Case 2: 24 yo pregnant female presenting with abnormal TFTs and tachycardia

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ENDORAMA 3/16/2017

Case 2: A different 24 yo pregnant female presenting with abnormal TFTs and tachycardia

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ENDORAMA 3/16

To earn credit for today's activity text code:

KAPBOQ to 773-245-0068

Chief Complaint

24 yo female, 7 weeks pregnant, presented to the ER from outside Ob clinic for chest pain and palpitations.

Heart rate was 128.

TSH checked and was <0.01

HPI

- She states she had had intermittent chest pain and SOB since before pregnancy, approximately 3 months prior to presentation
- Mild sweats intermittently
- Weight relatively stable, no diarrhea
- No eye symptoms, no pain over the neck
- No personal or family history of thyroid disease

Extended History

PMH: None

PSH: None

Allergies: None

Meds: Prenatal vitamin

Social History: No alcohol or cigarette smoking. Works as a home health aide

Family history: No family history of thyroid disease.

Physical Exam

Vitals: 36.6, HR 120-132, BP 114/64, RR 16, SpO2 100%, BMI 26.9

Gen: No acute distress

HEENT: EOMI, no increased insertions, no proptosis/exophthalmos

Neck: palpable thyroid but not enlarged, no nodules, no thyroid bruit

CV: regular rhythm, tachycardic, no murmurs

Abd: Soft, non-tender

MSK: Moving all extremities, no edema

Neuro: sensation intact to touch

Skin: warm, dry

Psych: normal mood and affect

Full set of TFTs

TSH <0.01

T3 619 (80-195)

T4 21.9 (5-11.6)

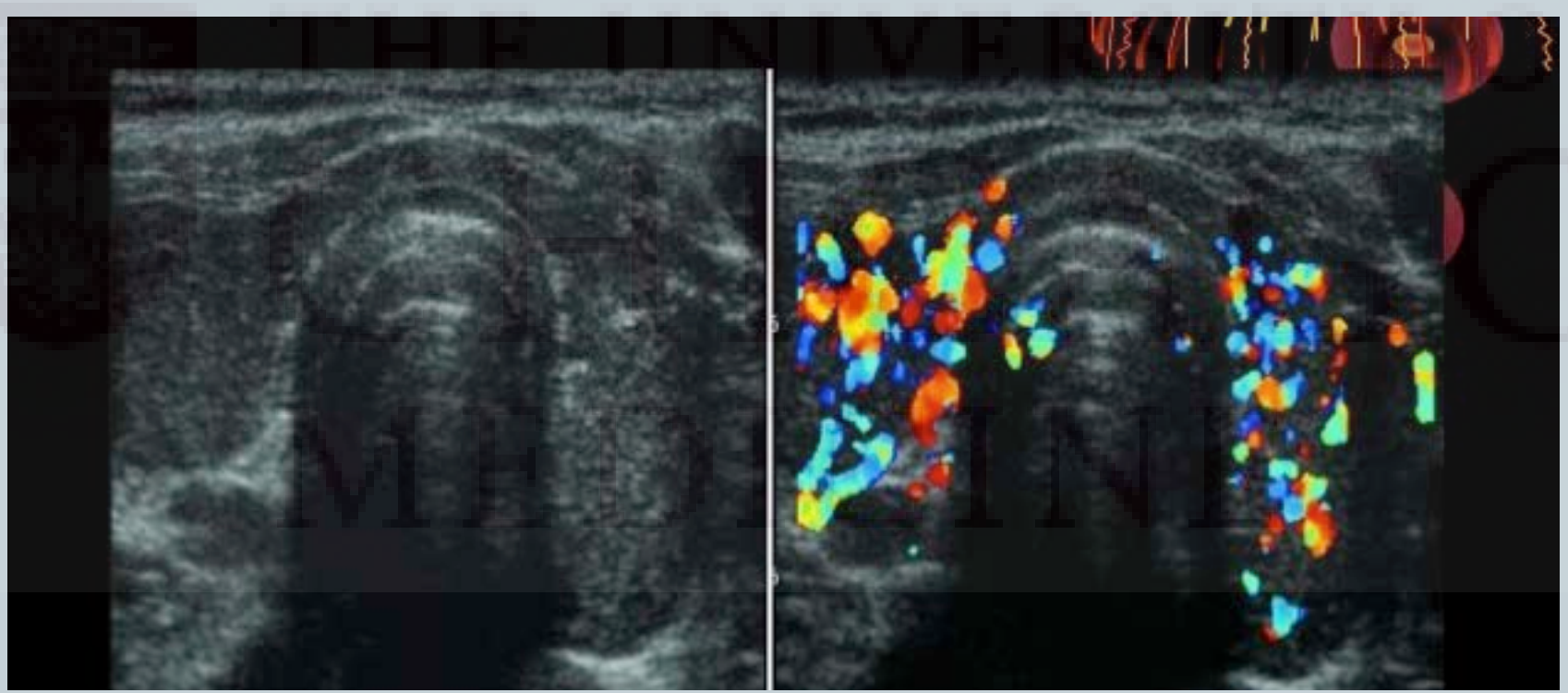
FT4 6.89 (0.9-1.7)

Further workup?

Further workup?

Patient course

- Sent TSI and bedside US done (official not available)



Now what?

US Bloodflow and Etiology of Thyrotoxicosis

65 patients with thyroid disease

Greater than 8% area with blood flow was 84% sensitive & 90% specific

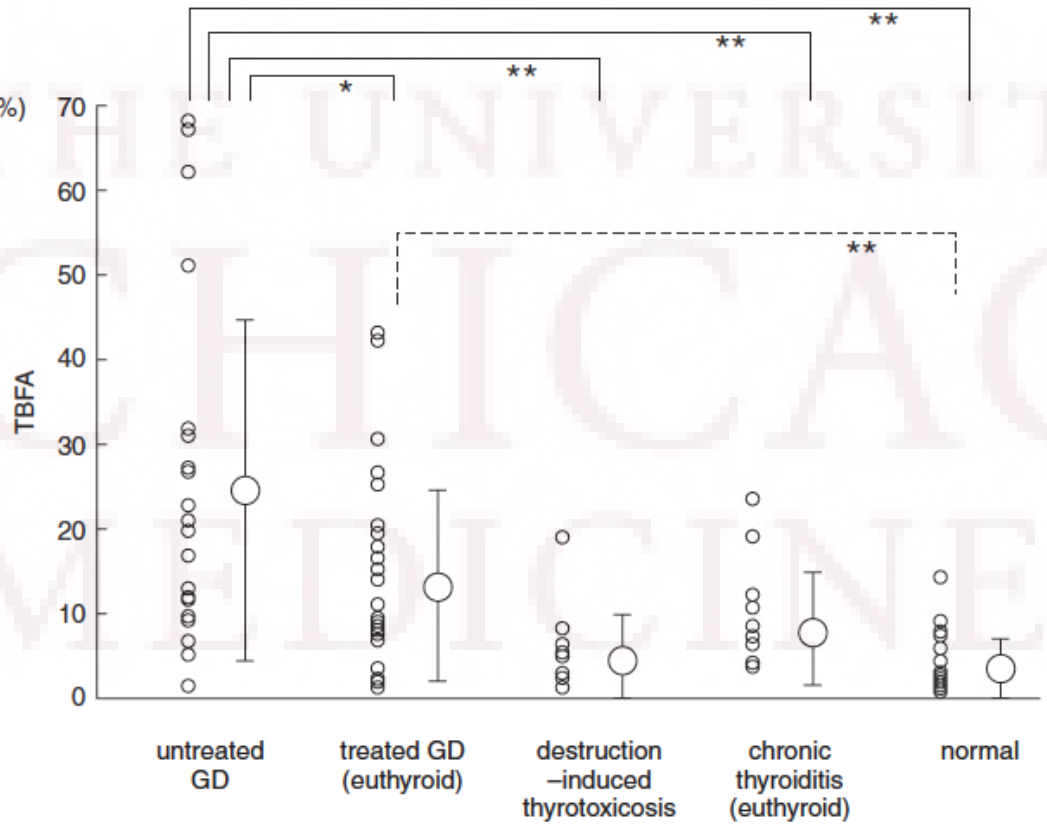


FIG. 1. Relative TBFA in patients with GD and other thyroid diseases. $*p < 0.05$; $**p < 0.001$.

Kurita et al. Measurement of thyroid blood flow area is useful for diagnosing the cause of thyrotoxicosis. Thyroid 2005.

Special obstetric considerations

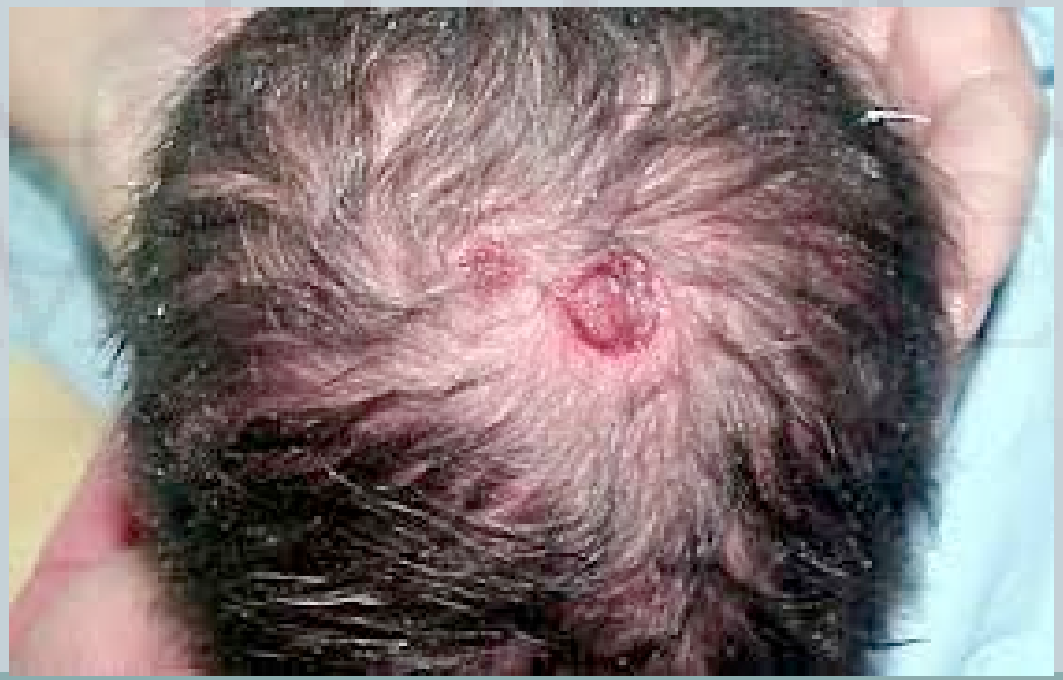
Poor control of thyrotoxicosis is associated with pregnancy loss, pregnancy-induced hypertension, prematurity, low birth weight, intrauterine growth restriction, stillbirth, thyroid storm, and maternal congestive heart failure.

Graves' disease in Pregnancy

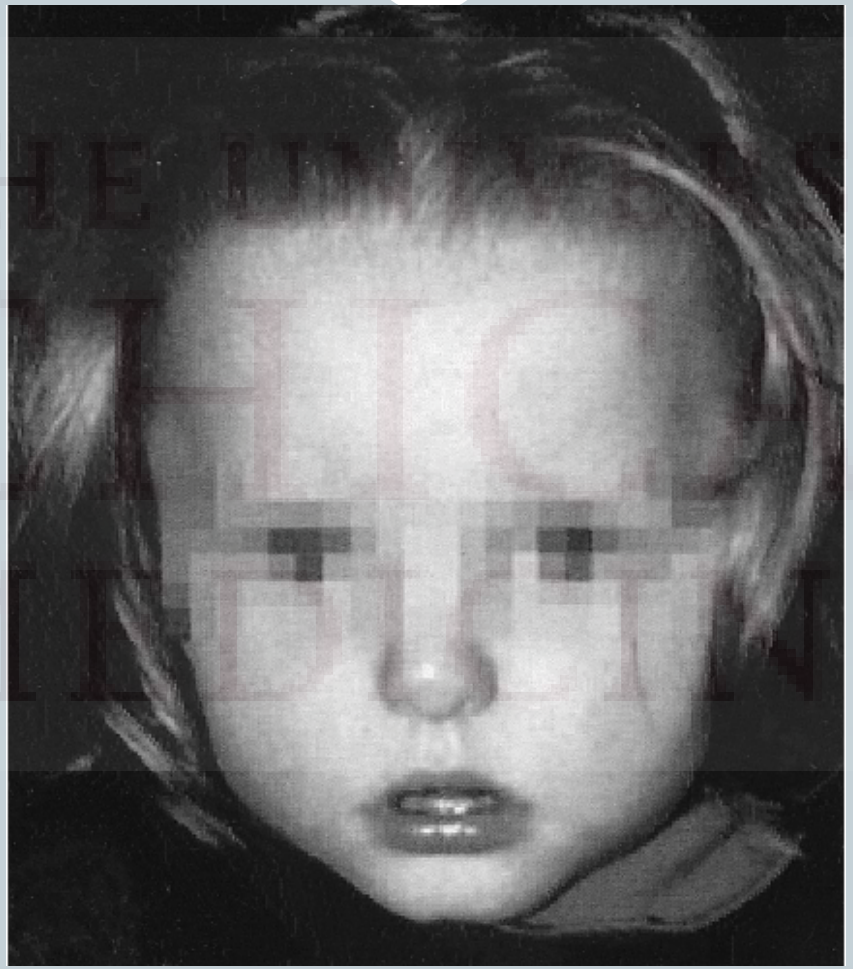
- How does management differ in pregnancy?

Graves' disease in Pregnancy

- PTU preferred in the first 16 weeks due to decreased severity of birth defects but no recommendation to switch after that.



“Methimazole embryopathy” – Dysmorphic facies



Bihan et al. Aplasia cutis congenita and dysmorphic syndrome after antithyroid drugs during pregnancy. The Endocrinologist 2002.

Other MMI induced malformations

- Based on case reports, there was concern for a "methimazole embryopathy" – a syndrome of minor dysmorphic features, choanal atresia and/or esophageal atresia, growth retardation, and developmental delay
- This was studied prospectively in 241 women exposed to MMI vs 1,089 women not exposed to teratogenic drugs.
  - No difference in spontaneous abortion rates
  - 8 of 204 exposed live births had a major malformation, compared to 23 children in the control group had major malformations

Di Gianantonio et al. Adverse effects of prenatal methimazole exposure. Teratology 2001.

TABLE 3. Major malformations identified in the exposed newborns

TIS	Case no.	Drug (dose)	g.w. From	g.w. To	Anomaly
Berlin	1	Carbimazole (40 mg/day)	1	11	Craniosynostosis-hypospadias
Berlin	2	Carbimazole (?)	0	30	Ventricular septal defect
Bilthoven	3	Methimazole (30 mg/day)	4	7	Choanal atresia
Jerusalem	4	Methimazole (10 mg/day)	0	4	Scrotal hypospadias
Lyon	5	Carbimazole (20 mg/day)	1	20	Spina bifida[a]
Milan	6	Methimazole (15 mg/day)	0	6	Scrotal hypospadias–hemivertebra
Paris	7	Methimazole (8 mg/day)	0	37	Atrioventricular canal
Paris	8	Methimazole (50 mg/day)	0	16	Esophageal atresia

?, unknown; g.w., gestational week.
[a]One twin pregnancy.

Exposed weeks 4-7

Rate of esophageal atresia in the general population: 1 in 2,500
Rate of choanal atresia: 1 in 10,000

Incidence of congenital abnormality

- Japanese study evaluated 1426 women with Graves' disease treated with PTU vs 1578 treated with MMI vs. 2065 women with no treatment in the first trimester of pregnancy

Yoshihara et al. Treatment of Graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformations. JCEM 2012.

TABLE 2. The number and prevalence of malformed infants in each of the exposed groups and the control group (multiple malformations included)

	Control group (without medicine)	MMI group	PTU group	All patients
Total no.	1906	1231	1399	5997
Mean birth weight (g)	2990	2939	3005	2990
Mean gestation length (wk)	39.1	39	39.1	39.3
Congenital malformation, yes (%)	40 (2.1%)	50 (4.1%)	26 (1.9%)	152 (2.5%)
OR (95% CI)	1	2.28 (1.54–3.33)	0.66 (0.41–1.03)	1.15 (0.68–1.86)
P value		0.0002	0.0786	0.58
Ventricular septal defect	11 (27.5%)	9 (18%)	8 (31.0%)	33 (18.1%)
Atrial septal defect	1 (2.5%)	0	2 (7.7%)	4 (2.2%)
Patent ductus arteriosus	0	4 (8%)	1 (3.9%)	6 (3.3%)
Cheiloschisis, palatoschisis	2 (5.0%)	0	1 (3.9%)	5 (2.8%)
Accessory ear	1 (2.5%)	2 (4%)	0	3 (1.6%)
Complete situs inversus	0	0	1 (3.9%)	1 (0.5%)
Omphalocele	0	6 (12%)	0	8 (4.4%)
Omphalomesenteric duct anomalies	0	7 (14%)	0	8 (4.4%)
Aplasia cutis congenita	0	7 (14%)	0	9 (4.9%)
Others	25 (62.5%)	15 (30%)	13 (50.0%)	75 (41.2%)

Others	25 (62.5%)	15 (30%)	13 (50.0%)
Trisomy 21	2	3	2
Syndactyly	1	0	3
Intestinal malrotation	3	0	1
Congenital cardiovascular deformity	3	0	0
Ventricular dilatation	3	1	0
Congenital megacolon	2	0	0
Imperforate anus	2	1	1
Hydronephrosis	0	1	2
Craniosynostosis	1	1	0
Kidney dysplasia	1	1	0
Biliary atresia	1	1	0
Talipes varus	1	0	0
Diaphragmatic hernia	1	0	0
Hypoplasia of the patella	1	0	0
Arachnoid cyst hemorrhage	1	0	0
Transposition of the great vessels	1	0	0
Cataracta congenita	1	0	0
Aortic stenosis	1	0	0
Pulmonary artery stenosis	1	0	0
Fallot's tetralogy	0	1	1
Sturge-Weber syndrome	0	1	0
Thoracocyllosis	0	1	0
Hearing loss	0	1	0
Esophageal stenosis	0	1	0
Esophageal atresia	0	1	0
Small bowel obstruction	0	1	0
Spina bifida occulta	0	1	0
Talipes valgus	0	0	1
Brachydactyly	0	0	1
Situs inversus viscerum	0	0	1
Schistorhachis	0	0	1
Hypospadias	0	0	1

PTU-related hepatotoxicity

Table 2. Substances and Drugs Other than Acetaminophen Reported as the Cause of Acute Liver Failure in Liver Transplant Recipients

	n = 137 (%)
Isoniazid	24 (17.5)
Propylthiouracil	13 (9.5)
Phenytoin	10 (7.3)
Valproate	10 (7.3)
Amanita mushrooms	9 (6.6)
Nitrofurantoin	7 (5.1)
Herbal	7 (5.1)
Ketoconazole	6 (4.4)
Disulfiram	6 (4.4)
Troglitazone	4 (2.9)
Halothane	3 (2.2)
Fialuridine	3 (2.2)
Sulfasalazine	3 (2.2)
Combination of non-APAP drugs	3 (2.2)
Methyldopa	3 (2.2)
Nefazodone	2 (1.4)
Labetolol	2 (1.4)
Cerivastatin	2 (1.4)
Other drugs (1 case each):	20 (14.6)
Amoxicillin-clavulinic acid, asparaginase, bromfenac, butorphanol, bupropion, carbemazepine, cocaine, hydrocodone, iron, isoflurane, ibuprofen, itraconazole, lisinopril, 6-mercaptopurine, naproxen paroxetine, pemoline, simvastatin, trimethoprim/sulfasoxazole, zafirkulast	1 (.7) each

Absolute risk of liver failure?

~1 in 10,000 (adults)

Russo et al. Liver transplantation for acute liver failure from drug induced liver injury in the United States. Liver Transplant 2004;10(8);1018-23.
Bahn et al. The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug administration. Thyroid 2009.

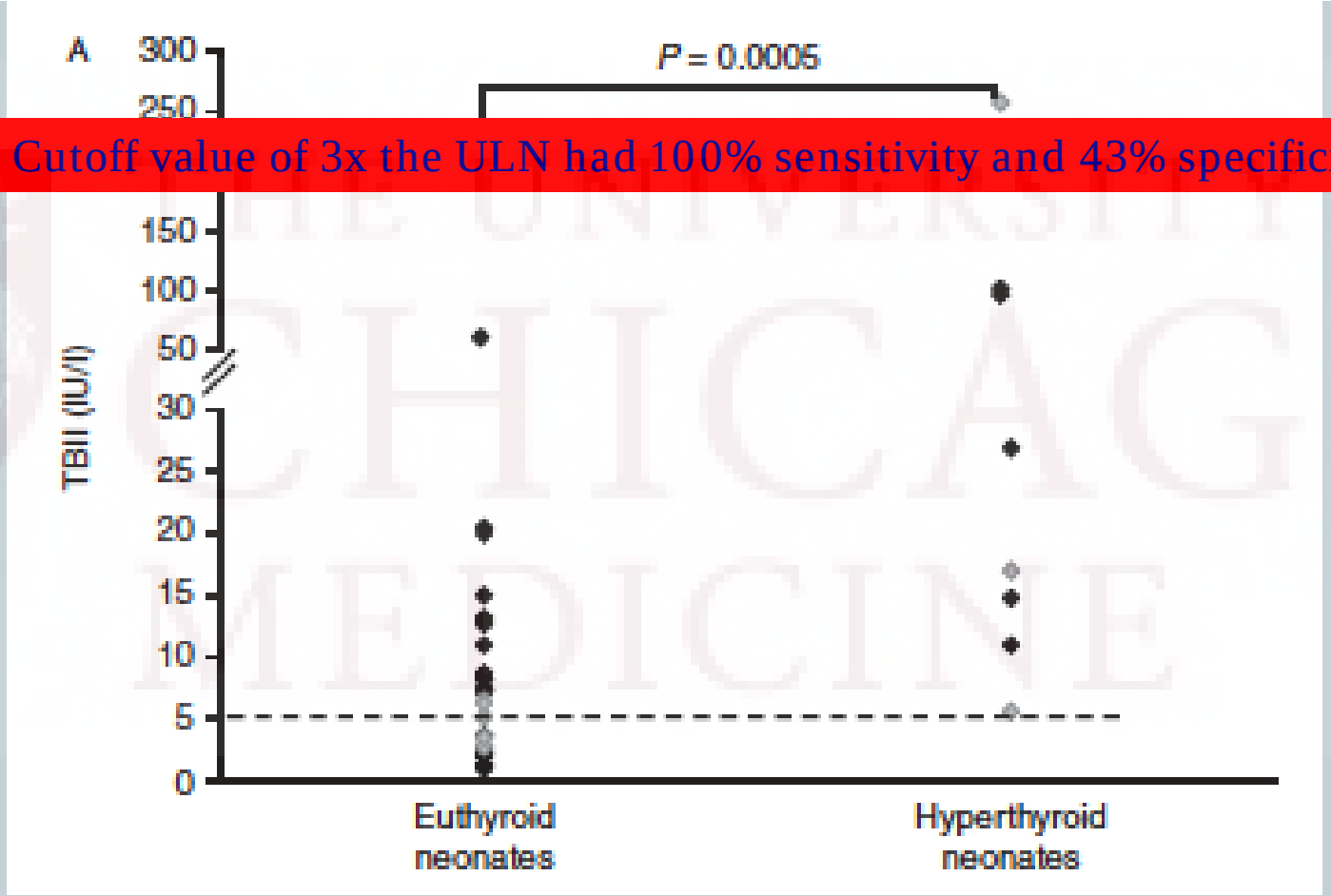
Graves' disease in pregnancy

- Antithyroid drugs are more potent in fetus than mother so goal is to maintain maternal TT4/FT4 values at, or just above, the pregnancy-specific upper limit of normal
- TFTs should be re-checked every 2-4 weeks following initiation and about every 4 weeks after
- As pregnancy advances, there is generally a suppression of autoimmune activity that may make cessation of all antithyroid drugs possible in the 3rd trimester (estimated 20-30% of cases)
- Long term treatment with beta blockers has been associated with IUGR, fetal bradycardia, and neonatal hypoglycemia

Fetal Considerations

- Fetuses can become:
  - Hyperthyroid (placental transfer of thyroid hormone)
  - Hypothyroid (placental transfer of antithyroid drugs)
  - Central hypothyroid (poor control of hyperthyroidism)
- Anti-thyroid drugs are cleared more rapidly in the fetus than TSI so fetuses can become hyperthyroid after delivery
- TSI recommended to be measured in early pregnancy, then again at weeks 18-22 if initially high, then again at weeks 30-34 if high or mother requiring antithyroid drugs

Predictive value of TSI for the neonate

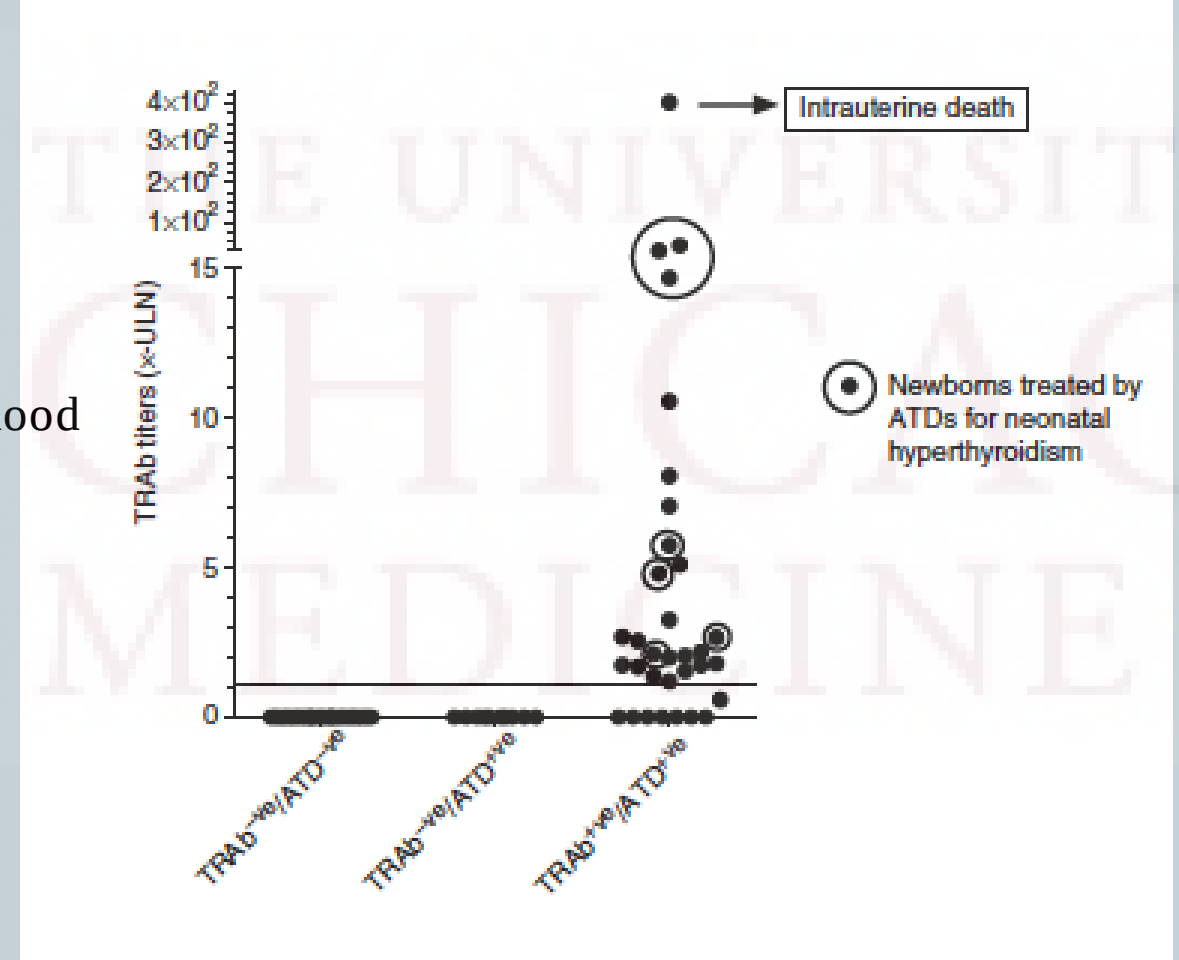


Cutoff value of 3x the ULN had 100% sensitivity and 43% specificity.

Abeillon-du Payrat et al. Predictive value of maternal second generation thyroid-binding inhibitory immunoglobulin assay for neonatal autoimmune hyperthyroidism. Eur J Endo 2014;171:451-60.

Value of TSI

Cord blood



Besancon et al. Management of neonates born to women with Graves' disease: a cohort study. Eur J Endo 2014;170:855-62

Other fetal surveillance

Recommendation 53

Fetal surveillance should be performed in women who have uncontrolled hyperthyroidism in the second half of pregnancy, and in women with high TRAb levels detected at any time during pregnancy (greater than 3x the upper limit of normal). A consultation with an experienced obstetrician or maternal-fetal medicine specialist is recommended. Monitoring may include ultrasound to assess heart rate, growth, amniotic fluid volume, and the presence of fetal goiter. ***(Strong recommendation, Moderate quality evidence)***

Patient course

- Patient was started on PTU 200 mg q8h and propranolol 60 mg TID
- Her TSI returned positive at 6.1
- Patient unable to follow for Endocrine here due to insurance but she already has followed up at Friend and Family for OB. Propranolol was reduced to 40 mg TID due to mildly low BP
- She was seen in MFM Clinic at Univ of Chicago this past Tuesday (now 1 month since diagnosis)

MFM Visit

- She is now 11 weeks by LMP
- At that visit, patient reports feeling well + compliance with PTU and propranolol.
- Patient's BP was 101/53, HR 83. Weight was 143 LB (down ~4 LB in 1 month)
- Early US of the fetus was normal and consistent with her LMP. Fetal HR 171. Fetal thyroid difficult to visualize before 20 weeks.
- TFTs re-checked

TFTs

Lab (wk pregnancy)	Lab RR	2/17/17 (7 wks)	3/14/17 (11 wks)
TSH	0.30-4.00	<0.01	0.01
Total T4	5.0-11.6	21.9	14.6
Total T3	80-195	619	308

Trimester Specific T3

Table 1
The reference intervals (2.5th and 97.5th percentiles) for TT4 and TT3 using isotope dilution tandem mass spectrometry and using immunoassays

Triiodothyronine TT3[a]	Reference intervals by IA, ng/dl (nmol/l)	Reference intervals by LC/MS/MS ng/dl (nmol/l)
First trimester	*n*=50, 92–218 (1.42–3.36)	*n*=52, 96–267 (1.48–4.12)
Second trimester	*n*=49, 112–278 (1.73–4.29)	*n*=51, 107–274 (1.64–4.22)
Third trimester	*n*=49, 111–265 (1.71–4.08)	*n*=51, 105–297 (1.62–4.57)
1 year postpartum	*n*=48, 74–146 (1.48–2.24)	*n*=52, 80–214 (1.23–3.29)

Soldin et al. Trimester-specific reference intervals for thyroxine and trioodothyronine in pregnancy in iodine-sufficient women using isotope dilution tanden mass spectrometry and immunoassays. Clinica chimica Acta 2004;349:181-89.

Patient course

- We reduced her PTU to 100 mg TID and propranolol cut to 20 mg TID and patient will follow up with MFM in 2 weeks
- I was able to speak with primary OB who sent referral so she could be seen for Endocrinology here

References

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum

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Lambert-Messerlian et al. First- and second-trimester thyroid hormone reference data in pregnant women: a FaSTER (First- and Second-Trimester Evaluation of Risk for aneuploidy) Research Consortium study. AJOG 2008;199:e1-62.

Kahric-Janicic et al. Tandem mass spectrometry improves the accuracy of free thyroxine measurements during pregnancy. Thryoid 2007.

Glinoer et al. Regulation of maternal thyroid during pregnancy. JCEM 1990;71:276-87.

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