). No thyroid function measures were performed in 4 pregnancies. In 5/23 pregnancies (22%) the patient was euthyroid around the time the pregnancy was diagnosed. Hypothyroidism, at any stage during pregnancy, occurred during 12/23 (52%) pregnancies with a TSH ranging from 4.1-81.8mU/L. Maternal hypothyroxinaemia during the first 20 weeks gestation was present in 7/24 (29%) pregnancies).

Pregnancy outcomes

There were no cases of fetal thyrotoxicosis diagnosed. Six pregnancies ended in miscarriage, there were two terminations (one of which was for a major congenital anomaly – hypoplastic left ventricle in a woman on propylthiouracil), and 21 live births (including two sets of twins). Neonatal thyroid function tests were performed on 7 babies. There were no cases of neonatal thyrotoxicosis or hypothyroidism diagnosed. Of the five pregnancies with markedly elevated TRAb levels: there were two miscarriages, one termination, one neonate had normal thyroid function and in the other no neonatal thyroid function tests were measured. Median birth weight was 2870g (range 1520 – 3710g), weight was unavailable for 8 births. Median gestation was 38.4 weeks (range 32-40.7 weeks) (missing data in 7 cases).

Discussion

The optimal management of women with Graves' disease who desire a future pregnancy is uncertain. A recent Danish study has raised additional concerns about the safety of anti-thyroid drugs in pregnancy, including propylthiouracil[13]. It is possible that definitive treatment prior to conception may be preferable to avoid potential teratogenicity of anti-thyroid drugs in early pregnancy[14]. However, there is limited data as to which option, radioactive iodine or surgery, is preferable in these women with Graves' disease.

In this small retrospective study we have identified a high rate of hypothyroidism during pregnancy (both at time of the pregnancy first being diagnosed and also during the subsequent gestation) irrespective of the treatment performed and a low rate of measurement of TRAb and referral of patients for endocrine assessment. Despite this there was only one case of neonatal thyrotoxicosis identified in this small cohort.

Pregnancy reference ranges for thyroid function tests are different from the non-pregnant normal range and have changed over the time period studied. Our laboratory does not give pregnancy-specific reference ranges and for the purposes of this study, given the time period studied we used a higher TSH cut-off of 4mU/L than that currently recommended (2.5mU/L for the first trimester and 3mU/L for the second and third trimesters). Despite this over a third of all patients had an elevated TSH at the time the pregnancy was diagnosed. More patients were euthyroid at the time of pregnancy diagnosis in the surgical group (68%) when compared to the radioiodine group (22%). Patients who have undergone a total or near-total thyroidectomy for Graves' disease and who are compliant with their medications are usually euthyroid on a stable dose of thyroid hormone replacement within the first 6-12 weeks after

surgery (Elston *et al.,* unpublished data) and the dose requirement does not typically change appreciably over time apart from during pregnancy. Patients who have undergone radioiodine therapy may remain thyrotoxic after a single dose as demonstrated here in which almost 20% of patients were still on anti-thyroid drugs around the time of conception. The remainder have a less predictable onset of hypothyroidism and may need increasing thyroid hormone replacement doses in the months to years after therapy as more endogenous thyroid function is lost. As such, one would expect that patients who have undergone surgery should have a higher rate of euthyroidism after the first three months following treatment as compared to those who have undergone radioiodine therapy. The higher rate of euthyroidism in the surgical group in this study is consistent with this hypothesis, despite the fact that in our unit surgery is often performed in young patients with poorly controlled thyrotoxicosis who may be less compliant than those who receive radioiodine. In addition, lower rates of euthyroidism were present in the radioiodine group despite approximately one-quarter of the radioiodine group being euthyroid on no therapy prior to pregnancy. Of concern in some pregnancies no prenatal thyroid function testing was performed in this study.

Surgical patients appeared more likely to have negative TRAb levels than those who had received radioiodine although this didn't reach significance possibly due to the small numbers in this study. This is consistent with the findings by Laurberg *et al.* where TRAb positivity may continue for many years following radioiodine[10]. The single surgical patient with an elevated TRAb level was receiving whole thyroid extract at presentation. This thyroid preparation may provide ongoing antigenic stimulation and explain why the TRAb level was still markedly elevated in this case.

Overall, when considering the TRAb data and the higher rates of euthyroidism around the time of conception, surgery may be the preferred option in this group if it can be performed safely by an experienced, high volume thyroid surgeon.

There are a number of limitations of this study including the small numbers and the likelihood that there were additional pregnancies post-definitive treatments not captured. We did not have accurate data on the dose of levothyroxine that patients were on and the timing and amount by which this was increased. Data on pregnancy outcomes was limited and we have no information on the subsequent neonatal development, in particular whether there was any intellectual impairment. Despite this, this small study shows that adherence to the current ATA guidelines is poor. It is possible that the low rates of thyroid function testing could be contributed to by the shift away from general practitioners and obstetricians to midwives as lead maternity carers in New Zealand. Midwives are currently unable to request thyroid function tests and may be less aware of the relevance of a previous diagnosis of Graves' disease especially when treatment for thyrotoxicosis has occurred in the distant past. We recommend that a clear advice statement detailing the recommended management in pregnancy is included following definitive therapy for thyrotoxicosis for all women who have undergone treatment for Graves' disease and who may have subsequent pregnancies. In addition a clinical alert could be added to the hospital and general practice electronic records. Further education of both patients and the clinicians involved in their care is required. Pre-pregnancy counseling of patients with a history of Graves' disease should be considered; for example by an experienced endocrine specialist nurse. In those patients who are TRAb negative and are either euthyroid on no treatment or are well-controlled on levothyroxine replacement, monitoring and

adjustment of the dose during pregnancy should be able to be performed by the general practitioner, with advice from the endocrine service as needed. Women with a positive TRAb level in the first trimester should be referred to an endocrinologist, obstetric medicine specialist or obstetrician who has experience with thyroid disease for assessment.

Conclusions

Adherence to the current ATA guidelines for monitoring of women who have previously received definitive treatment for Graves' disease is poor. Additional education and local guidelines are required in this area to optimise patient and baby outcomes.

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Table 1 Comparison of pregnancies after surgery and radioiodine

	Surgery (n=12, 22 pregnancies)	Radioiodine (n=17, 27 pregnancies)	
Median age at definitive treatment (range)	28 years (21-38)	31 years (21-40)	
Median time from definitive treatment to pregnancy (range)	19.6 months (-3-113.1)	32 months (0.5-96.2)	P=0.224
Not referred endocrinology (%)	19/22 (86%)	15/27 (56%)	P=0.02
Not referred obstetrics (%)	12/22 (55%)	9/27 (33%)	P=0.126
Not referred to endocrinology or obstetrics	11/22 (50%)	6/27 (22%)	P=0.03
TRAb not measured (%)	16/22 (73%)	16/27 (59%)	P=0.382
TRAb >3x ULN	1/6	5/11	P=0.261
Median TSH at pregnancy diagnosis (range)	2.1mU/L (0.1-38.8)	4.5mU/L (<0.01-59.8)	P=0.21
TSH >4mU/L at pregnancy diagnosis	3/19 (16%)	12/23 (52%)	P=0.014
Euthyroid around time conception	13/19 (68%)	5/23 (22%)	P=0.002
TSH >4mU/L at any stage during pregnancy	9/19 (47%)	12/24 (50%)	P=0.853

Highest TSH detected during pregnancy in hypothyroid patients	4.33-61mU/L	4.1-81.8mU/L	P=0.919
FT4 <10th centile during 1st 20 weeks gestation	5/18 (28%)	7/24 (29%)	P=0.987
Pregnancy outcome	14 live births 2 miscarriages 4 terminations 1 not known	21 live births (2 sets twins) 6 miscarriages 2 terminations (one for major congenital anomaly)	

TRAb = TSH receptor antibodies

Table 2. Paired TRAb data from diagnosis of Graves' disease and pregnancy

Patient	Treatment	Months between treatment and pregnancy	TRAb at Graves' diagnosis (U/L)	TRAb measurement in pregnancy (U/L)	Outcome
1	TT	45.1	>40	32	Neonatal thyrotoxicosis
2	TT	17.2	>40	<1	Live birth
3	NT	46.1	37	<1	Miscarriage
4	TT	13.1	24	<1	Live birth
5A	TT	19.6	12	<1	Live birth
5B	TT	4.2	12	<1	Live birth
6A	RAI	4.5	>40	>40	Miscarriage
6B	RAI	10.3	>40	14	Live birth*
7	RAI	9.6	27	<1	TOP*
8	RAI	94.7	24	<1	Live birth
9	RAI	0.5	22	14	TOP
10	RAI	3.1	8.2	16	Live birth
11	RAI	31.0	7.2	3.2	Live birth
12	RAI	92.8	5.9	<1	Live birth
13	RAI	0.7	3.5	26	Miscarriage
14	RAI	45.9	3.4	2.3	Live birth
15	RAI	33.2	1.7	<1	Live birth

TT = total thyroidectomy; NT = near-total thyroidectomy; RAI = radioiodine; patients with >1 pregnancy are defined as 5A, 5B etc; TOP = termination of pregnancy; *congenital heart disease and received anti-thyroid drugs during pregnancy