

## Preconception Management of DM, Obesity, and Thyroid Disease

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## Preconception Management of Type 1 and Type 2 Diabetes

## Pregestational DM

- Organogenesis occurs in first 8 weeks of pregnancy
- If inadequately controlled preconception, diabetes during pregnancy is associated with adverse outcomes
  - Miscarriage
  - Congenital anomalies
  - Neonatal death

## Adverse Outcomes

- UK Confidential Enquiry into Maternal and Child Health (CEMATCH) Survey data:



- Majority of malformations: cardiac and neural tube

BMJ 2006;333:177-80

## Adverse Outcomes



BMJ 2006;333:177-80

## Importance of Good Glycemic Control

- Miscarriage
  - Congenital anomaly
  - Therapeutic abortion
  - Stillbirth
  - Neonatal death
- 
- Adverse pregnancy outcome strongly correlated with A1C at conception
  - Risk increased by 5.5% for every 1% increase in 1<sup>st</sup> trimester A1c above 7%
  - Aim for an A1c of 7.0% preconception (<6.5% if it can be safely achieved)

Diabetes Care 2006;29(12):2612-6

## Preconception Care (PCC) Goals

- 1. Achieve A1C target
- 2. Optimize pharmacologic means of achieving glycemic targets: change OHA to insulin
- 3. Stop teratogenic medications
- 4. Start folic acid
- 5. Address for microvascular complications

\*\*\*REFER TO DM in PREGNANCY CLINICS\*\*\*

## Effectiveness of Preconception Care

- 680 pregnant women with DM1&DM2

A1C 7.2%

A1C 8.1%



Diabetes Care 2010;33(12):2514-19

## Preconception Care (PCC) Goals

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## ? Safety of OHAs

- Both Metformin and SU cross placenta



- Meta-analysis of early exposure to metformin, glyburide and glipizide showed no increase in major congenital malformations

Can J Clin Pharmacol 2003; 10(9):179-83

## Meta-Analysis of Metformin

- First trimester Metformin exposure (DM and PCOS) not associated with increased risk of major malformations (OR 0.50)

Fertility and Sterility 2006; 86(3):658-663

## CDA Position on OHAs

- Oral agents are not recommended for glycemic control in women with type 2 diabetes during pregnancy
- HOWEVER – based on currently available data, if a women with type 2 diabetes becomes pregnant while on metformin and/or SU these drugs should be continue until patient can be transitioned to insulin

Canadian Journal of Diabetes 2013;37:S168-183

## Which Insulins are Safe?

- **Basal Insulin:**
- NPH
- Detemir (Levemir) – RCT vs. NPH
- Glargine (Lantus) - Meta-analysis of observational data suggests safety
  - Theoretical concern: greater affinity for IGF-1 receptor
- **Bolus Insulin:**
- Regular
- Lispro (HL) – RCT vs. R
- Aspart (NR) – RCT vs. R
  - No pregnancy data with Glulisine (Apidra)

Canadian Journal of Diabetes 2013;37:S168-183

## Preconception Care (PCC) Goals

- 1. Achieve A1C target
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## ACEi/ARBs

- Negative effects with 2<sup>nd</sup>/3<sup>rd</sup> trimester exposure
  - renal failure
    - Oligohydroamnios/anuria
  - IUGR
  - limb defects
  - pulmonary hypoplasia/respiratory distress
  - fetal demise

Hypertension 2012;60(2):444-450



- First trimester exposure effects more conflicting

Hypertension 2012;60(2):444-450



## ACEi/ARB



- Overall – stop ACEi/ARBs pre-conception or upon pregnancy confirmation

NEJM 2006;354(23):2443-2451

## Statins

- Limited data
- 178 cases of 1<sup>st</sup> trimester statin exposure
- 52 cases after exclusion of elective/spontaneous abortions
- 20/52 cases reported malformations
  - severe CNS defects
  - complex limb defects

NEJM 2004;350(15):1579-1582

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## Folic Acid

- Folic acid reduces risk of NTDs
  - start 3 months preconception
- Current consensus for women with DM is 1mg

Journal of Obstetrics and Gynaecology Canada 2015;37(6):534-549

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## Retinopathy

- May progress during pregnancy and 1<sup>st</sup> year post partum
- RFs for progression during pregnancy:
  - poor glycemic control at baseline
  - more advanced retinopathy at baseline
  - rapid A1C correction may contribute

Diabetes Care 2000;23(8):1084-1091  
Diabetes Care 1995;18(5):631-637  
Diabetologia 2010; 53(6):1076-1083

## Retinopathy

- All women with DM should have ophthalmology exam:
  - prior to conception
  - in first trimester
  - in later pregnancy
  - post partum at discretion of ophthalmologist

## Nephropathy

- Very complex group
- Proteinuria with preserved renal function
  - increased risk of preeclampsia and preterm delivery
- Renal dysfunction (Cr > 124)
  - associated with significant risk of maternal renal function deterioration post partum
  - Significant risk of preterm delivery

Diabetes Care 2001;24(10):1739-1744; Diabetologia 2002; 45(1):36-41;  
NEJM 1996;335(4):226-232; Diabetes Care 1996;19(10):1067-1074

## Key Preconception Messages for Women With Pregestational DM

- 1. PLAN for pregnancy
- 2. Work with MD to achieve goals before trying to get pregnant
- 3. Use contraception until medically ready
- 4. A1C 7% or less prior to conception
- 5. Start folic acid 3 months prior to conception

## Preconception Management of Obesity

## BMI Classification of Obesity

- Obesity is associated with large spectrum of adverse pregnancy outcomes

## Congenital Birth Defects

- Data from National Birth Defects Prevention Study program in 8 US states
- Interviewed 3:1 cases : controls (1997-2002)
  - cases: mothers with children born with non-chromosomal congenital birth defects
- Compared congenital birth defect rate by self-reported maternal pre-pregnancy weight/height (BMI)
- Women with pregestational DM excluded from analysis

Arch Pediatr Adolesc Med 2007;161(8):745-750

## Congenital Birth Defects



- Outcomes adjusted for: maternal age, ethnicity, education level, smoking, alcohol, folic acid/PNV use

Arch Pediatr Adolesc Med 2007;161(8):745-750

### Audit of 30, 298 birth outcomes in N. Ireland (2004-2011) by BMI Category

**Statistically significant maternal outcomes by BMI category (OR (99%CI) relative to normal weight women)**

	Overweight BMI 25-29.9 N = 8415	Obese Class I BMI 30-34.9 N = 3333	Obese Class II BMI 35-39.9 N = 1194	Obese Class III BMI > 40 N = 586
GDM	1.7 (1.3-2.3)	3.7 (2.8-5.0)	6.0 (4.2-8.5)	8.5 (5.7-12.9)
HTN in pregnancy	1.9 (1.7-2.3)	3.5 (2.9-4.2)	5.0 (4.0-6.4)	6.6 (4.9-8.9)
IOL	1.2 (1.1-1.3)	1.3 (1.2-1.5)	1.4 (1.2-1.7)	1.6 (1.3-2.0)
C-section	1.4 (1.3-1.5)	1.8 (1.6-2)	2.5 (2.1-2.9)	2.8 (2.4-3.5)
Shoulder dystocia	1.5 (1-2.3)	-	-	-
PPH	1.4 (1.3-1.5)	1.8 (1.6-2.0)	2.4 (2.0-2.8)	2.7 (2.2-3.4)
Wound infection	-	-	3.5 (1.8-6.7)	6.0 (3.0-12.1)
Breastfeeding	0.8 (0.7-0.8)	0.6 (0.6-0.7)	0.5 (0.4-0.6)	0.4 (0.3-0.5)

\*ALL variables adjusted for age, parity, social deprivation, and smoking

\*IOL/C-section adjusted for pregestational DM and pregestational HTN

BJOG 2013;120:932-939

## Audit of 30, 298 birth outcomes in N. Ireland (2004-2011) by BMI Category

**Statistically significant fetal outcomes by maternal BMI category (OR (99%CI) relative to normal weight women)**

	Overweight BMI 25-29.9 N = 8415	Obese Class I BMI 30-34.9 N = 3333	Obese Class II BMI 35-39.9 N = 1194	Obese Class III BMI > 40 N = 586
Preterm delivery*	-	1.3 (1.0-1.6)	-	1.6 (1.1-2.5)
Macrosomia (>4kg)§	1.5 (1.3-1.6)	1.9 (1.6-2.2)	2.1 (1.7-2.6)	3.2 (2.4-4.1)
Stillbirth	-	-	-	3.0 (1.0-9.3)
NICU admission^	-	1.3 (1.1-1.7)	1.6 (1.2-2.2)	1.6 (1.0-2.6)

\*adjusted for elective C-section/IOL

§adjusted for gender and GA

^adjusted for preterm delivery, pregestational DM, GDM

BJOG 2013;120:932-939

## General Management Recommendations

- Aim for ideal body weight preconception
  - BMI 18.5-25
- Avoid pregnancy for 12-18 months post bariatric surgery
  - Surgical complications
  - Period or rapid weight loss

AJOG 2011;204(2):106-119



## CDA guidelines: GMD screening

- If there is a high risk of GDM based on multiple clinical factors, screening should be offered at any stage in the pregnancy [Grade D, Consensus]
- Risk factors include:
  - Previous GDM
  - Prediabetes
  - High-risk population (Aboriginal, Hispanic, South Asian, Asian, African)
  - Age  $\geq 35$  years
  - **BMI  $\geq 30$  kg/m<sup>2</sup>**
  - PCOS, acanthosis nigricans
  - Corticosteroid use
  - History of macrosomic infant
  - Current fetal macrosomia or polyhydramnios
- If initial screening is performed before 24 weeks and is negative, rescreen between 24 and 28 weeks gestation

Canadian Journal of Diabetes 2013;37:S168-183

## Preconception Management of Thyroid Disease

## Consequences of Overt Hypothyroidism on Conception/Pregnancy

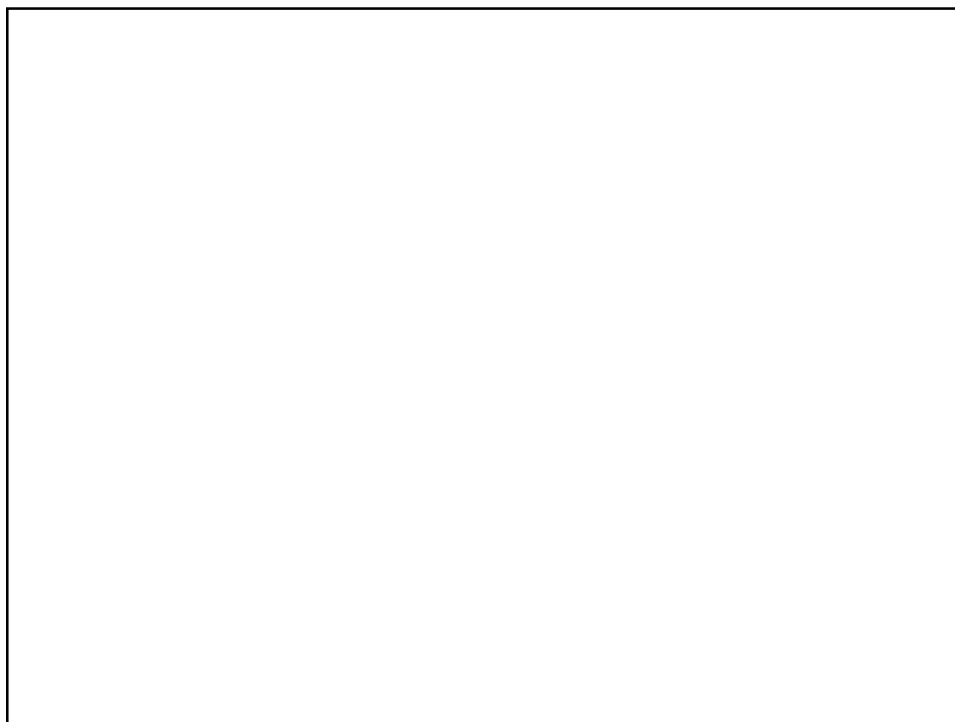
- Irregular menses
- Infertility
- Poor obstetrical outcomes:
  - pregnancy loss
  - gestational hypertension
  - premature birth
  - low birth weight

Thyroid 2017;27(3):315-389

## Consequences of Overt Maternal Hypothyroidism During Pregnancy

- Detrimental effects on fetal neurocognitive development
- Normal thyroid hormone levels are essential for:
  - neuronal migration
  - myelination

Thyroid 2017;27(3):315-389



## Study Details

- 2<sup>nd</sup> trimester screening program – 25 000 women – included TSH
- 75 women identified with TSH > 99.7% of all pregnant serum values
- 47 women participated in study
- 15 women with TSH 98-99.6% enrolled
- IQ testing performed on offspring at age 8+/-1

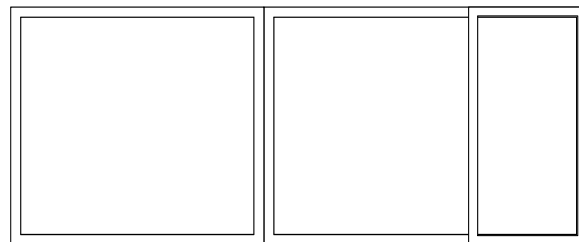
## Study Details

- Cases matched with 2 controls
- TSH <98%
- Matched for
  - GA at time of TSH measure
  - maternal age
  - years of maternal education
  - child gender

NEJM 1999;341:549-555

- 14/62 hypothyroid women treated ( o ) during pregnancy (but TSH still high when measured)

NEJM 1999;341:549-555



- Children of women with untreated hypothyroidism had significantly lower IQ than children of treated/control women
- Thyroid hormone replacement in hypothyroid pregnant women, even if insufficient, proved beneficial

NEJM 1999;341:549-555

## Thyroid Hormone Demand During Pregnancy

- Demand for thyroid hormone is increased during pregnancy
- Demand starts to rise by 5 weeks gestation
- Plateaus around 16 weeks gestation

NEJM 2004;351:241-249

## Iodine Requirement During Pregnancy

- Iodine is an essential for thyroid hormone production
- All women should get 250  $\mu\text{g}$  iodine daily during pregnancy

## Cretinism

- Consequence of severe maternal iodine deficiency which results maternal and fetal hypothyroidism
- Permanent intellectual disability
  - cretinism in most severe form

- Optimize iodine stores even prior to pregnancy – start PNV in preconception period



## Thyroid Hormone Optimization in Women With Pregestational Hypothyroidism

- Preconception: optimize Synthroid dosing
  - TSH <2.5
- Counsel to independently increase Synthroid when pregnancy suspected
  - 2 extra tabs Synthroid/week
  - 30% dose increase
- Contact MD right away for TSH check
  - increase monitoring frequency

Thyroid 2017;27(3):315-389

- 2 extra tab/week dosing strategy – effectively mimic physiologic changes in TSH in pregnancy

JCEM 2010;95:3234 –3241



## TSH Pregnancy Targets for Hypothyroid Women

- Aim for TSH in the “lower half of the trimester-specific reference range”  
OR
- TSH <2.5 when trimester-specific reference range not available

Thyroid 2017;27(3):315-389

## Pregnancy Planning in Women With Grave's Disease (GD)

- Women with GD should be rendered euthyroid before conception
  - two normal sets of tests at least 1 month apart
  - no change in therapy between tests
- Obstetrical concerns if hyperthyroid not controlled:
  - pregnancy loss
  - pregnancy-induced hypertension
  - low birth weight/IUGR
  - prematurity/stillbirth
  - maternal CHF, thyroid storm

Thyroid 2017;27(3):315-389

Post RAI: must delay pregnancy at least 6 months – time to achieve stable euthyroid state
Thyroid 2017;27(3):315-389

## MMT Associated Birth Defects

- Aplasia cutis
- Dysmorphic facies
- Choanal or esophageal atresia
- Abdominal wall defects (umbilicocele)
- Ventricular septal defects
- Urinary system defects
- Eye malformations

JCEM 2013;98(1):4373-4381

## PTU Associated Birth Defects

- Preauricular sinuses
  - minor birth defects
- Urinary tract defects
  - kidney cyst
  - hydronephrosis
  - megaloureter

JCEM 2013;98(1):4373-4381

## SUPPLEMENTAL SLIDES

### Normal TSH Reference Range In Pregnancy

- 2011 ATA guideline definition of pregnancy ULN in pregnancy:
- 2.5 – 1<sup>st</sup> trimester
- 3.0 – 2<sup>nd</sup>/3<sup>rd</sup> trimester
- Based on reference ranges from 6 prior studies (US/Europe)

## Normal TSH Reference Range In Pregnancy

- 2017 ATA guideline definition of pregnancy ULN in pregnancy:
- Preferred: compare to locally established pregnancy and trimester specific reference ranges
  - TPO Ab -/iodine sufficient pregnant women
- Second best: compare to “similar” population from past studies (next slide)
- Last option: TSH around 4.0



## 2017 ATA Definitions

- Overt Hypothyroidism
  - High TSH and low fT4
- Subclinical hypothyroidism
  - High TSH but fT4 still normal
- Isolated hypothyroxinemia
  - Normal TSH and a fT4 concentration in the “lower 2.5th–5th percentile of a given population”

## Potential Consequences of Subclinical Hypothyroidism in Pregnancy

- Multiple studies
- Variable definitions of subclinical hypothyroidism
- Overall impression:
  - increasing risk of pregnancy loss
  - preterm delivery
- Exacerbated by elevated TPOAb
  - risk apparent in TPOAb + women when TSH > 2.5
- In TPOAb – women, adverse risk not consistently apparent until TSH > 5–10

Thyroid 2017;27(3):315-389

## Treatment of Subclinical Hypothyroidism in Pregnancy

- **(a) LT4 therapy is recommended for**
- TPOAb + women with a TSH greater than the pregnancy-specific ref. range
  - Strong recommendation, moderate-quality evidence.
- TPOAb - women with a TSH greater than 10.0
  - Strong recommendation, low-quality evidence.
- **(b) LT4 therapy may be considered for**
- TPOAb + women with TSH concentrations >2.5 and below the upper limit of the pregnancy-specific ref. range
  - Weak recommendation, moderate-quality evidence.
- TPOAb - women with TSH concentrations greater than the pregnancy specific ref. range and below 10.0
  - Weak recommendation, low-quality evidence.
- **(c) LT4 therapy is not recommended for**
- TPOAb - women with a normal TSH (TSH within the pregnancy-specific ref. range or <4.0 if unavailable)
  - Strong recommendation, high-quality evidence.

Thyroid 2017;27(3):315-389

## Potential Consequences of Isolated Hypothyroxinemia in Pregnancy

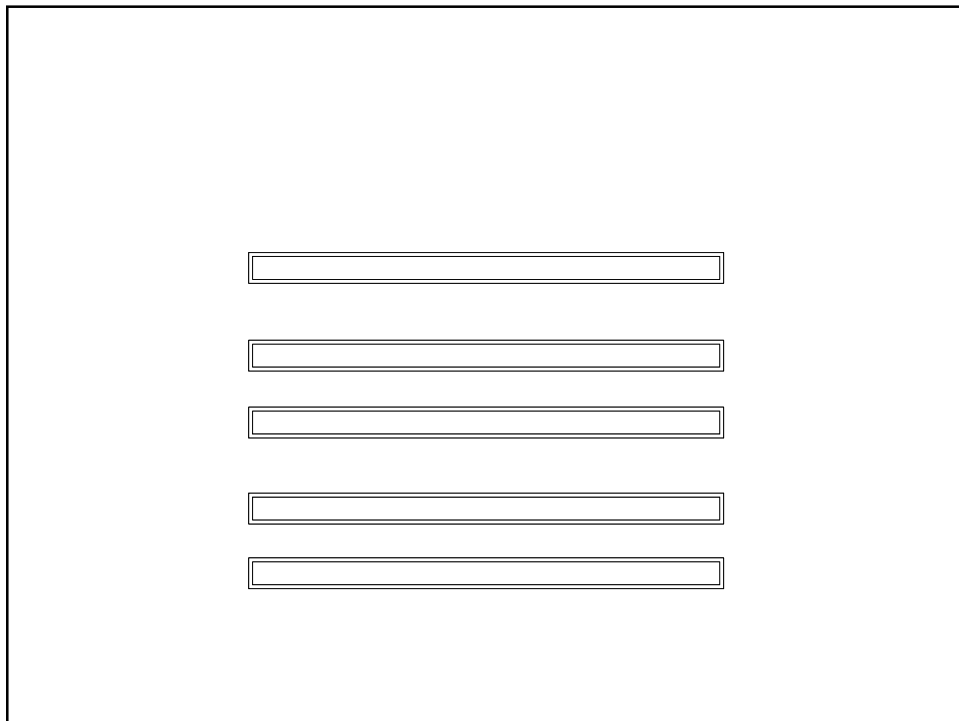
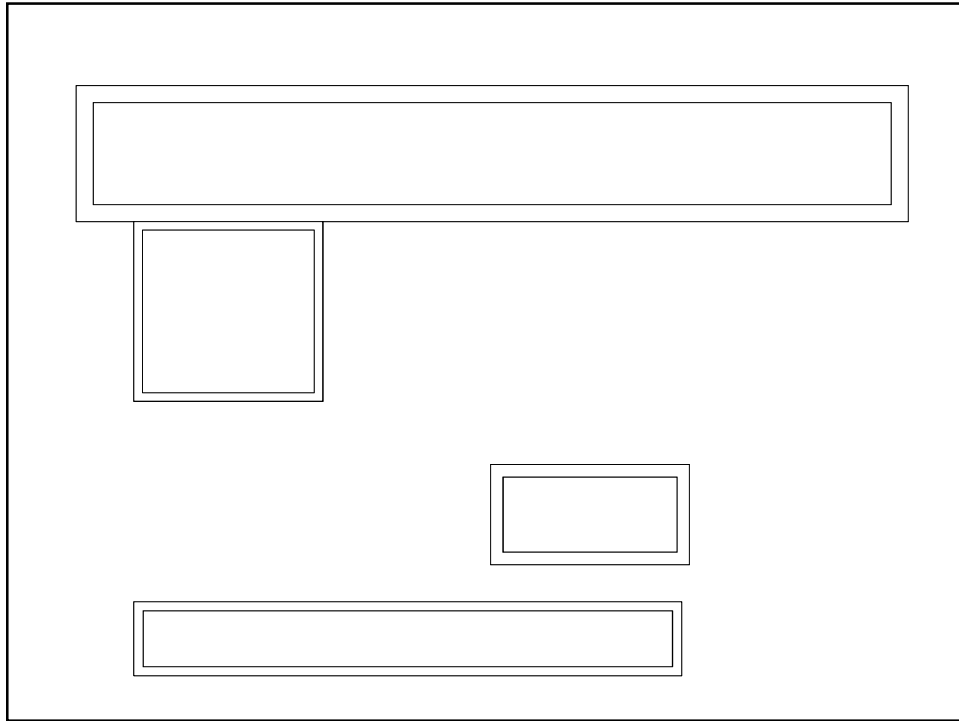
- Possible cognitive development issues
- maybe prematurity
- maybe low birth weight
- no studies exist in which demonstrate treatment reduces these adverse outcomes

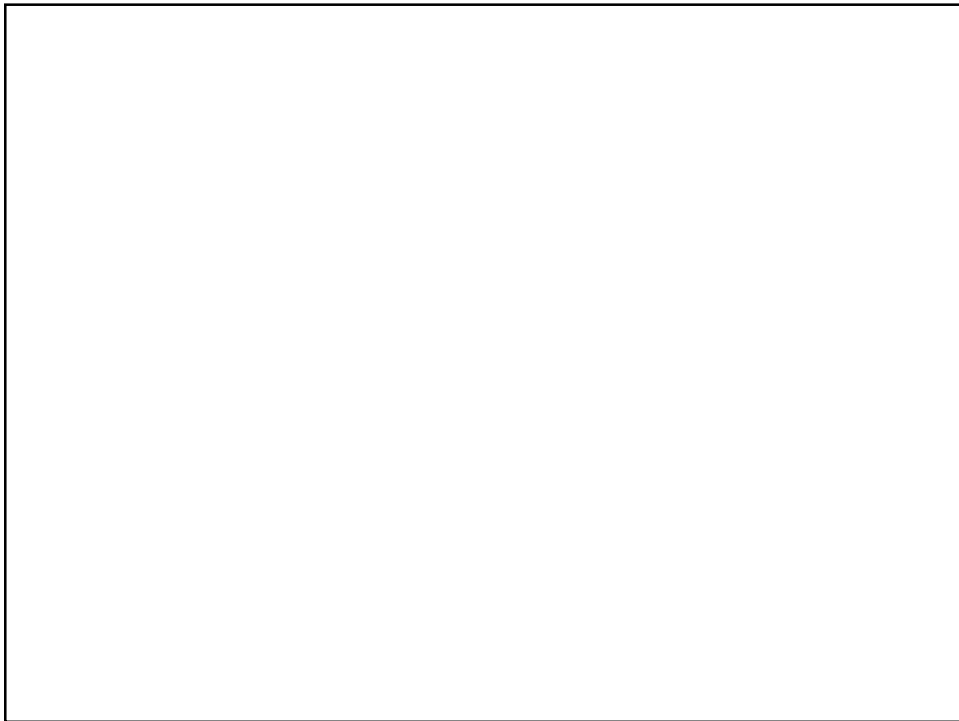
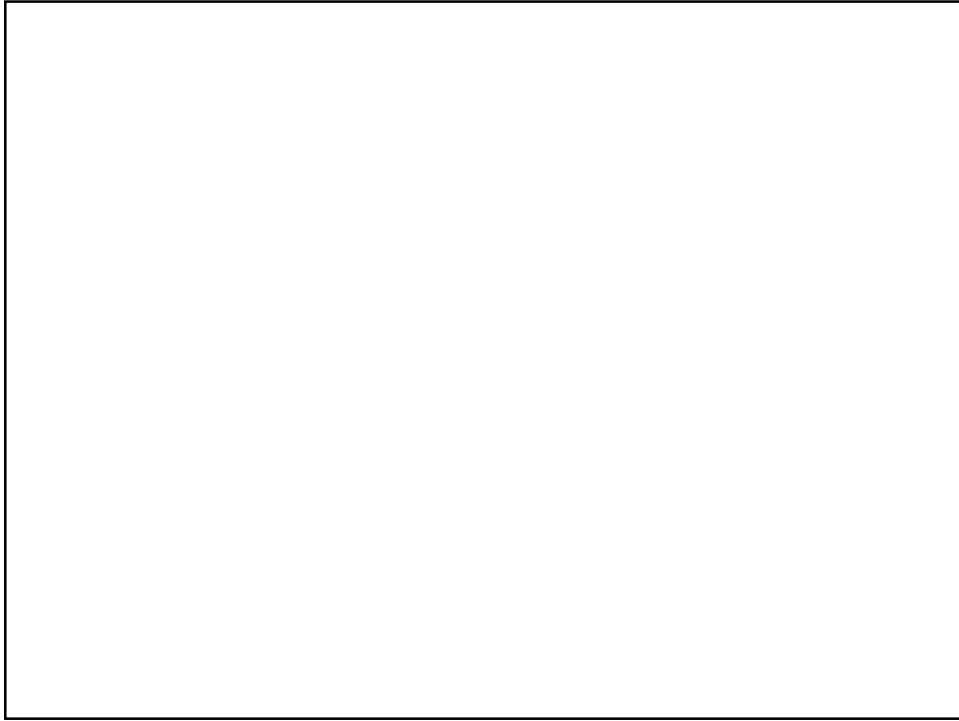
Thyroid 2017;27(3):315-389

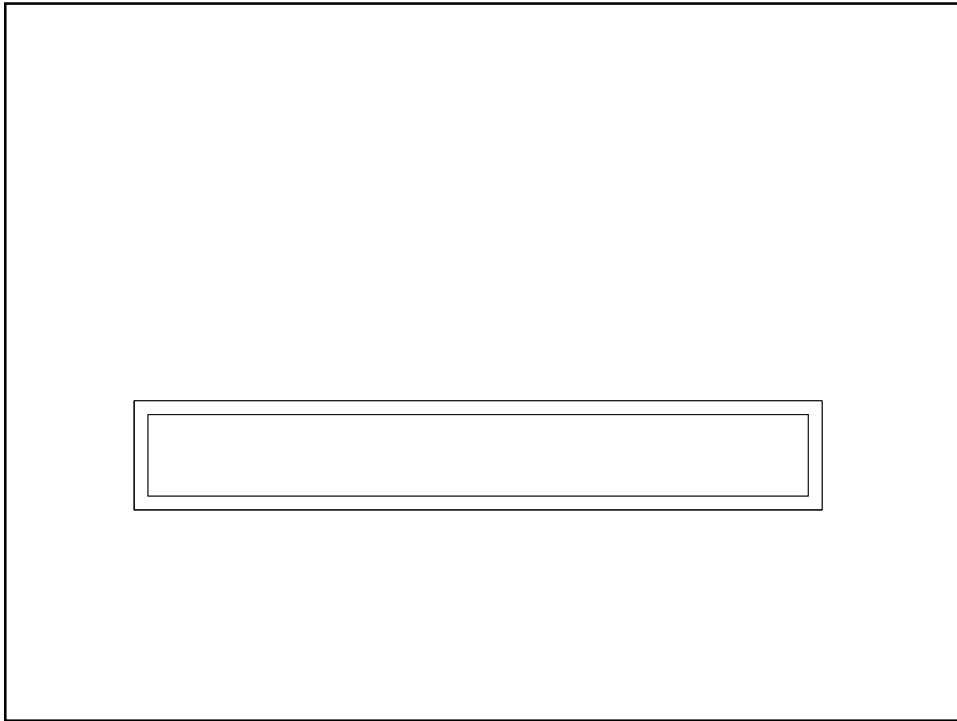
## Treatment of Subclinical Hypothyroidism/Isolated Hypothyroxinemia

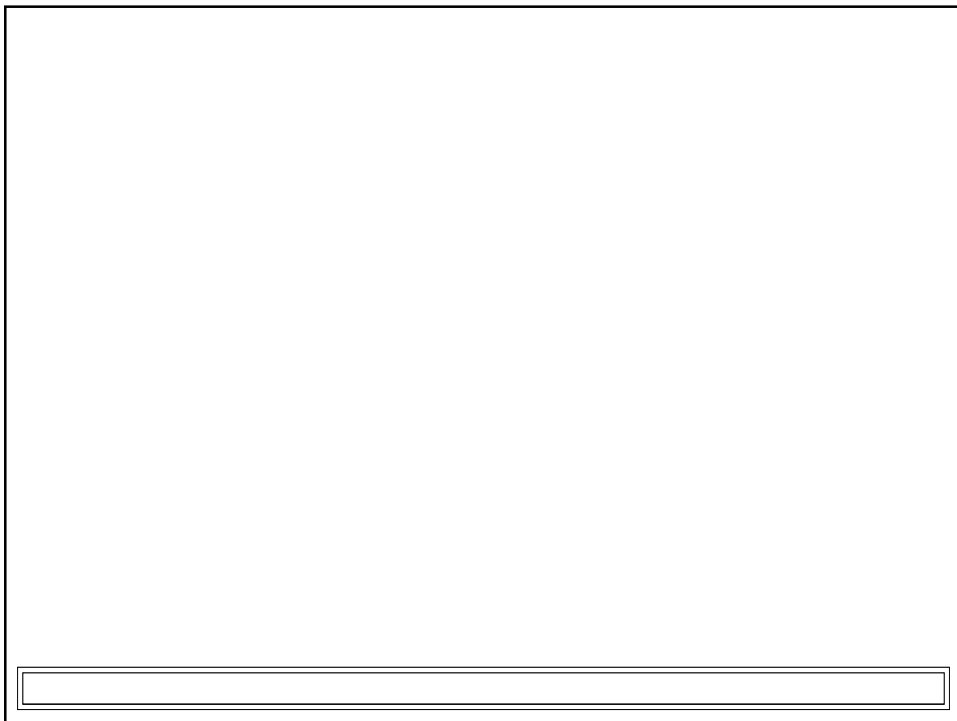
- Is there a neurocognitive benefit?
- 2 RCTs show no benefit

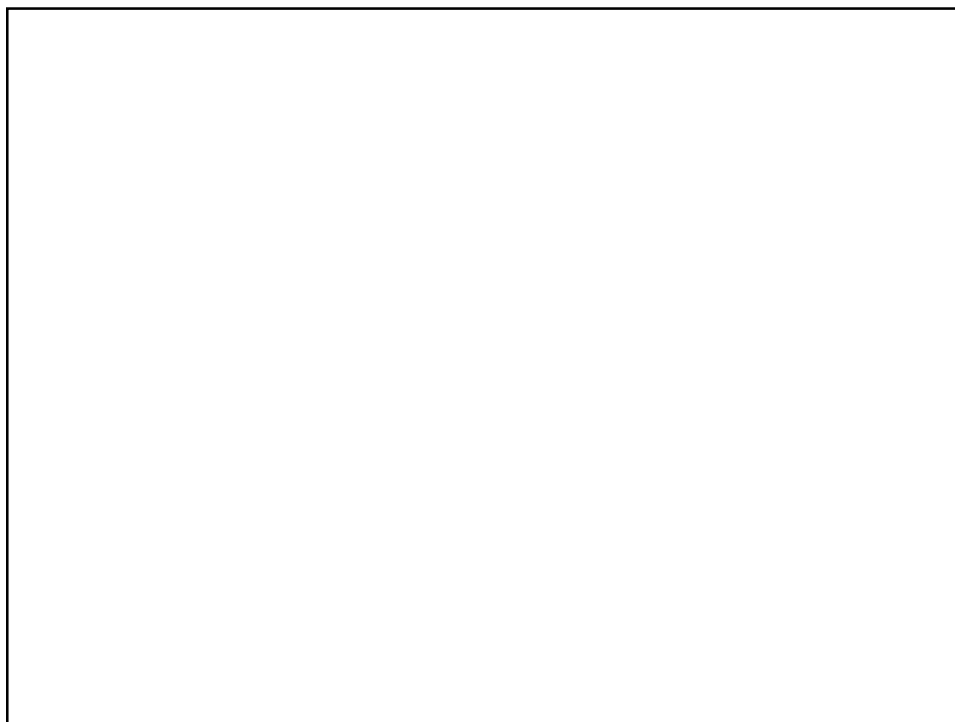












## TSH Monitoring – Euthyroid Women

- Euthyroid women with thyroid autoimmunity (TPO+) prior to pregnancy may develop hypothyroidism during pregnancy
- 2 prospective studies:
- 12% developed TSH >4 mU/L during gestation
- 19% developed supranormal TSH value at delivery
- Euthyroid TPO + pregnant women should have TSH checked
  - At pregnancy confirmation
  - Q4 weeks through midpregnancy

## Complications of TPO Ab Positivity?

- Associations between TPO antibodies in euthyroid women and:
  - spontaneous pregnancy loss
  - recurrent pregnancy loss
  - preterm delivery

## Interventions for TPO Ab + Euthyroid Pregnant Women?

- To decrease miscarriage?
- Very poorly studied
- Retrospective study of obstetrical outcomes in 65 euthyroid TPO Ab + pregnant women (TSH 1–3.5 at first visit) and 311 TPO Ab- pregnant women
- 34/65: treated with 50 mcg LT4 daily
  - mean 10 weeks gestation

Gynecol Obstet Invest 2012;74:265–273

## Does treatment with LT4 decrease the risk for pregnancy loss in euthyroid women with thyroid autoimmunity?

“ Insufficient evidence exists to conclusively determine whether LT4 therapy decreases pregnancy loss risk in TPOAb positive euthyroid women who are newly pregnant. However, administration of LT4 to TPOAb positive euthyroid pregnant women with a prior history of loss may be considered given its potential benefits in comparison with its minimal risk. In such cases, 25–50 mcg of LT4 is a typical starting dose”

- Weak recommendation, low-quality evidence.

## Interventions for TPO Ab + Euthyroid Pregnant Women?

- To decrease preterm delivery?
- Poorly studied – single prospective interventional trial
- Euthyroid TPOAb positive women randomized to treatment with LT4 or no treatment
- Obstetrical outcomes compared with euthyroid TPOAb negative women



- Preterm delivery rate: 22.4% in TPO+ untreated vs. 7% in TPO+ treated women ( $p < 0.01$ )
- Preterm delivery rate: 8.2% in TPO- woman

J Clin Endocrinol Metab 91: 2587–2591, 2006

Does LT4 treatment of euthyroid women who are thyroid autoantibody positive reduce risk for premature delivery?

“Insufficient evidence exists to recommend for or against treating euthyroid pregnant women who are thyroid autoantibody positive with LT4 to prevent preterm delivery”

- No recommendation, insufficient evidence.