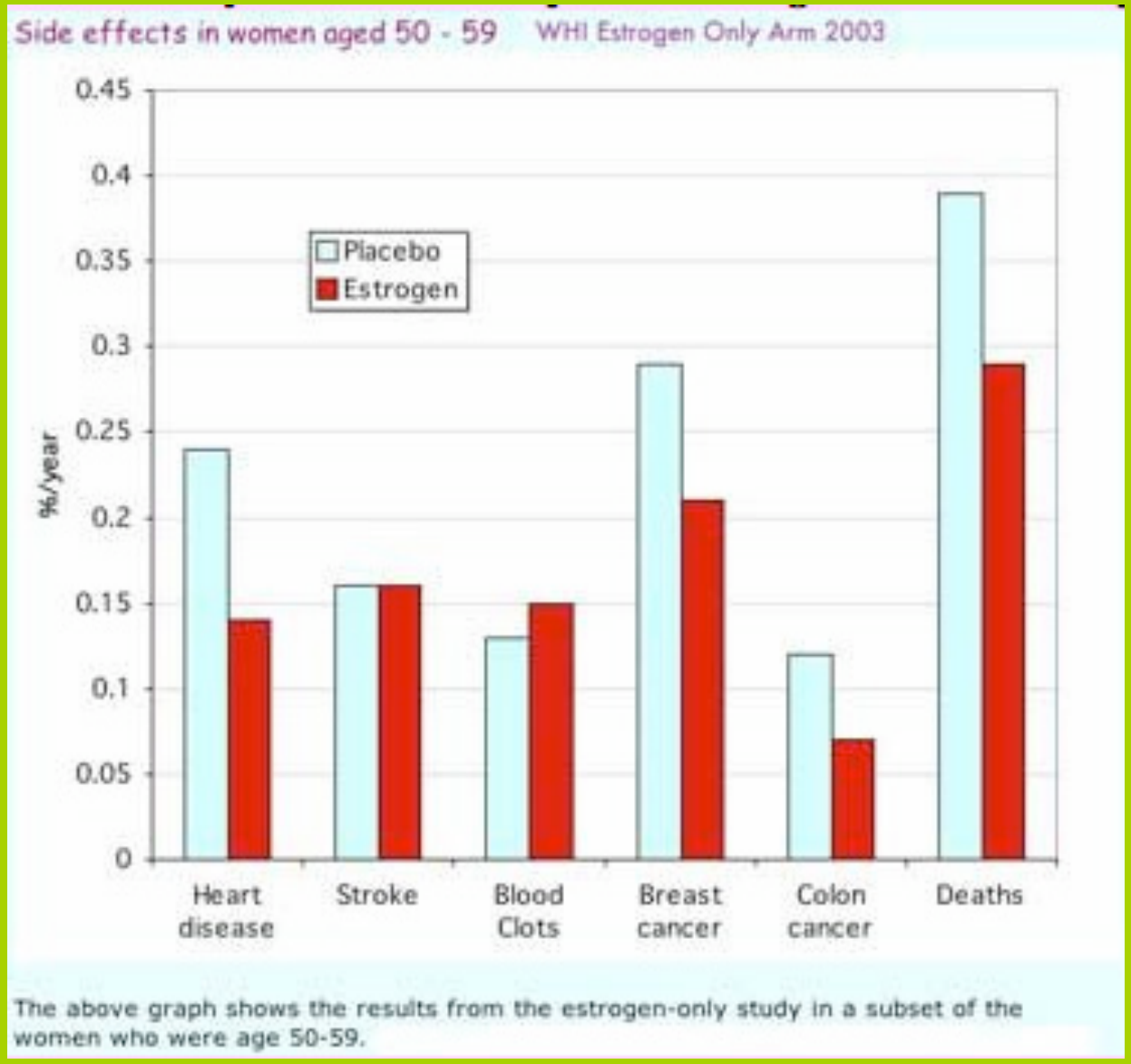
Thyroxine Deficiency in Pregnancy

Timothy Bilash MD MS OBG

Northern Inyo Hospital, Bishop, CA
October 20, 2006 1:30 PM

WHI Estrogen recap



In http://courses.washington.edu/bonephys/opestrogen.html. from:
Anderson GL et al, Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. Jama 2004;291:1701-12.

Clinical Significance

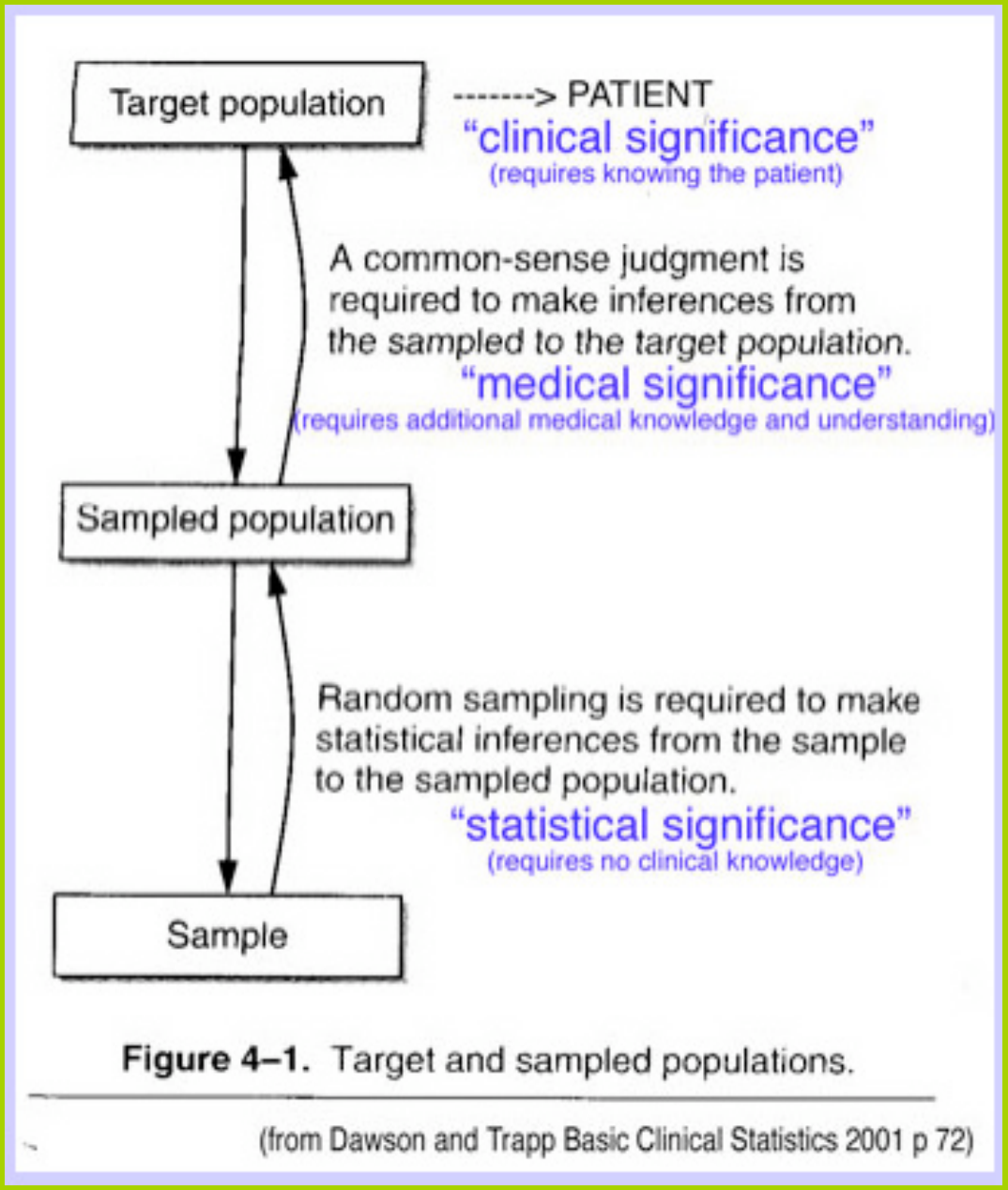
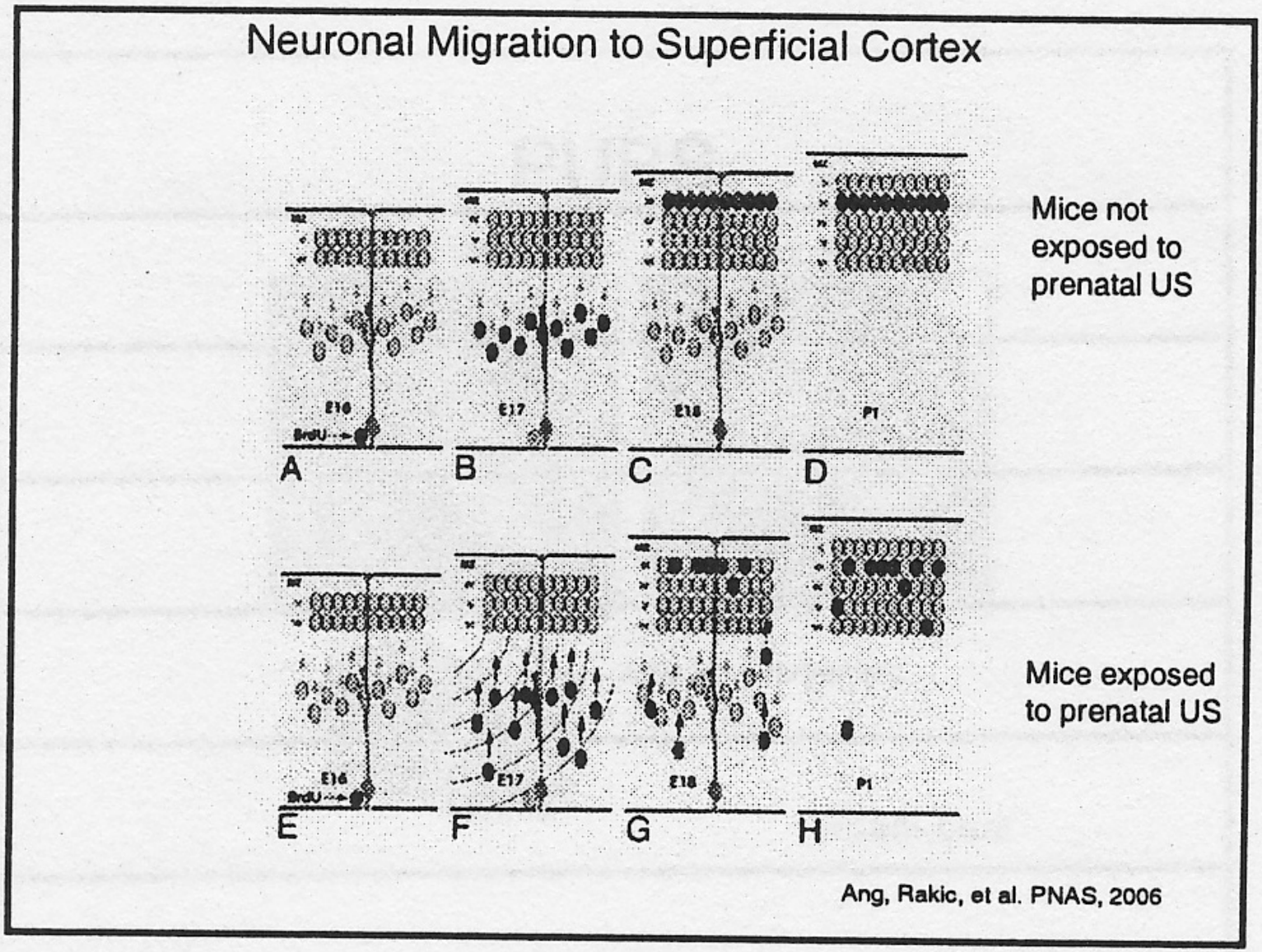


Figure 4–1. Target and sampled populations.

(from Dawson and Trapp Basic Clinical Statistics 2001 p 72)

Prenatal Ultrasound



Thyroxine Deficiency in Pregnancy

Timothy Bilash MD MS OBG

Northern Inyo Hospital, Bishop, CA
October 20, 2006 1:30 PM

Thyroid Gland Pic

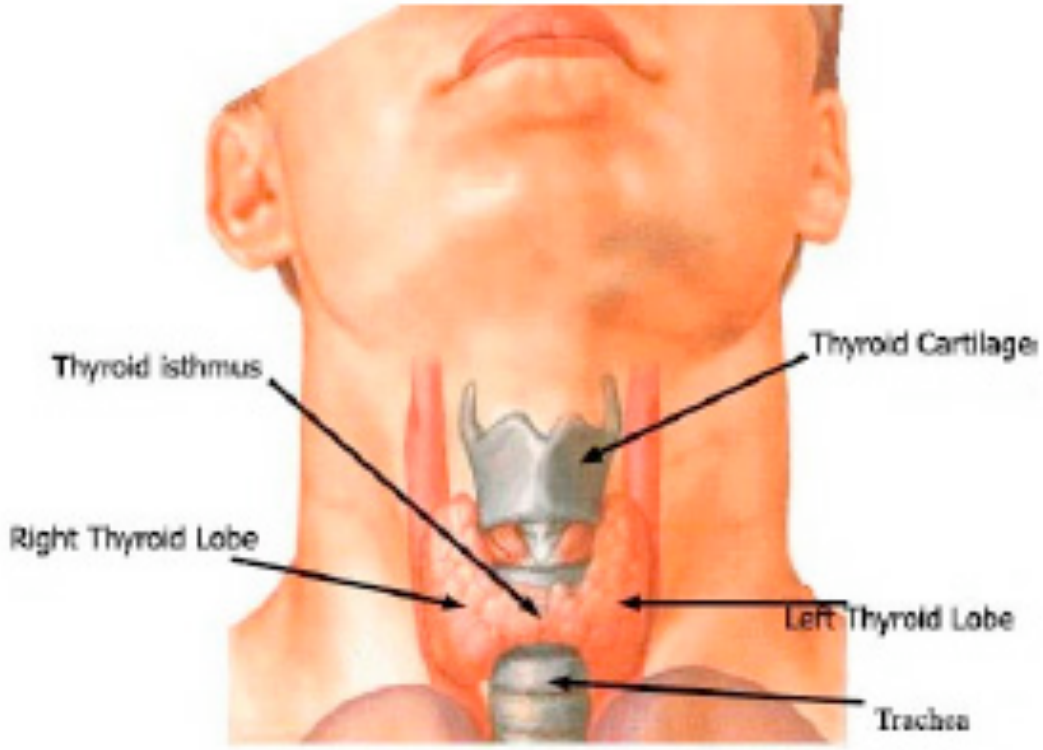


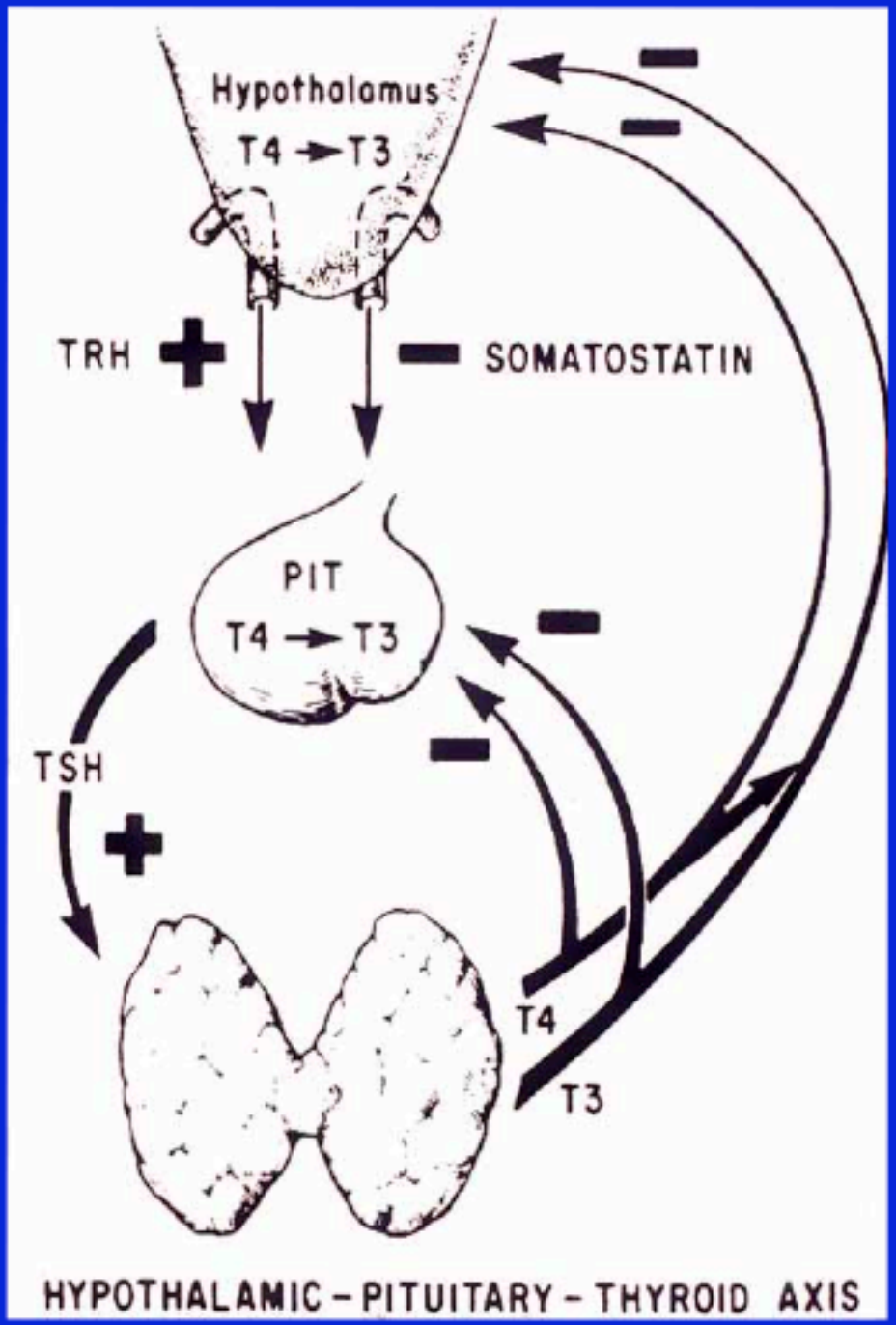
Figure 1: The human thyroid (1)

Thyroid Physiology

Thyroid has influences on:

- Carbohydrate metabolism
- Growth

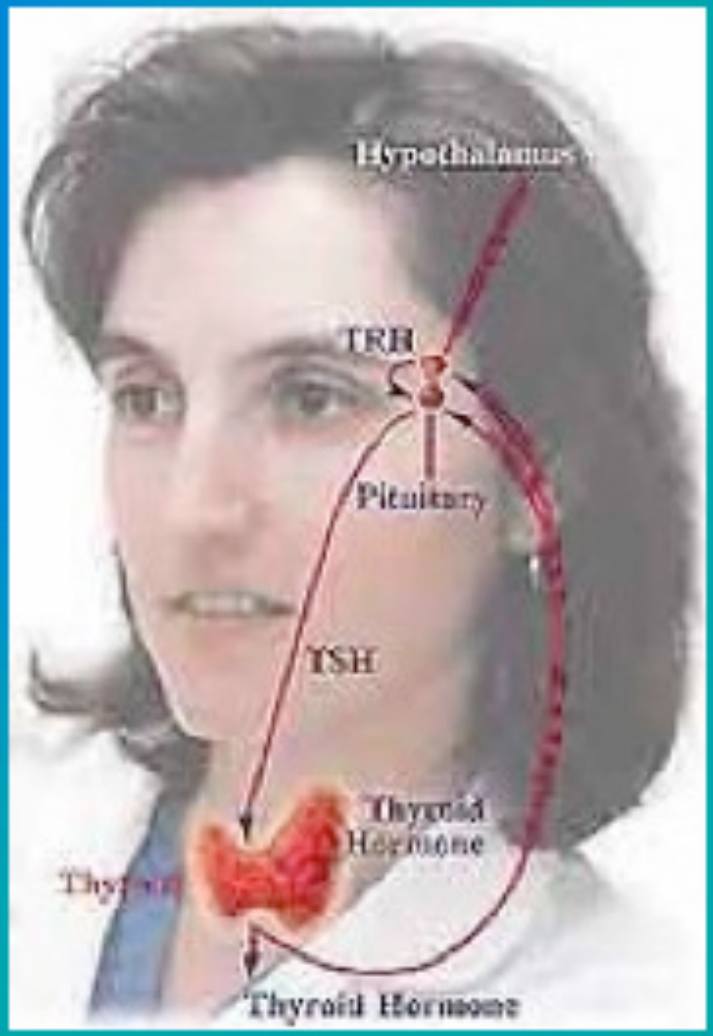
- …and just about everything else



HYPOTHALAMIC – PITUITARY – THYROID AXIS

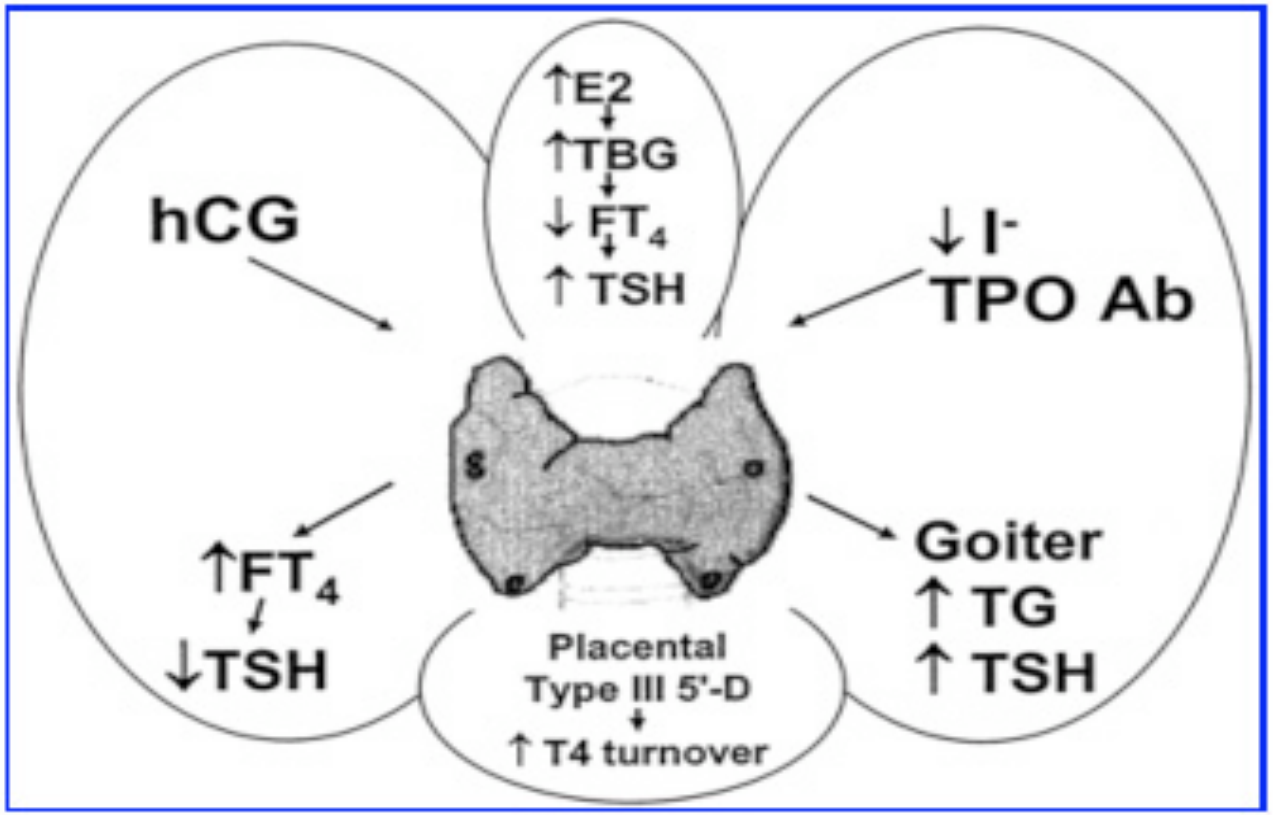
Thyroid Axis Regulation

- TRH → TSH → T4 → T3 + rT3.
- TSH : alpha / beta (unique) units.
- Highest levels occur at night: mild diurnal rhythm.
- Classic endocrine feedback loop.



PowerPoint Slide for Teaching

(Downloading may take up to 30 seconds.
If the slide opens in your browser, select File -> Save As to save it.)



Thyroid Physiology in Pregnancy

Important Hormones

Mother	Fetus
I_2	I_2
HCG	.
TSH	.
TBG	.
FT4	**FT4** (20-40 weeks)
Serum Proteins	Serum Proteins

Thyroid hormone Structures

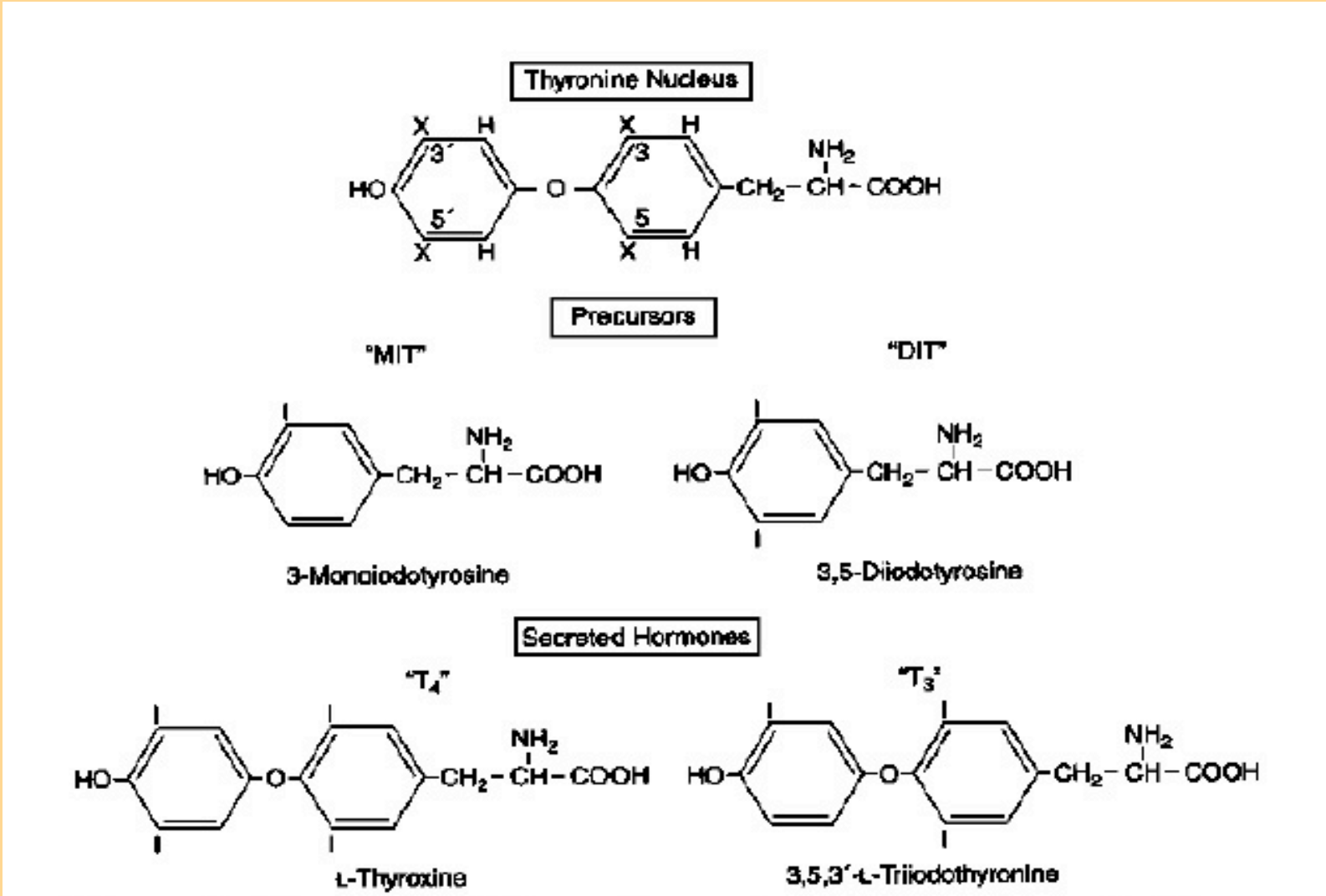


Figure 2: Structure of thyroxine and related compounds (4)

Thyroid Hormone in Pregnancy

2 Phases : *Production* + Conversion/*Modification*

Central Production

(0-10 weeks) Thyroid, (HCG stim)

(10-20 weeks) Thyroid, Liver

Peripheral Conversion

(20-40 weeks) Liver, Placenta

Bioactivity ? modified in Pregnancy

assay *immunoreactivity* vs *biological activity*

Thyroid peroxidase

Thyroid peroxidase or Thyroperoxidase (TPO) is an enzyme mainly expressed in the thyroid that liberates iodine for addition onto tyrosine residues on thyroglobulin for the production of thyroxine (T4) or triiodothyronine (T3) (thyroid hormones). This process is termed the "organification of iodine".

It is inhibited by the thioamide drugs, such as propylthiouracil. It is a frequent epitope of autoantibodies in autoimmune thyroid disease, reducing T4 levels.

- From Wikipedia, the free encyclopedia

Thyroid Metabolism

Activating Enzymes

- **D1**, inner and outer ring **Deiodinase** converts *T4 -> T3 + I* peripherally

  liver, no change in pregnancy

- **D2**, outer ring **Deiodinase**, intracellular conversion of *T4 -> T3* + I, rT3 -> T2 +I

  generates in cells locally (T3 determined by T4)

  important in pregnancy (esp 1st half)

  placenta (1st trimester), **amnion/chorion** membranes

Thyroid Metablism

De-activating Enzymes

- D3, Inner ring Deiodinase
- *Inactivates* ***T4 -> rT3 + I, T3 ->T2 +I***
  and limits excess in tissues locally
- *Provides* ***I_2 to Fetus*** (crosses Placenta)
- *Limits Placental Transfer* of active thyroid hormone to Fetus
- Important 20-40 weeks, placenta

Placental D3

The placenta contains high concentrations of the Type 3 or inner-ring iodothyronine deiodinase D3.

The inner-ring deiodination of T4 catalyzed by this enzyme is the source of high concentrations of reverse T3 present in the amniotic fluid. Reverse T3 levels parallel maternal serum T4 concentrations.

This enzyme may function to reduce the concentration of T3 and T4 in the fetal circulation (the latter being still contributed by 20-30% from thyroid hormones of maternal origin at the time of parturition), although fetal tissue T3 levels can reach adult levels due to the action of the Type 2 deiodinase D2.

The Type 3 deiodinase may also indirectly provide a source of iodide to the fetus via iodothyronine deiodination. In circumstances in which fetal T4 production is reduced or maternal free T4 markedly increased, transplacental passage occurs and fetal serum T4 levels are about one third of normal.

Thyroid Physiology

IODINE requirements

80 mcg/day **non-pregnant**

120 mcg/day **pregnant** (50% higher),

220 mcg/day pregnant *recommended*

150 mcg/day avg in US - iodine adequate

70 mcg/day avg in Europe - iodine restricted

empties stores by 2 months of pregnancy

(10mcg/day loss, despite improved uptake)

Sources: Iodized salt, Fish, Multivitamins

Thyroid Physiology

IODINE

There has been a marked

decline in Iodine excretion

1970 thru1990

Thyroid Buffer System

1) **Binding Proteins** are made in the liver, carry/store the bulk of ***inactive*** hormone

2) **Free hormone** is ***active***, a small percentage

3) Free hormone is ***metabolized*** and inactived (T4 ->T3, T3->rT3, gluconated, sulfated)

Thyroid Physiology

TBG (Thyroid Binding Globulin)

- E2 increases TBG (liver stim)
- 500-1000pg/nl threshold to increase TBG *
- Increase to plateau at 20 weeks preg
- TBG lowers FreeT4 after 20 weeks
- TBG lowers the T4/T3 ratio
- Large patient variation

Low Thyroid Symptoms

Hypothyroid

- **Fatigue**
- **Cold hands and feet (Cold Intolerance)**
- **Dry skin, Dry hair**
- **Constipation**
- **Weight Gain**
- **Depression / Memory Deficits**
- Infertility, Irregular Menses
- Elevated Serum Cholesterol
- Anemia

Low Thyroid Symptoms

Hypothyroid - Pregnancy

- Hypertension, Preeclampsia, Fluid Retention
- Diabetes Mellitus/ Glucose Intolerance
- Placental Abruption
- Hydramnios
- Arrythmias
- Failure to progress
- Large birthweight (mild), Low birthweight (severe)
- TTN

High Thyroid Symptoms

Hyperthyroid

- Insomnia/ Hyperactivity
- Diarrhea
- Hot sweats
- Weight loss
- Tachycardia/Palpitation
- Hypertension
- Seizures
- Irritability

Fetal Effects

Subclinical Hypothyroidism and Pregnancy. Two studies published in 1999 suggested that maternal hypothyroidism may impair fetal neuropsychological development. In one study, Pop and associates (1999) studied a group of women beginning at 12 weeks' gestation. Children born to women with free T_4 levels below the 10th percentile were at increased risk for impaired psychomotor development. In the other study, Haddow and colleagues (1999) retrospectively evaluated children born to 48 untreated women whose serum thyrotropin values exceeded the 98th percentile. Some offspring of these women had diminished school performance, reading recognition, and IQ scores. Importantly, while described as "subclinically hypothyroid," these women had significantly lower mean serum free thyroxine levels, and thus had overt hypothyroidism. Subsequently, Casey and co-workers (2003) identified subclinical hypothyroidism in 2.3 percent of 17,298 women screened before midpregnancy. These women had significantly higher incidences of preterm birth, placental abruption, and admission of infants to the intensive care nursery (Table 53–4).

Williams Obstetrics 22ndEd pg 1195

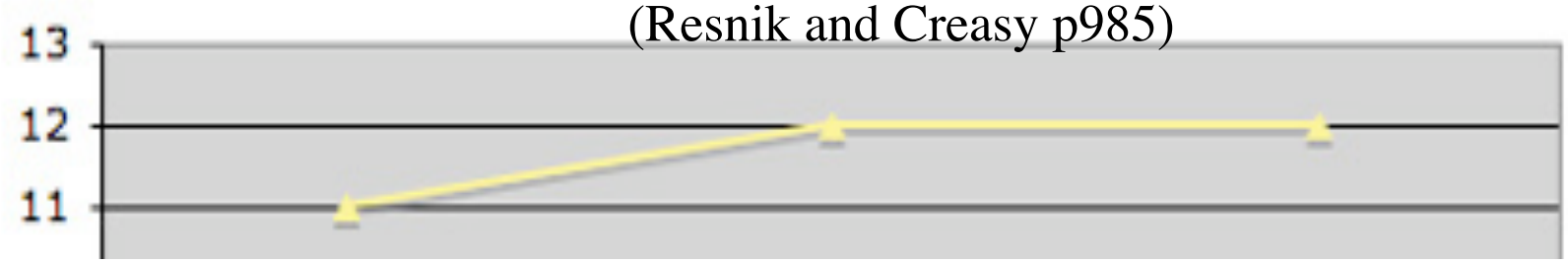
Thyroid Mean Values in Pregnancy

- Mean Values in Pregnancy (Resnik and Creasy p985, Glinoer 97)

	Trimester 1st	2nd	3rd	Term	
A. – TSH (0.2-4.0 mU/L)	.8	1.1	1.3		
(.1 - .6 pulsatile)				2.1	(I2 deficient)
B. – FT4 (0.8-2.0ng/dl)	1.4	1.1	1.0		
C. – TT4 (3.9-11.6 mcg/dl)	11	12	12		
D. – FT3 (1.9-7.1 ng/ml?)	3.3	2.7	2.5		
E. – T3/T4 molar ratio	2.3	2.4	2.5		

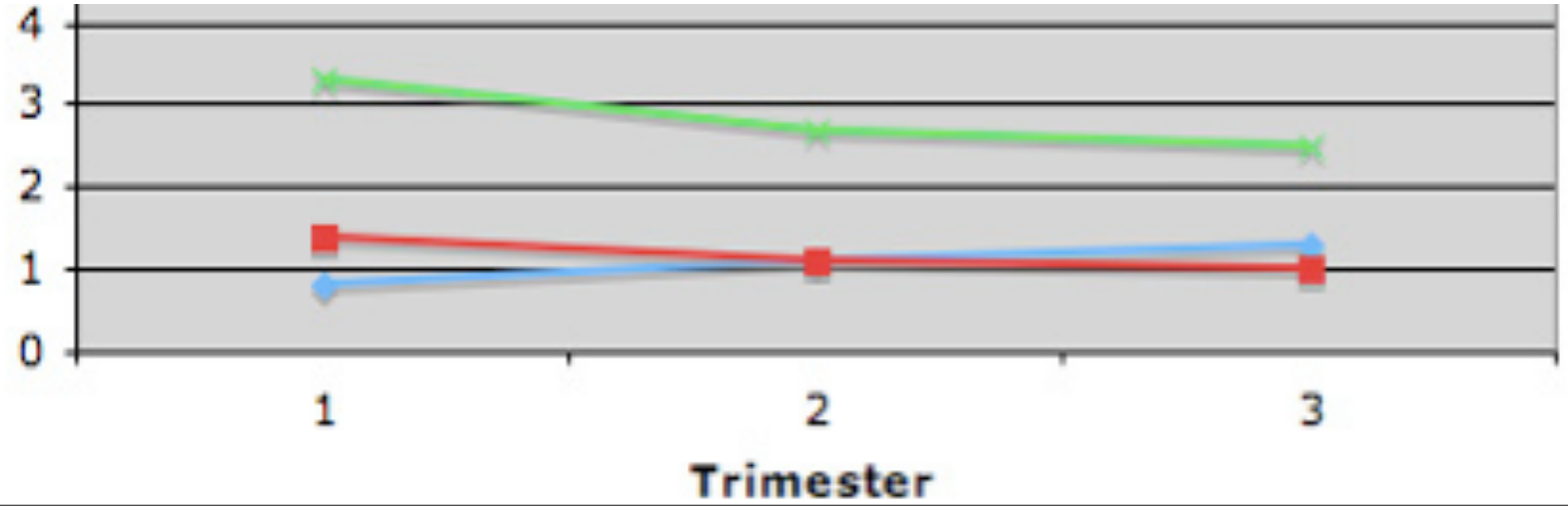
Thyroid Mean Values in Pregnancy

(Resnik and Creasy p985)



Trimester

	1st	2nd	3rd		Term
A. – TSH (0.2-4.0 mU/L)	.8	1.1	1.3	(.1 - .6, pulsatile)	
B. – TSH (I2 deficient Glinoer 97)					2.1
C. – FT4 (0.8-2.0ng/dl)	1.4	1.1	1.0		
D. – TT4 (3.9-11.6 mcg/dl)	11	12	12		
E. – FT3 (1.9-7.1 ng/ml?)	3.3	2.7	2.5		
F. – T3/T4 molar ratio	2.3	2.4	2.5		



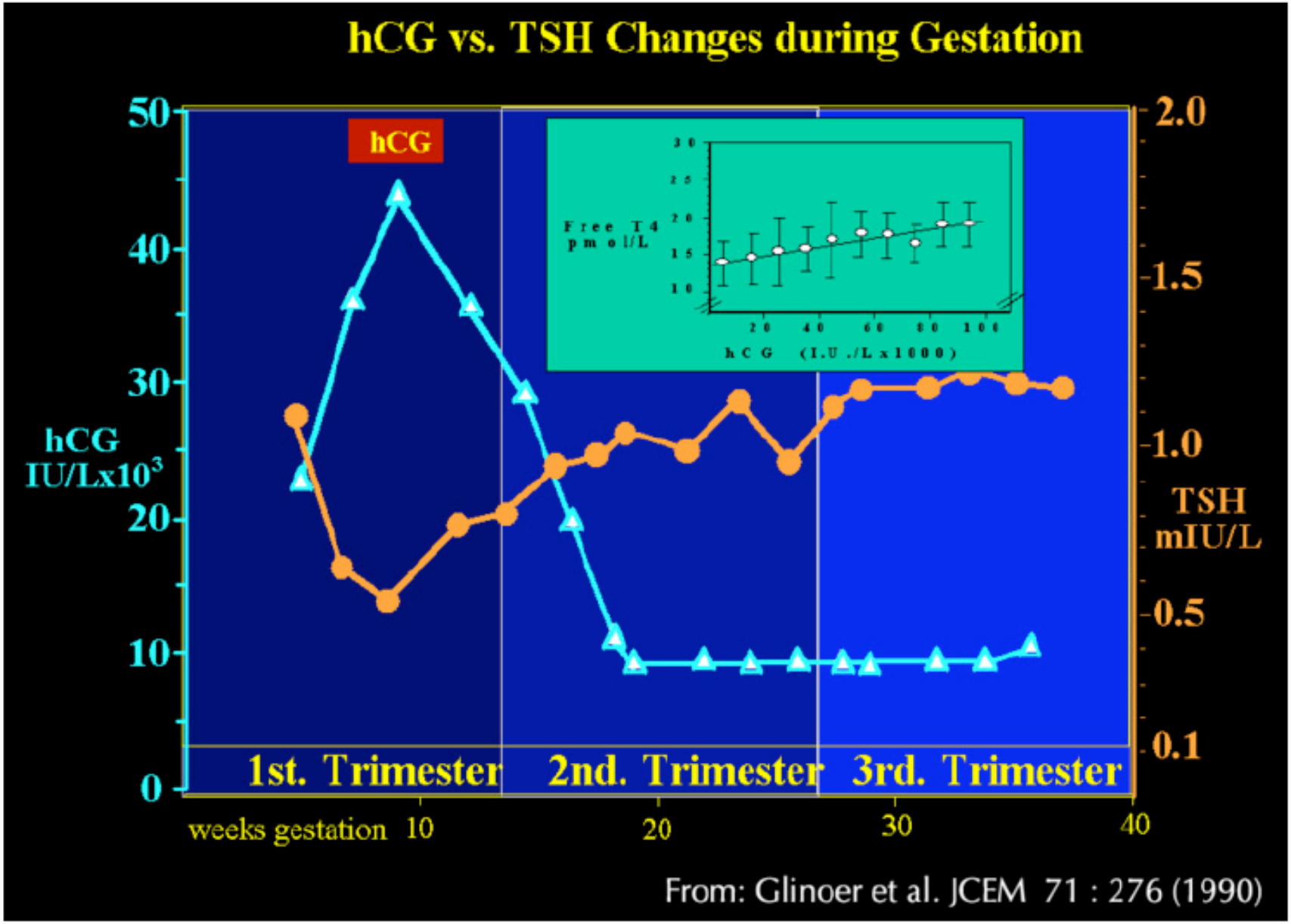
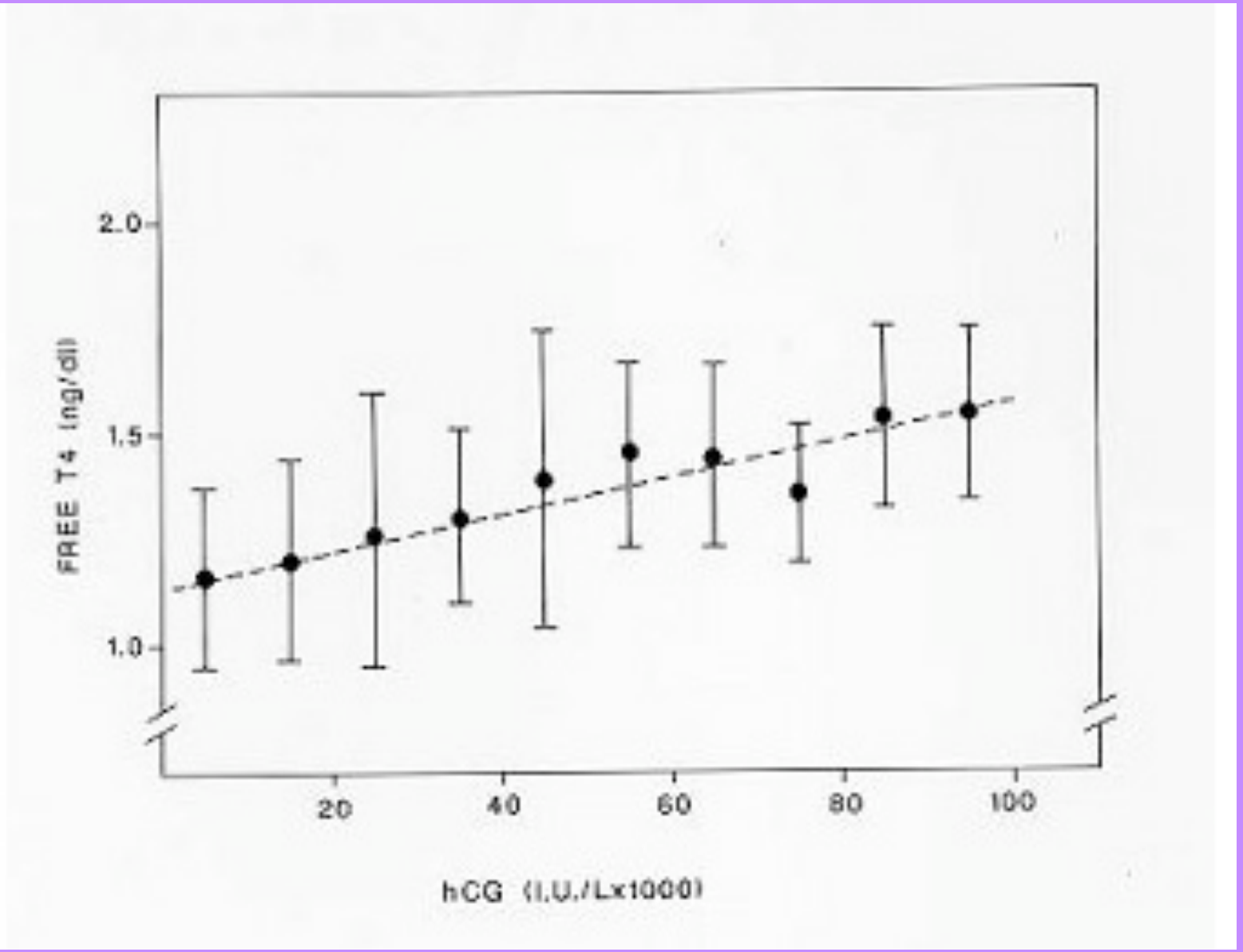


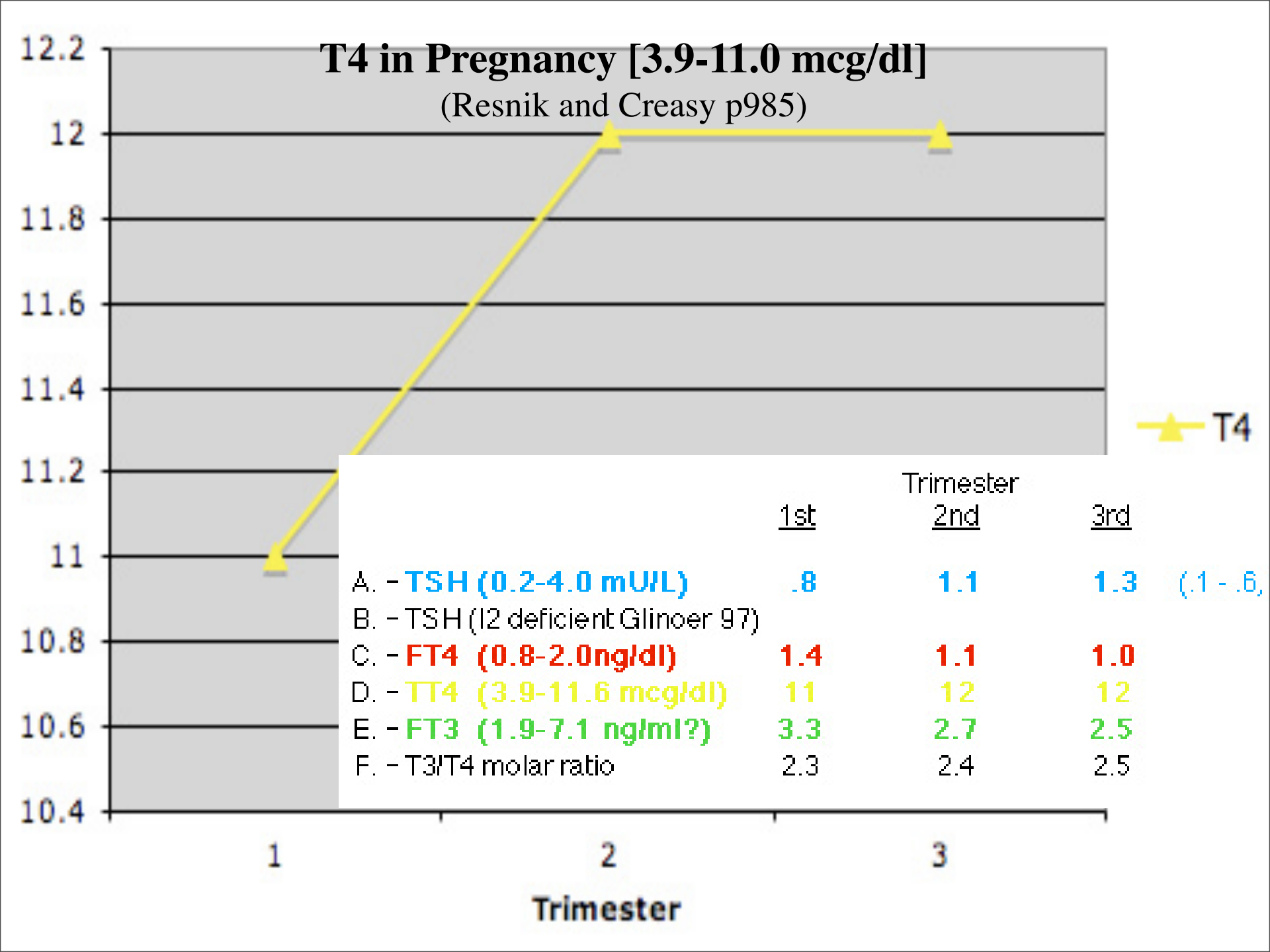
Figure 1. The pattern of serum TSH and hCG changes are shown as a function of

FT4 in Pregnancy



T4 in Pregnancy [3.9-11.0 mcg/dl]

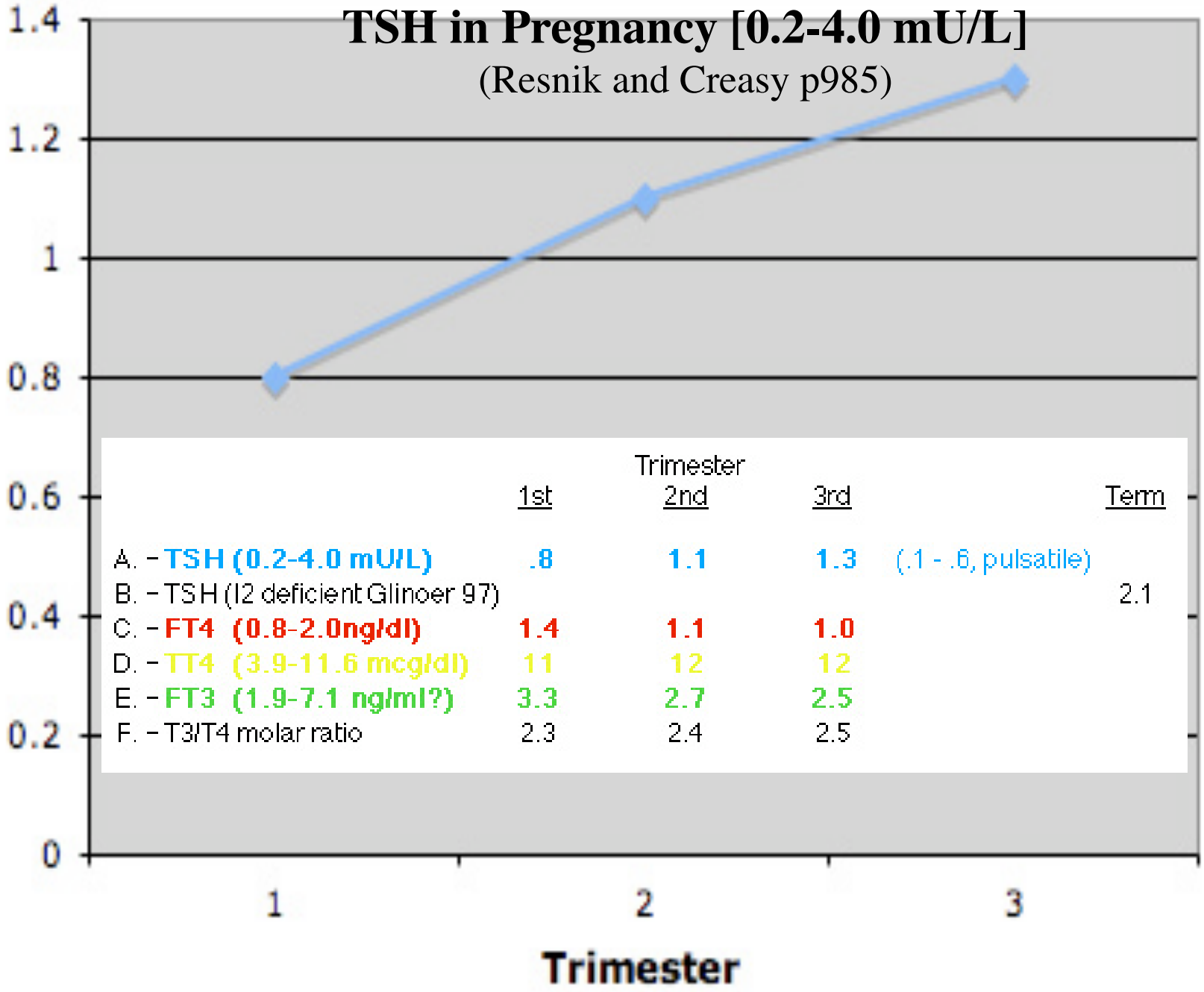
(Resnik and Creasy p985)



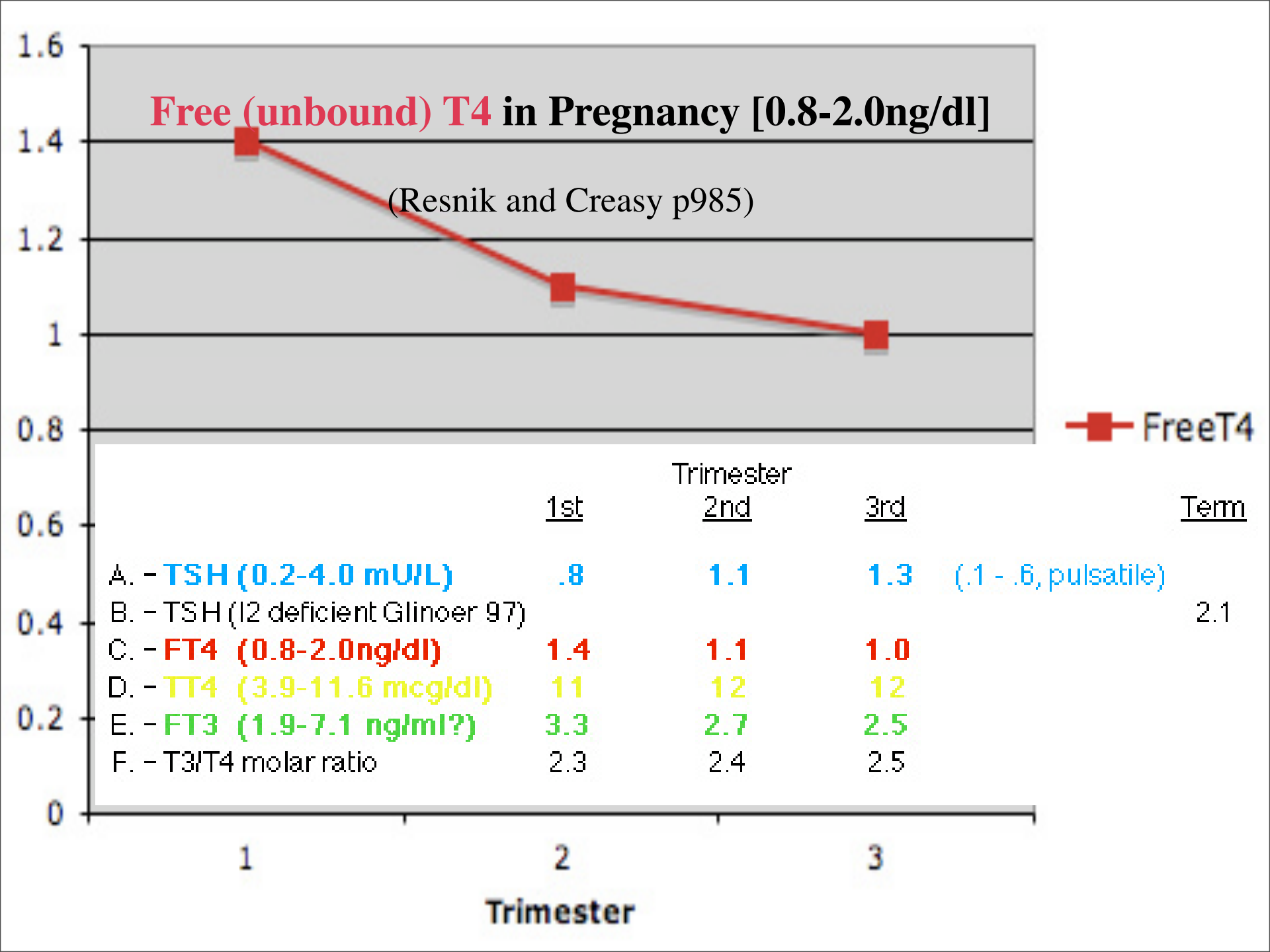
	Trimester 1st	2nd	3rd	
A. - TSH (0.2-4.0 mU/L)	.8	1.1	1.3	(.1 - .6,
B. - TSH (I2 deficient Glinoer 97)				
C. - FT4 (0.8-2.0ng/dl)	1.4	1.1	1.0	
D. - TT4 (3.9-11.6 mcg/dl)	11	12	12	
E. - FT3 (1.9-7.1 ng/ml?)	3.3	2.7	2.5	
F. - T3/T4 molar ratio	2.3	2.4	2.5	

TSH in Pregnancy [0.2-4.0 mU/L]

(Resnik and Creasy p985)

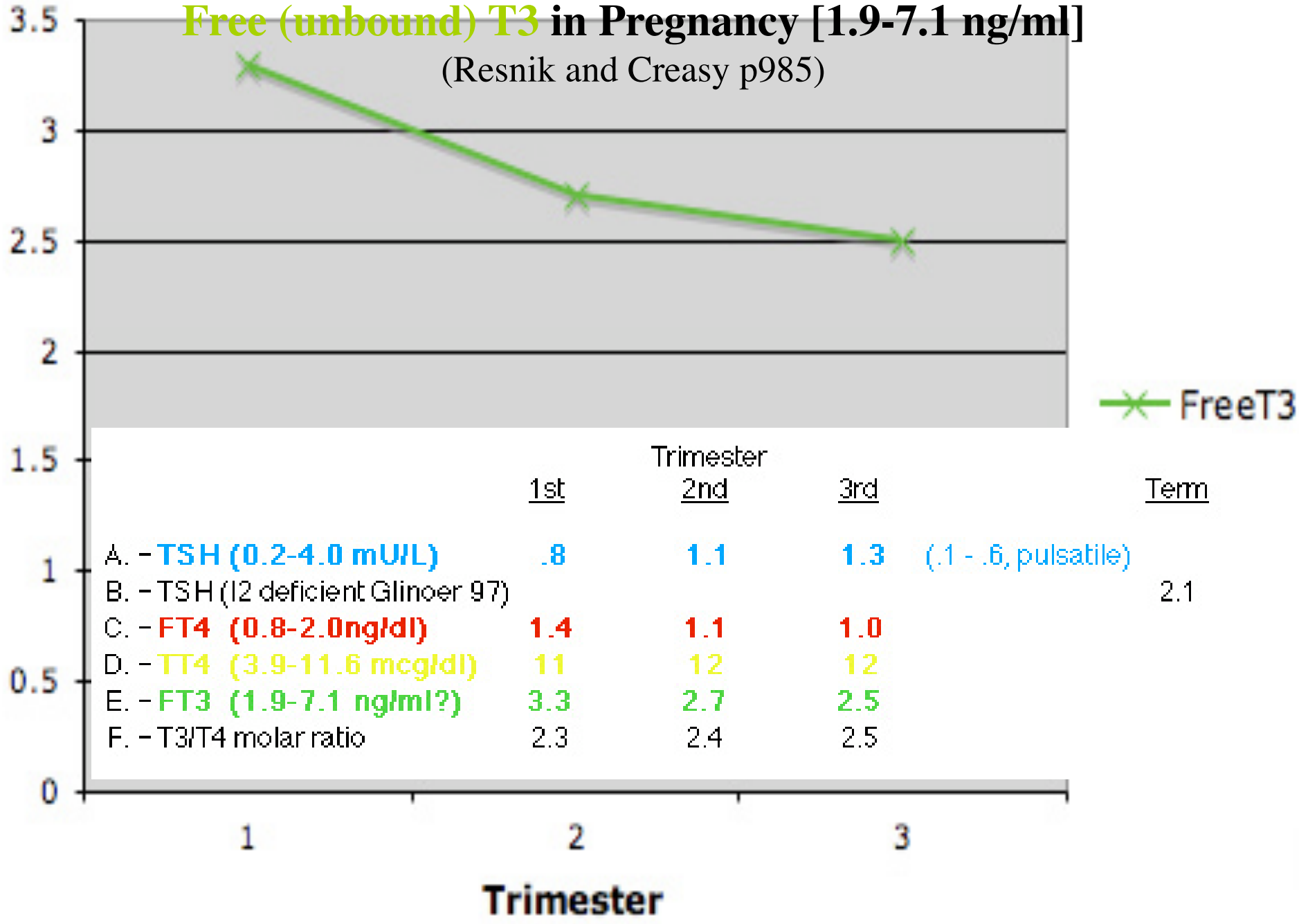


	Trimester 1st	2nd	3rd		Term
A. – TSH (0.2-4.0 mU/L)	.8	1.1	1.3	(.1 - .6, pulsatile)	
B. – TSH (I2 deficient Glinoer 97)					2.1
C. – FT4 (0.8-2.0ng/dl)	1.4	1.1	1.0		
D. – TT4 (3.9-11.6 mcg/dl)	11	12	12		
E. – FT3 (1.9-7.1 ng/ml?)	3.3	2.7	2.5		
F. – T3/T4 molar ratio	2.3	2.4	2.5		


Free (unbound) T4 in Pregnancy [0.8-2.0ng/dl]
(Resnik and Creasy p985)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
FreeT4
Trimester
1st
2nd
3rd
Term
A. - TSH (0.2-4.0 mU/L) .8 1.1 1.3 (.1 - .6, pulsatile)
B. - TSH (I2 deficient Glinoer 97) 2.1
C. - FT4 (0.8-2.0ng/dl) 1.4 1.1 1.0
D. - TT4 (3.9-11.6 mcg/dl) 11 12 12
E. - FT3 (1.9-7.1 ng/ml?) 3.3 2.7 2.5
F. - T3/T4 molar ratio 2.3 2.4 2.5
1
2
3
Trimester

Free (unbound) T3 in Pregnancy [1.9-7.1 ng/ml]

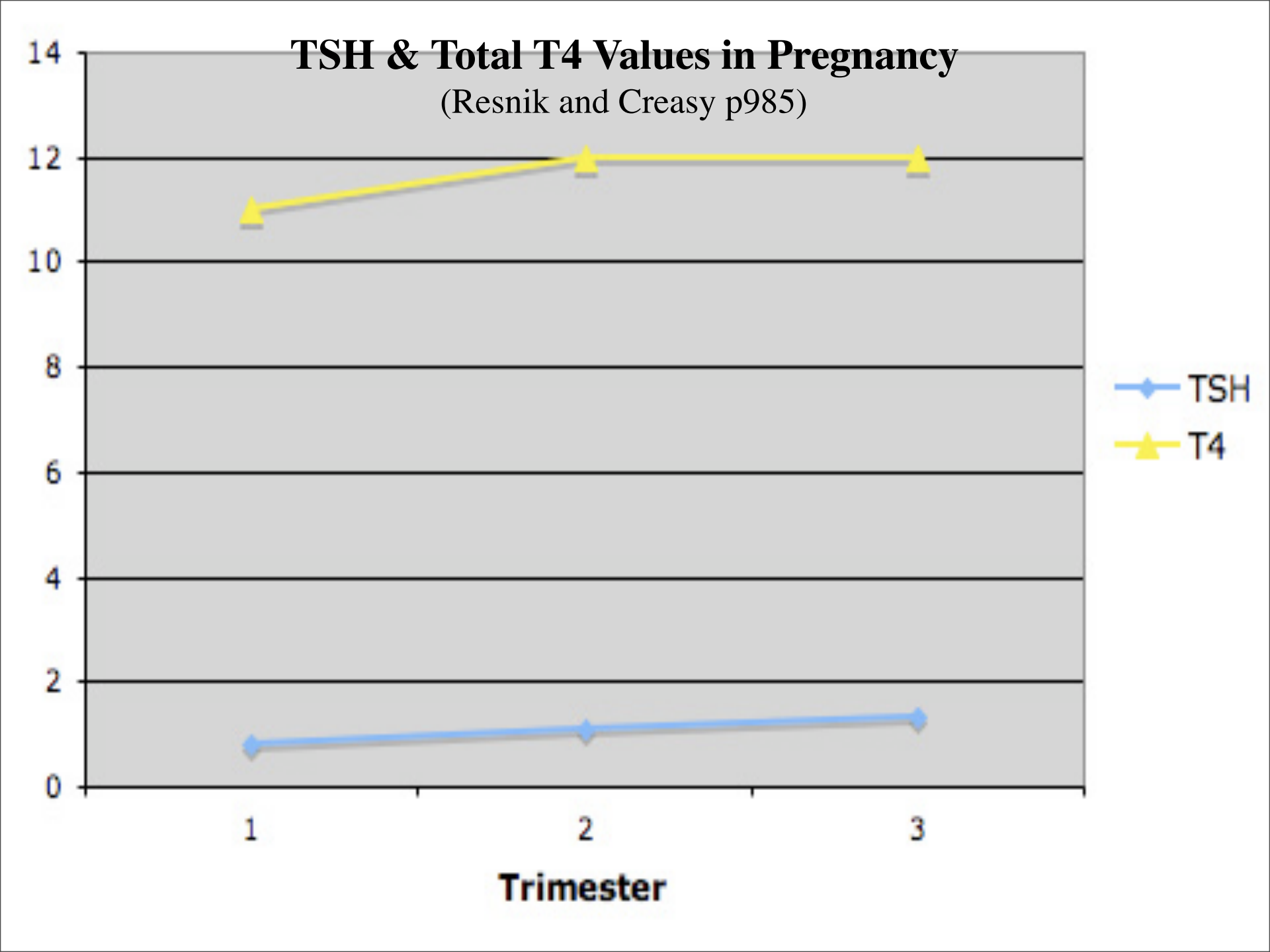
(Resnik and Creasy p985)



	Trimester 1st	2nd	3rd	Term
A. – TSH (0.2-4.0 mU/L)	.8	1.1	1.3	(.1 - .6, pulsatile)
B. – TSH (I2 deficient Glinoer 97)				2.1
C. – FT4 (0.8-2.0ng/dl)	1.4	1.1	1.0	
D. – TT4 (3.9-11.6 mcg/dl)	11	12	12	
E. – FT3 (1.9-7.1 ng/ml?)	3.3	2.7	2.5	
F. – T3/T4 molar ratio	2.3	2.4	2.5	

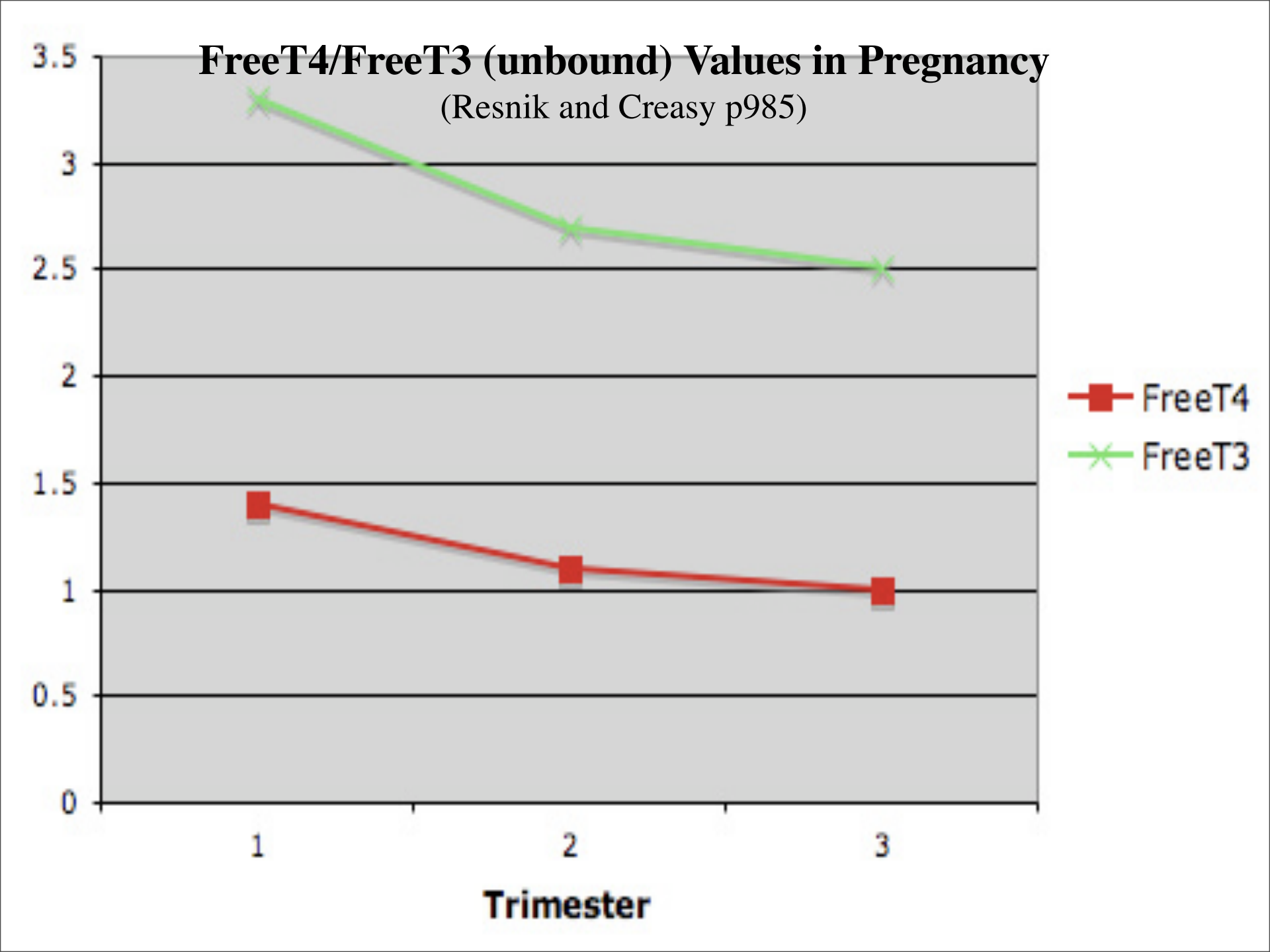
TSH & Total T4 Values in Pregnancy

(Resnik and Creasy p985)



FreeT4/FreeT3 (unbound) Values in Pregnancy

(Resnik and Creasy p985)

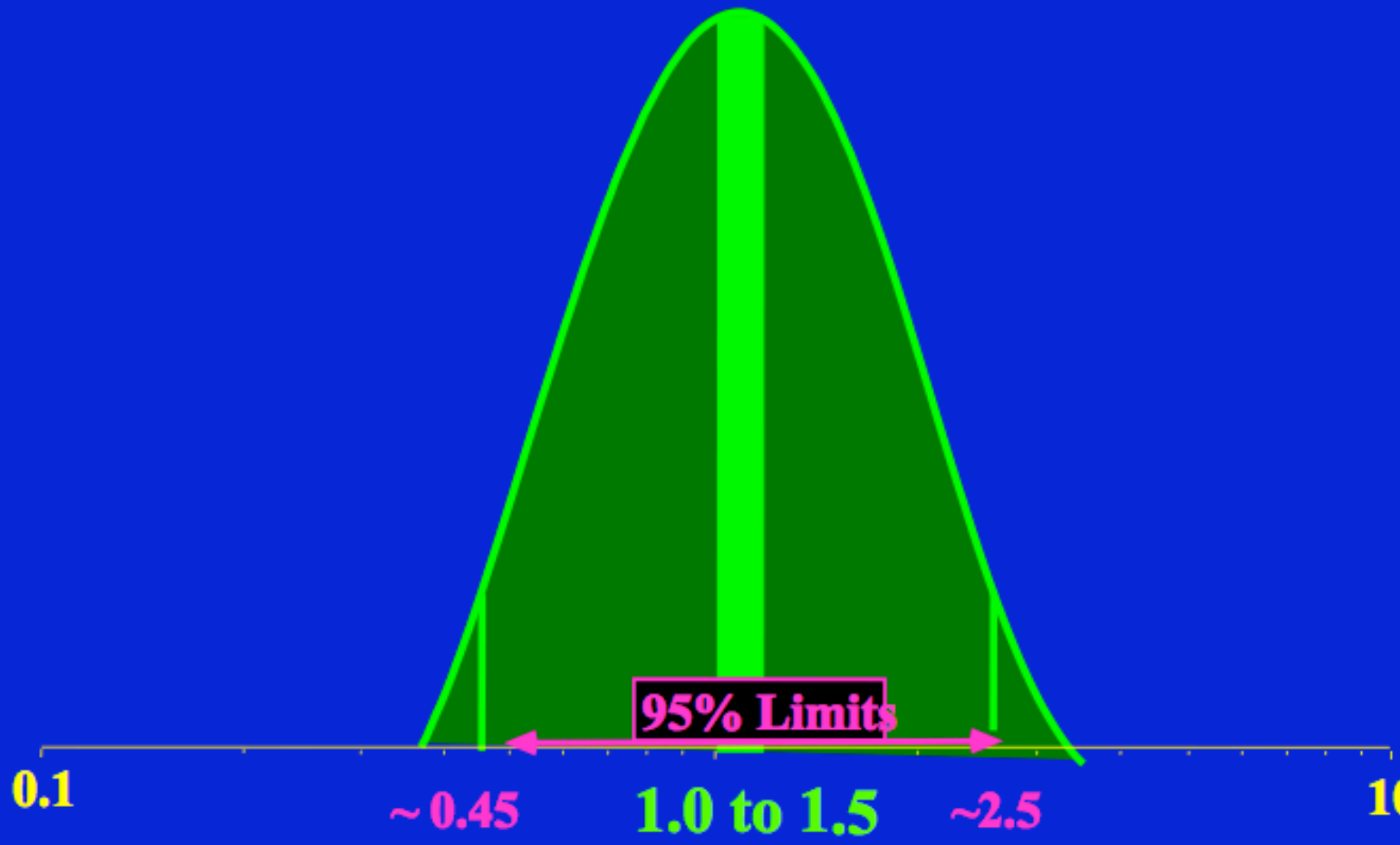


THYROID SCREENING TESTS

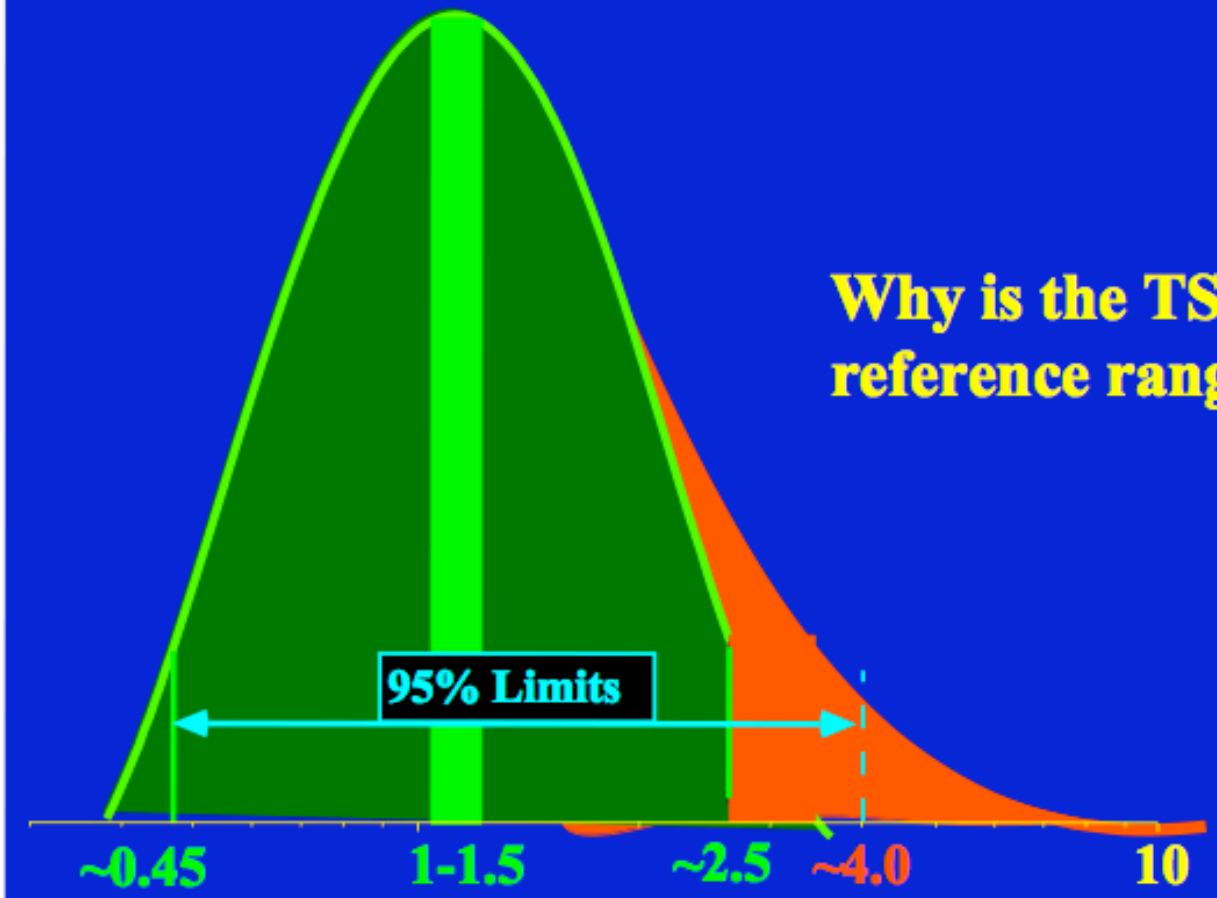
Use of TSH as the Screening Test for Hypothyroidism

- TSH is the "bioassay" for thyroid hormone effects on the body
- This assumes that all tissues require the same amount of thyroid hormone as the pituitary gland
- There are no other accurate, sensitive ways to assess thyroid hormone effects on the body
- There are clinical situations where TSH is not an adequate marker for thyroid function

TSH Normal (Gaussian) Distribution



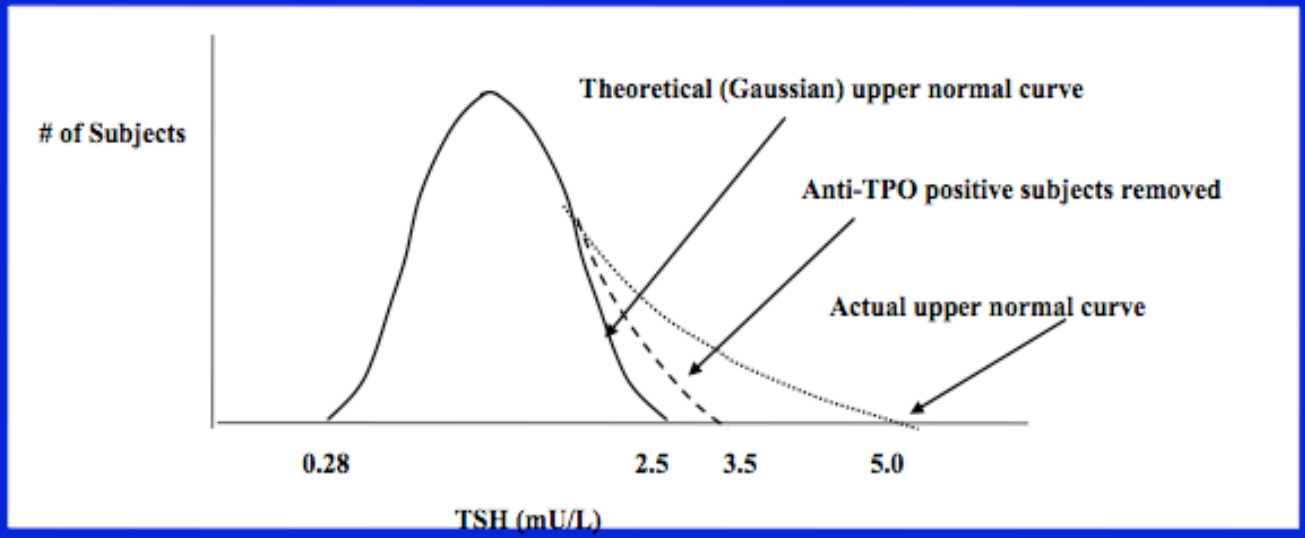
Current TSH Upper Reference Limits



Why is the TSH upper reference range skewed?

The True "Normal" TSH Range

- The "normal" TSH range is skewed at the upper range by subjects with early autoimmune thyroid disease
- In reference subjects ages 20-29 years, the normal TSH range is 0.40 – 3.56 mU/L (NHANES 2002)
- If TSH levels are normalized to a Gaussian distribution, the normal range is **0.40 – 2.5 mU/L**



American Thyroid Association

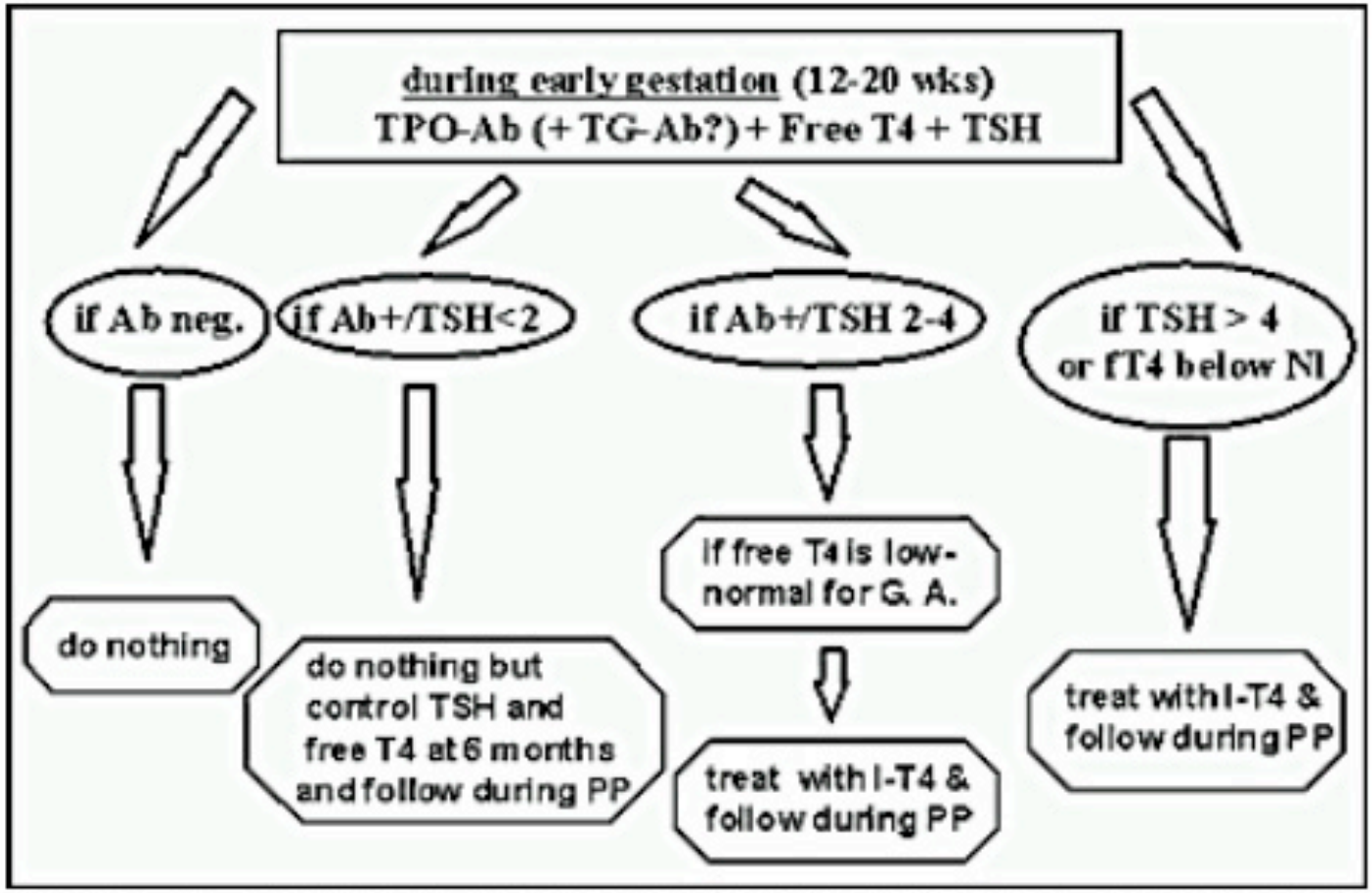


Figure 13. A proposed algorithm for the systematic screening of thyroid autoimmunity and hypothyroidism during pregnancy, based on the determination of thyroid antibodies (Ab), serum TSH and free T4 concentrations during the first half of pregnancy. GA = gestational age; NL = normal limits; PP = postpartum.
(Adapted, with modifications, and by permission of Glinoer; Trends in Endocrinology and Metabolism 9:403, 1998; Ref 134).

Thyroid Screening ACOG ?

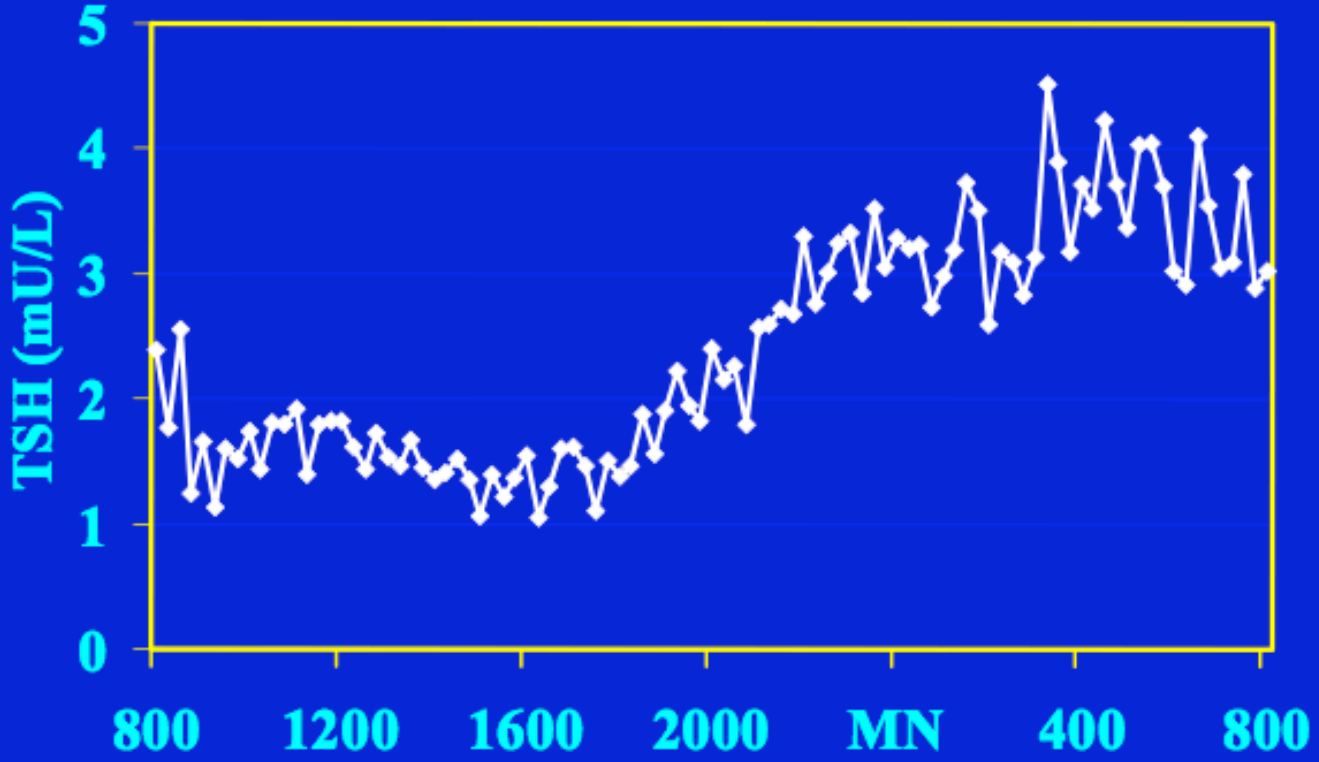
2000). Specifically, the American College of Obstetricians and Gynecologists (2002) concluded that observational data from the Haddow study were consistent with the *possibility* that subclinical hypothyroidism was associated with adverse neuropsychological development. The College thus recommended against implementation of screening until further studies were done to validate or refute these findings. One ma-

Williams Obstetrics 22ndEd p 1145

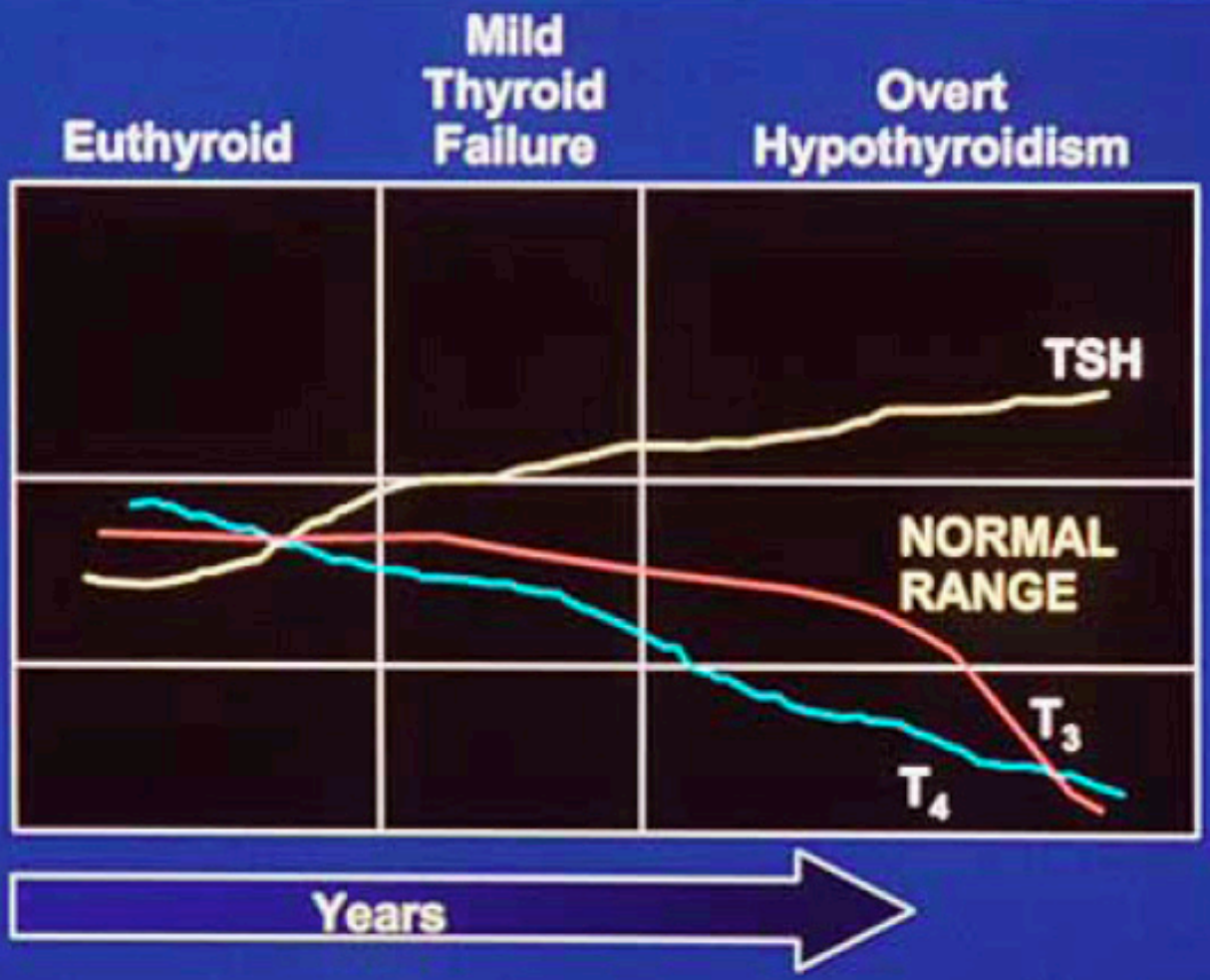
Use of TSH as the Screening Test for Hypothyroidism

- TSH is the "bioassay" for thyroid hormone effects on the body
- This assumes that all tissues require the same amount of thyroid hormone as the pituitary gland
- There are no other accurate, sensitive ways to assess thyroid hormone effects on the body
- There are clinical situations where TSH is not an adequate marker for thyroid function

24-hour TSH levels in a healthy subject



Progression of Mild Thyroid Failure



Adapted from Ayala AR, Wartofsky L. *The Endocrinologist.* 1997;7:44.

Tables for:
Free Thyroxine (FT4) and Free Triiodothyronine (FT3) Estimate Tests

[Thyroid 13(1):21-32, 2003. © 2003 Mary Ann Liebert, Inc.]

Table 1. Causes of FT4/TSH Discordance in the Absence of Serious Associated Illness

Mis-leading Test	Result		Likely Causes	Action
	TSH	FT4		
FT4	↑	N	1. Untreated—mild hypothyroidism 2. Treated—inadequate L-T4 dose or non-compliance	1. Measure TPO Ab. Confirm TSH after 6 weeks 2. Increase L-T4 dose/council compliance
	↓	N or ↓	1. Mild (subclinical) hyperthyroidism 2. Overtreatment with T3-containing preparation	1. ? Autonomous functioning goiter. 2. Measure FT3 to rule out T3-toxicosis.
	N	↑	1. Common during L-T4 treatent. 2. Abnormal binding proteins (i.e. FDH) 3. Antibody interferences (T4 antibody, HAMA or rheumatoid factor)	1. Expect higher FT4 with L-T4 Rx. for hypothyroidism 2 & 3. Check FT4 by alternate FT4 method ideally one using physical separation i.e. equilibrium dialysis or ultrafiltration
	N	↓	1. Binding-protein competitor drugs [see Section-3 B3(c)vi] 2. Pregnancy	1. Check FT4 by method using minimal dilution 2. Check FT4 by albumin-insensitive method. Use method- and trimester-specific reference ranges
TSH	↑	N	1. Dysequilibrium (first 6–8 weeks of L-T4 Rx. for primary hypothyroidism) 2. HAMA & other interferences	1. Recheck TSH before adjusting L-T4 dose. High TSH persists for months after Rx. for severe hypothyroidism 2. Check TSH (new specimen) by alternate method
	↓	N	1. Dysequilibrium (first 2–3 months post Rx. for hyperthyroidism) 2. Medications, i.e. glucocorticoids, dopamine	1. Use FT4 and FT3 during early Rx. of hyper to monitor thyroid status. TSH may take months to normalize after starting Rx. for severe hyperthyroidism
	N or ↑	↑	1. TSH-secreting pituitary adenoma	1. Check TSH (new specimen) by alternate method 2. TRH-stim or thyroid hormone suppression test 3. TSH alpha subunit 4. Pituitary Imaging.
	N	↓	1. Central hypothyroidism	1. Reduced bioactivity of immunoreactive TSH 2. ? other signs of pituitary deficiency 3. ? blunted (< 2 fold) TRH response

Table 3. Assay Results for Normal Subjects, Pregnant Women, and Severely Ill Patients

	Euthyroid (n = 6)		Pregnant (n = 10)		Severely Ill (n = 8)	
	Mean	SD	Mean	SD	Mean	SD
TBG, mg/L	22	(7)	53[b]	(6)	15.4[a]	(7)
T3 uptake	1.01	(0.07)	0.74[a]	(0.03)	1.08	(0.09)
T4 uptake	0.87	(0.2)	1.7[b]	(0.2)	0.6[a]	(0.1)
Total T4, nmol/L	125	(30)	144[a]	(20)	53[a]	(38)
FTI	125	(23)	108	(18)	56[a]	(36)
Free T4, ng/L, Abbott	113	(13)	81[a]	(40)	90	(42)
Free T4, ng/L, Corning	19	(6)	12[a]	(7)	56[a]	(3)
Free T4, ng/L, Amerlex	16	(2)	77[b]	(1)	53[b]	(4)
Total T3, nmol/L	2.1	(0.4)	3.0[b]	(0.4)	0.85[b]	(0.4)
Free T3, pmol/L, Corning	6.4	(1.0)	4.3[b]	0.7	1[b]	
Free T3, Amerlex	4.0	(0.7)	2.6[b]	(0.5)	1[b]	
TSH, milli-int. units/L	2.0	(0.8)	3.6[a]	(1.0)	2.9	(3)

TBG T3/T4

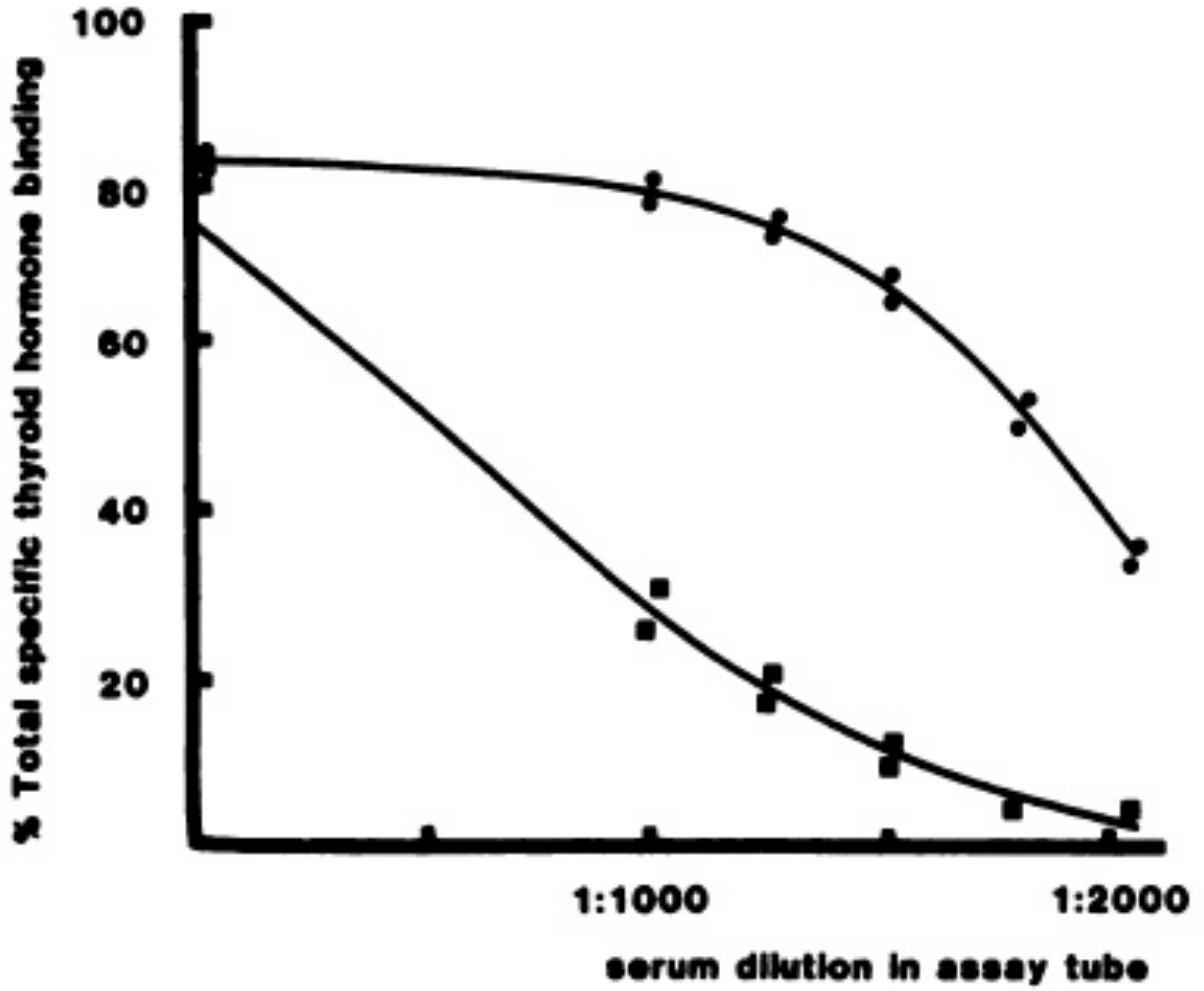


Fig. 1. Total specific T4 (●) and T3 (■) binding at increasing dilutions of sera in assay buffer, each dilution assayed in duplicate

Case Presentation

Thyroid Levels Change in Pregnancy

	Trimester 1st	2nd	3rd		Term
A. ▫ **TSH (0.2-4.0 mU/L)**	**.8**	**1.1**	**1.3**	(.1 - .6, pulsatile)	
TSH (I2 deficient Glinoer 97)					2.1
B. - **FT4 (0.8-2.0ng/dl)**	**1.4**	**1.1**	**1.0**		
C. - T4 (3.9-11.6 mcg/dl)	11	12	12		
D. - FT3 (1.9-7.1 ng/ml?)	3.3	2.7	2.5		
E. ▫ T3/T4 molar ratio	2.3	2.4	2.5		

Thyroid Screening Pregnancy

TSH (0.1-5.0) +/- 0.6

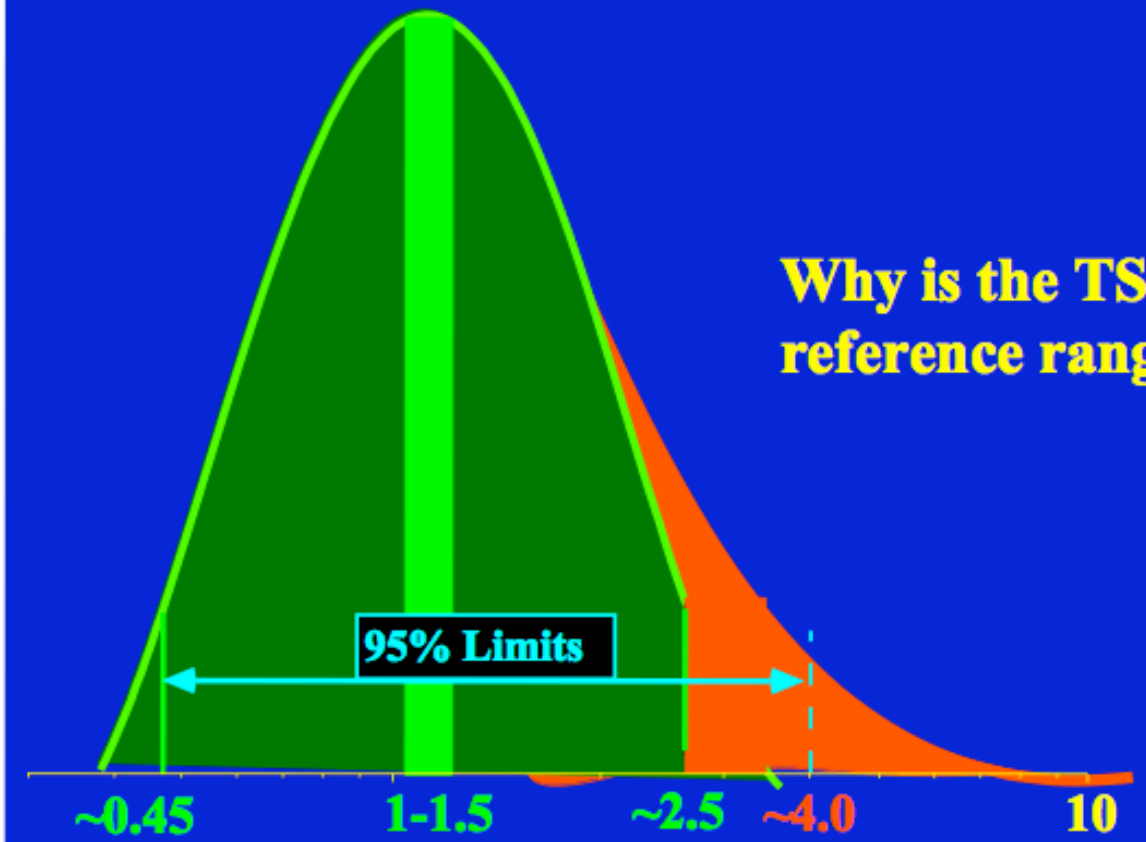
(Thyroid Stimulating Hormone)

TSH < 2.0 mIU	TSH < 2.5 mIU
< 20weeks	> 20weeks

0wk----------20wk----------40wk

- **HCG** supresses TSH (Pituitary), stimulates T4 (Thyroid)
- TSH increase from 10-20weeks (mirrors HCG)
- TPO-AB(+) skews TSH distribution to higher TSH
- TWINS, PIH, GTP, HYPEREMESIS (hi HCG lowers TSH)

Current TSH Upper Reference Limits



Why is the TSH upper reference range skewed?

Thyroid Screening Pregnancy 2

FT4 (0.6-1.6) +/- 0.1

"Free Thyroxine Estimate Test", FreeT4

FT4 >20% ile	FT4 >10% ile
<20 weeks	>20 weeks
>**0.8**	>**0.7**
[for 0.6-1.6 ng/ml]	[for 0.6-1.6 ng/ml]

0wk----------20wk----------40wk

HCG *increases* (T4-Thyr), Estradiol *decreases* (TBG-Liv)

Higher in early pregnancy than non-pregnant, then falls with GA, but remains in normal range

Thyroid Screening in Pregnancy
T4 Total Thyroxine

- +150% increase for Pregnancy normal range (upper normal or elevated)
- 7-18.5 mcg/dl approximate nl range
- Haddow identified 7.9mcg/dl (100nm/dl) as cutoff for hypothyroxinemia

Thyroid Screening in Pregnancy

- **Repeat q4-6 weeks** (non-pregnant and first trimester)
- q8weeks (2nd and 3rd trimester)
- as close to next dose as possible, late afternoon (diurnal, low at midnite)

Thyroid Screening

Non-Pregnancy

- **TSH**

  < 2.5 *(+/- 0.6)* (Consider AACE recs)

- **FreeT4**

  0.7-1.7 (in normal range) *(+/- 0.1)*

Other Tests to consider
Antibodies

- Antithyroid Antibodies **ATA** (-):
  TPO-microsomal
  ATG (antithyroglobin)
  if FreeT4 <10%ile
- Thyroid Stimulating Antibodies **TSI** (+)
- Thyroid Blocking Antibodies **TBI** (-)

Causes Fetal effects (IgG)

Other Tests to consider

Iodine Deficiency

- **Urinary iodide**: **<100mcg/24hr** (normal 100-500)
- **FT3/FT4 molar ratio >2.5** (FreeT3)
  (if Iodine deficient or subclinical)
- **TSH: increases** between 20-40 weeks
  (if Iodine deficient)
- **TG (Thyroglobin): elevation** correlates with degree of Iodine Deficiency

TREATMENT

Available Brands of L-T4

- Levothroid (Forrest)
- Levoxyl (King)
- Synthroid (Abbott)
- Unithroid (Watson)

Goals of Thyroxine Treatment

- **Replacement doses: hypothyroid patients**

  Goal: Mid - normal TSH

  Mean L-T4 dose = 1.7 ug/kg

- **Suppressive doses: thyroid cancer patients**

  Goal: Low or suppressed TSH

  Mean L-T4 dose = 1.9-2.4 ug/kg

THYROXINE DEFICIENCY

Treatment

- **L-thyroxine**, estimate **1.7mcg/kg/day** qhs (100-200mcg)
  - Pregnancy may require ~25% increase, more with increased GA
  - No food within 1 hour
  - Iron supplements inhibits absorption- take beyond 2 hours
  - Dose depends on brand
  - FreeT4 maintain upper normal vs clinical improvement?
  - TSH can be low in 10-20%, sub-normal in first trimester
  - ***? Newer recommendations 1.9-2.4mcg/kg/day***

- **Iodide**, **200mcg/day** (if deficient)

Thyroxine Deficiency

Problems to consider

- FreeT4 assays are *not standardized* for pregnancy
- Serum values have *non-normal* distribution
- Serum values are *skewed* to low values
- Labs *vary* in pregnancy, gestational age, albumin