Thyroid disease in pregnancy

Catherine Nelson-Piercy
Consultant Obstetric Physician
Guy’s & St Thomas’ Trust &
Queen Charlotte’s Hospital
London, UK
Physiological adaptation

Interpretation of TFTs in pregnancy

Hypothyroidism

Thyrotoxicosis

Postpartum thyroiditis
Physiological adaptation

- 2 x increase in urinary iodine excretion
- 3 x increase in iodine uptake by the thyroid
- Diversion of iodine to feto-placental unit
- Increased maternal iodine requirements
- Increase in thyroid volume
- Fetus dependent on maternal thyroxine < 12 weeks
Normal thyroid function in pregnancy

**Maternal**

↑ TBG means ↑ total T3 and T4  
↑ hCG results in ↓ TSH in 1<sup>st</sup> trimester  
↓ T4 in 2<sup>nd</sup> and 3<sup>rd</sup> trimester

<table>
<thead>
<tr>
<th>Normal ranges for fT4 (pmol/L) and TSH (mu/l)</th>
<th>Non-pregnant</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; trimester</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; trimester</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; trimester</th>
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<td>3&lt;sup&gt;rd&lt;/sup&gt; trimester</td>
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Biochemical thyrotoxicosis

- Suppressed TSH
- High fT₄ & fT₃
- Correlates with severity of hyperemesis
  Goodwin et al. AJOG 1992; 167: 648
- Abnormal TFTs in 40-60% with HG
- Correlates with hCG
- Increased oestradiol in HG vs controls
Gestational thyrotoxicosis vs Graves

**Graves / Hyperthyroidism**
- Symptoms pre date pregnancy
- Thyroid stimulating antibodies
- Goitre
- Tremor
- Thyroid eye disease

**Gestational /Hyperemesis**
- Onset first trimester
- Improves with treatment of hyperemesis
- No thyroid stimulating antibodies
- No pre-pregnancy thyroid disease
- Free T4 v high
Hypothyroidism

- Affects around 1% of Pregnancies in Europeans
  - TSH Screening studies (subclinical hypothyroidism)
    - 0.3% Japan
    - 2.2% Europe
    - 2.5% USA
- Usually identified and treated pre-pregnancy
- Usually due to Hashimoto’s thyroiditis or treated Thyrotoxicosis (surgery / radiiodine / drugs)
Hypothyroidism

- Majority have antithyroid antibodies
  - Thyroid microsomal (peroxidase) antibodies

- Women with antibodies convert from subclinical to clinical hypothyroidism at 5%/year
  - Important to monitor for hypothyroidism

- Type 1 diabetes high incidence of subclinical hypothyroidism so monitor in pregnancy
  - Of 82 type 1 diabetics 22.5% in T1 and 18.4% in T3 had thyroid dysfunction (usually subclinical hypothyroidism)

Gallas et al 2002
Hypothyroidism

- Clinically overt hypothyroidism rare in pregnancy due to subfertility

- Symptoms and signs similar to non-pregnant
  - Fatigue, weakness, cold intolerance, constipation, dry skin etc

- Overt hypothyroidism increased risk of miscarriage, pre-eclampsia, FGR

- Monitor fetal growth
Hypothyroidism in pregnancy

**Good control**
- normal maternal course
- thyroid function test in each trimester
- if euthyroid, T4 requirements usually stable
- monitor fetus/ neonate

**Overt maternal hypothyroidism**
- intellectual impairment in childhood
- pre-eclampsia
- FGR, abruption, prematurity
- fetal death
1.2.3. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T₄ dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter. USPSTF recommendation level: C; evidence, poor (2|⊙⊙⊙⊙).

1.2.4. The T₄ dose usually needs to be incremented by 4 to 6 wk gestation and may require a 30% or more increase in dosing. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕⊕).
I'm hypothyroid. Should I continue to take my levothyroxine during my pregnancy?

Yes! In fact, it is necessary to increase your dosage 25-50 mcg during the first twelve weeks, or first trimester, of your pregnancy. Check with your GP.

I'm hyperthyroid and take carbimazole. Is this okay during pregnancy?

Propylthiouracil is the medication of choice during pregnancy for the first trimester only in hyperthyroid (overactive) patients. Carbimazole is the drug used during the rest of pregnancy.

I have been treated with radioiodine for an overactive thyroid. Will this harm the baby?

You should not get pregnant for 6 months after this treatment. If you are in doubt check with your GP.

I have Graves' disease treated by surgery and am taking levothyroxine. Are there any problems for the baby?

Firstly you should increase the dose of thyroxine during pregnancy. There is also a very small chance that the baby could be born with an overactive thyroid but if so it would only last for about one month and can be treated easily. A blood test during the later part of pregnancy will indicate if there is a high risk of this.
Studies of maternal hypothyroxinaemia and subsequent IQ of their offspring

Haddow et al. *NEJM* 1999; 341: 549-555

- 25,216 women screened in 2nd trimester
- 62 with highest TSH compared with 124 controls
- 2/15 psychometric tests in the offspring aged 7-9 yrs showed impaired outcome
- effect more marked if not taking thyroxine
- i.e. impaired function in 8 tests and 7 point ↓ in IQ
Studies of maternal hypothyroxinaemia and subsequent IQ of their offspring


- prospective 3 year follow-up study
- compared 57 cases with FT4 <10th percentile and normal TSH at 12/40 with 58 controls
- thyroid function test in each trimester
- Bayley scales of infant development aged 1 and 2
- children had delayed mental and motor function
- BUT if maternal FT4 increased at 24 and 32/40 the scores did not differ from controls

- studied 1361 pregnant women with normal TSH
- compared 108 neonates of mothers with FT4 < 10th percentile, and 96 from controls
- Neonatal Behavioural Assessment Scale used at 3 wks
- Regression analysis showed that T1 maternal FT4 was a significant predictor of NBAS score
- Did not find any effect for TSH or FT4 later in gestation
Management of treated hypothyroidism

- No evidence for *routine* increase in thyroxine during pregnancy
- Monitor and adjust dose of T4 as required
  - 50/100 required dose increase (Kothari & Girling, 2008)
    - 11 diagnosed just before pregnancy
    - 9 raised TSH before conception
    - 8 sub-optimal compliance
- Other studies range from 20-75% (Girling JC & de Swiet M. BJOG 1992; Mandel NEJM 1990;)
- Little thyroxine crosses the placenta
Timing and Magnitude of Increases in Levothyroxine Requirements during Pregnancy in Women with Hypothyroidism

Erik K. Alexander, M.D., Ellen Marqusee, M.D., Jennifer Lawrence, M.D., Petr Jarolim, M.D., Ph.D., George A. Fischer, Ph.D., and P. Reed Larsen, M.D.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Cause of Hypothyroidism</th>
<th>Baseline Thyrotropin (μU/mL)</th>
<th>Baseline Thyroxine Dose (μg/day)</th>
<th>Baseline Thyroxine Dose (μg/kg/day)</th>
<th>Increase in Thyroxine Dose during Gestation (%)</th>
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Does thyroxine requirement increase in pregnant women with hypothyroidism?

Alexander et al. *NEJM* 2004; 351: 241-249

- prospective measurement of TFT, HCG, estradiol pre-conception and in 1st trimester
- 20 pregnancies in 19 women
- thyroxine dose ↑ if TSH > 5.0 µU/ml
- 6 cases had Ca - ↑ if TSH > 0.5 µU/ml

**Results:**

- 17/20 (85%) pregnancies required increased thyroxine
- mean thyroxine requirement ↑ by 47%
Does inadequate thyroxine replacement influence subsequent intelligence of the offspring?

Lazarus et al. – NEJM 2012; 366:493-501

- 21846 women screened at 12/40
- Randomly allocated to screened (results revealed and thyroxine given if TSH > 97.5th C or fT4 < 2.5th C) or control
- 390 screened; 404 control: no diff in IQ or RR of low IQ at 3 years of age

- Sensible to screen all women with hypothyroidism at booking and before conception to ensure TSH is normal and FT3 and FT4 are not low

- Ideally aim for fT4 level at the upper end of the normal range (gestation specific)

- **there are no studies to show that T4 treatment in pregnancy will influence subsequent long-term intelligence**
1.2.6. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored every 4–6 wk for elevation of TSH above the normal range for pregnancy. USPSTF recommendation level: A; evidence, fair (1|⊕⊕⊕⊕).
Hypothyroidism Summary: Practical management

- **Prepregnancy**
  - Good control and reassure re safety

- **Antenatally**
  - Monitor fT4 / TSH at first visit and in each trimester (more frequently if inadequate replacement)
  - Increase dose of T4 if required…Remember to avoid taking T4 with antacids or iron

- **Postpartum**
  - Review treatment and repeat TFTs
Hyperthyroidism in pregnancy

- In poorly / uncontrolled patients increased risk of preeclampsia, FGR, preterm labour, high output cardiac failure

- Study of 19 patients with uncontrolled thyrotoxicosis (Montoro and Mestman 1981)
  - 15 preterm delivery
  - 5 neonatal deaths
  - 5 severe neonatal morbidity

- Often improves in second / third trimesters

- Graves ophthalmopathy not affected by pregnancy
Hyperthyroidism in pregnancy

- Encountered in about 0.2% of pregnancies and 1% of women in reproductive age group.
- Most commonly Graves disease rather than toxic (multi)nodular goitre.
- Graves: Thyroid stimulating antibodies.
- Often diagnosed in 1st year after delivery.
Hyperthyroidism in pregnancy

Pregnancy mimics hyperthyroidism

- Heat intolerance, palpitations
- Emotional disturbance
- Bowel disturbance
- Goitre, palmar erythema
- Increased total T4, decreased TSH

But not: weight loss, eye signs, pretibial myxoedema
Hyperthyroidism in pregnancy: Treatment

- PTU or carbimazole: both safe
  - Not teratogenic
  - Aplasia cutis linked to Carbimazole
  - Side effects: eg agranulocytosis, thrombocytopenia, hepatitis
  - Doses less than 150mg/day PTU & 15mg/day Carbimazole will not affect the fetus
  - Breast feeding ok
  - DO NOT BLOCK & REPLACE

- Propranolol: initial treatment for tachycardia and tremor
PTU vs Carbimazole

- **Carbimazole**
  - Preferred in non-pregnant
  - Longer half life and ? Better compliance as once daily dosing
  - Fewer major adverse events (agranulocytosis)
  - Aplasia cutis very rare

- **PTU**
  - Preferred for new treatment in pregnancy
  - Short half life more frequent dosing
  - More minor adverse events (rashes)
  - Less placental and breast transfer (higher protein binding / less soluble)
  - Inhibits peripheral conversion of T4 to T3
Hyperthyroidism and pregnancy: treatment

- The place of surgery
  - Large goitre
  - Failed medical therapy
  - Side effects eg hepatitis

- No radio-iodine treatment in pregnancy and delay pregnancy for at least 4 months afterwards

- (NB diagnostic isotope scans should be avoided but if carried out risk of harm is low. If postpartum, avoid breast feeding for 24 hours)
Fetal Thyrotoxicosis

- Rare in contemporary practice especially if patient treated with antithyroid drugs. Beware post thyroidectomy / radioiodine pts

- **DIAGNOSIS** - suspect if high maternal levels of TSIs / active Graves’ Disease
  - Ultrasound - Increased AFI / non-immune hydrops, FGR, fetal goitre, FHR > 160
  - FBS for TFTs to confirm

- **TREATMENT** - maternal carbimazole + thyroxine

- **PROGNOSIS** - self-limiting after delivery but high mortality if untreated in utero (50%)
Neonatal thyrotoxicosis

*BMJ lesson of the week Smith et al 2000; 320: 1260-1*

- Transplacental transfer of maternal auto antibodies possible even if mother previously treated with radiol / surgery
- Take full history from women on thyroxine
- Very rare 1 in 70 of 0.1-0.2%
- Thyroid stimulating antibodies
- TBI index = TSH binding inhibiting Ig
- TBI > 30 predicts; >70 strongly predicts
Hyperthyroidism Summary: Practical Management

- **Prepregnancy**
  - Optimize control and reassure re antithyroid drugs
  - Discuss switch to PTU

- **Antenatally**
  - Check TFTs, discuss safety of treatment and risk of uncontrolled disease
  - Check TSI for risk of fetal hyperthyroidism
  - Ultrasound for fetal assessment

- **Postpartum**
  - Reassure re breast feeding if CBZ less than 15mg/day or PTU less than 150mg/day.
  - Check infant TFTs if higher doses given
Postpartum thyroiditis

- Occurs in up to 10% of all pregnancies

- Anti-microsomal antibodies and family history of autoimmune thyroid disease (70% risk)

- Type 1 diabetes increased risk

- Autoimmune thyroiditis with destruction of tissue and release of Thyroid hormone

- Lymphocytic infiltrate in the tissue

- Small goitre frequent
Postpartum thyroiditis

- Presents 3-6 months after delivery
- Transient hyper or hypothyroxinaemia
- May be biphasic with hyper then hypothyroidism
- Diagnosis: TFTs and differentiate from Graves (no TSI, low uptake on isotope scan)
- Role of screening with post natal TFTs
- Often remits after a year but may progress to permanent hypothyroidism (30% in 4 years)
POSTPARTUM THYROIDITIS

2 FORMS

- Destructive
  - activation of previously subclinical thyroiditis
  - remits spontaneously
  - low radioactive I uptake

- Postpartum exacerbation of autoimmune Graves’ disease
  - high radioactive I uptake
  - needs treatment
POSTPARTUM THYROIDITIS

TREATMENT

- **Hyperthyroid phase**
  - Beta blockers rather than antithyroid drugs
- **Hypothyroid phase**
  - Only give thyroxine if symptomatic

PROGNOSIS

- Tends to recur in subsequent pregnancies
- 25% progress to permanent hypothyroidism within 5 years
Postpartum thyroiditis

BMJ 2000; 320:1513
“...my vague acopia, the ebbing of my confidence, my gradually increasing bulk, my mad-professor hair. My daytime naps...”
“...how can I repay my daughter for growing up with a permanently exhausted mother?”