Table 1 Treatment preference in a woman diagnosed with Graves disease seeking pre-pregnancy counseling

Recommendation	Responders n (%)
Propylthiouracil	162 (52)
Methimazole/ carbimazole	123 (40)
Refer for definitive treatment with surgery before pregnancy	14 (4)
Refer for definitive treatment with radioiodine before pregnancy	12 (4)

Table 2 Different tests responders use to monitor antithyroid drugs dose in pregnancy

Tests	Responders n (%)
TSH and FT4	166 (53)
TSH, FT4 and FT3	62 (20)
FT4 alone	29 (9)
TSH, TT4, TT3	29 (9)
TSH and TT4	15 (5)
Others	12 (4)

FT4, free thyroxine; FT3, free triiodothyronine; TT3, total T3; TT4, total T4

Table 3 Target thyroid function tests in hyperthyroid pregnant women on antithyroid drugs

Targets	Responders n (%)
Low TSH and FT4(or TT4) in the upper end of normal range	197 (66)
TSH and FT4(or TT4) in the normal range	68 (24)
Low TSH and FT4(or TT4) in the normal range	16 (6)
Others	10 (4)

FT4, free thyroxine; FT3, free triiodothyronine; TT3, total T3; TT4, total T4

tion tests were in hyperthyroid range, with negative thyroid antibodies. Nearly 40% of physicians chose follow up, without treatment and 52% preferred treatment with propylthiouracil; of these 28% would change to methimazole/ carbimazole after first trimester (Table 4).

Checking of TSH receptor antibodies

Forty-three percent of responders did not routinely check TSH receptor antibodies (TRAb) in pregnant women with Graves' disease treated with antithyroid drugs (Table 5). Of around 53% who would check TRAb in the first trimester, 32% would repeat TRAb in the third trimester, only if positive in the first trimester.

Management of subclinical hyperthyroidism

Physicians were then asked if they recommend treatment or follow up of subclinical hyperthyroidism in pregnancy. About 80% of responders preferred follow up and 20% choose treatment.

Fetal ultrasound monitoring

Responders' approaches to ultrasonography monitoring of fetus in antithyroid treated women with Graves' disease varied. Nearly 55% of responders monitored the fetus routinely using ultrasound scan; 20% would do so in only when the mother was positive for TRAb, while 25% would not prescribe ultrasound monitoring.

Management of postpartum hyperthyroidism

There was inconsistency in responders' recommendations on how to manage a postpartum lactating woman with relapse of Graves' hyperthyroidism. Seventy-eight percent would start antithyroid medication (54%MMI and 24% PTU) and continue lactation; however, the remaining 22% would initiate antithyroid drugs (MM: I6% and PTU: 6%) but would stop lactation (Table 6).

Table 4 Responders' recommendations for treatment or follow up of an eight week pregnant woman with gestational thyrotoxicosis

Recommendation	Responders n (%)
Follow up, no treatment	127 (40)
Propylthiouracil in first trimester, then change to methimazole/ carbimazole	86 (28)
Propylthiouracil	74 (24)
Methimazole/ carbimazole	7 (2)
Others*	23 (6)

*Others include those who chose symptomatic therapy like as β-blocker and hydration therapy

Table 5 Routine checking of TSH receptor antibodies (TRAb) in a pregnant hyperthyroid woman

Response	Responders n (%)
No	135 (43)
Yes, in the first trimester, and if positive in the third trimester	101 (32)
Yes, in each trimester	34 (11)
Yes, in the first and third trimesters	32 (10)
Others	21 (4)

Table 6 Responders' recommendations to a postpartum lactating woman with Graves' hyperthyroidism

Recommendation	Responders n (%)
Start methimazole/ carbimazole but continue lactation	169 (54)
Start propylthiouracil but continue lactation	76 (24)
Start methimazole/ carbimazole and stop lactation	53 (16)
Start propylthiouracil and stop lactation	23 (6)

Discussion

The present study reports, for the first time, current clinical practices for management of hyperthyroidism during pregnancy in Asia. Guidelines from the ATA and ES published in 2011 and 2012 are alike in many aspects, and no disagreement or controversy have been found between the two guidelines [13]. Generally, there was a high degree of consistency between clinical practices of Asian physicians and guidelines, such as the initiation of antithyroid treatment in the first trimester, tests to monitor drug therapy and thyroid function for a pregnant hyperthyroid woman, lack of treatment of subclinical hyperthyroidism in pregnancy and management of postpartum hyperthyroidism.

Maternal hyperthyroidism diagnosed during pregnancy should be corrected, because hyperthyroidism has detrimental effects on both mother and fetal health [3-7]. Based on current data, MMI and PTU have equal efficacy in the treatment of pregnant women. The use of PTU has been recommended by both organizations during the first trimester, followed by MMI from second trimester onwards to the end of pregnancy. The greatest concern in the use of MMI in the first trimester of pregnancy is related to teratogenic effect called "methimazole embryopathy" that induces choanal or esophageal atresia, and dysmorphic faces [14-16]. On the other hand PTU hepatotoxicity that may occur anytime during treatment has caused concern regarding its use as the first line drug for treatment of hyperthyroidism, limiting its use to the first trimester of pregnancy [17-18]. Endocrine Society guidelines state that MMI may be administered if patient has an adverse response or cannot tolerate PTU or if this drug is not available. In addition, recommendations for change of PTU to MMI after first trimester has caused concerns for some thyroidologist; therefore the ES recommends that practitioners should use their clinical judgment in switching patients from one drug to another [11]. In the present survey, 96% of responders begin treatment of hyperthyroid pregnant women with

PTU and almost one third (38%) of them will switch to MMI after the first trimester.

For pre-conception counseling of a Graves' patient, 92% of Asian clinicians advised antithyroid drugs (52% PTU and 40% MMI) and only 8% will ablate the thyroid (radiation or surgery) before allowing the patient to consider pregnancy, this is in agreement with ATA, which recommends the use of MMI/CMZ and change to PTU once the pregnancy is confirmed [10]; however, it is not clear whether this approach would prevent MMI/CMZ associated embryopathy. It is noteworthy that following treatment of hyperthyroidism with antithyroid drugs or surgery, serum TRAb will decrease to normal values in the majority of patients [19] and TRAb titers will increase during the first year after radioiodine therapy followed by a subsequent gradual fall [20, 21]; however, even 4-6 years after radioiodine therapy many patients are still TRAb positive [22], an issue which is of utmost importance, as a high titer of TRAb is a risk factor for fetal and neonatal hyperthyroidism. Therefore clinicians advise women to postpone pregnancy for more than 6 month after ablation with ^{131}I.

More than half of the clinicians monitor antithyroid drug treatment by TSH and FT4 levels and another 20% with TSH, FT4 and FT3. Determination of serum TT3 levels used by 9% of physicians is not recommended as it has been reported that normalization of maternal TT3 leads to elevated serum TSH in infants [23]; in addition, 66% responders target achieving low TSH and FT4 (or TT4) in the normal range during such therapy. This is also considered as good practice, since guidelines recommend TSH and FT4 assessment as the main tests for such monitoring and advise aiming for FT4 within the upper end of normal range or just above the upper limit of normal, while utilizing the smallest possible dose of anti thyroid drugs during pregnancy [10, 11]. It was distressing to find that 24% of Asian clinicians target normal range for serum TSH and FT4 concentrations, an approach which could increase the chance of fetal goiter and hypothyroidism [24]. Inconsistency in test combinations used by the responders (Table 2) for monitoring anti thyroid drugs' doses during pregnancy may to some extent be due to the availability of tests in different settings. On the other hand, despite the controversy on the accuracy of FT4 assays during pregnancy about 82% of physicians used FT4 alone or in combination with other tests [25, 26].

Differentiation of Graves' disease and gestational thyrotoxicosis may be difficult during the first half of pregnancy. Severe nausea, vomiting, weight loss and palpitation, along with negative thyroid antibodies favor gestational thyrotoxicosis, a self limiting condition which is less severe than Graves' disease [27, 2]; however, current clinical evidence of autoimmunity, typical goiter, ophthalmopathy and TRAb supports the diagnosis of Graves' disease. In most cases of gestational thyrotoxicosis no treatment is indicated; antithyroid drugs are not indicated as serum T4 returns to normal around 14-18 weeks of pregnancy and the available evidence shows no improvement of pregnancy outcomes in treated cases [28, 29]. This approach was selected only by 40% of responders, while 54% preferred treatment with antithyroid medications.

Increased serum TRAb is a risk for fetal and neonatal hyperthyroidism and can be detected in up to 95% of hyperthyroid pregnant women with Graves' disease. The titer decreases with the progression of pregnancy. Routine measurement of TRAb in a hyperthyroid pregnant woman under antithyroid drug therapy is recommended by major professional endocrine organizations. Mothers with active hyperthyroidism, a history of radioiodine therapy, thyroidectomy for hyperthyroidism or delivery of a hyperthyroid infant should undergo further evaluation [30-32]. The prevalence of fetal and neonatal hyperthyroidism ranges between 1-5% in women with current or past history of Graves' disease and lack of treatment will increase morbidity and mortality in the fetus and infants [33, 34]. Serum TRAb titers increase following ^{131}I therapy and may remain high for many years thereafter. It is recommended to measure TRAb by 24-28 weeks of gestation to detect pregnancies at risk. A titer over 3 times that of upper normal limits warrants close follows up of the fetus. It is worrying that 43% of clinicians surveyed indicated that they do not routinely check TRAb, mainly due to lack of availability of this test.

Although there is not enough evidence to recommend or advise against the use of thyroid ultrasound in differentiating the cause of hyperthyroidism in pregnancy, it has been recommended to use ultrasound scan for monitoring of fetus in women with Graves' disease under antithyroid drug therapy; ultrasonography should be performed in those with uncontrolled hyperthyroidism or with high TRAb titers, both of which can compromise fetal well being [35]. Only 25% of Asian responders did not adhere to this recommendation.

In this survey, for the management of hyperthyroidism in a postpartum lactating woman, 78% of the

Table 7 Comparison of Asian and European responders in management of hyperthyroidism in pregnancy

Variables	Responders (%)	
	Asian[†]	European[*]
Pre-pregnancy approach for a newly diagnosed Graves' disease		
Propylthiouracil	52	42
Methimazole/ carbimazole	40	36
Surgery	4	9
Radioiodine	4	13
Treatment for Graves' hyperthyroidism in first trimester[†]		
Propylthiouracil	58	53
Propylthiouracil in the first trimester then Methimazole/ carbimazole	38	34
Methimazole/ carbimazole	4	12
Tests to monitor antithyroid drugs dosage in pregnancy		
TSH and FT4	53	27
TSH, FT4 and FT3	20	41
FT4 alone	9	8
TSH, TT4, TT3	9	4
Target thyroid function in treated hyperthyroidism		
Low TSH and FT4(or TT4) in the upper end of normal range	66	64
TSH and FT4(or TT4) in the normal range	24	13
Low TSH and FT4(or TT4) in the normal range	6	19
Treatment for gestational thyrotoxicosis		
Follow up, no treatment	40	50
Propylthiouracil, in first trimester, then methimazole/ carbimazole	28	17
Propylthiouracil	24	18
Methimazole/carbimazole	2	7
Checking TRAb in hyperthyroid pregnant		
No	43	11
Yes, in the first trimester, and if positive in the third trimester	32	42
Yes, in each trimester	11	17
Yes, in the first and third trimester	10	15
Postpartum lactating woman with Graves' hyperthyroidism		
Methimazole/ carbimazole but continue lactation	54	38
Propylthiouracil but continue lactation	24	30
Methimazole/ carbimazole and stop lactation	16	21
Propylthiouracil and stop lactation	6	3

[*]Ref no: [12]; [†]Data derived from current survey

responders chose antithyroid therapy and continuing lactation; however, 24% of them preferred treatment with PTU. ATA and ES both recommended treating lactating hyperthyroid women with MMI, because treatment with PTU may cause liver damage [17]. It has been shown that MMI therapy up to 30 mg daily does not cause any alterations in thyroid function and mental or physical development of children, aged 48-86 months, breast-fed by lactating hyperthyroid mothers [36, 37]. Checking thyroid functions of breast-feeding infants of mothers taking antithyroid drugs is recommended. Prescribing the treatment in divided doses immediately after breast feeding is also suggested. It is unfortunate, however that 22% of responder physicians surveyed recommended stopping lactation while treating the lactating mother with antithyroid medications.

Compared to the survey reported management of hyperthyroidism in pregnancy in Europe [12], the results of this study did not differ greatly in various aspects of management of hyperthyroidism during pregnancy except for TRAb monitoring, which unfortunately most Asian physicians did not check it routinely in hyperthyroid pregnant women, contrary to European clinicians who also assessed FT3 more in combination with TSH and FT4 for monitoring the dose of anti thyroid drugs (Table 7).

There are several limitations that should be considered in analyzing the results of this survey. First, the clinician responders were not randomly selected from all countries of this large continent (Asia) and may not represent all physicians in Asia. The Asian – Ocean Thyroid Association has over 4000 members of which just 321 practitioners participated in this study which may not be representative of all; however we did not receive responses from some of these practitioners. Our results are hence somewhat limited as regards generalization. Second, variations in the clinical practices of different countries especially, those with larger number of responders, could have influenced the overall results of this study. Third, majority of participants of this survey were endocrinologists, and the approach of other healthcare professionals for management of hyperthyroidism in pregnancy, may differ from that of the endocrinologists surveyed; on the other hand, none of the responders were obstetricians, although some of them do manage these patients in multidisciplinary settings. We believe that this survey with participants from 21 Asian countries may provide a snapshot of current practices in the management of hyperthyroidism in Asia, however larger surveys are clearly warranted.

It is concluded that although most Asian clinicians adhere to the clinical practice guidelines recommended by major professional organizations, the lack of adherence of a considerable number of physicians should be considered in the strategic plans of continuing medical education in related professional societies of various countries of Asia.

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Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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ORIGINAL

Screening and management of hypothyroidism in pregnancy: Results of an Asian survey

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Abstract. Maternal hypothyroidism in pregnancy is associated with several adverse outcomes. The American Thyroid Association and the Endocrine Society Guidelines for the management of thyroid diseases in pregnancy were published in 2011 and 2012, respectively; however, impact of the guidelines in routine clinical practice is unknown. We therefore carried out a survey to study current practices in the screening and management of hypothyroidism in pregnancy. We collected completed questionnaire survey based on clinical case scenarios from 321 members of the Asia-Oceania Thyrpid Association (AOTA). Responses from 310 clinician members (from 21 Asian countries) were analyzed. For a woman with hypothyroidism planning pregnancy, 54% favored testing thyroid function before adjusting the dose, whilst 32% recommended increasing the dose of L-thyroxine (L-T_4) as soon as pregnancy is confirmed. For a pregnant woman with newly diagnosed overt hypothyroidism, most responders initiated a full dose of L-T_4. One half of responders used serum TSH and free T_4 to monitor the dose of L-T_4. Although the target of thyroid function tests that responders aimed to achieve with L-T_4 was inconsistent, but a majority aim to keep TSH within recommended trimester specific range. Twenty-one % responders or their institutions screened all pregnant women for thyroid dysfunction, 66% performed targeted screening of only the high-risk group, whilst 13% did not carry out systemic screening. Majority of responders practices within recommendations of major professional societies; however, there is wide variation in the clinical practice in the treatment and screening of hypothyroidism during pregnancy in Asia.

Key words: Hypothyroidism, Screening, Survey, Pregnancy

MATERNAL thyroid hormone deficiency is common in pregnancy. Hypothyroidism during pregnancy is associated with several adverse outcomes, including gestational hypertension, miscarriage, placental abruption, premature birth, fetal growth retardation, and impaired neuropsychological development of the offspring [1]. Optimal treatment of maternal hypothyroidism is important to achieve a successful pregnancy outcome; however, detection and treatment of maternal hypothyroidism in pregnancy remain controversial [2, 3]. Two guidelines from American Thyroid Association (ATA) and Endocrine Society (ES) for the management of thyroid diseases, including hypothyroidism, in pregnancy were published in 2011 and 2012 [3, 4]. However, it is not clear as to what extent clinicians follow these guidelines in their routine clinical practice. Therefore, we have carried out a sur-

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Abbreviations: ATA, American Thyroid Association; ES, Endocrine Society; AOTA, Asia-Oceania Thyroid Association; AFES, Asian Federation of Endocrine Societies

vey of Asian members of the Asia-Oceania Thyroid Association (AOTA) to study the prevalent current practices relating to the screening and treatment of hypothyroidism during pregnancy in Asia.

Subjects and Methods

An electronic questionnaire survey was emailed to members of the AOTA Council and presidents of member endocrine societies in March, 2013 asking them to distribute the questionnaire to endocrinologists in their countries. This was followed by a reminder email in September 2013. In addition, during Asian Federation of Endocrine Societies (AFES) meeting in Jakarta Indonesia, November 13-16, 2013, questionnaire was distributed to endocrinologists, internists and general practitioners attending the meeting. The survey was based on clinical case scenarios, and asked questions about the clinical practices related to the management of hypothyroidism and hyperthyroidism in pregnancy. Only results concerning the treatment and screening of hypothyroidism during pregnancy are presented in this report. 'The survey questionnaire was validated in a recent survey of members of the European Thyroid Association [5]. In total, there were 16 multiple choice questions on screening thyroid function and management of hypothyroidism during pregnancy. Responders were asked to select single (13 questions) or multiple (3 questions) answers. However, for most questions, they were also able to provide their own answer if it was not included in the questionnaire. A copy of the questionnaire is available on request from the authors.

All frequencies were adjusted on a 100% basis excluding the non-responders. Results are predominantly presented as percentages, rounded up to a whole number in the text and up to one decimal point in the tables.

Results

Characteristics of responders

We received 321 responses from 21 countries. Nine responders were not involved in the management of thyroid diseases in pregnancy. Two responders were from a non-Asian country (Australia), and were not included in the current analysis. Therefore, responses from 310 responders practicing in 21 Asian countries were analyzed. There were 277 (89%) endocrinologist and 33 (11%) internists and general practitioners. The countries with ten or more responders included: Iran (44), Indonesia (43), Philippines (40), Taiwan (38), Malaysia (23), Japan (14), Singapore (12), India (11), Thailand (11), and Srilanka (10).

Screening pregnant women for thyroid dysfunction

Whilst 21% of responders or their institutions screened all pregnant women for thyroid dysfunction, 66% performed targeted screening of only the high-risk group and 13% did not carry out systemic screening. More than 80% of responders carrying out the targeted screening used personal history of thyroid disease, presence of goiter, history of a thyroid disease in first degree relatives, previous thyroid surgery, history of neck irradiation and history of miscarriage as risk factors to classify the 'high-risk' group (Table 1).

Responders' timing of screening thyroid function in pregnancy was variable; 51% screened in a pre-pregnancy visit, 36% in the first antenatal visit, and 11% did not have specific timing. Table 2 shows tests used for screening a pregnant woman for thyroid dysfunction. About half use TSH and free or total T_4 and another half order TSH alone or in combination with thyroid antibodies. Responders were asked whether they would routinely repeat thyroid function tests during the pregnancy if the initial screening was normal; 27% would routinely repeat the tests in later pregnancy, 53% would repeat only in the presence of thyroid antibodies, and 32% would not repeat.

Responders were asked at when they would start L-T_4 replacement. They used varied criteria to start L-T_4 replacement following the screening: TSH above the trimester-specific reference range, 36%; TSH above the population reference range, 5%; TSH above 2.5 mIU/L, 33%; TSH above 5 mIU/L, 16% and free T_4 (FT_4) below the trimester-specific reference range, 10%.

Treatment of hypothyroidism in pregnancy

Physicians were asked what dose of L-T_4 they would start for a 24-year-old woman, who is 12 weeks pregnant and has just been diagnosed with overt hypothyroidism. Responders suggested variable doses to initiate L-T_4 replacement for the woman, although most recommended starting on a full replacement dose, empirically or based on pregnancy adopted body weight (Table 3). Only 19% of responders recommended a small starting dose of L-T_4 (25–50 μg/daily), and 3% suggested the starting dose based on pre-treatment TSH concentration.

Although a majority of responders (84%) would not endorse abortion in overt hypothyroid patient in the late first trimester, 8% would recommend abortion, and a further 8% would discuss the option of abortion.

There was inconsistency in responders' recommendations on how to adjust the dose of L-T_4 in a hypothyroid woman, who is planning pregnancy (Table 4). About 54% would first check thyroid function tests before adjusting the dose. Nearly 32% of responders would recommend the woman to increase the dose of L-T_4 by 30-50% as soon as pregnancy is confirmed, only 11% would increase L-T_4 dose by two tables per week as soon as pregnancy is confirmed (Table 4).

Eighty two percent of responders used 4 different combinations of tests to monitor the dose of L-T_4 in pregnancy (Table 5), with almost half choosing TSH and free T_4 measurements. The target thyroid function test results that responders aim to achieve with L-T_4 in pregnancy was inconsistent, although a majority of responders (63%) aim to keep TSH <2.5 mIU/L in the first trimester and <3 mIU/L in the later trimesters (Table 6). Almost one fourth of the responders wanted

Table 1 Risk factors used by responders carrying out targeted screening of pregnant women for thyroid dysfunction to stratify the high-risk group

Risk factors	Responders n (%)
Personal history of a thyroid disease	194 (98)
Personal history of an autoimmune disease	147 (74)
History of a thyroid disease in first degree relatives	171 (86)
Presence of goiter	188 (95)
History of neck irradiation	169 (85)
Previous thyroid surgery	170 (88)
Obesity	79 (40)
Family history of an autoimmune disease	147 (74)
History of miscarriage	166 (84)
History of infertility	138 (70)
Notion of inadequate iodine nutrition	137 (69)

Table 2 Tests used for screening pregnant women for thyroid dysfunction

Tests	Responders n (%)
TSH alone	88 (29)
Free T_4	45 (15)
Total T_4	7 (2)
TSH and free or total T_4	137 (46)
Free or total T_3	5 (2)
TSH and thyroid antibodies	92 (30)
Urinary iodine excretion	3 (<1)

Table 3 Starting dose of L-thyroxine (L-T_4) in a pregnant woman diagnosed with overt hypothyroidism (TSH 86mIU/L) at 12 weeks gestation

Starting dose of L-T_4	Responders n (%)
Start on a small dose (*e.g.* 25–50μg daily)	61 (19)
Start on a full dose (*e.g.* 100–125μg daily)	104 (33)
Start on a dose based on pregnancy adopted body weight	50 (15)
Start for a few days on a double dose (*e.g.* 200μg daily), then a dose based on pregnancy adapted body weight	96 (30)
Start on a dose based on pre-treatment TSH level	13 (3)

Table 4 Responders' recommendations to a hypothyroid woman treated with L-T_4 (TSH 2.4mIU/L), who is planning pregnancy

Recommendations	Responders n (%)
	Planning pregnancy
Increase L-T_4 dose by 30–50% as soon as pregnancy is confirmed	101 (32)
Increase L-T_4 dose by two tablets per week as soon as pregnancy is confirmed	34 (11)
Check thyroid function as soon as pregnancy is confirmed	169 (54)
Increase L-T_4 dose before pregnancy	9 (3)

Table 5 Different tests responders use to monitor L-T_4 dose and to screen thyroid dysfunction in pregnancy

Tests	Responders n (%)
	Monitoring L-T_4 dose
TSH alone	43 (14)
TSH, FT_4	139 (46)
TSH, FT_4, FT_3	44 (14)
TSH, FT_4, TT_3	16 (4)
TSH and TT_4	27 (8)
Trimester specific TSH ranges	16 (4)
Others	44 (14)

FT_4, free thyroxine; FT_3, free triiodothyronine; TT_3, total T_3; TT_4, total T_4

Table 6 Target thyroid function test results in hypothyroid pregnant women on L-thyroxine replacement

Targets	Responders n (%)
TSH and FT_4 within laboratory reference range	26 (8)
TSH and FT_4 within the trimester-specific reference range	78 (25)
TSH <2.5 mIU/L in the first trimester and <3 mIU/L in the second and third trimesters	189 (63)
Other variable TSH, FT_4, and FT_3 targets	12 (4)

FT_4, free thyroxine; FT_3, free triiodothyronine

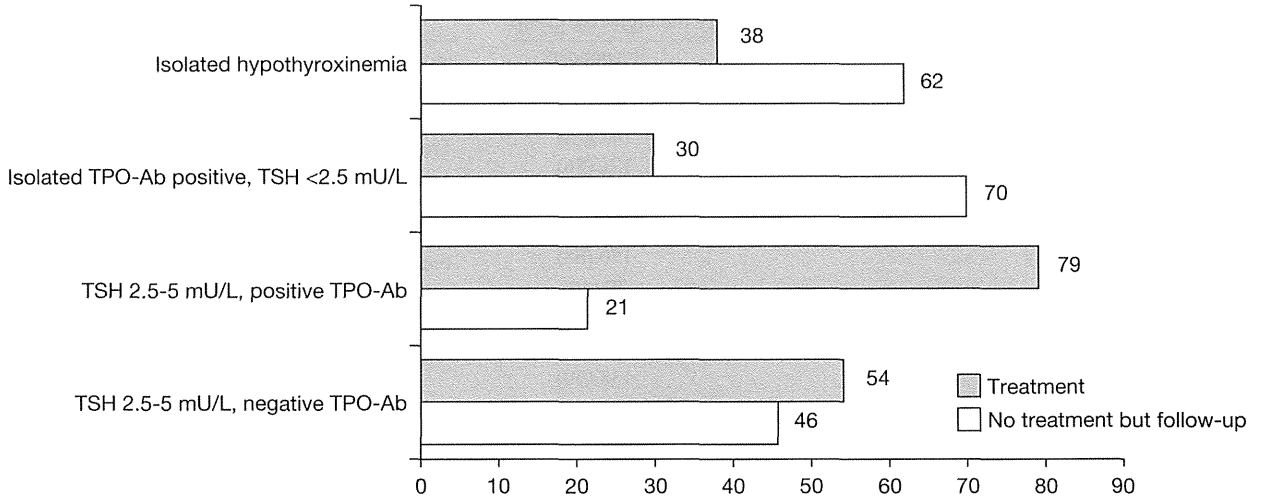

Fig. 1 Percentage of responders recommending treatment or follow-up only for various outcomes following thyroid screening in pregnancy

to keep both TSH and free T_4 within the trimester-specific reference range.

Responders' approach to various outcomes of screening thyroid function in pregnancy was variable (Fig. 1). Thirty-Eight percent of the responders would treat isolated hypothyroxinemia; whilst 62% would follow-up without treatment; 30% would treat isolated thyroid antibodies positive with normal TSH; 79% would treat TSH level >2.5 (but <5 mIU/L) with positive thyroid antibodies; and 54% would treat TSH level>2.5(but <5 mIU/L) with negative antibodies and no other thyroid disease.

Discussion

This survey, for the first time reports clinical practices relating to the treatment and screening of maternal hypothyroidism in pregnancy in Asia. The American Thyroid Association [3] and the Endocrine Society Guidelines [4] had been published 1 and 2 years prior to the time of the survey. There was a high degree of consistency between the guidelines and some aspects of the responders' clinical practice, such as the target thyroid function for pregnant hypothyroid women on L-T_4 treatment, and targeted screening of pregnant women for thyroid dysfunction.

Universal screening for thyroid dysfunction in pregnant women has been hotly debated in recent years [6, 7], ATA and some members of ES have recommended targeted case-finding, although some of the latter society members recommended universal screening in pregnancy [3, 4]; although several studies have shown that the targeted case-finding approach misses a signif-

icant proportion of pregnant women with thyroid dysfunction [7, 8].

The association between mild maternal thyroid hormone deficiency in pregnancy and impaired neuropsychological development of the offspring [9, 10] as well as other adverse obstetric outcomes have been reported previously [11]. Only one randomized controlled trial has suggested that identification of mild thyroid hormone deficiency in the low-risk pregnant women by screening and treatment with L-T_4 may reduce obstetric complications [6]. In the present survey, 66% of the responders or their institutions perform targeted screening of only the high-risk group, in accord with recommendations of ATA and some members of ES. It is, however, unfortunate that 13% of responders do not carry out systematic screening.

There are several other uncertainties surrounding screening thyroid function in pregnancy in the current study. These include timing, type of tests, and criteria for starting treatment. Half of the responders reported that they screened thyroid function during pre-pregnancy visit, but 36% would do so in the first antenatal visit. One could argue that the identification and treatment of hypothyroidism in the first antenatal visit may be too late to prevent the associated adverse effects; however, implementing systemic screening of thyroid function in all women contemplating pregnancy would be an enormous challenge, especially for developing countries of Asia. A recent study has suggested that, if screening is limited to first trimester, over 40% of pregnant women with hypothyroidism could be missed [12] and 68% of our responders agreed that thyroid function tests should be repeated in later stages of pregnancy if the initial screening was normal, 27% routinely and 41% in the presence of thyroid antibodies.

Maternal hypothyroidism diagnosed in pregnancy should be corrected as promptly as possible [3, 4, 6] because maternal thyroid hormones play an important role in the early fetal neurological development [9, 13]. In this survey, most responders initiated full replacement dose of L-T_4 for pregnant women newly diagnosed with overt hypothyroidism. However, a small minority still started on a small dose of L-T_4 (Table 1). It is unfortunate that 16% of responders would recommend or discuss the option of abortion in overt hypothyroid pregnant patients in the first trimester, despite the absence of published studies to support such a practice. Indeed, a study has found that IQs of the children whose mothers had been hypothyroid during early pregnancy were normal and similar to those of their siblings who were not exposed to maternal hypothyroidism in utero [14]. Most recent antenatal thyroid screening study reported that treatment of maternal hypothyroidism did not improve IQ or impaired cognitive function in 3 old offspring [15].

Most hypothyroid women need an increased dose of L-T_4 from very early pregnancy [16, 17]. Indeed, about 25% women on L-T_4 replacement have biochemical evidence of under replacement at their first antenatal visit [7], which may be prevented by optimizing the L-T_4 dose before pregnancy [18]. In the present study, 32% of responders would advise woman to increase the dose of L-T_4 by 30–50% and 11% by two tablets per week as soon as pregnancy is confirmed according to previous recommendations [3, 4, 19]. In the absence of studies comparing these different approaches, this survey has highlighted inconsistency in clinicians' approach for optimizing L-T_4 replacement in hypothyroid women planning pregnancy with a little more than half of responders choosing thyroid function as soon as pregnancy is confirmed (Table 2).

In regard to the target thyroid function for pregnant hypothyroid women, most responders (78%) aimed to achieve TSH and free T_4 within the trimester-specific reference range or TSH <2.5 mIU/L in the first trimester and <3 mIU/L in the later trimesters (Table 4), as recommended by the guidelines [3, 4].

An increased risk of miscarriage in TPOAb negative women with TSH 2.5–5 mIU/L has been reported [20] but, there is no randomized controlled trial evidence to show benefit of L-T_4 in these women. In contrast, there is growing evidences for an association between thyroid autoimmunity and adverse obstetric outcomes such as miscarriage [21-23], recurrent pregnancy loss [24, 25], preterm delivery and low birth weight [20, 26]. A randomized controlled trial has shown that L-T_4 treatment may reduce miscarriage and preterm delivery in euthyroid TPOAb positive pregnant women [26]. In another prospective trial, L-T4 treatment reduced the risk of preterm delivery in euthyroid TPOAb positive women undergoing assisted reproduction technologies [27]. In this survey, most responders (70%) would not treat euthyroid pregnant women with isolated TPOAb positivity (Fig. 1). This practice is in agreement with guidelines, which do not recommend L-T_4 for these pregnant women [3, 4], underlining the need for further studies.

Although maternal hypothyroxinemia has been shown to be associated with impaired neuropsycho-

Table 7 Comparison of Asian and European responders in the screening and management of hypothyroidism in pregnancy

Variable	Responders (%)	
	Asian	European*
Screening for thyroid function in pregnancy		
All	21	42
Targeted screening	66	43
Choice of treatment of overt hypothyroidism		
Start on a full dose	33	46
Double dose first	30	25
Pre-pregnancy recommendation to a hypothyroid women with TSH 2.4 mIU/L		
Check thyroid function when pregnant	54	43
Increase L-T_4 by 30-50% (or two tablets weekly)	43	50
Tests to monitor L-T_4 dose		
TSH, FT_4	46	43
TSH alone	14	12
TSH, FT_4, FT_3	14	29
Target thyroid function in treated hypothyroidism		
TSH< 2.5 mIU/L in the first trimester and <3.0 mIU/L therefore	63	57
TSH and FT_4 within the trimester specific range	25	30
L-T4 treatment in pregnancy		
Isolated hypothyroxinemia	38	38
TPOAb positive, TSH <2.5 mIU/L	30	10
TPOAb positive, TSH 2.5-5 mIU/L	79	85
TPOAb negative, TSH 2.5-5 mIU/L	54	40

* Ref. No. 5

logical development of offspring [10], there is a lack of consensus on the definition and management of isolated maternal hypothyroxinemia [28]. Furthermore, a large observational study has failed to show an association between maternal hypothyroxinemia and obstetric adverse outcomes [29]. The prospective nonrandomized Generation R study, reported increased risk of lower communication development in children born to women with isolated hypothyroxinemia [30]. Although 62% of the responders practice in accord with guidelines recommending against the treatment of maternal hypothyroxinemia in pregnancy, it is remarkable that nearly 38% of the responders reported that they would treat isolated maternal hypothyroxinemia.

Compared to the survey reported treatment and screening of hypothyroidism in pregnancy in Europe [5], the results of this study is not much different in various aspects of management of hypothyroidism in pregnancy (Table 7). Most Asian responders prefer targeted screening for thyroid function in pregnancy, while European responders screen all pregnant women twice as many as Asian ones.

This study has several limitations. First, the responders may not represent all physicians in all countries in a large continent such as Asia. The Asian – Ocean Thyroid Association has over 4000 members of which just 321 practitioners participated in this study which may not be representative of all; however we did not receive responses from some of these practitioners. Our results are hence somewhat limited as regards generalization. Secondly, variation in the clinical practices in different countries could have influenced the overall results of the survey. Thirdly, most of the responders of the survey are endocrinologists, and their approach to the management of hypothyroidism in pregnancy may be different from that of other healthcare professionals, such as obstetricians, internists and general practitioners. Finally, clinical practices of members of a learned thyroid association may differ from those of non-member endocrinologists.

With responders from 21 Asian countries, we believe that this survey provides a snapshot of current practice in the management of hypothyroidism during pregnancy in Asia and demonstrates further that alike European physicians [5], Asian clinicians often do not adhere to clinical practice guidelines [31]. This nota-

ble deficiency may be considered in the strategic plans of related professional societies of various countries.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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INTERNAL MEDICINE

□ REVIEW ARTICLE □

Graves' Ophthalmopathy: Epidemiology and Natural History

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Abstract

Graves' ophthalmopathy (GO) is an autoimmune disorder of the orbit that is clinically relevant in 25-50% of patients with Graves' disease and 2% of patients with chronic thyroiditis. The age-adjusted annual incidence of clinically relevant GO is 16 per 100,000 population in women and 2.9 in men. At the onset of ophthalmopathy, 80-90% of patients have hyperthyroidism, with the rest having euthyroidism or hypothyroidism. The natural history of GO consists of two phases: an active inflammatory phase and a static phase. Anti-inflammatory therapy is indicated for the first phase of GO. Approximately 5% of patients experience late reactivation of GO. Asians appear to have less severe manifestations, with milder orbital edema, proptosis and muscle restriction. Genetic, anatomic and environmental factors influence the development of GO. Aging, thyroid dysfunction, thyroid stimulating hormone (TSH) receptor antibodies, smoking and radioiodine treatment for hyperthyroidism also influence the development and course of GO.

Key words: Graves' ophthalmopathy, Graves' disease, epidemiology, prevalence, ethnicity

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Introduction

Graves' ophthalmopathy (GO), also known as Graves' orbitopathy, Graves' eye disease, thyroid eye disease and thyroid-associated ophthalmopathy, is an autoimmune disorder of the orbit that is closely associated with autoimmune thyroid diseases. GO is clinically relevant in 25-50% of patients with Graves' disease and 2% of patients with chronic thyroiditis (1-4). A subclinical form of GO can be detected on orbital imaging in more than 70% of patients with Graves' disease. At the onset of ophthalmopathy, 80-90% of GO patients have hyperthyroidism, with the rest having euthyroidism or hypothyroidism. GO precedes the onset of hyperthyroidism in 20% of patients; however, it more frequently develops concomitantly or following the onset of hyperthyroidism. GO is usually bilateral, although it may be asymmetric or unilateral in 15% of patients. Sight is threatened in 3-5% of GO patients, with these patients requiring urgent treatment (1). There is considerable evidence that both genetic (5) and environmental (6) factors are involved in the development of GO. Although the primary autoantigen(s) and precise mechanisms underlying the association between GO and autoimmune thyroid diseases remain unclear, thyrotropin (TSH) receptors are thought to be the primary target of autoimmune reactions in GO patients.

In this review, we present the prevalence and natural history of GO, as well as risk factors that may influence its prevalence, including genetic factors, cigarette smoking and radioiodine treatment of hyperthyroidism. The definition of GO and the methods used to diagnose this condition also influence its estimated prevalence. Ethnic differences in the clinical presentation of GO are also described.

Epidemiology

Incidence of GO: The age-adjusted annual incidence of clinically relevant GO in a representative county in the United States (USA) was estimated to be 16 per 100,000 population in women and 2.9 per 100,000 in men, with an estimated prevalence of 0.25% (7). Subsequent studies in Europe (8-12), the USA (13, 14), India (15), Malaysia (16) and Japan (17) have reported prevalence rates ranging from

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Table. Clinical Presentation of Eye Changes in Patients with Graves' Ophthalmopathy

	Dickinson[53] Caucasian GO patients in adults	Krassas[34] Caucasian 77 GO patients in children	Kozaki[29] Japanese 10921 GO patients in adults
Lid retraction	90-98%	-	57.0%
Lid swelling	75%	60%	47.0%
Proptosis	63%	52%	74.0%
Extraocular muscle involvement	40-60%	6.5%	40.8%
Corneal involvement	10-17%	30%	-
Optic nerve involvement	5%	0%	7.3%

GO: Graves' ophthalmopathy

0.1% to 0.3%, although one study from the USA reported a prevalence of 5.75% (14), likely due to environmental and/or anatomic factors.

Thyroid function at the onset of GO: The onset of GO in most patients is closely related to Graves' hyperthyroidism. GO often develops concomitantly with hyperthyroidism, although it may precede or follow hyperthyroidism (18). In a study from Pisa, Italy, GO was found to be associated with hyperthyroidism in 202 of 221 (91.4%) patients (19). In another cohort study, 90% of the GO patients had hyperthyroidism, 3.3% had Hashimoto's thyroiditis and 5.8% were euthyroid (20). GO and hyperthyroidism occur within 18 months of each other in 60% to 85% of patients (19, 21-23). GO can occur in patients who develop hyperthyroidism at a later age or may develop some time after the treatment of hyperthyroidism (22-24).

The overall incidence of GO in patients who have never been hyperthyroid (euthyroid Graves' disease and hypothyroid Graves' disease) varies from 2.5% to 34.3% (20, 25-28), with differences being due to referral biases or other factors. Up to 50% of initially euthyroid patients develop hyperthyroidism within 18 months (23).

Clinical presentation

The clinical presentation of GO varies by age, gender and race. Several differences in clinical presentation have been observed between Asian and Caucasian patients.

Age and sex distribution: GO patients are older than patients with GD without ophthalmopathy (mean age: 46.4 years vs. 40.0 years) (28). Bimodal peaks in age onset have been observed in both men and women, with both peaks occurring five years earlier in women than in men (40-44 years vs. 45-49 years and 60-64 years vs. 65-69 years) (7). In an observational case series of 10,931 consecutive Japanese patients with GO treated at one clinic from 1993 to 2002, the mean age at GO onset was 39.1 years in women and 43.0 years in men (29).

Most patients with GO exhibit both enlargement of extraocular muscle and expansion of adipose tissue, with some showing a predominance of one feature or the other. Patients under 40 years of age tend to demonstrate fat expansion, whereas patients over 60 years of age display more extraocular muscle swelling (2, 30).

GO is more common in women than in men. The female to male ratio is 4.2 in Swedish patients (31) and 3.9 in Japanese subjects (29). Moreover, the female to male ratio varies according to the severity of ophthalmopathy, being 9.3, 3.2 and 1.4 in patients with mild, moderate and severe ophthalmopathy, respectively (28). Another study reported female to male ratios of 3.4 and 2.1 among patients with hyperthyroid Graves' disease without and with ophthalmopathy, respectively, and 0.7 among patients with euthyroid Graves' disease (19). In a recent cohort of 2,045 patients with Graves' disease, the rates of NOSPECS classes IV-VI were 30.4% in men and 21.3% in women (32). Taken together, these studies indicate that GO tends to be more severe in older patients than in younger patients and in men compared to women. The higher prevalence of smoking in men, as well as gender-related genetic factors, may play a role in the severity of GO.

GO in children: GO is rare in children, occurring in 0.1 per 100,000 prepubescent and 3.0 per 100,000 postpubescent children (33). No ethnic differences have been reported in children or adolescents. The clinical manifestations of GO are less severe in children and adolescents than in adults (Table) (34). Soft tissue involvement and proptosis were the predominant eye changes in 77 GO patients described in five studies (35-39). More severely restricted eye muscle movement and optic dysfunction almost never occur in children. The prevalence of GO in children and teenagers is related to the prevalence of smoking among teenagers in various countries (34).

Anatomical differences between races: Racial differences in ocular anatomy in normal subjects and GO patients have been extensively reviewed (40, 41). Normal exophthalmometry values vary significantly among races, with Asians having low values and blacks having relatively shallow orbits and higher values (42-45). Furthermore, there are differences in the eyelid and orbital septum between Caucasians and Asians. Apical compression and optic neuropathy occur more frequently in Asians due to their shallower orbits and narrower apices (41, 46).

Clinical features: GO is clinically relevant in 25% of unselected patients with Graves' disease if eyelid signs are excluded and 40% if eyelid signs are included (47). Orbital imaging, such as magnetic resonance imaging (MRI) and

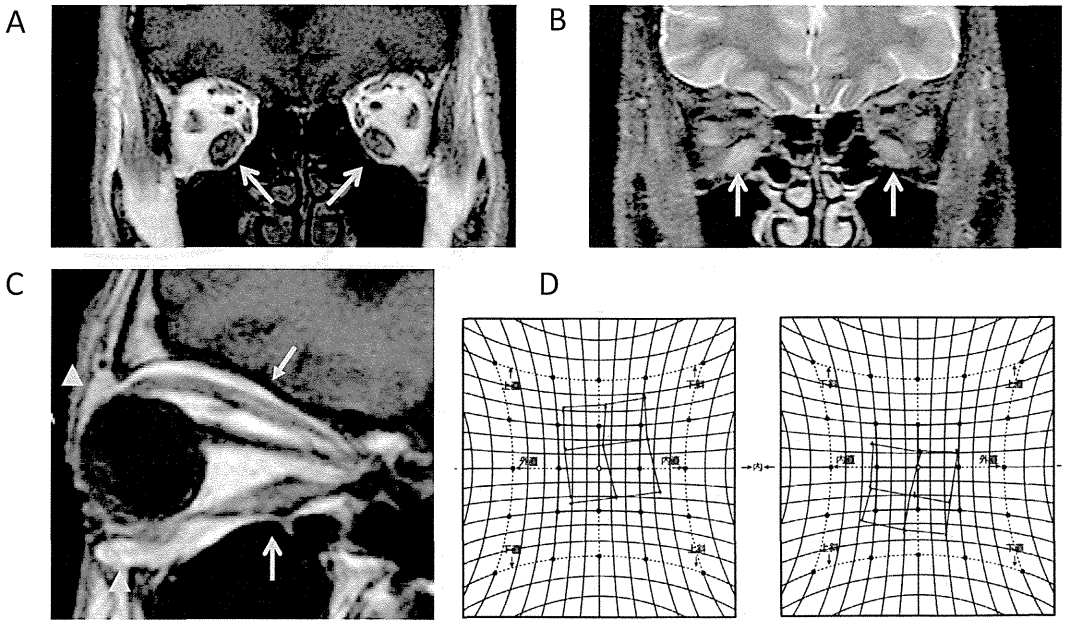

Figure 1. A 73-year-old man with Graves' disease visited our clinic with diplopia upon an upward gaze. He had conjunctival injection and proptosis (right: 22 mm, left: 19 mm) with eye muscle dysfunction. Orbital MRI showed enlargement of the bilateral inferior rectus muscles (arrows) and fat tissue accumulation in the eyelids (▲). A: T1-weighted image in a coronal section. B: Short inversion time inversion recovery (STIR) image showing high intensity with enlarged inferior rectus muscles. C: T1-weighted image in a sagittal section. D: Hess chart showing the presence of extraocular muscle dysfunction. The clinical activity score was 1. The NOSPECS class was II_a, III_c, IV_b, V_0, VI_0.

computed tomography (CT) show enlargement of the extraocular muscles, an increase in the orbital fat tissue volume and enlargement of the lacrimal glands (48, 49) (Fig. 1A, C). In addition, orbital imaging reveals abnormalities in almost all patients with GO. The clinical activity score (CAS) is useful for assessing the GO activity. If the CAS is more than 3, immunosuppressive therapy is recommended for the treatment of GO in Europe (50). The CAS values, however, tend to be low in Japanese GO patients who are receiving intravenous steroid pulse therapy (51). The NOSPECS classification remains a useful reminder of the features that should be assessed (52, 53).

Class 0: More than half of patients with Graves' disease do not have evident ophthalmopathy. However, approximately 70% of patients with untreated Graves' disease without signs or symptoms of ophthalmopathy exhibit an enlargement of the extraocular muscles, a condition termed 'occult thyroid eye disease' (54-56). Imaging modalities, such as CT and MRI, are useful for evaluating these conditions.

Class I (Only signs): Upper lid retraction, staring and eyelid lag are observed in 35-53% of patients with Graves' disease (16) and in 90-98% of Caucasian patients (19, 20) and 57% of Japanese patients (29) with GO.

Class II (Soft tissue involvement): Class II signs are common, affecting 32% of patients with Graves' disease (47). Lid swelling is observed in 47% of GO patients, with injection and edema of the conjunctiva observed in 32% (29).

Class III (Proptosis): Proptosis is observed in 24% of untreated patients with Graves' disease and 63-74% of patients with GO (29, 47).

Class IV (Extraocular eye muscle involvement): Approximately 22% of patients suffer from diplopia. Enlargement of the extraocular muscles is observed in 41% of GO patients (29). The enlarged eye muscle is no longer able to lengthen and causes diplopia (Fig. 1D). In most patients with this class of disease, several extraocular muscles are affected to various degrees. Therefore, MRI is useful for evaluating orbital lesions in patients with GO. A high signal intensity on STIR images may indicate inflamed extraocular muscles (48) (Fig. 1B).

Class V (Corneal involvement): Although punctuate staining is observed in 10-17% of patients, the incidence of sight-threatening ulceration was <2% a century ago and it is probably lower now (1).

Class VI (Sight loss): Optic nerve involvement, so-called dysthyroid optic neuropathy, is observed in 3-7% of GO patients (1, 29).

Caucasians have been reported to be at greater risk of developing GO than Asians (42% vs. 7.7%) (57). Moreover, Asians appear to have less severe manifestations, with milder features of orbital edema, proptosis and muscle restriction (46). A cross sectional study of Malay, Chinese and Indian GO patients with Graves' disease in Malaysia showed that the prevalence of GO ranged from 35.1% to 40.0% in the three populations, similar to the prevalence observed in Caucasians (16). A similar frequency of GO of 33% has been documented in juvenile patients with Graves'

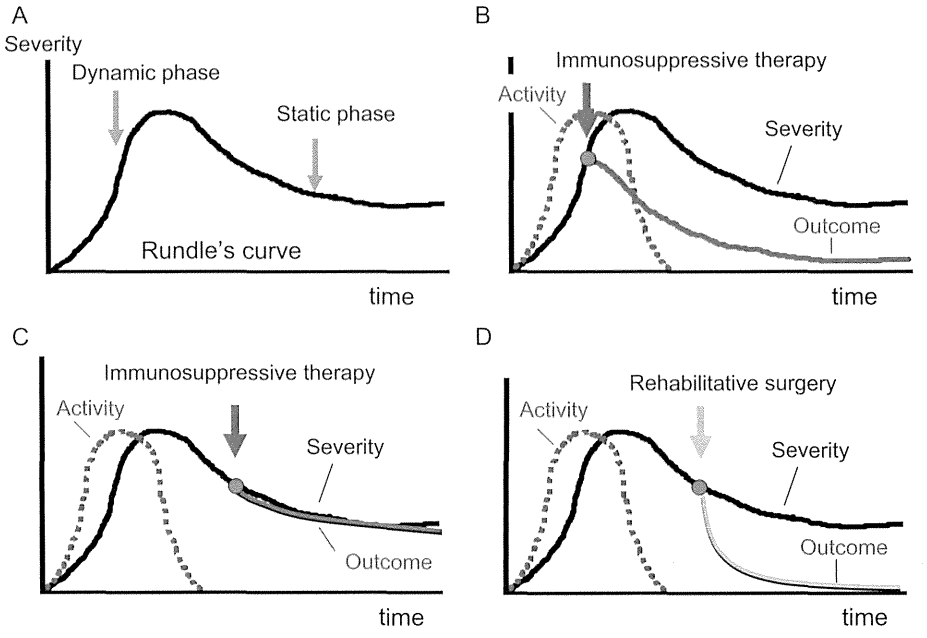

Figure 2. Natural history of Graves' ophthalmopathy (GO) depicting the severity of GO over time (Rundle's curve) (A). The administration of immunosuppressive treatment during the early active phase of GO results in a reduction of both the disease activity and severity (B). The administration of immunosuppressive treatment during the late inactive phase of GO does not result in any benefits for the course of GO (C). During the late inactive phase, rehabilitative surgery results in great benefits (D). (Modified from ref. 64 with permission)

disease (58). The incidence of GO in Japanese is similar to that observed in Caucasians (Table). Taken together, these studies show that, although the prevalence of GO may not differ among ethnic groups, the clinical features of GO differ, being milder in Asians than in Caucasians.

A study conducted in Sweden based on the registry of a Swedish Multicenter Study found that 20% of patients with GD had orbitopathy, with 4.9% having infiltrative signs and/or symptoms and 15.2% having non-infiltrative symptoms (31). In that study, there were geographic differences in the incidence of GD. The study also found that smoking did not significantly influence the incidence of GO.

A prospective, population-based study conducted in Denmark found that approximately 5% of patients with Graves' disease develop moderate to severe GO, with similar risks observed in women and men. The risk of GO is much higher in patients 40-60 years of age than in younger patients with Graves' disease (59).

In one clinic in the United Kingdom (60) the prevalence of GO fell from 57% in 1960 to 37% in 1990, a decrease that may be related to the decrease in smoking in Western countries during this period of time. In contrast, the prevalence of GO increased in Poland and Hungary where the prevalence of smoking also increased (61). Other factors, such as a greater awareness of GO in Graves' disease patients as well as improved laboratory testing of the thyroid function may also have contributed to the decline in prevalence in individual clinics (47).

Natural history

The natural history of GO was first described by Rundle (62, 63). Progressive deterioration may occur over 6-24 months, due to the development of the autoimmune process (dynamic active progressive phase, Fig. 2A). This stage is characterized by lymphocyte infiltration, with the cells secreting various cytokines, along with fibroblast proliferation and edema. As the inflammatory activity subsides, a plateau is reached, followed by a phase of spontaneous slow improvement that may last a year or more. Regression of the inflammatory process may lead to fibrosis, preventing affected tissues from returning to their previous healthy state (static phase). Anti-inflammatory therapy is indicated in the first phase and corrective surgery may be indicated in the second phase (Fig. 2B-D) (64).

A long-term follow-up study showed that the general appearance of the patients had improved after 15 years, although approximately 50% still had obvious signs of orbitopathy (63).

In a study of 122 patients with thyrotoxicosis, exophthalmos remained stable in 78.7% of the patients, improved in 5.7% of the patients and worsened in 15.6% of the patients (65). In a small series of 59 patients with mild GO referred to a combined thyroid eye clinic and assessed every three months for one year or more, 13 (22%) experienced substantial improvement, 25 (42%) experienced a slight improvement, 13 (22%) exhibited unchanged ocular involvement and eight (14%) demonstrated progression to a more

severe form of GO (66). In contrast, a study involving 81 patients followed-up for 2.7 years found that 25 of 53 (47%) patients showed improvements in ophthalmopathy with no therapy or only local protective agents, 26 (49%) showed no changes and two (4%) showed deterioration (67). In a more recent cohort study of 346 patients with newly diagnosed and recent onset Graves' hyperthyroidism, 255 (73.7%) had no ocular involvement, 70 (20.2%) had mild and inactive GO, 20 (5.8%) had moderate-to-severe and active GO and one (0.3%) had sight-threatening GO with dysthyroid optic neuropathy (68). Progression from moderate to severe GO occurred in 2.6% of patients without orbitopathy and in 2.3% of those with mild GO at baseline (68). These findings indicate that a spontaneous improvement occurs in approximately 30% of patients with mild to moderate GO.

Several studies have suggested that prompt restoration and stable maintenance of euthyroidism is important for the natural history of GO. Anti-thyroid drugs (ATDs) and thyroidectomy do not influence the natural history of GO. Radioiodine therapy can induce the progression or de novo development of GO, particularly in smokers (69, 70). This effect can be prevented by the administration of oral steroid prophylaxis. Two cohort studies in which the patients received levothyroxine therapy soon after radioactive iodine with the specific intent of preventing hypothyroidism found that deterioration of GO was rare (0-2%) (71, 72). A randomized trial of patients newly diagnosed with Graves' disease found that radioactive iodine did not increase the risk of worsening GO compared with methimazole [relative risk (RR), 0.95], when the development of hypothyroidism was actively prevented by the administration of thyroid hormone two weeks after radioactive iodine treatment (RAI) (73).

In patients with mild orbitopathy, the choice of thyroid treatment is largely independent of GO. A series of 72 patients with inactive GO according to the CAS were treated with radioactive iodine without concurrent glucocorticoid administration (69). GO activation was observed in approximately 7% of the patients considered to be at low risk and therefore given no steroid prophylaxis. Whether concomitant treatment of hyperthyroidism in these patients should be conservative (ATDs) or ablative (RAI and/or thyroidectomy) is presently based on expert opinion rather than evidence. The American Thyroid Association and American Association of Clinical Endocrinologists have provided guidelines to assist health care professionals in making medical decisions for specific clinical conditions in patients with GO (74).

Late reactivation of GO, defined as active orbitopathy occurring after more than five years of quiescent disease, appears to be uncommon, being reported in only 5% of GO patients (75).

Risk factors

Several risk factors may influence the occurrence of GO. These include genetic factors, smoking, the presence of TSH receptor antibodies [TSH binding inhibitor immunoglobulins (TBII) >50% or thyroid stimulating immunoglobulin (TSI) >8.8 IU/L] (76), a high pretreatment T3 concentration (≥325 ng/dL or ≥5 nmol/L) (69), an advanced age, stress, drugs, iodine intake, ^{131}I therapy (66) and hypothyroidism following radioiodine treatment (68).

Genetic factors: GO is generally regarded to be an autoimmune disease and genes related to its immunopathogenesis in the orbit may be involved in susceptibility to GO (5). The human leukocyte antigen (HLA)-DRB1*03, DRB1*04 and DRB1*07 genotypes have been shown to be related to the development of GO in Caucasians. In Asian populations, the association between HLA and GO is less clear. Polymorphisms in immunomodulatory genes have been reported to be associated with GO, including genes encoding cytotoxic T lymphocyte antigen (CTLA-4), interleukin-1 (IL-1) and members of the IL-1 family, interferon (IFN)γ, IL-23R, CD40, protein tyrosine phosphatase, non-receptor type 22 (PTPN22), nuclear factor-kappa B (NF-κB) and tumor necrosis factor α (TNFα) (77), as well as thyroid specific genes (TSH receptor gene) and adipogenesis-related genes, such as peroxisome proliferator-activated receptor γ (PPARγ). These findings are based on small case-controlled association studies and suggest racial differences in genetic associations (41). These results, however, require confirmation in large-scale studies.

Cigarette smoking: Cigarette smoking is the strongest modifiable risk factor for the development of GO. A meta-analysis (78) of case control studies as well as cohort studies (71, 72) demonstrated strong links between tobacco smoking and the development and deterioration of GO. One study reported that 64% of patients with GO and 48% of Graves' disease patients without orbitopathy were smokers, compared with approximately 30% of patients with nontoxic goiters, toxic goiters or Hashimoto's thyroiditis (79). Smoking causes GO progression following radiotherapy for Graves' disease and attenuates the efficacy of orbital radiotherapy and high-dose systemic glucocorticoids (80). The pathogenic mechanisms underlying the effects of smoking on GO are not fully understood.

Anti-TSH receptor antibodies: Since TSH receptor mRNA and proteins are present in orbital adipose tissue and an increased expression of this receptor has been reported in the orbital adipose tissue of patients with GO (2), autoimmunity against the TSH receptor may play a major role in the development of GO. The TBII titers and TSI concentrations have been reported to be associated with GO development (81-84), and TSI has been found to be directly associated with the CAS and response to anti-inflammatory therapy (85-87).

^{131}I therapy for hyperthyroidism: The development or worsening of GO after radioiodine therapy for hyperthyroidism has been reported in 15-39% of patients (69, 70, 73). Randomized controlled trials found that the risks of radioiodine were greater than those for anti-thyroid drugs, e.g., 15% vs. 3% (67), 33% vs. 10% (69) and 38.7% vs. 21.3% (73), respectively. Radioiodine therapy is also associ-

ated with a greater risk of ophthalmopathy than anti-thyroid drugs [RR, 4.23; 95% confidence interval (CI), 2.04-8.77] (88). Glucocorticoid prophylaxis is beneficial for patients with mild pre-existing GO (70). A transient increase in the level of TSH receptor antibodies has been reported after radioiodine therapy (89). Therefore, radioiodine therapy may trigger the development of autoimmune inflammation in the orbit and result in the worsening of GO. The ability to prevent the deterioration of GO with the early administration of T4 suggests that the development of hypothyroidism after radioiodine therapy may be a more important risk factor for the development of GO (71, 72).

Conclusion

GO is an autoimmune disease of the orbit that is frequently associated with Graves' disease. The age-adjusted annual incidence of clinically relevant GO in a representative county is estimated to be 16 per 100,000 population in women and 2.9 per 100,000 in men. The estimated prevalence of clinically relevant GO ranges from 0.1% to 0.3%. At the onset of orbitopathy, 80-90% of GO patients have hyperthyroidism, with the rest having either euthyroidism or hypothyroidism. Approximately 5% of patients exhibit late reactivation of GO.

Lid retraction is observed in 57-98% of adults with GO, with proptosis in 63-74%, extraocular muscle involvement in 40-60% and optic neuropathy in 5-7%. However, a subclinical form of GO is demonstrated on orbital imaging in more than 70% of patients with Graves' disease.

The natural history of GO consists of two phases: an active inflammatory phase and a static phase. The rate of development or progression to a more severe form of GO is 4% to 15%. Anti-inflammatory therapy is indicated in moderate to severe GO patients in the first phase.

Several racial and/or geographic differences are observed in the clinical presentation of GO. Genetic, anatomic and environmental factors are involved in the development of GO. Aging, thyroid dysfunction, TSH receptor antibodies, cigarette smoking and radioiodine treatment for hyperthyroidism also influence the development and course of GO.

The authors state that they have no Conflict of Interest (COI).

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