“Mother’s little helper”
Endocrine disease in pregnancy

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ABCD Spring meeting
22/4/2016

University of Glasgow

Topics

- Thyroid disease
  - Hyperthyroidism
  - Hypothyroidism
  - Subclinical hypothyroidism
- Pituitary disease
  - Prolactinomas
  - Diabetes insipidus
  - Hormone replacement
- Adrenal disease

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Thyroid in pregnancy

- More TBG
- More inactivation of T_4 and T_3
- Placental transfer of T_4 to foetus
  - Baby doesn't produce T_4 until 18-20 weeks
  - Baby deiodinases T_4 to T_3

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24 yr old woman

- 14 weeks' first pregnancy
  - Vomiting, tachycardia
  - fT_4 26pmol/l, TSH <0.01mU/l
- 18 weeks'
  - Feeling better
  - fT_4 18pmol/l, TSH 0.02mU/l

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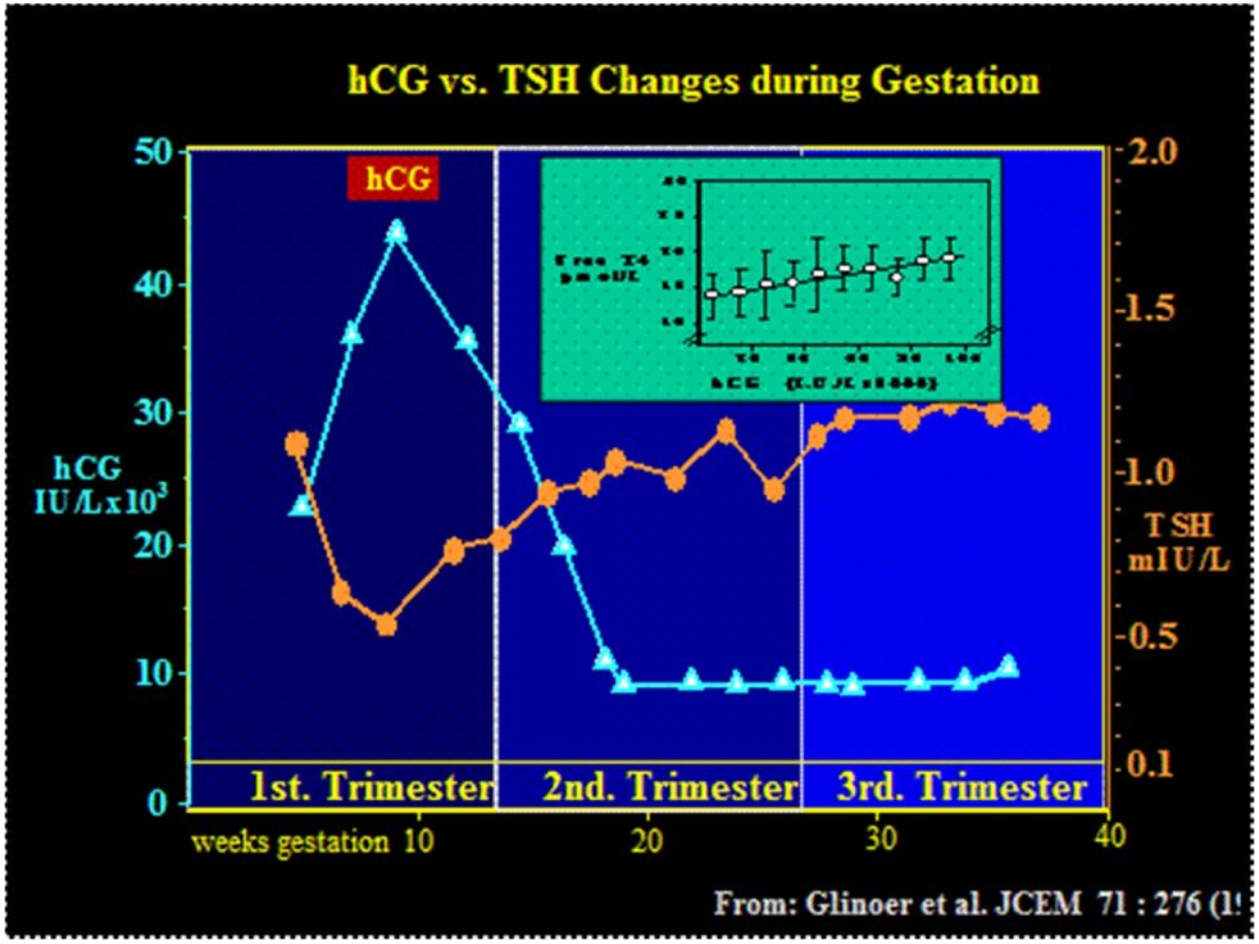
hCG



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Hyperemesis gravidarum (Gestational transient thyrotoxicosis)

- Early pregnancy
  - XS vomiting
  - Non-specific symptoms

- Treat with fluids ± β-blockers
- Need to differentiate from Graves'

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Hyperemesis *vs* Graves'

- Graves' suggested by:-
  - Goitre
  - +ve TRAbs
  - Eye signs
  - Weight loss / myopathy
  - Symptoms prior to pregnancy
  - Increased vascularity on USS

If fT_4 > 1.5 times reference range *and* TRAb +ve
"treat as clinically necessary"

De Groot et al, JCEM 2012

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Graves' disease in pregnancy

- 0.2% of pregnancies

- Risk factor for
  - Pre-eclampsia, IUGR, miscarriage, preterm delivery
  - Foetal thyrotoxicosis

- How to treat…

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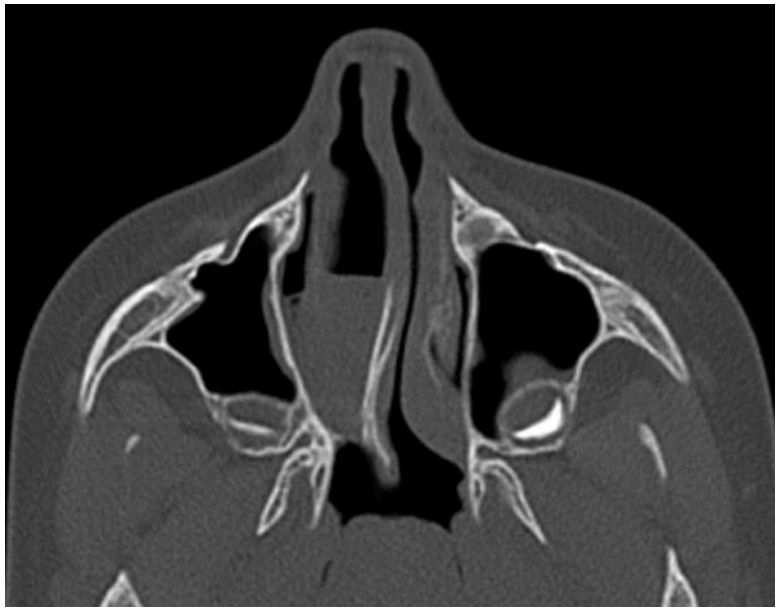

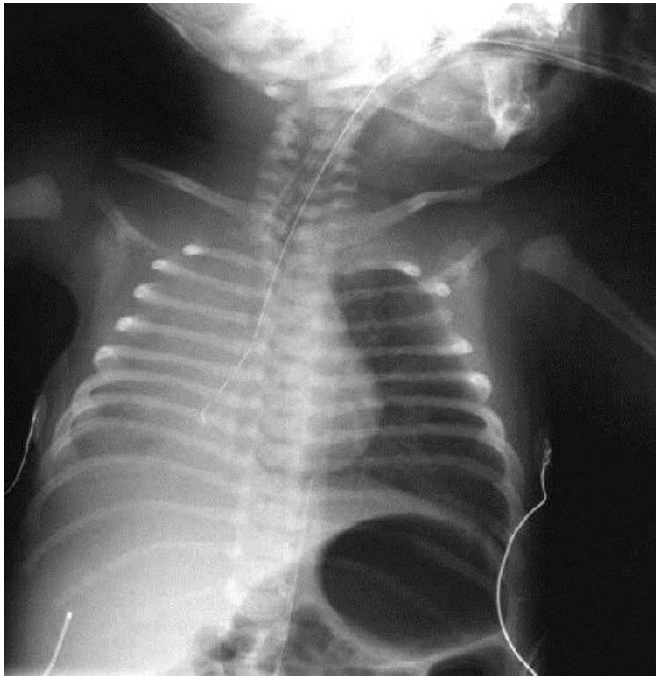

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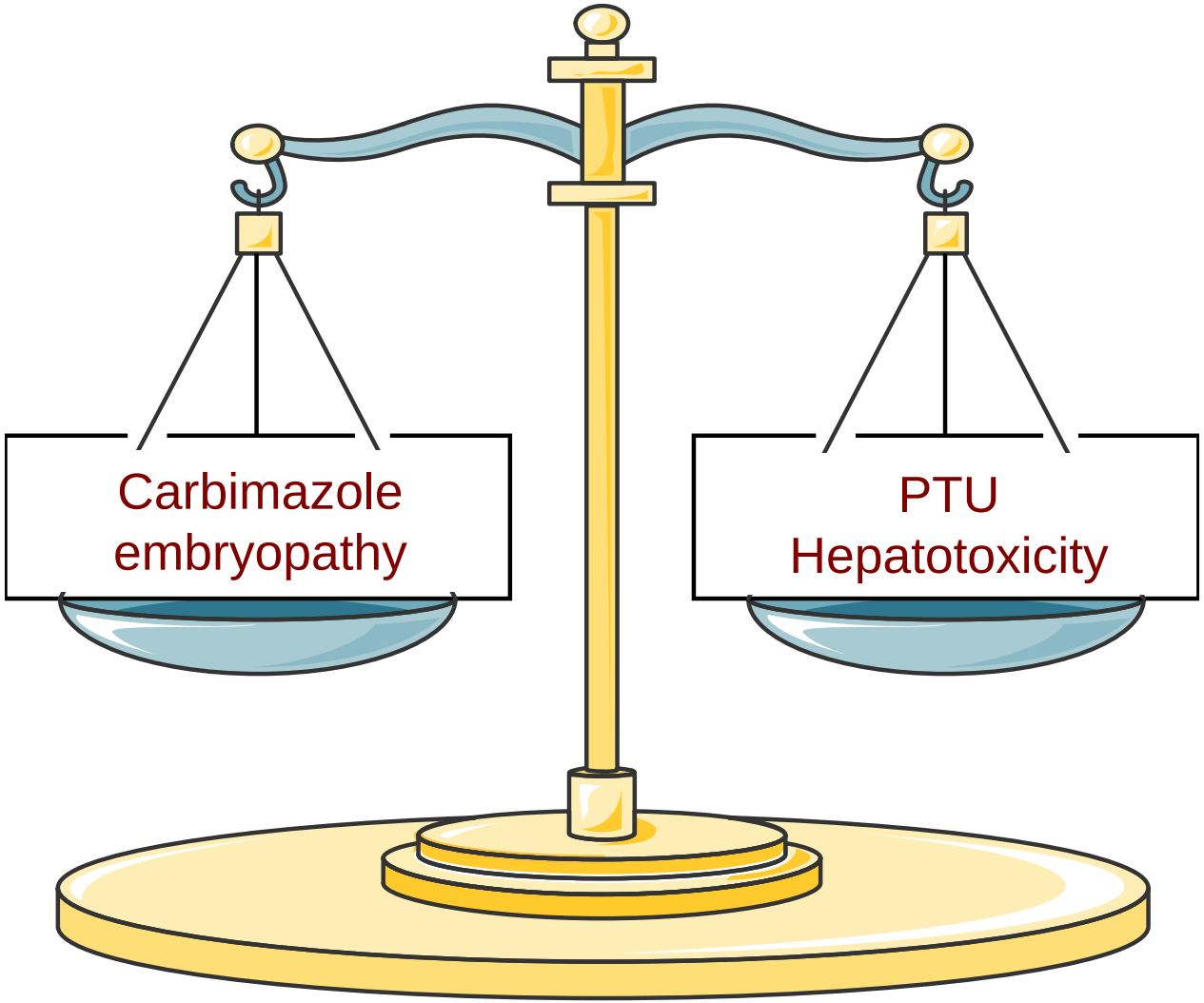
Drugs in pregnancy

- Both carbimazole and PTU cross placenta



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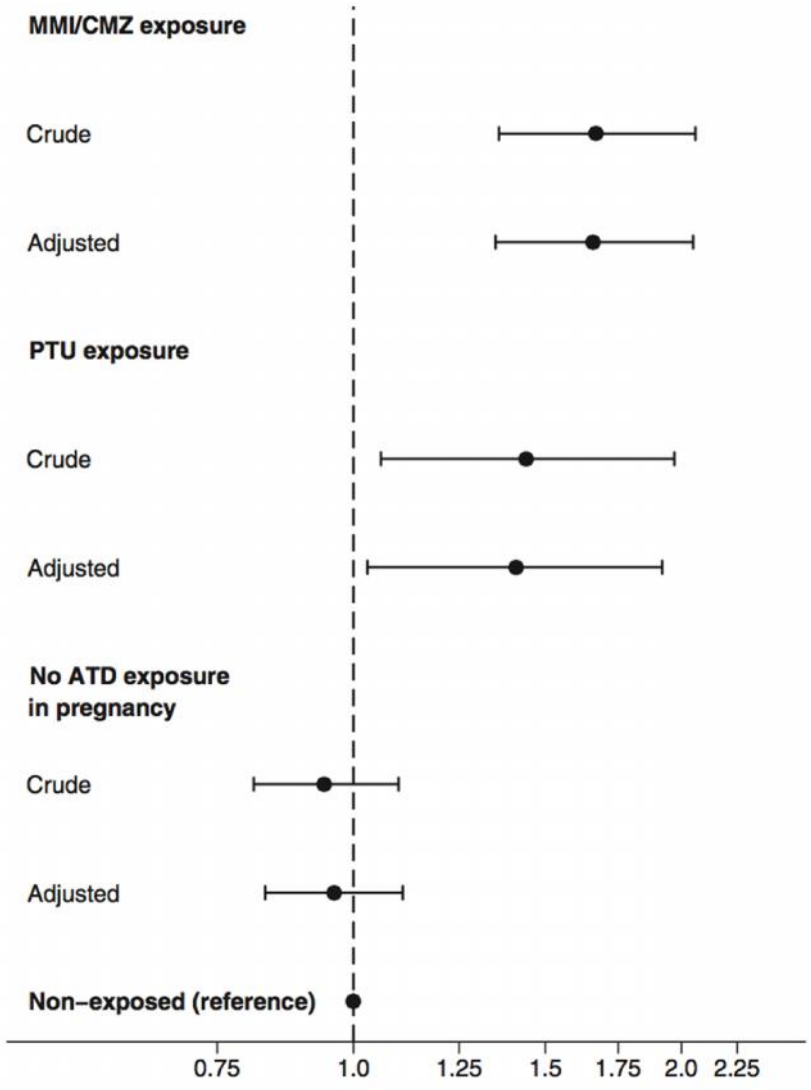

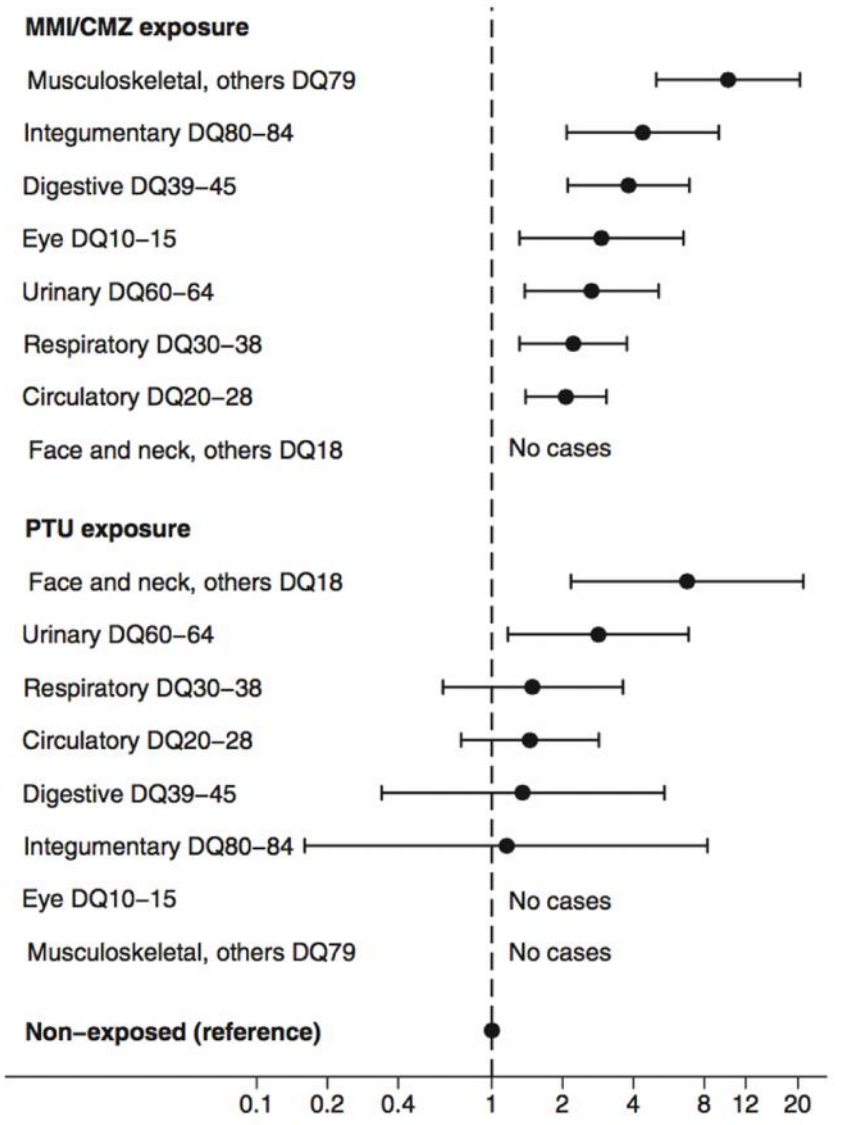

Anderson et al JCEM 2013 98 (11):4373-4381

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Treatment of Graves' disease

- PTU pre-pregnancy and in first trimester
- Carbimazole thereafter

- Lowest dose possible
  - Aim for fT_4 towards upper end of (non-pregnant) reference range
  - Check TFTs every 4 wks

- Risk of recurrence in post-partum period

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TRAb antibodies

- Cross placenta & stimulate foetal thyroid

- In women with Hx of Graves' check TRAb at time of initial TFTs
  - If negative then no need to repeat
  - If positive recheck at 18-22 weeks to establish foetal monitoring

ATA Draft guidelines presented Endo 2016

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Case

- 24 yr old woman
- Hypothyroid since 2009
  - 100 mcg thyroxine daily
  - TPO +ve

- 6 weeks pregnant
- Feels more tired
- fT_4 15pmol/l, TSH 5.3mU/l

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TSH target ranges

- First trimester 0.1 - 2.5 mU/l
- Second trimester 0.2 - 3.0 mU/l
- Third trimester 0.3 - 3.5 mU/l

American Thyroid Association 2011

Thyrotropin reference ranges in different populations

Reference	Population	Thyrotropin reference range (mIU/L)		
		1st trimester	2nd trimester	3rd trimester
Stagnaro-Green[8]	US*	0.1-2.5	0.2-3.0	0.3-3.0
De Groot[9]	US†	0.1-2.5	0.2-3.0	0.3-3.5
Yan[19]	Chinese	0.03-4.51	0.05-4.50	0.47-4.54
Li[20]	Chinese	0.14-4.87		
Marwaha[21]	Indian	0.6-5.0	0.44-5.78	0.74-5.7
Korevaar[22]	Mixed (Dutch, Moroccan, Turkish, Surinamese)	0.06-4.51		

*American Thyroid Association guideline recommendations.
†Endocrine Society guideline recommendations.

Negro & Stagnaro-Green, BMJ 2014

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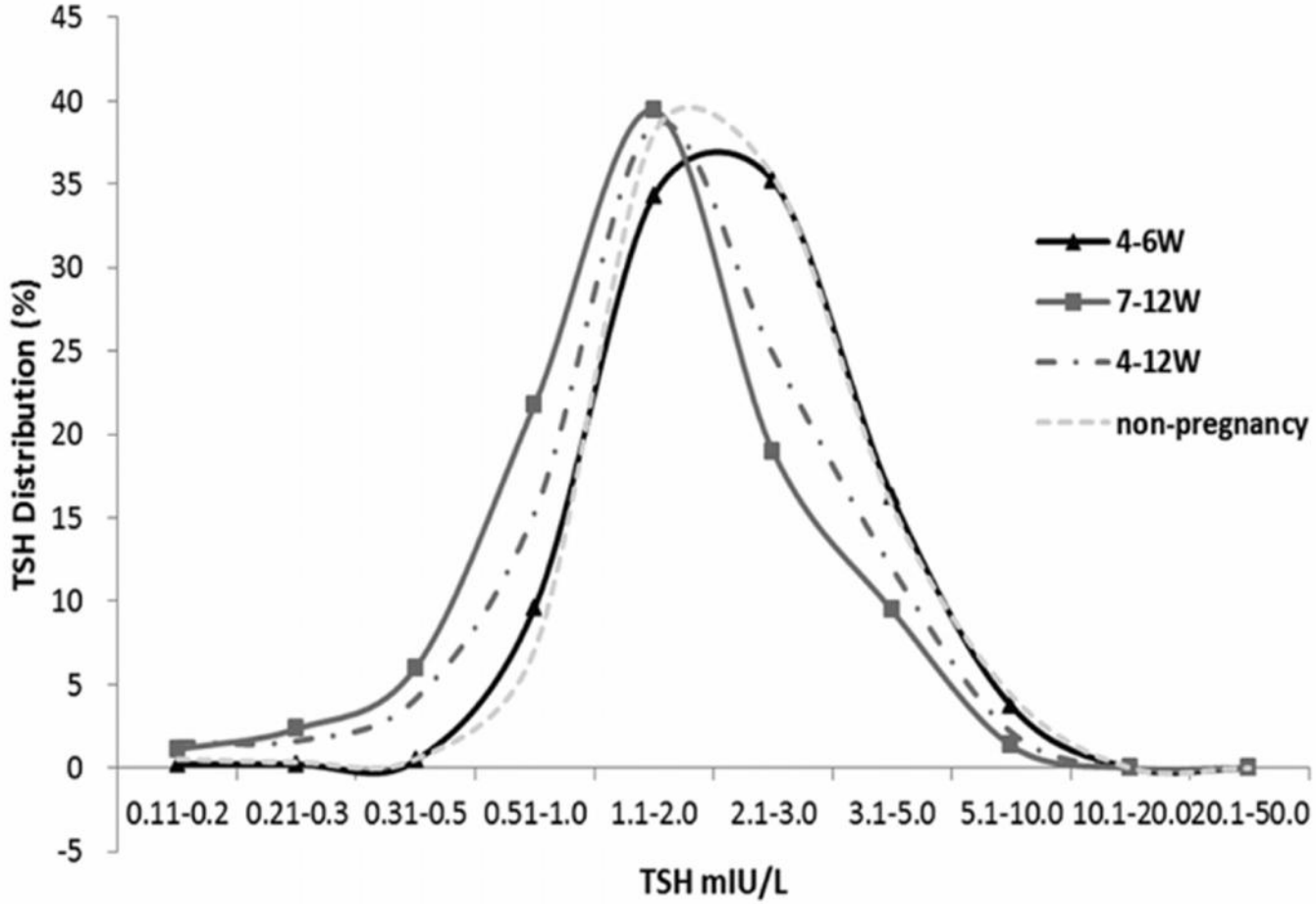

Figure 1. The distribution of TSH in different subgroups. Compared with pregnant women during 7 to 12 gestational weeks, the distribution of TSH at 4 to 6 gestational weeks moves to the right significantly and almost coincides with nonpregnant women.

Li et al, JCEM 2014 99 (1):73-79

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

- 16 women
  - 9 had thyroid cancer

- 50-85% of women need a dose increase
  - Mean 28mcg increase needed

- Higher increment needed if no residual thyroid tissue

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What should we do?

- ATA guidelines 2011
  - 2 extra tablets per week (29%)
- US Endo 2012
  - increase by 30%
- John Lazarus (UK)
  - “take extra 50mcg when +ve pregnancy test”
  - Then tell GP
  - Recheck a month later

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Any harm in empirically increasing dose?

- Probably not
- No evidence of iatrogenic hyperthyroidism
- Main risk is patient anxiety about under / late treatment

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Case

Dear Dr Carty

This 45 yr old is undergoing IVF at a private L*nd*n clinic. Her TSH was 3.5mU/l. She is well. They've told me to start her on thyroxine and she's to come back once her TSH is <2mU/l

- **Subclinical hypothyroidism**
  - Elevated TSH, normal fT_4, few or no clinical symptoms

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What's the evidence?

- SCH associated with ↑ miscarriage risk

- Treatment in fertility setting
  - ↑ live delivery rate (NNT 3)
  - ↓ miscarriage rate

Velkeniers et al, Hum Reprod Update 2013

- In general obstetric setting
  - One trial in TPO+ve women
  - ↓ miscarriage rate

Negro et al, JCEM 2006

- Meta-analysis
  - No overall benefit

Reid et al, Cochrane Collaboration 2012

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How common is SCH?

- Previous reports 2-3% of pregnant women affected

- If TSH>2.5mU/l used as cut off
  - 15% of pregnant women in Netherlands
  - 28% of pregnant women in China

Li C et al, JCEM 2014,
Negro R et al, BMJ 2014

The NEW ENGLAND JOURNAL of MEDICINE

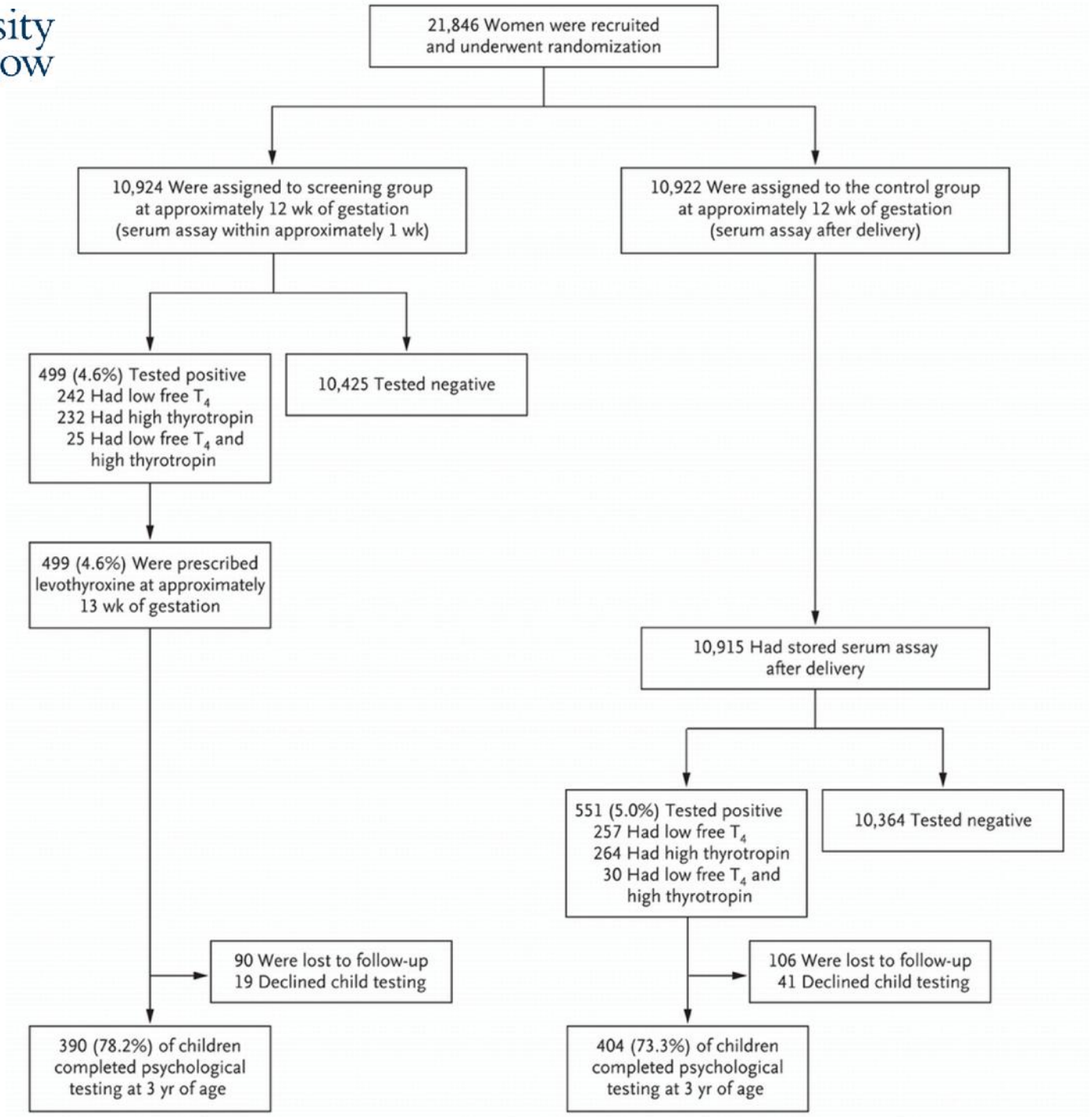
ORIGINAL ARTICLE

A Correction Has Been Published

Antenatal Thyroid Screening and Childhood Cognitive Function

John H. Lazarus, M.D., Jonathan P. Bestwick, M.Sc., Sue Channon, D.Clin.Psych., Ruth Paradice, Ph.D., Aldo Maina, M.D., Rhian Rees, M.Sc., Elisabetta Chiusano, M.Psy., Rhys John, Ph.D., Varvara Guaraldo, M.S.Chem., Lynne M. George, H.N.C., Marco Perona, M.S.Chem., Daniela Dall'Amico, M.D., Arthur B. Parkes, Ph.D., Mohammed Joomun, M.Sc., and Nicholas J. Wald, F.R.S.

N Engl J Med 2012; 366:493-501 | February 9, 2012 | DOI: 10.1056/NEJMoa1106104


21,846 Women were recruited and underwent randomization
10,924 Were assigned to screening group at approximately 12 wk of gestation (serum assay within approximately 1 wk)
10,922 Were assigned to the control group at approximately 12 wk of gestation (serum assay after delivery)
499 (4.6%) Tested positive
242 Had low free T4
232 Had high thyrotropin
25 Had low free T4 and high thyrotropin
10,425 Tested negative
499 (4.6%) Were prescribed levothyroxine at approximately 13 wk of gestation
90 Were lost to follow-up
19 Declined child testing
390 (78.2%) of children completed psychological testing at 3 yr of age
10,915 Had stored serum assay after delivery
551 (5.0%) Tested positive
257 Had low free T4
264 Had high thyrotropin
30 Had low free T4 and high thyrotropin
10,364 Tested negative
106 Were lost to follow-up
41 Declined child testing
404 (73.3%) of children completed psychological testing at 3 yr of age

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Why was it negative?

- Wrong assessment of child intellectual function?
- Thyroxine started too late?
- Due to incomplete follow-up?
- IQ assessed too early?

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NIH Multicentre Study

- 97,226 pregnancies screened for
  - Low fT4(<0.86ng/dl) *or*
  - Raised TSH (>4mU/l)
  - IQ assessed age 5 years

Table: Median IQ Scores According to Trial and Treatment Group

Study Group	Placebo	Levothyroxine
Subclinical Hypothyroidism*	N=325 94 [85, 107]	N=323 97 [85, 105]
Hypothyroxinemia*	N=253 91 [82, 101]	N=254 94 [83,101]

* Data shown as Median IQ Score [25th %ile, 75th %ile]

Casey et al Am J Obstet Gynecol S2 Abstracts Feb 2016

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Guidelines

- American Thyroid Association (2011)
  - Treat SCH (TSH>2.5 mU/l) if AB+ve or if TSH>10 mU/l
- US Endocrine Society (2012)
  - Treat SCH (TSH>2.5 mU/l) regardless of AB status
- European Thyroid Association (2014)
  - Treat SCH (TSH>2.5 mU/l) regardless of AB status
- ACOG (2015)
  - Do not treat SCH

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Treatment of SCH in pregnancy

- Pros
  - Cheap and safe
  - Potential benefits (esp if AB+ve)
- Cons
  - Lack of evidence
  - Potential of over-treatment / anxiety
  - What happens after the pregnancy?
- Trimester / ethnicity specific ranges needed

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TABLET trial

Randomised Controlled Trial of the Efficacy and Mechanism of Levothyroxine Treatment on Pregnancy and Neonatal Outcomes in Women with Thyroid Antibodies (TABLET)

In 'TABLET'

- Birmingham Clinical Trials Unit (BCTU)
- **TABLET**

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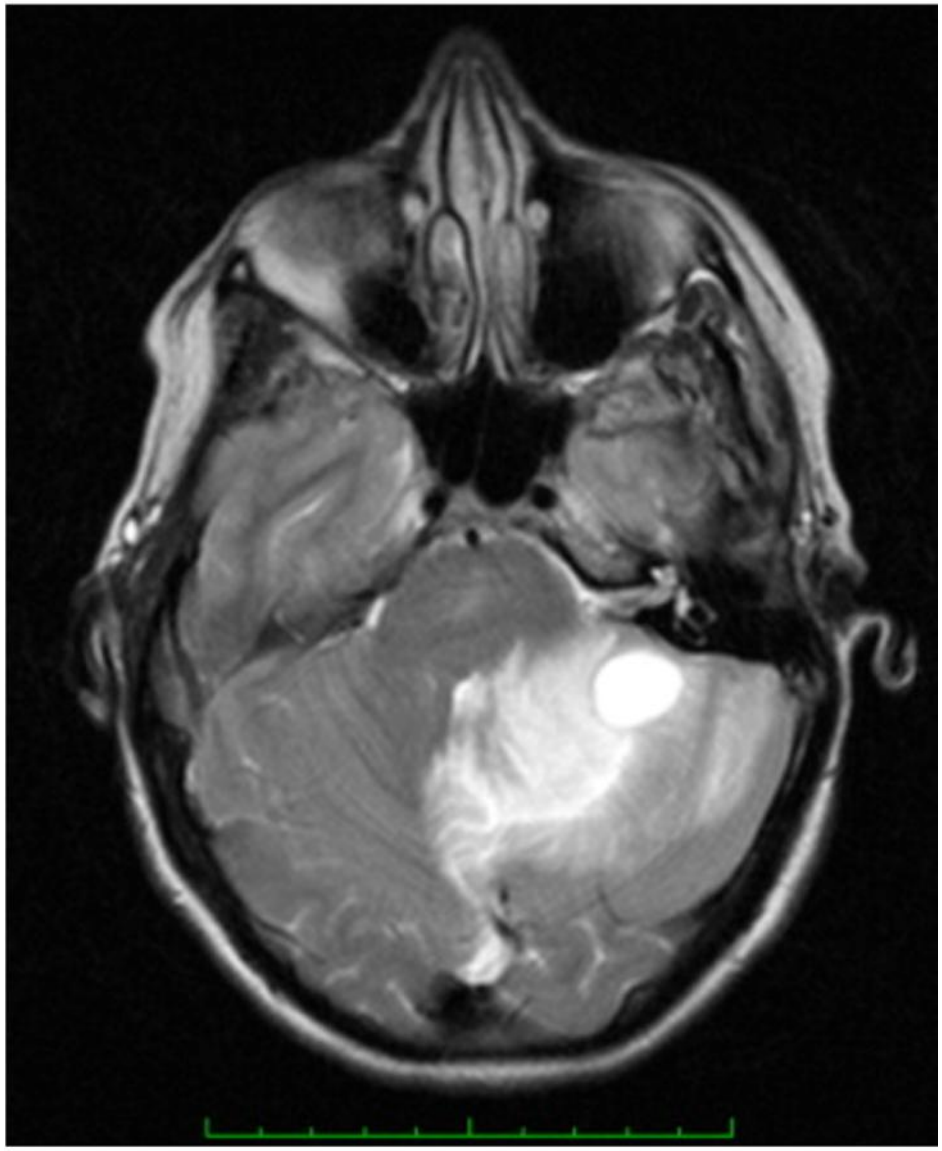

Carty DM et al, EJOG 2011

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Prolactinoma in pregnancy

- Pituitary expands by ≈30%
  - Peak in second week post-partum
- Bromocriptine crosses placenta
- Cabergoline?

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Safety of DAs in pregnancy

	Bromocriptine (*n* (%))	Cabergoline (*n* (%))	Normal (%)
Pregnancies	6239 (100)	968 (100)	100
Spontaneous abortions	620 (9.9)	73 (7.5)	10–15
Terminations	75 (1.2)	63[d] (6.5)	20
Ectopic	31 (0.5)	3 (0.3)	1.0–1.5
Hydatidiform moles	11 (0.2)	1 (0.1)	0.1–0.15
Deliveries (known duration)	4139 (100)	705 (100)	100
At term (>37 weeks)	3620 (87.5)	634[e] (89.9)	87.3
Preterm (<37 weeks)	519 (12.5)	71 (10.1)	12.7
Deliveries (known outcome)	5120 (100)	629 (100)	100
Single births	5031 (98.3)	614 (97.6)	96.8
Multiple births	89 (1.7)	15 (2.4)	3.2
Babies (known details)	5213 (100)	822 (100)	100
Normal	5030 (98.2)	801 (97.4)	97
With malformations	93 (1.8)	21 (2.4)	3.0

Molitch et al, EJE 2015 (172): R205-13

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Prolactinoma in pregnancy

- Enlargement in pregnancy
  - High oestrogen levels
  - Discontinuation of DA
- Risk of symptomatic enlargement
  - 2.4% for microadenomas
  - 20% for macroadenomas without previous surgery

Molitch, Best Prac Clin Endo & Metab 2011(25):885-96

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- Microprolactinoma
  - Routine clinical assessment
- Macroprolactinoma
  - Visual field assessment
  - MRI if symptoms or VF impairment
  - Reinstitute DA if enlargement
- Post-partum monitoring

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- Non-functioning pituitary adenomas
  - Rare
  - Unlikely to grow in pregnancy

- Acromegaly
  - Rarer
  - Risk of GDM and PIH
  - Safety of SSA?

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Case

- 25 yr old, 36 weeks pregnant
- Polyuria, nocturia, polydipsia
- Blood sugar normal

- Na 147 mmol/l
- Urine Osmo 89 mOsm/kg
- Serum Osmo 293 mOsm/kg

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Diabetes insipidus in pregnancy

- Transient DI of pregnancy
  - Placenta produces vasopressinase
  - Established DI often worsens / unmasked
- Acute fatty liver pregnancy
- Sheehan’s syndrome
- Lymphocytic hypophysitis

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Sheehan's syndrome

- Pituitary necrosis 2^0 to hypotension
- Within hours of delivery
- Rare nowadays

Harold Leeming Sheehan (1900-1988)

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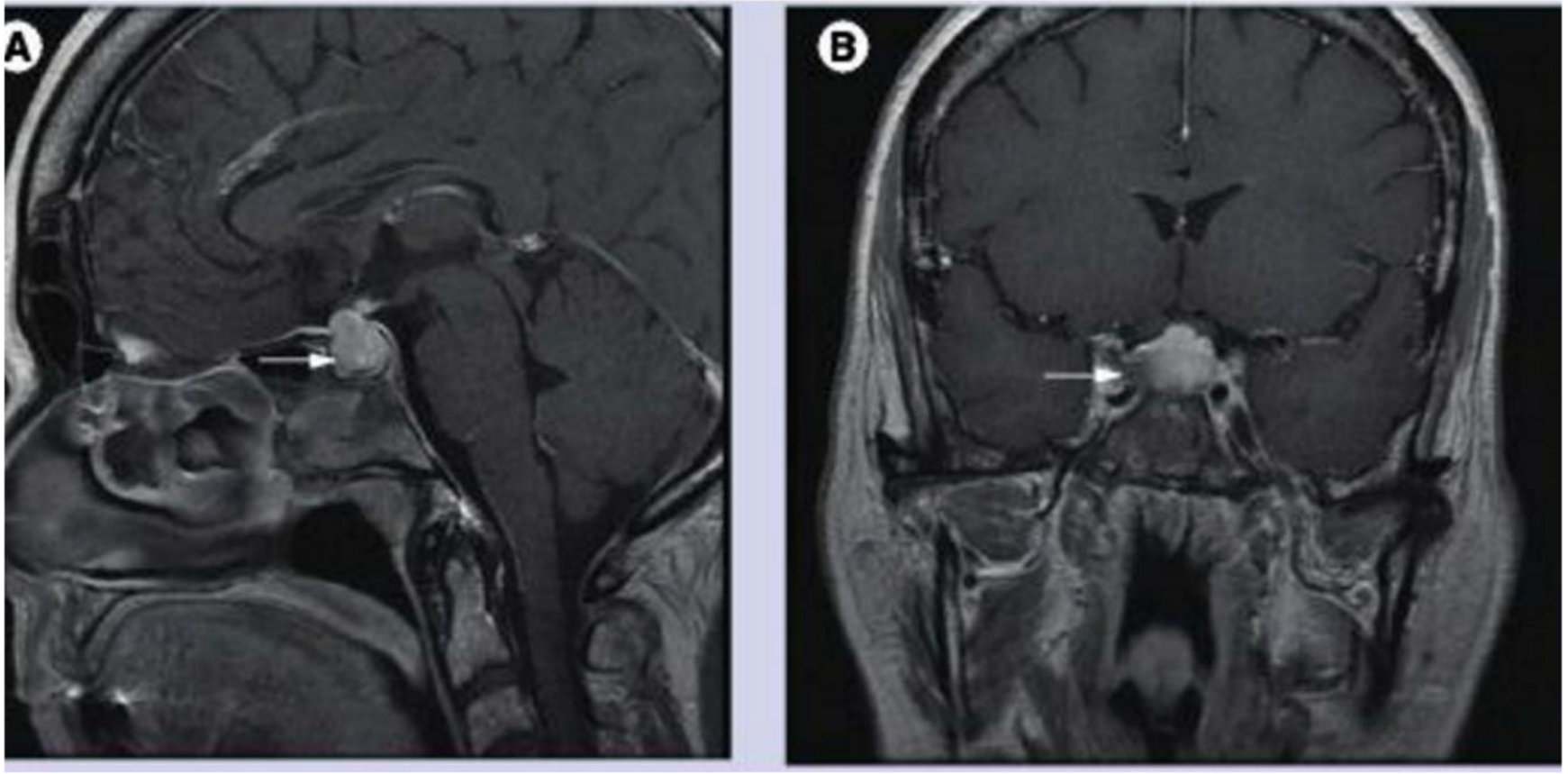
Lymphocytic hypophysitis



Expert Rev Endcrinol Metab, 2011

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Lymphocytic hypophysitis

- Lymphocytic infiltration
  - Probably autoimmune
- Presents with hypopituitarism / DI / symptoms from mass effect
  - Mostly 3rd trimester or in post-partum period
- Diffuse enhancement / enlargement of pituitary
- Often associated with empty sella

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Pituitary hormone replacement

- Hydrocortisone
  - Stress dose (50mg) in 2nd stage labour
- Thyroxine
  - Check TFTs every 4-6 weeks
- Growth Hormone
  - Avoid
- DDAVP
  - Continue and adjust dose if required

Endocrine Society Guidelines 2016

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Cushing's syndrome

- Levels of free and total cortisol and ACTH rise throughout normal pregnancy
  - Inactivated by 11-β-HSD2
  - Circadian rhythm maintained in normal pregnancy
  - Dexamethasone suppression testing unreliable
  - Reference ranges for UFC not established

- Adrenal sources more common in pregnancy

- Metyrapone not teratogenic

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Adrenal insufficiency

- Diagnosis in pregnancy difficult
  - Vague symptoms
  - Higher cortisol levels than outwith pregnancy
- HC is replacement steroid of choice
  - Increase in HC dose not routinely required
  - Use of IM HC
- Give 50mg IV HC in 2nd stage of labour
  - Repeat every 6-8 hrs

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Primary aldosteronism

- Primary aldosteronism
  - Diagnose with renin / aldo / MRI
  - Treat with conventional BP meds
  - May improve due to progesterone blocking MR receptor

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Summary

- Thyroid disease common in pregnancy
  - Need local trimester and ethnicity specific TFT ranges
  - Should we screen TFTs for all pregnant women?
  - Should we treat SCH?

- Prolactinomas common in pregnancy
  - Microprolactinoma unlikely to enlarge
  - DAs appear to be safe

Questoins?


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