Endocrine Disorders in Pregnancy

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Having taught board review programs for the AAFP for more than 20 years, Dr. Weismiller is the founding and current chair of the AAFP Family Medicine Board Review Express™, as well as the AAFP's annual Family Medicine Update live course. He is a frequent presenter at AAFP Family Medicine Experience (FMX) and teaches American Board of Family Medicine (ABFM) Knowledge Self-Assessments throughout the country. He is the author of numerous publications on issues related to women’s and children’s health, and he is an advocate for empowering individuals to make sound health care choices.

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Learning Objectives

1. Develop screening protocols to identify patients at risk for developing pregnancy-related endocrine disorders.
2. Order appropriate laboratory or radiologic tests to confirm diagnosis us suspected endocrine disorders.
3. Recognized indication for referral and possible admission, coordinating care and follow-up as necessary.
4. Develop collaborative care plans that foster patient adherence to prescribed lifestyle modifications and pharmacotherapy.

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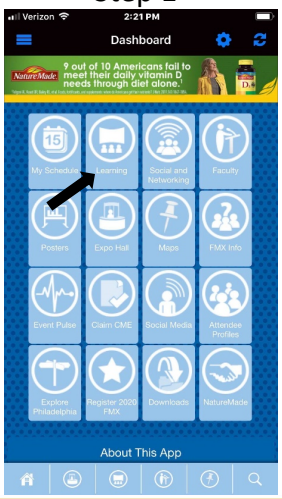
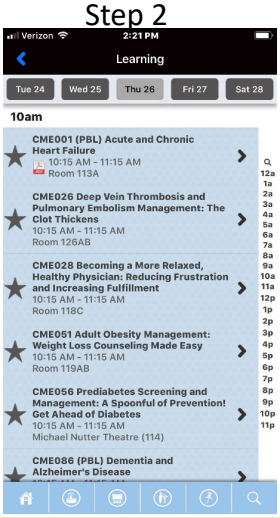
Audience Engagement System

Step 1



Step 2



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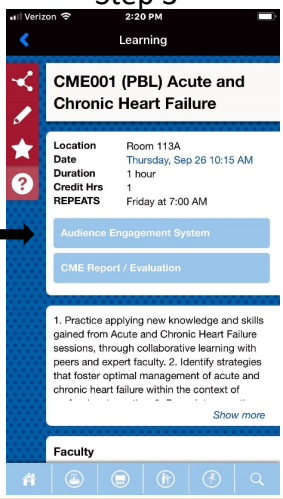

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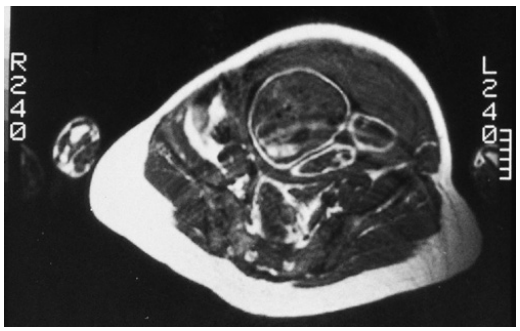
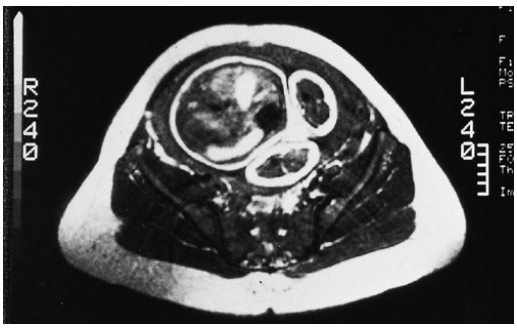


Fetus of a diabetic woman in excellent glucose control

Affects 7% of pregnancies[7]



Fetus of a diabetic woman in poor glucose control

Diabetes mellitus

Diabetes mellitus

Pregestational

- 10% of pregnancies complicated by DM
  - Major congenital malformations remain the leading cause of mortality and serious morbidity in infants of mothers with type 1 and type 2 diabetes
- Because few well-designed studies have been performed, many of the guidelines are based on expert and consensus opinion

Gestational

- 90% of pregnancies complicated by DM
  - > 50% eventually develop type 2 DM

AES Question #1

Prepregnancy counseling for women with pregestational diabetes mellitus has been reported to be beneficial and cost effective and should be encouraged. *(Level B evidence)* Which one of the following targets is recommended as the optimal HbA_{1c} entering pregnancy?

A. ≤ 5.7%
B. ≤ 6%
C. ≤ 6.5%
D. ≤ 7%

Pregestational Diabetes

Prepregnancy visit

- Counsel – potential complications in pregnancy
  - Fetal anomalies
    - most common cause of neonatal death in children of mothers known to have DM before pregnancy is congenital anomalies
  - PTD
  - Preeclampsia
    - 15-20% of pregnancies
  - Fetal macrosomia
    - Shoulder dystocia - >2x
  - Mode of delivery
  - Hyperglycemia
  - Worsening diabetic retinopathy and nephropathy
  - Neonatal complications
- Evaluate for baseline complications: hypertension, nephropathy, retinopathy, CVD
- Ensure adequate contraception if NOT planning pregnancy immediately *(LARC preferred)*
- Plan to optimize HbA_{1c} *(< 6% - anomaly rate 2-3%)*
  - HbA1c near 10% - anomaly rate 20-25%
- Discuss plan to increase folic acid when attempting to get pregnant (800 ug to 1 mg)

Pregestational DM

Neonatal Consequences

- Poorly controlled Pregestational DM
  - Profound hypoglycemia
  - Increased rate of RDS
  - Polycythemia
  - Organomegaly
  - Electrolyte disturbances
  - Hyperbilirubinemia
  - Long-term outcomes
    - Obesity
    - CHO intolerance

Pregestational Diabetes

First trimester

- Prenatal labs/tests include $HgbA_{1c}$,TSH, 24-hour urine (if no baseline), EKG
- Evaluation
  - Ophthalmologist
  - Dietician
    - dietary approach to glycemic control is focused on careful carbohydrate counting and allocation of appropriate ratios of carbohydrates to meals and snacks (Level B)
  - Possibly endocrinologist, cardiologist, nephrologist

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Pregestational Diabetes

Second trimester

- Start low-dose aspirin 12-28 weeks of gestation – optimally 16 weeks EGA (Level B)
  - high-risk factor for the development of preeclampsia
- US including a detailed anatomical survey
- Consider fetal echocardiography

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Pregestational Diabetes

Third trimester

- Evaluate fetal growth
- Start low-dose aspirin by 28 weeks of gestation if NOT started in the second trimester
- Fetal monitoring (nonstress test, MBPP, BPP)
  - usually once or twice per week (Level B)

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Pregestational Diabetes

- Treatment (Level B)
  - Use of all oral hypoglycemic agents for control of pregestational type 2 diabetes mellitus during pregnancy should be ***limited and individualized*** *until data regarding the safety and efficacy of these drugs become available*
  - Insulin is the **preferred** treatment for pregestational diabetes in pregnancy not controlled by diet and exercise

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Pregestational Diabetes

Delivery

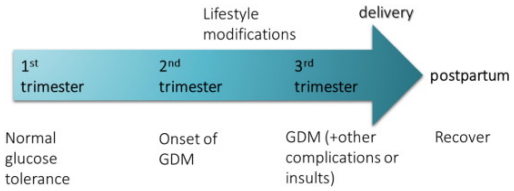
- If EFW ≥ 4500 g, consider cesarean delivery *(Level C)*
- Without vascular complications and well controlled blood glucose levels, deliver at 39 0/7 weeks to 39 6/7 weeks EGA
- In women with vascular complications or poorly controlled blood glucose, consider delivery at 36 weeks 0/7 weeks to 38 6/7 weeks EGA, and in rare cases, even earlier

AES Question #2

Gestational diabetes has been associated with each of the following perinatal complications EXCEPT:

A. Increased frequency of maternal hypertensive disorders
B. Increased risk of operative delivery
C. Increased frequency of neonatal hyperglycemia
D. Increased risk of intrauterine fetal death during last 4-8 weeks of gestation

Gestational Diabetes



- Condition is increasing as obesity and older age at pregnancy become more common
- Increased risk:
  - Gestational hypertension
  - Preeclampsia
  - Cesarean delivery
  - 7-fold increased risk of developing diabetes later in life

Why All the Fuss …

Adverse Outcomes

Maternal

- Increased frequency
  - Maternal hypertensive disorders
  - Cesarean delivery
- Increased risk of intrauterine fetal death during last 4-8 weeks of gestation
  - Fasting hyperglycemia (> 105 mg/dL)

Fetal

- Excessive fetal growth (macrosomia)
  - Increased risk for operative delivery
  - Shoulder dystocia
  - Birth trauma
- Neonatal morbidity
  - Hypoglycemia
  - Hypocalcemia
  - Hyperbilirubinemia
  - Polycythemia

Detection of GDM

Organization	Recommendation	Comments
ACOG (2018)	• Use a 2-step method at 24-28 weeks (Level B). • Screen for undiagnosed type 2 diabetes at the first prenatal visit in those with risk factors	Use a blood glucose level of either 135 or 140 mg/dL with factors such as community prevalence rates of GD determining the cutoff.
USPSTF (2014)	• Screen asymptomatic women after 24 weeks (Grade B). • Current evidence is insufficient to assess the balance of benefits and harms of screening for GD in asymptomatic pregnant women before 24 weeks of gestation (Grade I).	Goal was not to look at the performance or whether one method was better than another for screening. Found treating can significantly reduce the risk of preeclampsia, macrosomia, shoulder dystocia.
ADA (2014)	• Screen for undiagnosed type 2 diabetes at the first prenatal visit in those with risk factors • Screen at 24-28 weeks if not previously known to have diabetes.	Updated Guidelines: Use either: 1. 1-step method (75g OGTT) 2. 2-step method

RISK FACTORS (Screen early)…ACOG, NIDDK,ADA

- Patient is overweight with BMI of 25 (23 in Asian Americans), and ONE or more of the following:
  - Physical inactivity
  - First-degree relative with diabetes
  - Known impaired glucose metabolism
  - Previous pregnancy history of
    - GDM
    - Macrosomia (≥4000 g)
    - Stillbirth
  - Hypertension (>140/90 or being treated)
  - HDL cholesterol ≤ 35 mg/dL
  - Fasting TG ≥ 250
  - PCOS, acanthosis nigricans, nonalcoholic steatohepatitis, morbid obesity and OTHER conditions associated with insulin resistance
  - HgbA1C>5.7%, impaired glucose tolerance or impaired fasting glucose on previous testing
  - ASCVD
  - High risk ethnicity

ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. **2018**;131(2):e49-e64.

Two-Step Approach in USA

ACOG 2018, ADA 2014

- 24-28 weeks (routine)
- Initial screening: 50 g oral glucose load (glucose challenge test)
  - > 135 or > 140 mg/dL* ➔ 3-hour OGTT
  - Note: **> 190**, > 90% abnormal 3-hour
- 3-hour OGTT ± ➔ 2 or more abnormal values = (+) GDM
  - Overnight fast, 100 g glucose polymer
  - Abnormal plasma blood glucose: > fasting
    95 mg/dL, 1h 180, 2h 155, 3h 140

*Either threshold acceptable, ACOG 2018 (Level C).

± Can also be used as a 1-step method for high-risk women or in areas in which the prevalence of insulin resistance is 5% or higher (eg, southwestern and southeastern US).

One abnormal value on 3-hour OGTT?

- One abnormal value - significantly increased risk of adverse perinatal outcomes compared with women without GDM.
- *Although a higher level of scrutiny may be focused on this subset of women, further research is needed to clarify the risk of adverse outcomes in patients with one abnormal value on the 100-g, 3-hour OGTT and whether they would benefit from treatment.*

Cheng YW, Block-Kurbisch I, Caughey AB. Carpenter-Coustan criteria compared with the national diabetes data group thresholds for gestational diabetes mellitus.Obstet Gynecol 2009;114:326–32.

Gestational Diabetes Mellitus Treatment
ACOG 2018

- Initial management (Level A)
  - Nutritional counseling by registered dietician
  - Advice on moderate exercise program (if possible); minimum of 150 minutes per week
- No conclusive evidence for the threshold value at which clinicians should start pharmacologic therapy
- Pharmacologic treatment
  - Insulin is considered **PREFERRED** treatment in pregnancy (Level A)
  - Glyburide treatment should **NOT** be recommended as a first-**CHOICE** pharmacologic treatment because, in most studies, it DOES NOT yield equivalent outcomes to insulin (worse outcome including macrosomia and birth injury (Level B)
  - In women who decline insulin therapy **or** if unable to safely administer, metformin is a reasonable second-line choice (Level B)

ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. **2018**;131(2):e49-e64.

Gestational Diabetes Mellitus
Maternal Surveillance – Glucose Monitoring

- **Glucose Target Levels**
  - Fasting or preprandial < 95 mg/dL
  - 2-hour postprandial BG < 120 mg/dL (1 hour < 140mg/dL)
  - 1-2 times per week versus daily; review weekly
- **Pharmacologic Treatment (if on more than 3 occasions)**
  - ≥ 95 mg/dL fasting whole blood glucose or
  - ≥ 120 mg/dL 2 h postprandial
  - Daily glucose monitoring

Gestational Diabetes Mellitus

Fetal Surveillance/Assessment (Level C)

- **Third trimester**
  - Increased risk for fetal demise
    - Preexisting DM
    - Fasting glucose >105 mg/dL
- Delay delivery safely in order for the fetus to mature
- Abnormal results are rare when diabetes well-controlled, no vascular disease or hypertension

- **Antenatal Testing**
  - Modified Biophysical Profile (MBPP)
    - NST and AFI
  - Biophysical Profile (BPP)
  - Contraction Stress Test (CST)
- **Ultrasound**
  - Amniotic Fluid Index (AFI)
  - Asymmetric fetal growth
  - Estimated fetal weight (EFW)

Gestational Diabetes Mellitus

Fetal Surveillance/Antepartum

- Well-controlled A_1 GDM (Level C)
  - no consensus regarding criteria for initiation and frequency (MBPP, BPP)
  - beginning 34-40 weeks versus none
- More intensive biophysical testing
  - beginning at 32-34 weeks, twice weekly?
    - insulin requirement (A_2, B)
    - hypertension
    - previous stillbirth or other adverse obstetrical history

Gestational Diabetes Mellitus
Fetal Surveillance/Ultrasound

- Assessment for asymmetric fetal growth (early third trimester) may aid in identifying fetuses that can benefit from maternal insulin therapy
- Aid in the timing and route of delivery????
  - Estimate fetal size
    - CPD and birth trauma increase after 4000g
  - ≥ 4500 g - C-section *may* be best option (Level C; previously Level B)*
    - May reduce likelihood of permanent brachial plexus injury in the infant
  - 4000 to 4500 g – consider:
    - Past delivery history
    - Clinical pelvimetry
    - Progress of labor

ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. **2018;131(2):e49-e64*

Gestational Diabetes Mellitus
Timing of Delivery?

- Timing of delivery in women with GDM that is controlled with only diet and exercise **(A1GDM)** should NOT be before 39 weeks gestation, unless otherwise indicated. Expectant management up to 40 6/7 weeks of gestation in the setting of indicated antepartum testing is generally appropriate (Level C)
- GDM well controlled on medications **(A2GDM) or Type 2**, delivery is recommended at 39 0/7 to 39 6/7 weeks of gestation (Level C)

ACOG – 2018

Gestational Diabetes Mellitus

Timing of Delivery?

- **Poorly controlled** – Expert guidance supports earlier delivery but data lacking regarding precise timing
  - Delivery between 37 weeks 0 days and 38 weeks 6 days may be justified
  - Delivery between 34 weeks 0 days and 36 weeks 6 days reserved for (1) failure of in-hospital glycemic control or (2) abnormal fetal testing
- Council regarding risks/benefits of **scheduled cesarean delivery** when EFW > 4500 g (Level C)

ACOG – 2018

Long-Term Considerations

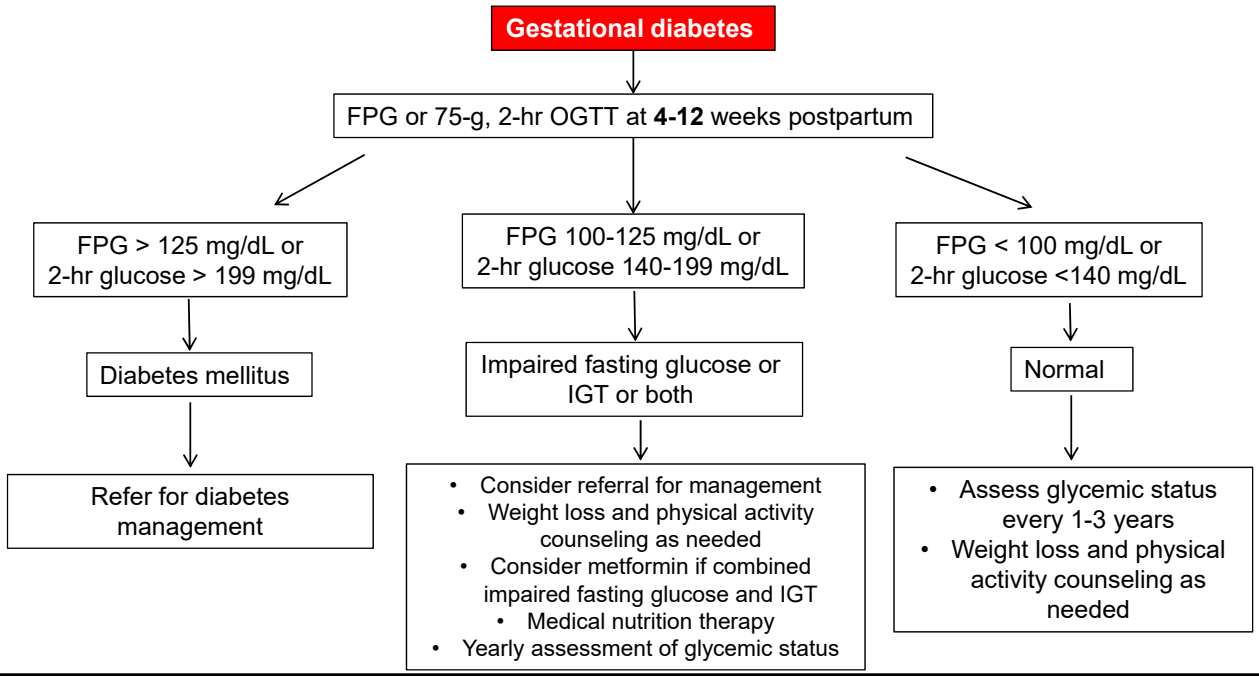
- Increased risk for recurrence of GD
  - 33%-50% likelihood
- Increased risk for development of diabetes after pregnancy
  - Up to 1/3 will have diabetes or impaired glucose metabolism at postpartum screening
  - 35% of women 5-10 years after parturition
- Offspring – increased risk
  - Obesity
  - Glucose intolerance
  - Diabetes in late adolescence and young adulthood

Postpartum

- Reclassification of maternal glycemic status at least 4 weeks after delivery (preferred 4-12 weeks, ACOG 2018) [Level C]
  - FPG or 2-hr OGTT
- Reassessment of glycemia every one (USPSTF) to three years (ADA) [SOR:C], if above normal; yearly assessment (ADA) if impaired fasting glucose or impaired glucose tolerance at 6-12 weeks

ACOG – 2018

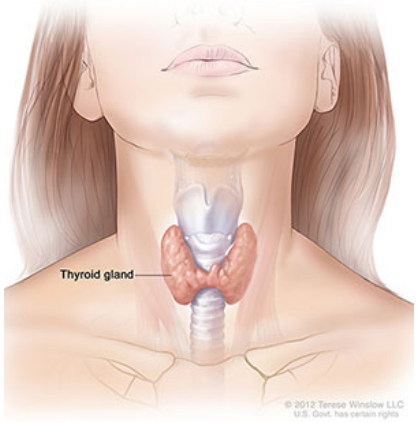
Management of Postpartum Screening Results



Best Practice Recommendations

- Nutritional Counseling
- Insulin is the preferred pharmacologic therapy
  - Human preferable
  - Insulin analogs have not been adequately tested
- Oral agents have not been generally recommended
- Glucose monitoring
- Programs of moderate physical activity have been shown to lower maternal glucose concentrations
  - Impact on neonatal complications awaits rigorous clinical trials
- Delivery during the 38th week is recommended

Thyroid Disorders

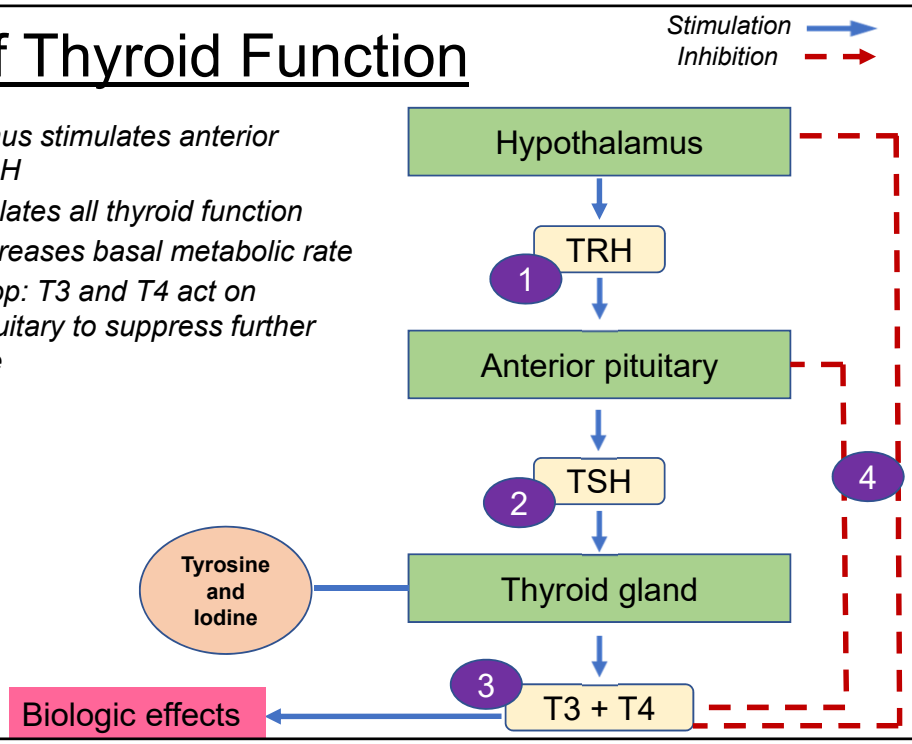


Thyroid Disorders

- Fetus dependent on maternal thyroxine (T4) in early pregnancy.
- Maternal thyroid gland is required to increase thyroid hormone synthesis by up to 50% to meet the increased demands of pregnancy due to placental transfer of T4, increased thyroid hormone metabolism, increased renal iodine losses and changes in levels of T4 binding proteins. These changes also affect laboratory thyroid function test assays.
- Thyroid stimulating hormone (TSH) is the most reliable measure of thyroid function during pregnancy. Pregnancy- and trimester-specific laboratory reference ranges should be used if available.

Regulation of Thyroid Function

1. *TRH from hypothalamus stimulates anterior pituitary to release TSH*
2. *Release of TSH stimulates all thyroid function*
3. *T3 and T4 release increases basal metabolic rate*
4. *Negative feedback loop: T3 and T4 act on hypothalamus and pituitary to suppress further TRH and TSH release*

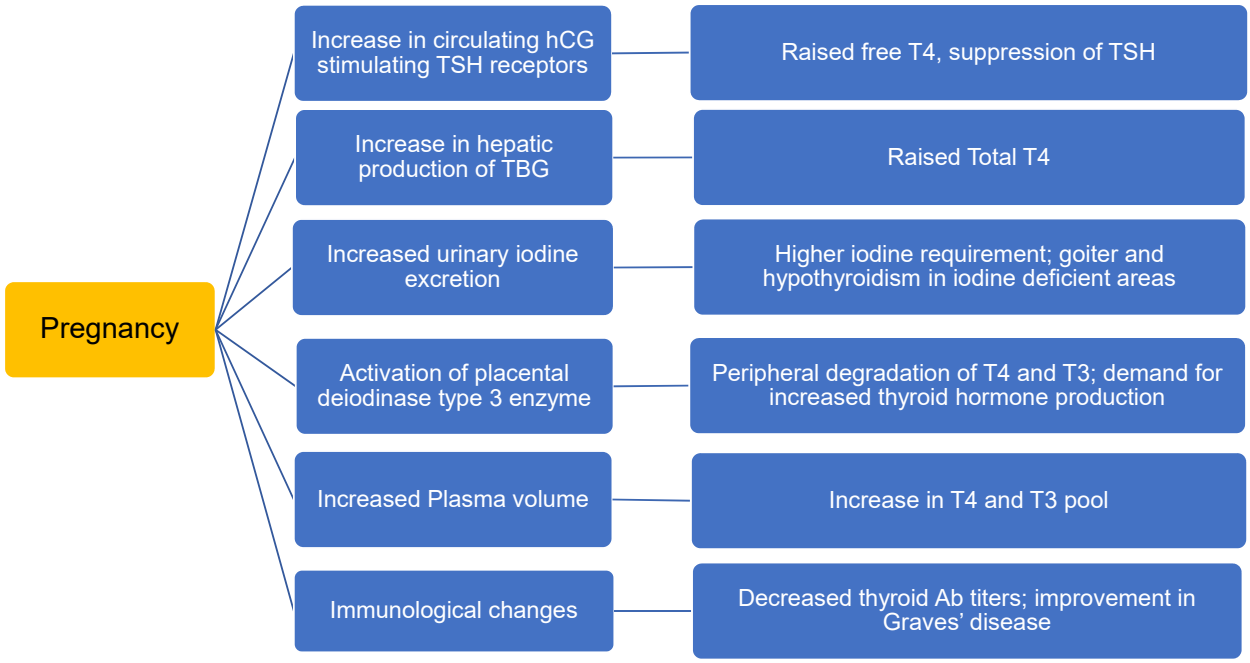


Changes in Thyroid Function Test Results in Normal Pregnancy and in Thyroid Disease

Maternal Status	TSH	Free T4
Pregnancy	Varies by trimester*	Raised to no change
Overt Hyperthyroidism	Decrease	Increase
Subclinical hyperthyroidism	Decrease	No change
Overt hypothyroidism	Increase	Decrease
Subclinical hypothyroidism	Increase	No change

**The level of TSH decreases in early pregnancy because of weak TSH receptor stimulation due to substantial quantities of human chorionic gonadotropin during the first 12 weeks of gestation. After the first trimester, TSH levels return to baseline values.*

Physiological changes in pregnancy and their impact on the thyroid



Thyroid Gland and Pregnancy

- Glandular hyperplasia and increased vascularity result in moderate thyroid enlargement but not thyromegaly
  - Thyroid function tests are NOT indicated in asymptomatic pregnant women with slightly enlarged thyroid glands (Level B)
  - Maternal thyroid volume is 30% larger in the third trimester than in the first
- Any goiter or nodule recognized during pregnancy should be considered pathologic

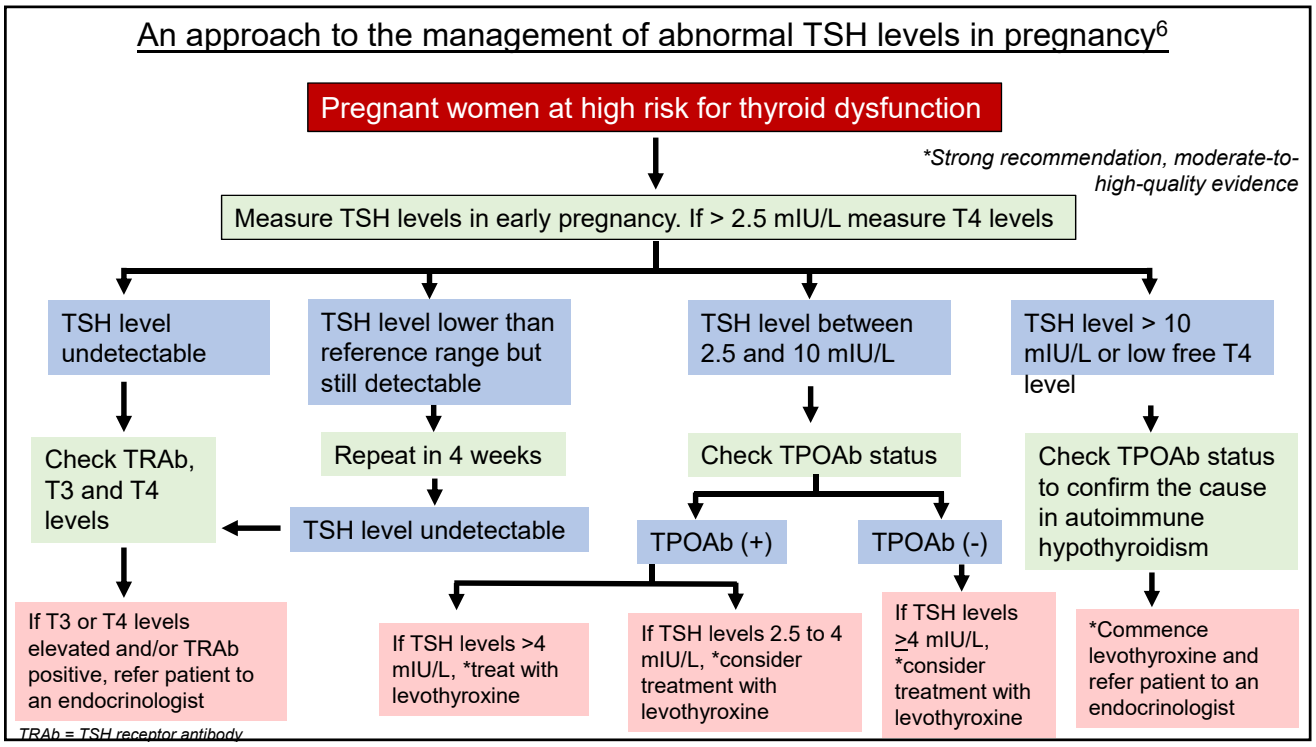
Thyroid function and the Fetus

- Maternal T4 is transferred to the fetus throughout the entire pregnancy and is important for normal fetal brain development
  - The high placental content of D3 inactivates most maternal T3 and T4, and very little free hormone reaches fetal circulation
- It is especially important before the fetal thyroid gland begins concentrating iodine and synthesizing pituitary TSH and thyroid hormone at approximately 12 weeks of gestation
- After 15-18 weeks, the fetus controls most of its own thyroidal secretion

Whom to screen in early pregnancy for thyroid dysfunction

- No evidence for universal screening
- Women at high risk – **TSH** BEFORE conception and as soon as pregnancy is confirmed.
  - TSH > 2.5 IU/L – obtain FT4 and Thyroid peroxidase antibody (TPOAb)

- **High Risk**
  - History of previous thyroid dysfunction
  - Current symptoms suggestive of hyper- or hypothyroidism
  - Known (+) thyroid antibodies
  - Age $\geq$ 30 years
  - Any history of autoimmune disease
  - History of previous pregnancy loss, preterm delivery, or infertility
  - Use of lithium, amiodarone or recent iodinated contrast use
  - History of head and neck radiation
  - Molar pregnancy
  - Goiter



AES Question #3

In considering a pregnant patient with hyperthyroidism, which one of the following statements is true?

A. Serum Free T4 will be decreased
B. Inadequately treated, it is associated with a greater risk of preterm delivery
C. Toxic nodular goiter is the most common cause
D. It often improves in the second and third trimester due to the immunosuppressive effects of pregnancy

Hyperthyroidism

- **Etiology**
  - Graves' Disease (30-80 per 100,000 person-years) – accounts for 95% of cases
  - Toxic nodular goiter (1-2 per 100,000 person-years)

✓ Often improves in the second and third trimester due to the immunosuppressive effects of pregnancy

- Signs and Symptoms are similar to the nonpregnant state
  - Problem is that some symptoms of hyperthyroidism are similar to symptoms of pregnancy
  - Serum TFTs differentiate thyroid disease from nonthyroid disease
- Best treated prior to pregnancy
- **Goal of Treatment:**
  - Control thyrotoxicosis while avoiding fetal or neonatal transient hypothyroidism

Hyperthyroidism
Diagnosis

- Clinical suspicion
  - Infertility
  - Hyperemesis gravidarum
  - Failure of nonobese women to gain weight
  - Classic Signs of Graves Disease
- Highly sensitive third generation tests
  - TSH (Low)
  - Free T4 or FTI (Increased)
    - Monitored to manage thyroid disease in pregnancy

Thyroid Disease

Effects of Pregnancy and Hyperthyroidism on Tests commonly used to evaluate Thyroid Function

Test	Normal Pregnancy	Hyperthyroidism
TSH	**No change**	**Decreased**
TBG	Increased	No change
Total T4	Increased	Increased
Free T4	**No change**	**Increased**
FTI	No change	Increased
Total T3	Increased	Increased or no change
Free T3	No change	Increased
RT_3U	Decreased	Increased

- *Most of the pregnancy-induced changes in thyroid physiology are stimulated by hyperestrogenemia which in turn causes production of altered TBG.*
- *Changes in structure and function of the gland during pregnancy can mimic some of the effects of hyperthyroidism*

Transient gestational hyperthyroidism

- Common cause of mild hyperthyroidism secondary to thyroid stimulation by beta human chorionic gonadotrophin
- Generally limited to the first half of pregnancy
- Seen more often in women with hyperemesis and those with high beta human chorionic gonadotrophin levels due to molar pregnancy or multiple gestation
- Antithyroid medications are NOT indicated for women with gestational hyperthyroidism

Thyrotoxicosis
Management

- Controlled medically, does not pose a serious threat to the mother
  - Use the least amount of medication required to achieve clinical euthyroidism (Level B)
    - —may take 3-4 weeks to be reflected in labs
  - Aim of treatment with antithyroid medications - maintain a free T4 level at the upper end (or within 10%) of the nonpregnant reference range
  - Mechanisms:
    - —directed at blocking thyroid hormone production
      - e.g., thioureas
    - —directed at peripheral manifestations of disease
      - e.g., beta blockers

Maternal thyrotoxicosis

- Inadequately treated – associated with a greater risk:
  - Preterm delivery
    - Including medically indicated preterm deliveries
  - Severe preeclampsia
  - Heart failure
  - Miscarriage – (no data to support this claim)
  - Fetal
    - LBW

Hyperthyroidism
Treatment

- **Propylthiouracil** (PTU)
  - Start 100-150 mg q 8 hours (300-450 mg/day)
    - ✓Increase to control thyrotoxicosis
    - ✓May require doses of 600-900 mg per day
    - ✓Monitor free T4 and TSH q month
    - ✓Titrate downward as soon as possible
  - The birth defects associated with propylthiouracil are generally milder and more easily corrected so it is used ***preferentially*** before a planned pregnancy and during the first trimester
- **Methimazole** – Second and third trimesters (if needed, when risk of malformation lower, preferred due to lower risk of hepatotoxicity)
- **Beta blockers** may be used for rapid control of adrenergic symptoms

Hyperthyroidism
Effects on Fetus and Infant

- Thioureas cross the placenta
  - can cause fetal hypothyroidism and goiter
  - appear to have no subsequent growth and development adverse effects
- Morbidity and mortality - infants born to women:
  - who remain thyrotoxic despite therapy
  - who do not receive adequate prenatal care/treatment
- Fetal Thyrotoxicosis
  - in about 1% of mothers with Graves' disease
  - Consider in all women with a history of Graves' disease
  - If diagnosed – consultation with a clinician with expertise in such conditions warranted

History of Graves' Disease
Treated with surgery or radioactive iodine

- TRAb levels measured in early pregnancy – if (+), repeat at 18-22 weeks' gestation
  - Can cross placenta cause fetal hyperthyroidism and neonatal Graves' disease
- Women with active Graves' disease or (+) TRAb at 18-22 weeks – monitoring for fetal hyperthyroidism (MFM specialist)
- TRAb level is elevated at 18 to 22 weeks' gestation or in women with active Graves' disease **on treatment**, measurement of TRAb levels at 30 to 34 weeks' gestation can guide decisions about neonatal and postnatal monitoring

Hypothyroidism in Pregnancy

- Difficult to diagnose
  - Subclinical disease (elevated TSH with normal free T4) more common than overt disease
    - Subfertility
    - Poor pregnancy outcomes: increased risk of SpAB, PTD, preeclampsia, GDM, IUGR, PROM
- Untreated hypothyroidism
  - Low-birth-weight infants
    - Medically indicated preterm delivery, preeclampsia, placental abruption
    - ? IUGR (not clear if independent of other complications)
  - Pregnancy loss
  - Impaired fetal neurocognitive development
- Hashimoto's thyroiditis is the most common cause of hypothyroidism in pregnancy

Hypothyroidism
Diagnosis

- Rise in the level of circulating T4 expected during pregnancy fails to take place (low free T4) ***and*** level of TSH is elevated *OR*
- TSH > 10 mIU/L regardless of free T4 level
- *NOTE:* There is insufficient data to warrant routine screening of asymptomatic pregnant women for hypothyroidism (Level C)

Thyroid Disease

Effects of Pregnancy and Hypothyroidism on Tests commonly used to evaluate Thyroid Function

Test	Normal Pregnancy	Hypothyroidism
TSH	**No change**	**Increased**
TBG	Increased	No change
Total T4	**Increased**	**Decreased**
Free T4	No change	Decreased
FTI	No change	Decreased
Total T3	Increased	Decreased or no change
RT_3U	Decreased	Decreased

- *Most of the pregnancy-induced changes in thyroid physiology are stimulated by hyperestrogenemia which in turn causes production of altered TBG*
- *Changes in structure and function of the gland during pregnancy can mimic some of the effects of hyperthyroidism*

Using TPOAb

- Women who are (+) TPOAb – increased rates if miscarriage and PTD – independent of thyroid function
- Thus, measurement recommended to assist with decision making on when to treat subclinical hypothyroidism
- High-quality randomized clinical trials on levothyroxine replacement to treat subclinical hypothyroidism during pregnancy are limited

Levothyroxine in pregnancy – data is mixed

Trial	Results	Lmitations
Controlled Antenatal Thyroid Screening (CATS)-I and CATS-II trials Hales C, Taylor PN, Channon S, et al. Controlled antenatal thyroid screening II: effect of treating maternal suboptimal thyroid function on child cognition. J Clin Endocrinol Metab 2018; 103: 1583-1591. 8. Lazarus JH, Bestwick JP, Channon S, et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med 2012; 366: 493-501.	No significant difference in intelligence quotient in children aged 3 and 9.5 years of mothers with subclinical hypothyroidism randomized to levothyroxine treatment or placebo	Late commencement of levothyroxine at 13 weeks of gestation
Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy Casey BM, Thom EA, Peaceman AM, et al. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. N Engl J Med 2017; 376: 815-825.	No improvement in cognitive outcomes in children of mothers treated for subclinical hypothyroidism at 5 years of age	Late commencement of levothyroxine at 17 to 18 weeks of gestation
Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease Nazarpour S, Tehrani FR, Simbar M, Tohidi M, Majd HA, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. Eur J Endocrinol 2016; EJE-16-0548.	Levothyroxine replacement may reduce the rates of preterm delivery in women with subclinical hypothyroidism and positive TPOAb	

Hypothyroidism detected in early pregnancy

Treatment[6]

- TSH > 10mIU/L
  - Begin full dose* replacement

TSH Level (mIU/L)	Initial dose
Upper limit of normal to 5	1 to 1.5 mcg/kg daily (range 50 to 75 mcg daily)
5-10	1 to 1.7 mcg/kg daily (range 75 to 100 mcg daily)
>10	1.7 to 2.5 mcg/kg daily (range 100 to 200 mcg daily) and consider referral to endocrinologist

** Based on lean bodyweight*

Hypothyroidism detected in early pregnancy

Treatment

- TSH > 10mIU/L
  - Begin full dose replacement
  - Goal is to maintain the TSH in the low normal range
  - Monitor TSH every 4-6 weeks until stable then every 8 weeks with a final check at 28-32 weeks
- Thyroxine requirement usually increases as the pregnancy advances
- Fetal surveillance????
- Following delivery, dose of levothyroxine can be halved, or ceased if on 50mcg daily or less during pregnancy, and thyroid function checked two to three months' postpartum

Treatment of pre-existing hypothyroidism

- Levothyroxine dose increase
  - 20-30% increase when pregnancy is confirmed
  - 50% increase if no thyroid tissue (congenital hypothyroidism, post total thyroidectomy, post radioactive iodine ablation)
- Thyroid function monitored q four to six weeks until the TSH level is stable, then q 8 weeks with a final check at about 28 to 32 weeks' gestation
- Postpartum
  - Levothyroxine dose returned to the prepregnancy dose
  - Thyroid function should be checked two to three months' postpartum

Hypothyroidism

Effects on Fetus and Infant

- No evidence of thyroid dysfunction
- Mass screening to minimize sequelae of congenital hypothyroidism (1/4,000 infants) and prompt aggressive T4 replacement
  - Sequelae can be prevented with treatment in the first few weeks of life

Nodular Thyroid Disease

- Evaluate by ultrasound and fine-needle aspiration or tissue biopsy
- Avoid radioiodine scanning
- (+) thyroid cancer
  - Differentiated (papillary or follicular) – surgery can be delayed until postpartum period as such a delay is unlikely to affect long-term prognosis
  - Advanced differentiated, medullary, or poorly differentiated – surgery in the second trimester may be considered

Postpartum Thyroid Dysfunction

Postpartum Thyroiditis

- Autoimmune inflammation
- Affects 5-10% of women in postpartum period
- Presents as new-onset:
  - Painless hypothyroidism (25%) *or*
  - Transient thyrotoxicosis (50%) *or*
  - Thyrotoxicosis followed by hypothyroidism within one year postpartum
  - Eventual return to euthyroidism
- Transient and recurrent in subsequent pregnancies
  - 70% risk of recurrence
- May occur after pregnancy loss

Postpartum Thyroid Dysfunction

Postpartum Thyroiditis

- Risk
  - (+) TPOAb – 50% risk of developing
  - Past history of PP Thyroiditis – 70% risk of developing
- Treatment unclear
  - Permanent hypothyroidism is uncommon
  - Thyrotoxicosis and hypothyroidism are mild
  - Toxic phase – no antithyroid medications
  - Check TSH q 2 months AFTER toxic phase
  - May try to wean from replacement at 6-12 months after initiating treatment

Postpartum Thyroiditis

Diagnosis/Screening

- Document new-onset abnormal levels of TSH or FT_4 or both
- Screening with TFTs and antimicrosomal antibodies in asx women NOT warranted

Could she have Graves' Disease?

- This is the main differential diagnosis
  - (+) TRAb
  - Signs – Goiter with a bruit or ophthalmopathy
  - Uncertainty about diagnosis – technetium uptake scan
    - Breastfeeding – breastmilk expressed and discarded during scan + 48 hours afterwards
- (+) thyrotoxicosis > 6months postpartum – Graves' is most likely diagnosis

Antithyroid medications are needed?

- Graves' disease in Breastfeeding mothers
  - Lowest effective dose
  - Ingest FOLLOWING a breastfeed
- Doses – safe in breastfeeding; less than 1% of parent drug transferred to breastmilk
  - PTU 300 mg
  - Methimazole 20 mg

What can we say -

- TSH goal in pregnancy < 3.0
- Levothyroxine is indicated for subclinical hypothyroid with (+) thyroid peroxidase antibodies
- Gravid women with subclinical hypothyroidism not treated
  - Check TSH and T4 q 4 weeks until 16-20 weeks and then AT LEAST once between 26 and 32 weeks
- No radioactive iodine scanning or ablation

Best Practice Recommendations

- Women at high risk of thyroid dysfunction should undergo screening with measurement of thyroid stimulating hormone (TSH) levels in early pregnancy.
- If the TSH level is 2.5mIU/L or more on early pregnancy screening, levels of thyroid peroxidase antibodies should be measured to identify women who may benefit from treatment for subclinical hypothyroidism.
- Transient gestational hyperthyroidism is a common cause of mild hyperthyroidism in early pregnancy. Referral of the patient to an endocrinologist is recommended if TSH levels remain persistently undetectable and/or T3 or T4 levels are elevated and/or TSH receptor antibodies (TRAb) are positive.
- Women with active Graves' disease or a history of Graves' disease treated with surgery or radioactive iodine may be at risk of fetal hyperthyroidism. If TRAb level is elevated at 18 to 22 weeks' gestation, endocrinology and maternal-fetal medicine input are required.

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Thank you

Questions

FMX