Endocrine Complications: Pregnancy and the Thyroid
Drugs and the Thyroid

Endocrine and Diabetes
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Outline

• Changes in Pregnancy
• Trimester specific Targets
• Common drugs affecting the thyroid
• New update
• Cases
You are the Endocrine Reg on call

- GP phones you for advice
- 28 F
- 5 ½ weeks pregnant
- TSH is 5.5 miU/L
- She has had a previous miscarriage
- What are you going to say?

- A. Don’t worry pregnancy really early
- B. Be concerned but miscarriage is common not for thyroxine
- C. Start Thyroxine and see in the joint clinic
- D. Get more details re neck, TPO and give thyroxine, pregnancy vitamins arrange joint clinic ANC
- E. Phone a friend
Pregnancy

Metabolic Changes
• Increased erythropoetin, cortisol, noradrenaline
• High cardiac output
• Plasma volume expansion
• High cholesterol and triglycerides
• Pro thrombotic and inflammatory state
• Insulin resistance

Gestational Syndromes
• Pre-Eclampsia
• Gestational Diabetes
• Obstetric cholestasis
• Gestational Thyrotoxicosis
• Transient Diabetes Insipidus
• Lipid disorders
• Postnatal depression
• Postpartum thyroiditis
• Postnatal autoimmune disease
• Paternal Disease
Thyroid gland development

- Fetal thyroid follicles and thyroxine synthesis occurs at 10 weeks
- Axis matures at 15-20 weeks
- Maternal T4 0-12 weeks regulates neurogenesis, migration and differentiation then fetal T4
Thyroid hormone changes during pregnancy

- NEJM 1994
- Mother
- TBG, Total T4, HCG
- Free T4, thyrotropin
- Fetus
- TBG, Total T4
- Thyroptropin, T4, TT3
- FT3
- Importance of Iodine
Glycoprotein hormones

Glycoprotein hormones contain two subunits, a common $\alpha$ subunit and a distinct $\beta$ subunit: TSH, LH, FSH and hCG.
Managing Thyroid Levels during Pregnancy is very crucial.
Hypothyroidism

• Prevalence during pregnancy 2-3 %
• Overt hypothyroidism 0.3-0.5 % pregnancy
• Subclinical hypothyroidism 2-3 %
• Signs and symptoms
• Usually predate the pregnancy:
• Weight gain, cold intolerance, poor concentration, poor sleep pattern, dry skin, constipation, tiredness,
2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum

Authors: Erik K. Alexander MD¹ (co-chairperson), Elizabeth N. Pearce MD, MSc² (co-chairperson and corresponding author), Gregory A. Brent MD³, Rosalind S. Brown MD⁴, Herbert Chen MD⁵, Chrysoula Dosiou MD, MS⁶, William A. Grobman MD⁷, Peter Laurberg MD⁸, John H. Lazarus MD⁹, Susan J. Mandel MD¹⁰, Robin P. Peeters MD, PhD¹¹, and Scott Sullivan MD¹²
ATA guidelines Thyroid 2011

- 1\textsuperscript{st} trimester 0.1-2.5 mIU/L
- 2\textsuperscript{nd} trimester 0.2-3.0 mIU/L
- 3\textsuperscript{rd} trimester 0.3-3.0 mIU/L
- 4 weekly for 20 weeks gestation
- Again 26-32 weeks

- 25-30 % increase if miss period and no recent test
- Urgent blood test and review
FIG. 1. Testing for thyroid dysfunction in pregnancy. ULRR, upper limit of the reference range.
## Aetiology of Hypothyroidism

<table>
<thead>
<tr>
<th>Primary</th>
<th>Transient</th>
<th>Secondary</th>
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<tbody>
<tr>
<td>Autoimmune</td>
<td>Post partum thyroiditis</td>
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<tr>
<td>Hashimoto's Atrophic thyroiditis</td>
<td></td>
<td>Hypopituitarism</td>
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<td>Drugs</td>
<td>Subacute thyroiditis</td>
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<tr>
<td>Lithium</td>
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<tr>
<td>Amiodarone</td>
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<tr>
<td>Iodine Deficiency</td>
<td></td>
<td></td>
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<tr>
<td>Congenital</td>
<td></td>
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<tr>
<td>Toxic nodule</td>
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Hypothyroidism in pregnancy

How does it affect the pregnancy

• Inadequate treatment
• Gestational hypertension
• Placental abruption
• Post partum haemorrhage
• If untreated
• Low birth weight
• Preterm delivery
• Neonatal goitre
• Neonatal respiratory distress

What to do?

• Preconception counselling ideal pre-conception TSH <2.5 mIU/L
• Increase dose by 30 %
• arrange TFT early preg and titrate
• women require a dose increase in their thyroxine during pregnancy

• If overt in pregnancy aim to normalise asap

• Commence at 50-100mcg measure TFT at 4-6 weeks
Subclinical Hypothyroidism

- Controlled Antenatal Thyroid Screening Study (CATS)
- Screening not indicated
- Maternal treatment did not improve cognitive function at the age of 3 years
- Cochrane review 2012
- “There is insufficient evidence to recommend the use of one intervention over another”
- New data in Iodine and TSH upper limits 2017
Targeted Screening

- Age >30
- BMI >40
- Miscarriage preterm labour
- Personal or family history
- Goitre
- Anti TPO
- Type 1 DM
- Head and neck irradiation
- Amiodarone, Lithium or contrast use
What does this show?
Case

• Case 1
• 28 year old lady presents at 23 weeks gestation known asthma
• Second pregnancy
• Known Graves thyrotoxicosis
• Lost to F/U at another Anc clinic
• Looks tremulous, sweaty, tachycardic, large goitre with bruit
Results

• TSH < 0.02
• Ft4 > 60
• FT3 > 32
• TBII positive or 3

• What is the diagnosis?
• What will you do?
Options

- Urgent surgery
- Radioiodine
- PTU and B blocker asap
- Carbimazole and B blocker
- Observe
- Repeat tests
- PTU, B blocker and consider surgery
Try treatment

• Start PTU at high dose- baseline LFT
• Initially check TFT in 2 weeks
• Some change
• FT4 32
• FT3 15
• TSH<0.02
• Setting mobile phone as a reminder
• Goes away for a long weekend and forgets meds!
What are the options?

• A. Surgery asap
• B. Section her under the mental health act 5:2 and treat as inpatient
• C. Continue medications and see weekly
• D. Change the medication
• E. Something else
Outcome

• Control improved
• Underwent SVD at 36.5 weeks in the back of an ambulance!
• DNA all FU appts
• Baby born neonatal transient thyrotoxicosis treated with carbimazole for 6 weeks weight 71B 7oz
• Agreed to undergo thyroidectomy
Hyperthyroidism

• Prevalence in pregnancy is 0.1-0.4 %
• Female Population 2%
• 85-90% due to Graves
• Less common toxic adenoma, MNG, gestational thyrotoxicosis, trophoblastic neoplasia, TSH-oma
Effects

How does the disease effect pregnancy?
• If inadequately treated:
  • IUGR
  • Low birth weight
  • Preecclampsia
  • Preterm delivery
  • Risk of stillbirth
  • Risk of miscarriage

How does pregnancy effect the disease?
• Tends to worsen in the first trimester
• Improves latter half of pregnancy
Management

• Symptomatic treatment- beta blockers are safe eg propranolol 10-20 mg tds
• Anti-thyroid medication
• Choices PTU Carbimazole (prevent thyroid peroxidase enzyme coupling and iodinating tyrosine residues on thyroglobulin reduce T3 and T4)
• RAI is contraindicated during pregnancy
• Surgical interventions- if intolerant optimal timing 2nd trimester

• Carbimazole
• Increased risk of congenital abnormalities
• Aplasia cutis
• Choanal atresia
• Intestinal anomalies
• Propylthiouracil
• Rare hepatotoxicity
What about antibodies??

• TSH-R antibodies (TRAB/TBII)
• Are measured at 22-26 weeks
• If raised 2-3 fold or present fetal/neonatal thyrotoxicosis risk increased and surveillance needed
• Who to test-
• Current Graves, past Graves, previous neonate with Graves, etc
Fetal Thyrotoxicosis

- Transplacental cross over of TSH-R antibodies
- Occurs in 0.01 % of cases
- Management options anti-thyroid medication
- Associated with:
  - IUGR
  - Fetal goitre
  - Fetal Tachycardia
  - Fetal hydrops
  - Preterm delivery
  - Fetal demise
Gestational Thyrotoxicosis

Cause
- Limited to the first half of the pregnancy
- Raised T4, Low/suppressed TSH
- Absence of thyroid autoimmunity
- Associated with hyperemesis gravidarum
- 5-10 cases/1000 pregnancies
- Multiple gestation
- Hydatidaform mole
- Hyperplacentosis
- Choriocarcinoma

Issues
- Benefits of treating
- Hyperemesis gravidum
- Extreme- Wernicke’s encephalopathy electrolyte imbalance low K and IUGR
- Thyrotoxicosis risks
Distinguish Between Them?

<table>
<thead>
<tr>
<th></th>
<th>Graves Disease</th>
<th>Gestational Thyrotoxicosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms predate pregnancy</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Symptoms during pregnancy</td>
<td>+/+++</td>
<td>-/+</td>
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<tr>
<td>N and V</td>
<td>+/-</td>
<td>+++++</td>
</tr>
<tr>
<td>Goitre with bruit TED</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>TSH-R antibody</td>
<td>+</td>
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</table>
Post Partum Thyroiditis

• Prevalence 7%
• High risk women are
• Type 1 diabetics
• Graves disease in remission
• Chronic viral hepatitis
• Measure TSH 3 months post partum
Drugs and the Thyroid

• Commonly
• Amiodarone
• Lithium
• Interferon
• Immune therapies (oncology, rheumatology)
• Lots more.....
# Drugs and the Thyroid

<table>
<thead>
<tr>
<th>Effect on thyroid function</th>
<th>Drugs</th>
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</thead>
<tbody>
<tr>
<td>Increase or decrease thyroid hormone secretion</td>
<td>Iodide, amiodarone, lithium (rare increase)</td>
</tr>
<tr>
<td>Decrease TSH secretion</td>
<td>Dopamine, propranolol, dopaminergic agonists, glucocorticoids, cytokines, octreotide</td>
</tr>
<tr>
<td>Increase hepatic metabolism of T4</td>
<td>Rifampin, phenytoin, carbamazepine, barbiturates</td>
</tr>
<tr>
<td>Decrease thyroidal synthesis</td>
<td>Carbimazole, propylthiouracil, lithium</td>
</tr>
<tr>
<td>Impair T4 to T3 conversion</td>
<td>Beta-blockers, glucocorticoids, amiodarone, propylthiouracil, radiocontrast dyes</td>
</tr>
<tr>
<td>Displacement of T4/T3 from plasma proteins</td>
<td>Furosemide, NSAIDs, mefenamic acid, carbamazepine, beta-blockers</td>
</tr>
<tr>
<td>Increase thyroxine-binding globulin (TBG), total T3, total T4</td>
<td>Estrogens, tamoxifen, heroin, methadone, raloxifene</td>
</tr>
<tr>
<td>Decrease TBG, total T3, total T4</td>
<td>Androgens, anabolic steroids, glucocorticoids</td>
</tr>
<tr>
<td>Impair absorption of thyroxine</td>
<td>Cholestyramine, aluminum hydroxide, ferrous sulfate, sucral fate, calcium carbonate, protein pump inhibitors</td>
</tr>
<tr>
<td>Autoimmunity altered</td>
<td>Interleukin 1, interferon-alpha, interferon-beta, TNF-alpha</td>
</tr>
<tr>
<td>Modify thyroid hormone action</td>
<td>Amiodarone</td>
</tr>
</tbody>
</table>
Amiodarone and thyroid function

• *Dirty drug*
• Potent anti-arrhythmic- AF
• 37 % iodine by weight
• 200mg tablet 75 mg iodide
• Lipid soluble
• Long elimination half life
• 14-18 % get abnormalities
• AIT or AIH
Amiodarone Induced Hypothyroidism (AIH)

• Susceptibility
• Inhibitory effect on thyroid hormone synthesis
• Inability of gland to escape Wolf-Chaikoff effect
• Accelerate Hashimotos trend
• Reduction in Thyroid hormone synthesis
• Downregulation of peripheral receptors
Amiodarone Induced Thyrotoxicosis

• AIT type 1
  • Latent pre-existing
  • Low iodine areas
  • Iodine induced excess
  • Thyroid hormone release
  • Jode-Basedow phenomenon

• AIT Type 2
  • Normal Thyroid
  • Destructive
Key points

• Amiodarone - Iodine Rich often used to treat Atrial fibrillation
• SE: pulmonary, GI, ophthalmic, neurologic, dermatologic, thyroid
• Incidence AIT 3 % M>F
• AIH 22 % F>M
• Prognosis
• Dronedarone does not contain Iodine
Ipilimumab (and Nivolumab)

• Recently recommended by NICE for advanced melanoma
• Mode of action: monoclonal antibody, activates immune system by inhibiting CTLA-4 which normally downregulates immune system
• Target CTLA-4 – keeps T Cell active to destroy cancer cells
Ipilimumab Hypophysitis: Literature

• New Entity
• Original description 2008
• 64 hits on pubmed review
• Most in 2014-2015
• Recent review article
• To date no biopsy samples
Ipilimumab

Most common Endocrinopathies:

• Hypophysitis 0-17 %
• Hypothyroidism (thyroiditis related) 2.7 %
• Hyperthyroidism (thyroiditis related) 0.3 %
• Primary Adrenal Insufficiency 2.1 %

Ipilimumab Hypophysitis (IH)

- Can occur as early as 4 weeks after
- Median 11 weeks
- Most remain on Glucocorticoids
- Males>Females (unlike lymphocytic hypophysitis)
- More frequent with increased usage given overall survival benefit
- Strategies for early detection
Summary

• Headache common presentation
• Can occur as early as 3 weeks but most 11 weeks*
• If doubt take bloods and give steroids
• Discuss with Endocrine
• MRI pituitary
• Visual fields
• Thyroid – hypo/hyper after thyroiditis 2.7 % and 0.3 %
• Hypophysitis with hypopituitarism in up to 17 %*
• Recovery may occur

Unknowns

• True incidence of all hormone deficiencies
• True recovery and how often to assess for recovery
• Whether high dose steroid really needed (..give only if vision were compromised ?)
• Patchy initial investigation and follow up investigation
Summary

• Awareness pregnancy ranges for TFT are lower
• Impact of thyroid disease on fetus and mother
• Many drugs can affect thyroid particularly amiodarone
• Newer immune therapies
• Future drugs

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WELL, MR AND MRS SPRAT, IT APPEARS TO HAVE BEEN YOUR THYROIDS ALL ALONG.