Graves’ Disease – Special Features

Kenneth A. Woeber, MD, FRCPE

Epidemiology of Graves’ Disease

• Cause of up to 80% of cases of hyperthyroidism in iodine-sufficient areas of the world
• Prevalence: ~ 0.5% of population
• Incidence: ~ 20/100,000/year
• Female/male ratio: 5/1 – 10/1
• Concordance rate: monozygotic twins 35%; dizygotic twins 3% (Brix et al., J Clin Endocrinol Metab 86: 930, 2001); concordance rate in monozygotic twins higher than in HLA-identical sibs
• Predisposition: 79% genetic; 21% nongenetic
• Female siblings and female children have 5 – 8% risk
Pathogenesis of Graves’ Disease

Autoreactive T cells and B cells escape tolerance and infiltrate the thyroid gland (as well as extrathyroidal tissues) and elaborate cytokines that ultimately lead to production of TSH receptor antibodies (TSHRAb) as a result of:

Genetic susceptibility
Environmental factors: stress, smoking
Endogenous factors: female gender, postpartum

Clinical Manifestations of Graves’ Disease

- Diffuse toxic goiter in > 90%
- Thyrocardiac disease in < 30%*
- Overt infiltrative ophthalmopathy in ~ 30%
- Overt infiltrative dermopathy (pretibial myxedema) in < 5%

* may also occur in other forms of thyrotoxicosis
## Prevalence of Cardiac Disease in Thyrotoxicosis

<table>
<thead>
<tr>
<th></th>
<th>Series of Sandler and Wilson(^1)</th>
<th>Series of Summers and Surtees(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>462</td>
<td>200</td>
</tr>
<tr>
<td>Patients with cardiac abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with pre-existing conditions</td>
<td>150 (32%)</td>
<td>60 (30%)</td>
</tr>
<tr>
<td>without pre-existing conditions</td>
<td>86 (14%)</td>
<td>31</td>
</tr>
<tr>
<td>Cardiomegaly alone</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>48</td>
<td>9</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>26</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^1\)QJ Med 28:347, 1959

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**Figure 1. Schema of the Factors That Produce the Cardiovascular Effects of Thyrotoxicosis.**

## Frequency of Atrial Fibrillation in Hyperthyroidism

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auer et al. (Am Heart J 142:838, 2001)</td>
<td>100 of 725 patients</td>
<td>14%</td>
</tr>
<tr>
<td>Frost et al. (Arch Int Med 164:1675, 2004)</td>
<td>3,362 of 40,628 patients</td>
<td>8%</td>
</tr>
</tbody>
</table>

## Frequency of Arterial Embolism in Hyperthyroidism with Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staffurth et al. (Br Med J 2:688, 1977)</td>
<td>21 of 262 patients</td>
<td>8%</td>
</tr>
<tr>
<td>Yuen et al. (Med J Aust 1:630, 1979)</td>
<td>5 of 21 patients</td>
<td>24%</td>
</tr>
<tr>
<td>Bar-Sela et al. (Arch Int Med 141:1191, 1981)</td>
<td>12 of 30 patients</td>
<td>40%</td>
</tr>
<tr>
<td>Petersen et al. (Stroke 19:15, 1988)</td>
<td>12 of 91 patients</td>
<td>13%</td>
</tr>
</tbody>
</table>
Prothrombotic State in Hyperthyroidism

(Stuijver et al., Thrombosis and Haemostasis 108:1077, 2012)

Hypercoagulable State

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Hypofibrinolytic State

Increased factors VIII & IX, fibrinogen, & von Willebrand factor

Decreased plasminogen activator

ACC / AHA / ESC 2006 GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION

“In patients with AF associated with thyrotoxicosis, oral anticoagulation (INR 2.0 to 3.0) is recommended to prevent thromboembolism, as recommended for AF patients with other risk factors for stroke.”
### OUTCOME OF POST-THYROTOXIC ATRIAL FIBRILLATION
(From Nakazawa et al., Am. J. Med. 72: 903, 1982)

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous Version (n, 101)</th>
<th>Persistence (n, 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Gender (F:M)</td>
<td>71:30</td>
<td>38:24</td>
</tr>
<tr>
<td>Mean duration of symptoms (mo)</td>
<td>18</td>
<td>52</td>
</tr>
<tr>
<td>Mean duration of atrial fibrillation (wk)</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>Pre-existing heart disease (%)</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Presence of heart failure (%)</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Time to return to euthyroidism (wk)</td>
<td>Cumulative % in sinus rhythm</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>
Pathogenesis of Graves’ Ophthalmopathy

- Characterized by increased orbital fat and increased extraocular muscle volume
- Orbital preadipocyte fibroblasts express TSHR and expression correlates with eye disease activity
- Infiltration of autoreactive T cells targeted through recognition of TSHR-expressing fibroblasts results in cytokine-mediated adipogenesis and hydrophilic glycosaminoglycan production

(adapted from Stan and Bahn, Thyroid 20: 777, 2010)
10-Point Clinical Activity Score (CAS) for Graves’ Ophthalmopathy

(Mourits et al., Br J Ophthalmol 73: 63, 1989)

- **Pain (2 points):** pain on or behind globe; pain on lateral or vertical gaze
- **Redness (2 points):** eyelids; conjunctiva
- **Swelling (4 points):** chemosis; swollen caruncle; eyelid edema; increase in proptosis of > 2 mm during 1- to 3-month period
- **Impaired Function (2 points):** decrease in visual acuity during 1- to 3-month period; decrease in eye movements in any direction during 1- to 3-month period

mild, < 3 points; moderate, 3 – 5 points; severe, > 5 points

Factors that Worsen Graves’ Ophthalmopathy

- Cigarette smoking (Bartalena et al., J Endocrinol Invest 12: 733, 1998)
- Greatly elevated TSHRAB
- Elevated TSH
- Thiazolidinediones (Starkey et al., J Clin Endocrinol Metab 88: 55. 2003)
Smoking Behavior and Effect of $^{131}$I Treatment on Graves’ Ophthalmopathy

*(adapted from Bartalena et al., Ann Int Med 129: 632, 1998)*

<table>
<thead>
<tr>
<th>Behavior of 150 patients</th>
<th>No change in eyes</th>
<th>New or worsened eye disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>82 smokers</td>
<td>63</td>
<td>19 (23%)</td>
</tr>
<tr>
<td>68 nonsmokers</td>
<td>64</td>
<td>4 (6%)</td>
</tr>
</tbody>
</table>

Figure 1. Kaplan–Meier Plots of the Development or Worsening of Ophthalmopathy in Patients with Hyperthyroidism Caused by Graves’ Disease.

### Effects of Treatment on Graves’ Ophthalmopathy during 4-years Follow-Up

(adapted from Traisk et al., J Clin Endocrinol Metab 94: 3700, 2009)

<table>
<thead>
<tr>
<th>313 newly diagnosed patients with Graves’ hyperthyroidism</th>
<th>New ophthalmopathy</th>
<th>Worsened ophthalmopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>163 patients treated with $^{131}$I followed by levothyroxine</td>
<td>53/163 (33%)</td>
<td>10/163 (6%)</td>
</tr>
<tr>
<td>150 patients treated with 18-months of methimazole and levothyroxine</td>
<td>23/150 (16%)</td>
<td>9/150 (6%)</td>
</tr>
</tbody>
</table>

### Effects of Treatment or Smoking on Graves’ Ophthalmopathy

(adapted from Traisk et al., J Clin Endocrinol Metab 94: 3700, 2009)

<table>
<thead>
<tr>
<th>313 newly diagnosed patients with Graves’ hyperthyroidism</th>
<th>Odds Ratio (95% CI) of new or worsened ophthalmopathy during 4-years follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{131}$I (163 pts) vs. methimazole (150 pts)</td>
<td>4.05 (1.95 – 8.43)</td>
</tr>
<tr>
<td>smokers (121 pts) vs. nonsmokers (192 pts)</td>
<td>5.20 (2.35 – 11.53)</td>
</tr>
</tbody>
</table>
Glucocorticoid Use to Prevent Progression of Graves’ Ophthalmopathy after $^{131}$I Treatment

(Shiber at al., Thyroid 24: 1515, 2014)

- Moderate ophthalmopathy, 0.4 – 0.5 mg/Kg daily tapered over 3 months
- Mild ophthalmopathy or presence of risk factors (cigarette smoking, greatly elevated TSHRAb), 0.2 – 0.3 mg/Kg daily tapered over 4 – 6 weeks
Management of Established Graves’ Ophthalmopathy

• Active Mild Disease, CAS < 3 (~90% of cases)
  - cessation of tobacco use
  - artificial tears and ointments
  - dark glasses
  - elevation of head of bed
  - prisms for diplopia
  - diuretics

Management of Established Graves’ Ophthalmopathy (continued)

• Active Moderate-to-Severe Disease, CAS > 3 (<10% of cases)
  - glucocorticoids, preferably methylprednisolone infusions over 12 weeks to cumulative 7.5 g in severe cases
    (Bartalena et al., J Clin Endocrinol Metab 97: 4454, 2012)
  - total thyroid ablation, through near total/total thyroidectomy followed by rhTSH stimulated $^{131}$I treatment; improvement in 70% vs 20% with thyroidectomy alone at 12 months (p<0.01)
    (Moleti et al., J Clin Endocrinol Metab 99: 1783, 2014)
Management of Established Graves’ Ophthalmopathy (continued)

• Active Moderate-to-Severe Disease, CAS > 3 (< 10% of cases)
  – rituximab, conflicting findings in 2 randomized controlled studies
    (Salvi et al., J Clin Endocrinol Metab 100: 422, 2015; Stan et al., J Clin Endocrinol Metab 100:432, 2015)

Accordingly, near total/total thyroidectomy should be recommended treatment of Graves’ hyperthyroidism with active moderate-to-severe ophthalmopathy followed with rhTSH stimulated ¹³¹I treatment in severe cases.

Management of Established Graves’ Ophthalmopathy (continued)

• Dysthyroid Optic Neuropathy (sight-threatening disease, < 1% of cases)
  – iv methyl-prednisolone pulses of 500 – 1000 mg daily for 3 days and repeated after 1 week and tapered for a total dose of up to 10 g
  – if unresponsive after 2 to 4 weeks, urgent surgical decompression should be undertaken
    (Curro et al., Thyroid 24: 897, 2014)

• Inactive Disease
  – eye lid surgery, eye muscle surgery, orbital decompression
Pathogenesis of Infiltrative Dermopathy

Infiltration of autoreactive T cells in cutaneous tissues targeted by TSHR-expressing fibroblasts results in cytokine-mediated hydrophilic glycosaminoglycan production, causing edema and ultimately fibrosis.
Clinical Features of Graves’ Dermopathy
(Fatourechi, Best Pract Res Clin Endocrinol Metab 26: 353, 2012)

• Virtually always associated with severe Graves’ ophthalmopathy
• Onset follows Graves’ ophthalmopathy
• Usually localized to pretibial area but can also occur elsewhere
• Occurs in areas subject to repeated trauma
• Usually presents as lymphedema with hyperpigmented plaques or nodules secondary to accumulation of hydrophilic glycosaminoglycans and to proliferation of connective tissue
• Obstruction of the lymphatic microcirculation and fibrosis may lead to development of elephantiasis
• Clubbing of the fingers and toes (thyroid acropachy) occurs in approximately 20% of patients with dermopathy

Treatment of Infiltrative Dermopathy

• Topical glucocorticoid under occlusive dressing
• Multipoint subcutaneous injection of triamcinolone (Deng and Song Thyroid 21: 83, 2011)
• Multipoint intradermal injection of dexamethasone with mesotherapy needles (Vannucchi et al., Thyroid 23: 626, 2013)
Hyperthyroidism in Pregnancy

• Graves’ hyperthyroidism occurs in < 1% of all pregnancies – gradual improvement during pregnancy with exacerbation in late postpartum period  
  
(Andersen et al., J Clin Endocrinol Metab 100: 1164, 2015)

• Gestational transient thyrotoxicosis occurs in 1% - 3% of all pregnancies, especially in multiple pregnancies and molar pregnancy – begins in first trimester correlating with rising hCG, is associated with hyperemesis gravidarum, and resolves spontaneously in early second trimester  
  
(Tan et al., BJOG 109: 683, 2002)

Differential Diagnosis of Hyperthyroidism in Pregnancy

• Graves’ hyperthyroidism – diffuse goiter, presence of exophthalmos, undetectable serum TSH, elevated T4 and T3, and positive TSH receptor antibody (TSHRAb)

• Gestational transient thyrotoxicosis – absent goiter and exophthalmos, undetectable serum TSH and elevated T4 and T3 that resolve in early second trimester, and negative TSHRAb
Adverse Consequences of Maternal Hyperthyroidism in Pregnancy

- Miscarriage
- Intrauterine growth restriction
- Fetal goiter
- Fetal hyperthyroidism
- Central hypothyroidism in fetus
- Accelerated bone maturation
- Preterm birth
- Low birth weight
- Still birth

Treatment of Hyperthyroidism in Pregnancy

- Thionamide drugs, methimazole, carbimazole, and propylthiouracil, are the cornerstone and first line of treatment.
- Thyroidectomy is indicated for serious adverse reactions to or high dosage requirement for a thionamide or for noncompliance and should only be undertaken in second trimester.
- Radioiodine is contraindicated.
Adverse Consequences of Fetal Exposure to Thionamides

The association between the use of methimazole in early pregnancy and birth defects was first reported in 1972. Subsequent studies confirmed this finding with methimazole or carbimazole but the association was considered to be rare and propylthiouracil appeared not to be implicated. Two recent studies, however, have indicated that the association of birth defects with the use of methimazole in the first trimester may be more common, and one of the studies reported that propylthiouracil may result in milder birth defects.

Adverse Consequences of Fetal Exposure to Thionamides (continued)

Data from Japan on pregnancy outcome in 6,744 women with Graves’ disease revealed overall rate of birth defects resulting from prenatal exposure were: 50/1231 (4.1%) for methimazole, 21/1399 (1.5%) for propylthiouracil, and 40/1906 (2.1%) for no medication.

- methimazole vs. controls, p=0.002
- propylthiouracil vs. controls, p=0.709

Birth defects with methimazole included aplasia cutis, omphalocele, omphalomesenteric duct anomaly, and esophageal atresia.

(Yoshihara et al., J Clin Endocrinol Metab 97: 2396, 2012)
Adverse Consequences of Fetal Exposure to Thionamides (continued)

Danish nationwide register-based cohort study of 817,093 children born between 1996 and 2008 of whom 1097 were exposed to methimazole/carbimazole, 564 to propylthiouracil, 159 to both, and 3543 to neither during gestation with median followup of 8.3 years. Prevalence of birth defects:

- 9.1%* with methimazole/carbimazole (aplasia cutis, choanal atresia, esophageal atresia, omphalocele, omphalomesenteric duct anomalies)
- 8.0%* with propylthiouracil (malformations of face and neck and urinary system)
- 10.1%* with both
- 5.4% with neither during gestation

* p<0.001 vs neither during gestation

(Andersen et al., J Clin Endocrinol Metab 98: 4373, 2013 and Thyroid 24: 1533, 2014)

Adverse Consequences of Maternal Exposure to Thionamides

- Adverse Event Reporting System of the FDA has drawn attention to acute liver failure related to propylthiouracil with estimated prevalence of 1 in 10,000 adults and 1 in 2,000 children whereas it has not been reported with methimazole (see Bahn et al., Thyroid 19: 673, 2009).
- Accordingly, propylthiouracil should be only used in first trimester.
Treatment of Hyperthyroidism in Pregnancy

- Use lowest dosage of thionamide drug to maintain total T4 within reference range for pregnancy.
- Recommended dosage of methimazole (or carbimazole) is 5 – 15 mg daily.
- Equivalent dosage of propylthiouracil is 100 – 300 mg daily in divided doses.
- Consider switching from methimazole to propylthiouracil before the 6th week of the first trimester and then back to methimazole in the second trimester on basis of methimazole associated “embryopathy” and of propylthiouracil induced liver failure.

Thyroidectomy in Pregnancy

- Optimal time is second trimester
- Prepare with 7-10 day course of propranolol and Lugol’s iodine
- Prolonged propranolol may lead to intrauterine growth restriction, fetal bradycardia, and fetal hypoglycemia
- Prolonged Lugol’s iodine will lead to fetal goiter and hypothyroidism due to failure of fetal thyroid to escape from Wolff-Chaikoff effect
Monitoring of Hyperthyroidism during Pregnancy

- Measure serum total T4 and TSH every 4 – 6 weeks. Dosage requirement for methimazole will decrease in third trimester and increase postpartum.
- Measure TSHRAb in first trimester and if elevated measure again between 20 and 26 weeks of gestation.
- Very high TSHRAb in women with active or past history of Graves’ hyperthyroidism may lead to fetal and neonatal hyperthyroidism. Ultrasound monitoring of fetus for tachycardia (>160/min) and goiter is indicated (Luton et al., J Clin Endocrinol Metab 90: 6093, 2005).

Breast-feeding and Methimazole Treatment

- Study by Azizi et al. of 82 children aged between 48 and 86 months demonstrated that thyroid function and physical and intellectual development of the 42 breast-fed infants whose lactating mothers were being treated with methimazole were normal and not different from those of 40 control infants (J Pediatr Endocrinol Metab 16: 1239, 2003).
- Methimazole should be taken in divided doses immediately after a feeding.
Postpartum Hyperthyroidism

- New onset of Graves’ hyperthyroidism occurs in < 1% of patients, usually presents 7 – 9 months postpartum, and is characterized by positive TSHRAb (Andersen et al., J Clin Endocrinol Metab 100: 1164, 2015).
- Postpartum thyroiditis occurs in 1 - 17% of patients, presents with thyrotoxicosis in ~ 50% of cases, usually presents 2 - 4 months postpartum, and is characterized by negative TSHRAb.