تازه های تیروئید و بارداری

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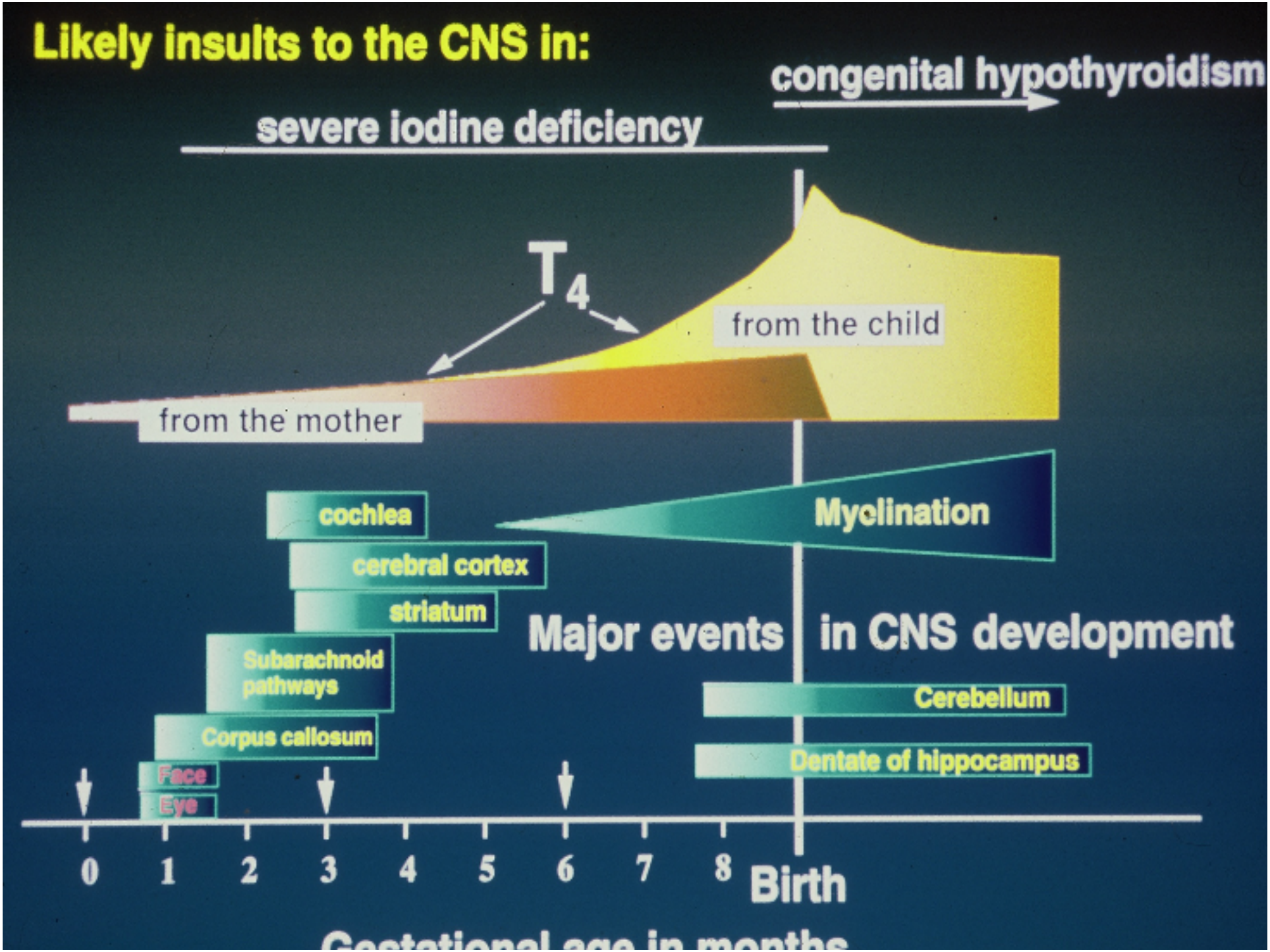
دانشگاه علوم پزشکی شهید بهشتی

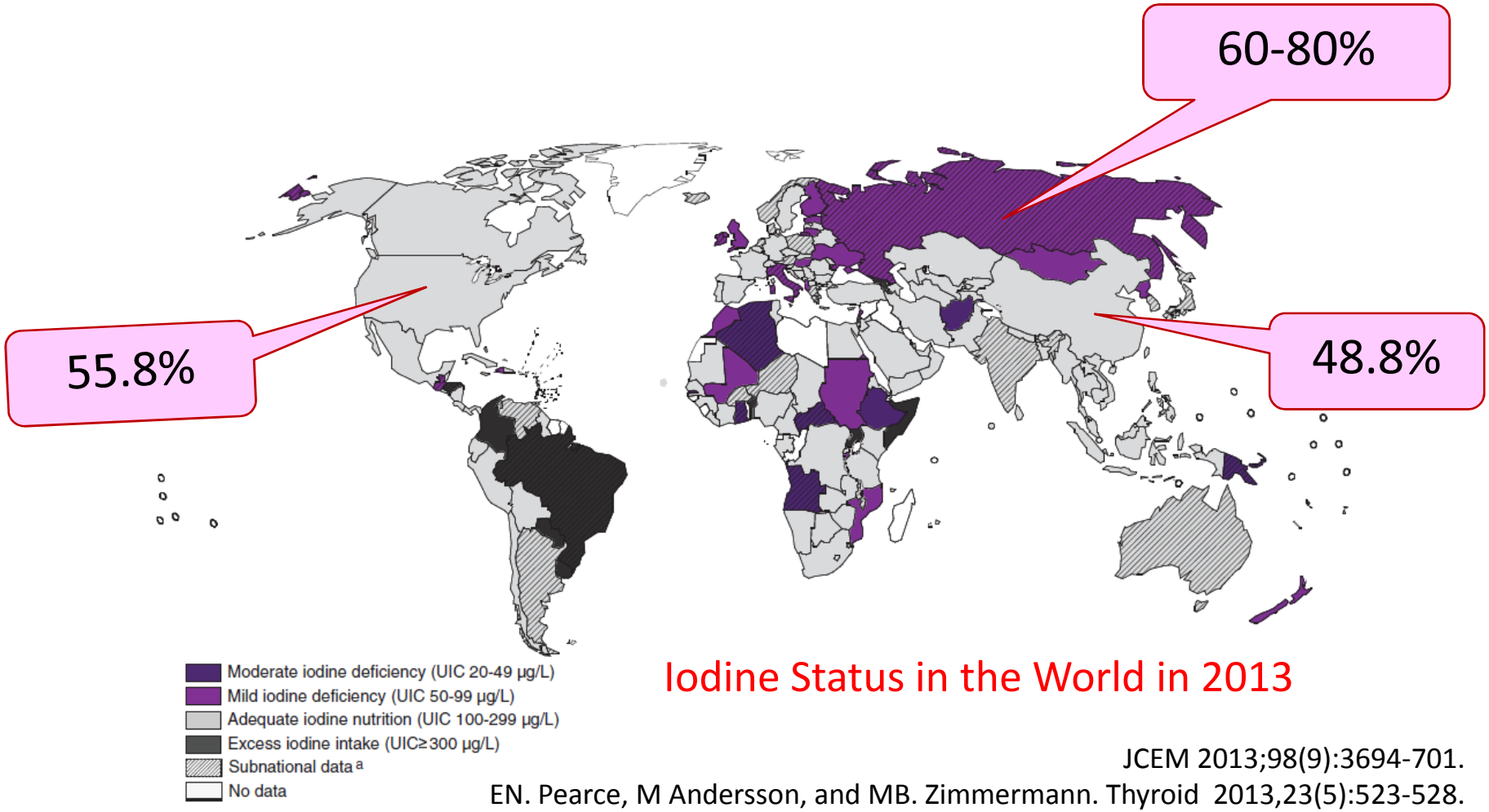
وبینار تخصصی بیماری های تیروئید در بارداری
انجمن متخصصین زنان و زایمان ایران
۶ آذر ۱۳۹۹

Important and/or Controversial Issues in Pregnancy:

1. The importance of iodine
2. Thyroid function tests
3. Screening for thyroid Dysfunction
4. Management of hyperthyroidism


Likely insults to the CNS in:
congenital hypothyroidism
severe iodine deficiency
T4
from the child
from the mother
cochlea
Myelination
cerebral cortex
striatum
Major events
in CNS development
Subarachnoid pathways
Cerebellum
Corpus callosum
Dentate of hippocampus
Face
Eye
0
1
2
3
4
5
6
7
8
Birth
Gestational age in months

Prevalence of Iodine Deficiency in Pregnancy



Iodine Status in the World in 2013

JCEM 2013;98(9):3694-701.
EN. Pearce, M Andersson, and MB. Zimmermann. Thyroid 2013,23(5):523-528.
Caldwell KL：Thyroid，2013，23：927-937
Endocrinol Nutr. 2009; 56(1):9-12. Thyroid. 2009; 19(2):157-63.
Clin Endocrinol (Oxf). 2009, 70(5):776-80.
J Clin Endocrinol Metab.1992, 75(3):800-805.

Importance of iodine and thyroid hormones in brain development

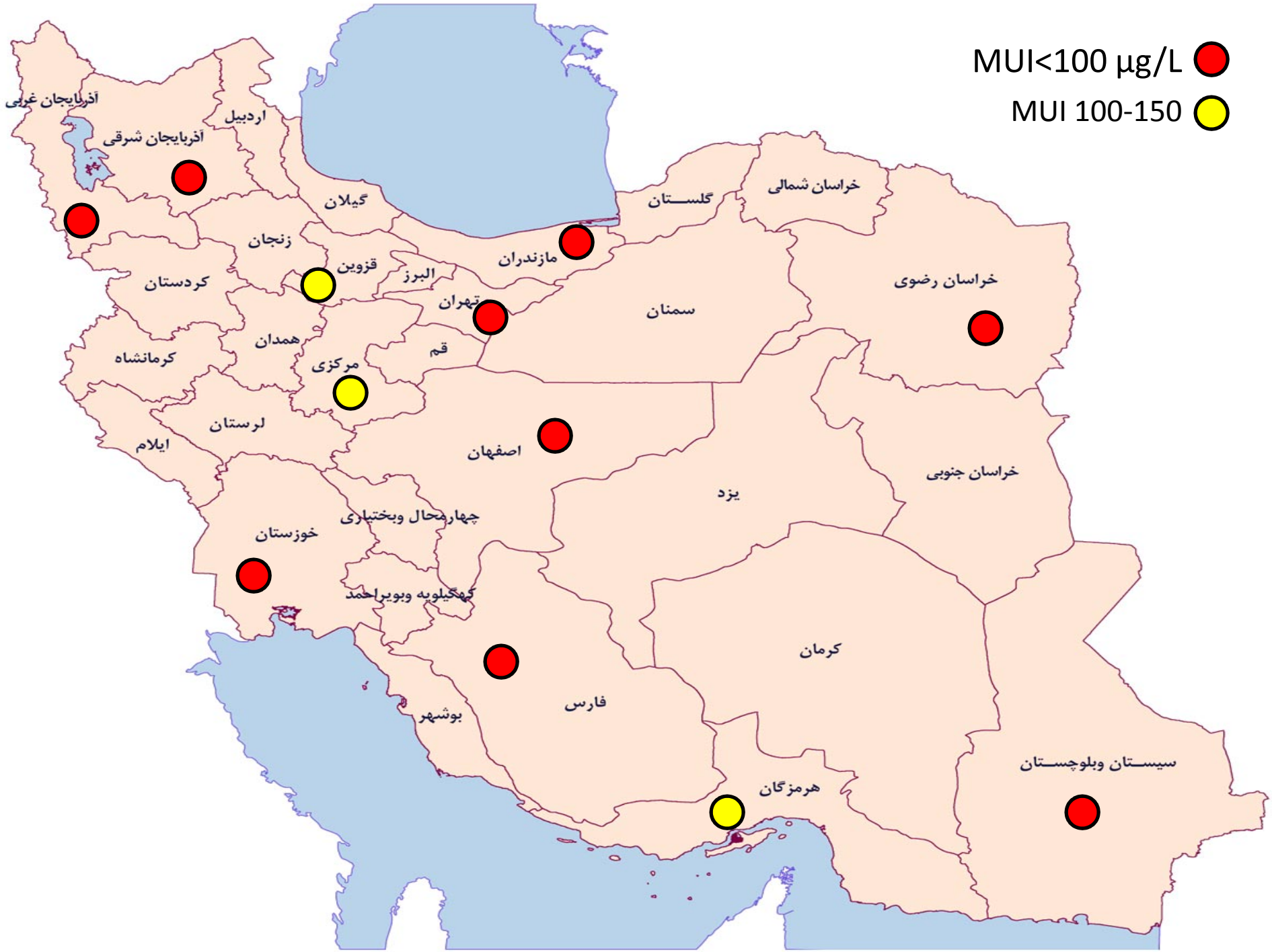
- **50,000 brain cells produced/second in developing fetal brain**
- **100 billion brain cells in adult**
- **One million billion connections between these brain cells: Determine IQ**

Iodine Requirement in Pregnancy (μg/day)

During pregnancy

Basal	150
40-50 % increased T4 requirements	50-100
Transfer of T4 and I from mother to fetus	50
Increased renal clearance of I	50
Total requirement	**250-300**

Delange: Int.J. Endocrinol. Metab. 2: 1, 2004


MUI<100 µg/L
MUI 100-150
آذربایجان غربی
آذربایجان شرقی
اردبیل
گیلان
زنجان
قزوین
کردستان
البرز
مازندران
گلستان
خراسان شمالی
خراسان رضوی
تهران
سمنان
همدان
قم
کرمانشاه
مرکزی
لرستان
ایلام
اصفهان
یزد
خراسان جنوبی
چهارمحال وبختیاری
خوزستان
کهگیلویه وبویراحمد
کرمان
فارس
بوشهر
سیستان وبلوچستان
هرمزگان

How much iodine we get from iodized salt?

(numbers in red are daily iodine intake)*

Daily salt intake (gm)	Amount of iodine in table salt		
	20 ppm	30 ppm	40 ppm
2	40	60	80
4	80	120	160
6	120	180	240

* Daily requirement of pregnant women: 200-300 μg/day

Iodine Supplementation in Pregnancy

Before conception & First trimester:

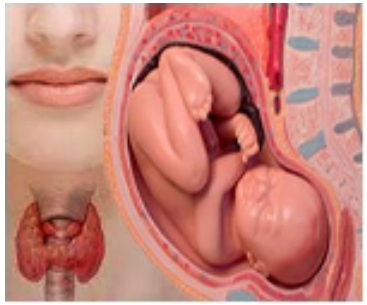
Folic Acid + Iodine 150 µg

Second and third trimesters:

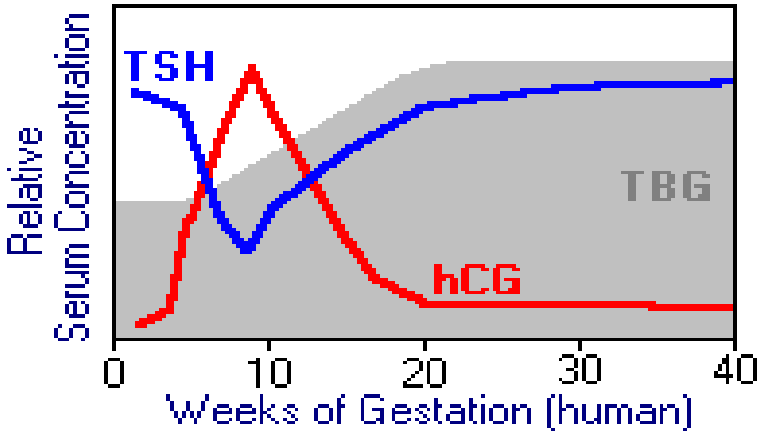
Multivitamins + Iodine 150 µg

or Folic Acid + Iodine 150 µg

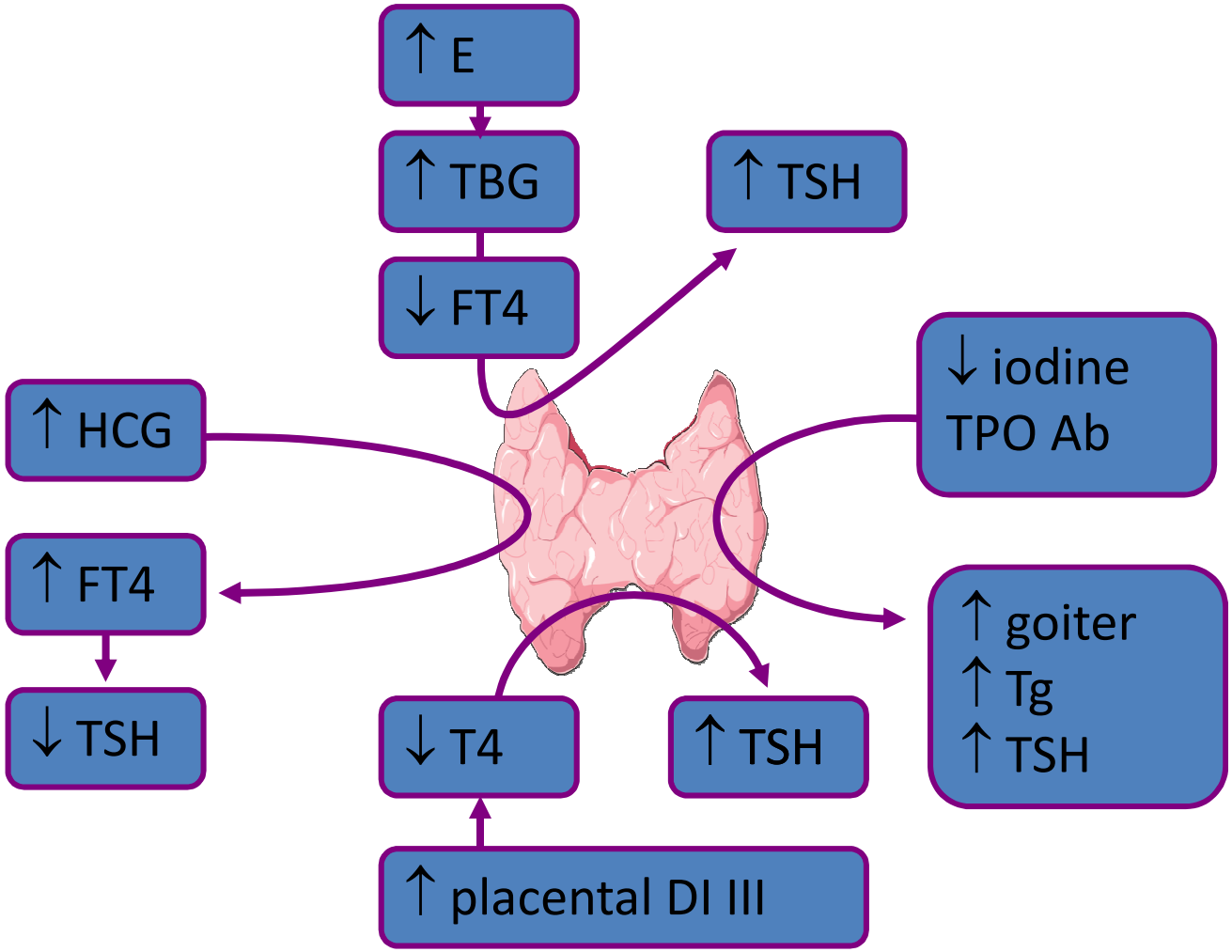
بیان مسئله



- بدنبال تغییرات فیزیولوژیک و هورمونی ناشی از بارداری و گنادوتروپین جفتی انسانی (HCG) تولید تیروکسین (T4) و تری یدوتریونین (T3) تا ۵۰ درصد افزایش یافته و منجر به افزایش ۵۰٪ در نیازهای روزانه ید در زن می گردد، در حالی که سطح تیروتروپین (TSH) به ویژه در سه ماهه اول کاهش می یابد، در سه ماهه دوم و سوم حاملگی با کاهش غلظت hCG ، مقدار تیروکسین محدوده طبیعی برمیگردند.



Factors for thyroid stimulation during pregnancy



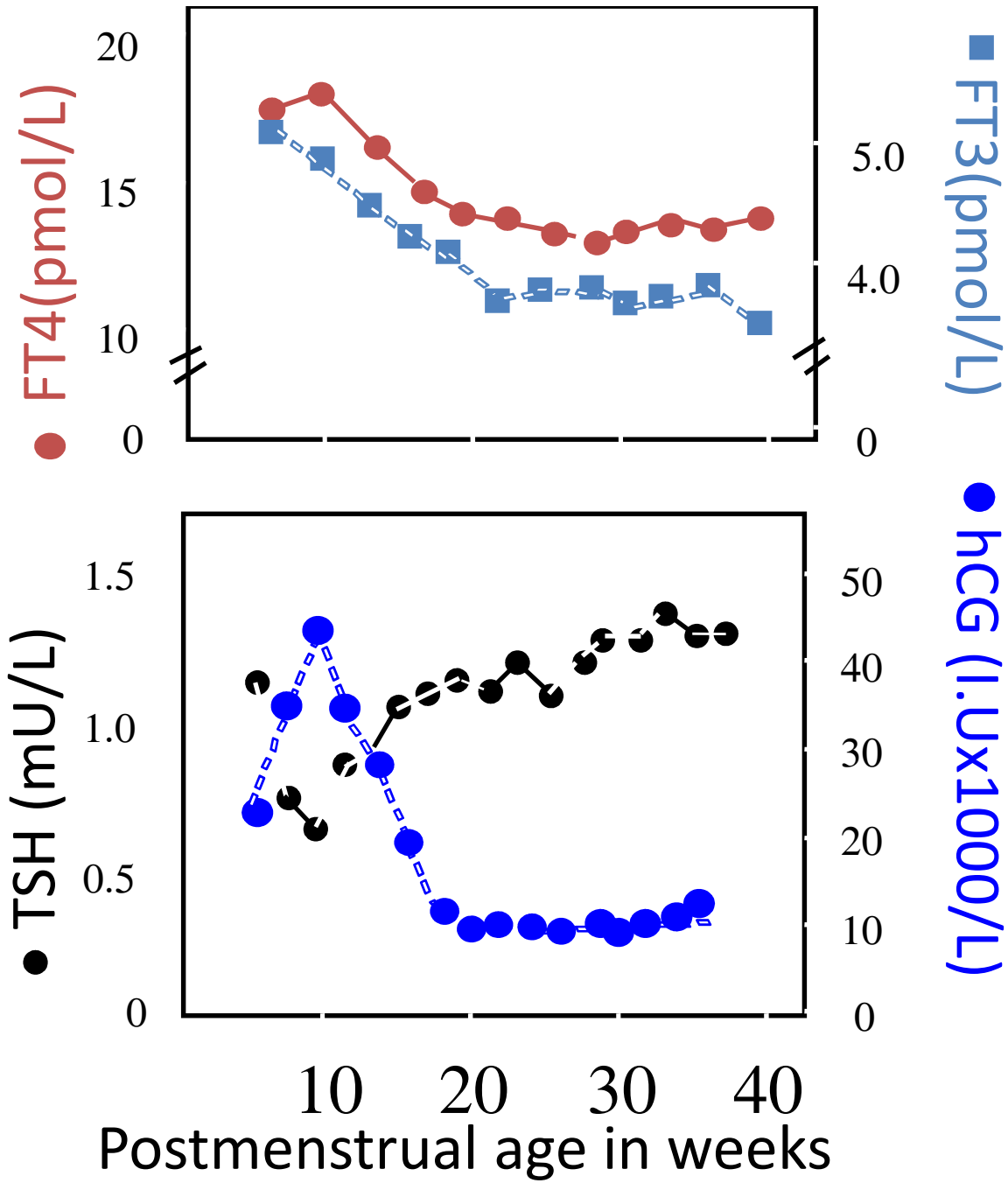
Delange: Int.J. Endocrinol. Metab. 2: 1, 2004

Thyroid

function tests

In pregnancy

A 25 year-old woman in the 8th week of pregnancy has serum TSH of 0.1 mU/L (normal 0.5-4.0) and serum free T4 of 2.5 and 1.4 ng/dl normal (0.8-1.9) by two different laboratories. Pulse rate is 90/min, thyroid in not enlarged and there are no physical findings for Graves' disease or hyperthyroidism.



Glinoer, Endocr Rev 1997;18:404-433

Recommendation 26

Pregnancy-specific TSH reference range :

- **When available, population and trimester-specific reference ranges for serum TSH during pregnancy**
- **If internal or transferable pregnancy-specific TSH reference ranges are not available, an upper reference limit of ~ 4.0 mU/l may be used.**

ATA Guidelines, Thyroid 2017; 27: 315

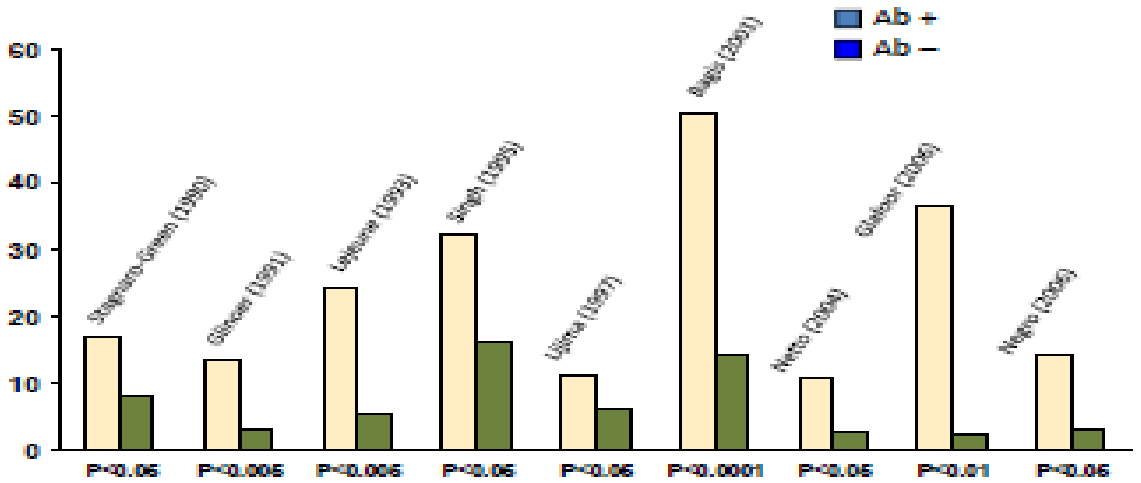
Screening for thyroid dysfunction in Pregnancy

چرا غربالگری تیروئید برای بارداری انجام شود؟

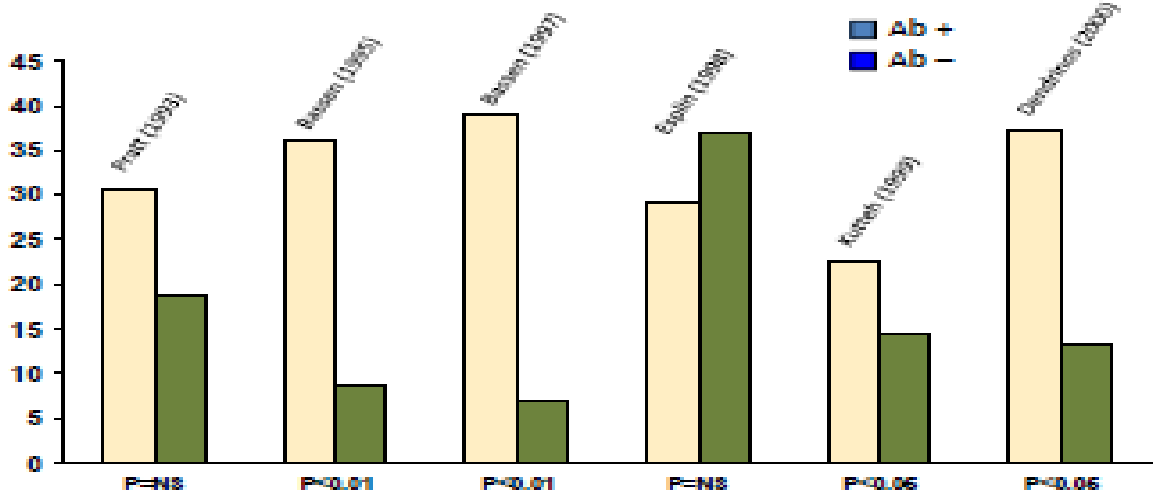
Issues of thyroid screening in pregnancy

- Overt hypothyroidism: Rare, clinical evidences
- Clinical hyperthyroidism: Rare, clinical evidences
- Subclinical hyperthyroidism: Harmless
- Subclinical hypothyroidism:
  - Effect on fetus and offspring: none
  - Effect on pregnancy outcome: mostly in TPOAb+ woman

Thyroid Antibodies and Spontaneous Miscarriage



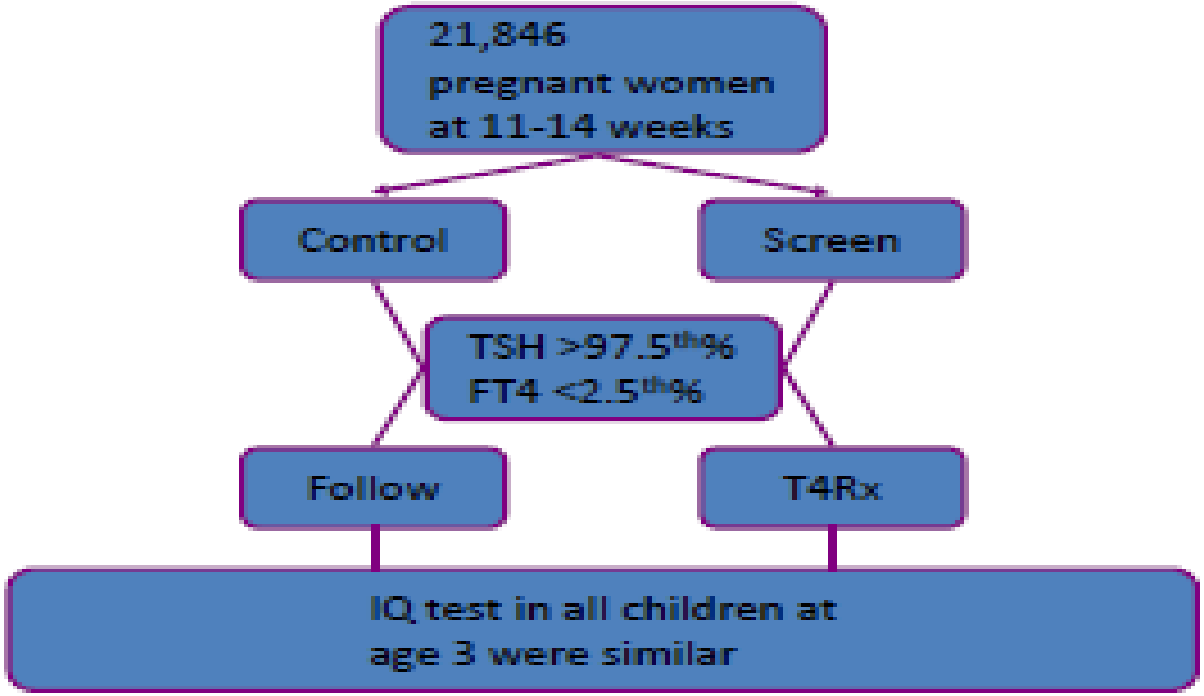
Recurrent Abortion and Thyroid Antibodies



Antenatal thyroid screening and childhood cognitive function

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

N Engl J Med 2012; 366:493-501



Lazarus et al: N Engl J Med 2012;366:493-501

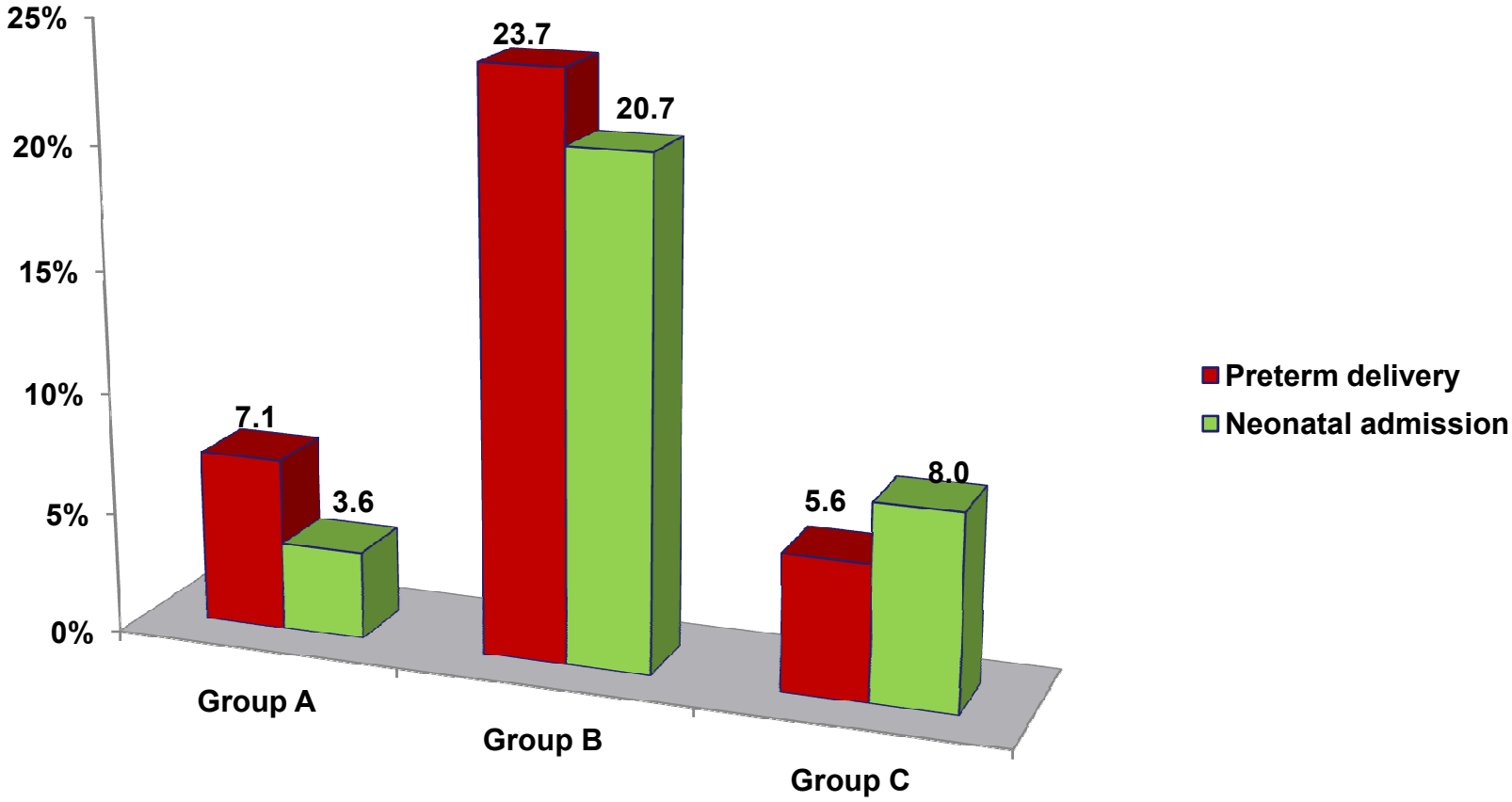
Standardized Full-Scale Child IQ and Scores on the Child Behavior Checklist (CBCL) and the Behavior Rating Inventory of Executive Function, Preschool Version (Brief-P), According to Study Group*

Test	Screening Group (N = 390	Control Group (N = 404)	Difference (95% CI) (Control Group − Screening Group)†	P Value
IQ				
Mean	99.2±13.3	100.0±13.3	0.8 (−1.1 to 2.6)	0.40
<85 (% of children)	12.1	14.1	2.1 (−2.6 to 6.7)	0.39
CBCL T score‡				
Mean	44.4±12.4	45.1±13.6	0.7 (−1.2 to 2.5)	0.49
Brief-P T score§				
Median	40	40	0	0.59
Interquartile range	47–55	47-55		

* Plus–minus values are means ±SD. The full-scale child IQ test was standardized so that for each psychologist, the mean score among the children in the control group whom they tested was 100. In the screening group, the women were assigned to treatment with levothyroxine.
† For percentages of children with an IQ below 85, the absolute (percentage-point) differences are shown.
‡ For the CBCL, a T score above the 98th percentile is indicative of a clinically significant problem.
§ For the Brief-P, a T score above 65 is indicative of a clinically significant problem.

N Engl J Med 2012; 366:493-501

Preterm delivery and neonatal admission among study groups



TPOAb+ T4 treated | TPOAb+ No T4 | Control

Nazarpour S, et al. Eur J Endocrinol 2017; 176: 253

Indications for treatment with levothyroxine during pregnancy

TPOAb	Serum TSH mU/L	LT4 therapy
Positive		
	>10	Strongly recommended
	4-10	Recommended
	2.5-4	May be considered
	<2.5	Not recommended
Negative		
	>10	Strongly recommended
	4-10	Recommended
	2.5-4	Should not be used
	<2.5	Not recommended

Velasco U & Taylor P. Europ J Endocrinol, 2018
Alexander EK, et al. Thyroid 2017 January 6
Cooper DS, et al. N Engl J Med 2017; 376; 876

Recommendation 96 & 97

All pregnant women should be verbally screened at the initial prenatal visit for any history of thyroid dysfunction, and prior or current use of either thyroid hormone (LT4) or anti-thyroid medications (MMI, carbimazole, or PTU).

All patients seeking pregnancy, or newly pregnant, should undergo clinical evaluation. If any of the following risk factors are identified, testing for serum TSH is recommended.

1. **A history of hypothyroidism/hyperthyroidism or current symptoms/signs of thyroid dysfunction**
2. **Known thyroid antibody positivity or presence of a goiter**
3. **History of head or neck radiation or prior thyroid surgery**
4. **Age >30 years**
5. **Type 1 diabetes or other autoimmune disorders**
6. **History of pregnancy loss, preterm delivery, or infertility**
7. **Multiple prior pregnancies (≥ 2)**
8. **Family history of autoimmune thyroid disease or thyroid dysfunction**
9. **Morbid obesity (BMI ≥ 40 kg/m2)**
10. **Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast**
11. **Residing in an area of known moderate to severe iodine insufficiency**

2017 ATA Guidelines, Thyroid

The American College of Obstetricians and Gynecologists

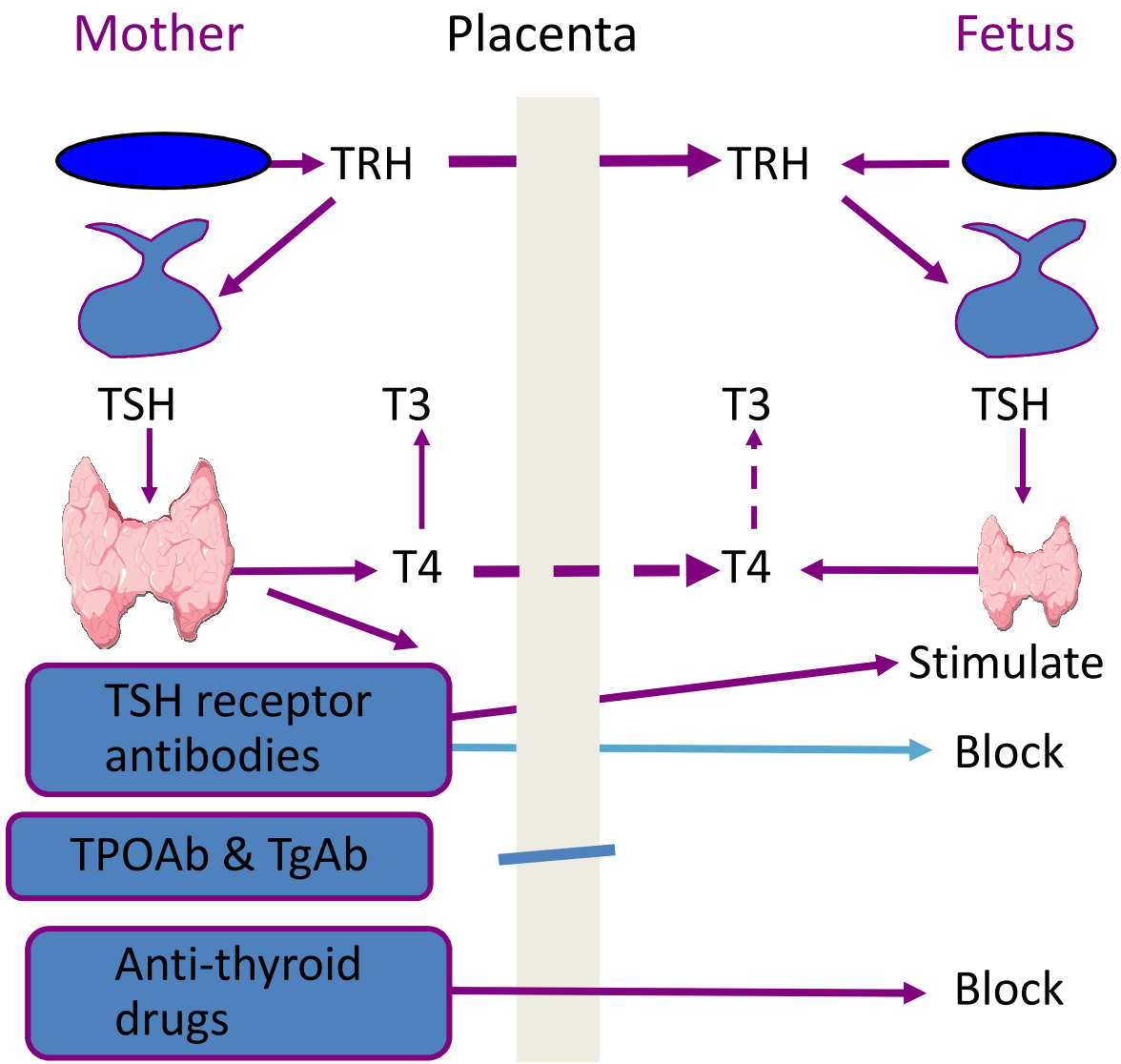
- **Universal screening for thyroid disease in pregnancy is not recommended because identification and treatment of maternal subclinical hypothyroidism has not been shown to result in improved neurocognitive function in offspring.**
- **The first-line screening test used to assess thyroid status in patients is measurement of the TSH level.**

Thyroid disease in pregnancy. Obstet Gynecol 2015;125(4):996-1005.

Management of hyperthyroidism in pregnancy

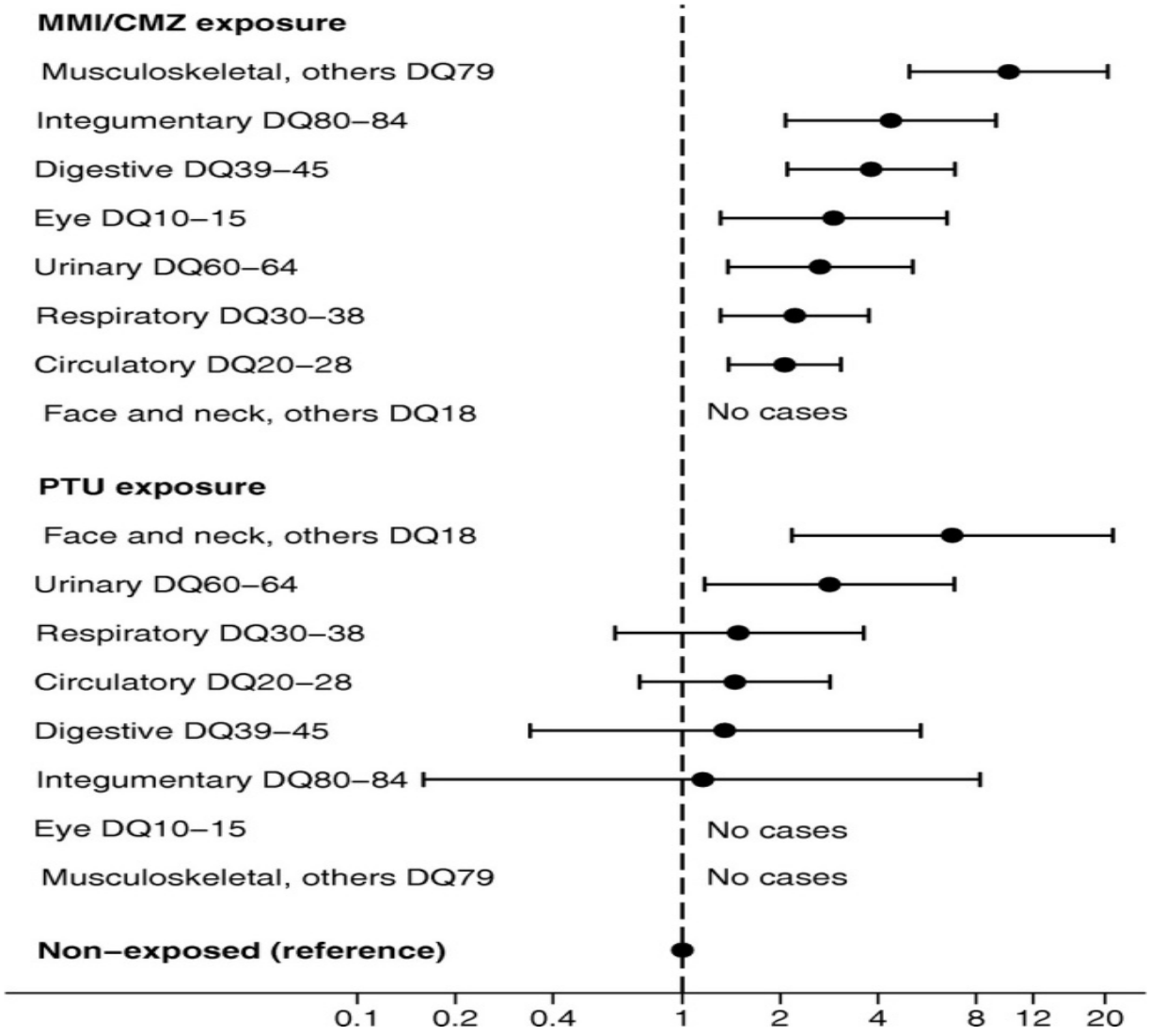
Thyrotoxicosis in pregnancy

- Occurs in 0.2-0.4% of women
- Mostly caused by Graves' disease



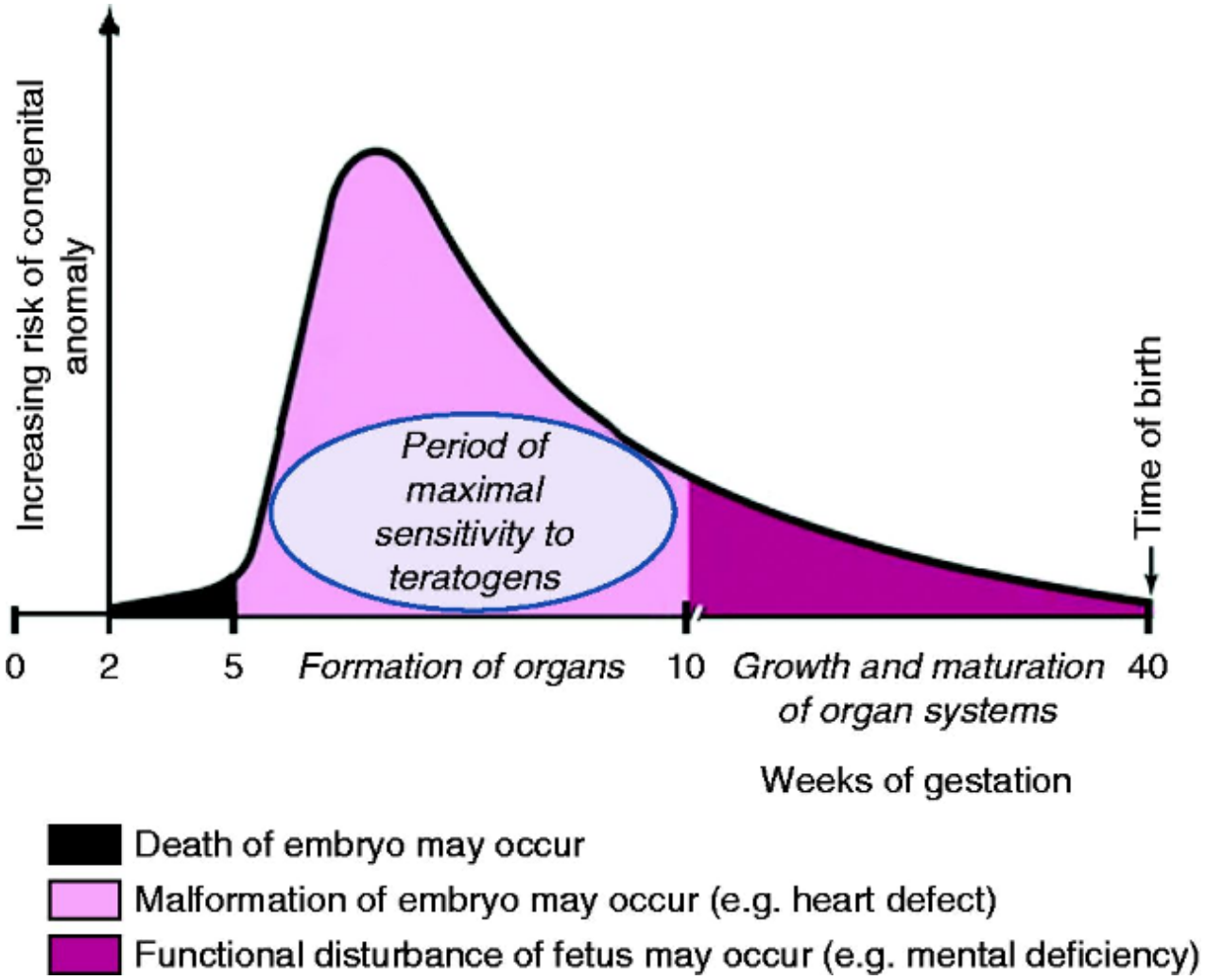
Spencer CA 2006

Subgroups of birth defects with significant association to antithyroid drug (ATD)



Andersen SL, et al. Andersen SL, et al. J Clini Endocrinol Metab 2013, 98:4373-4381.

Schematic illustration showing the time period in gestational weeks of maximal sensitivity to abnormal development in humans



Peter Laurberg, and Stine Linding Andersen .Eur J Endocrinol 2014;171:R13-R20

Ways to restrict the teratogenic effect of ATD in early pregnancy

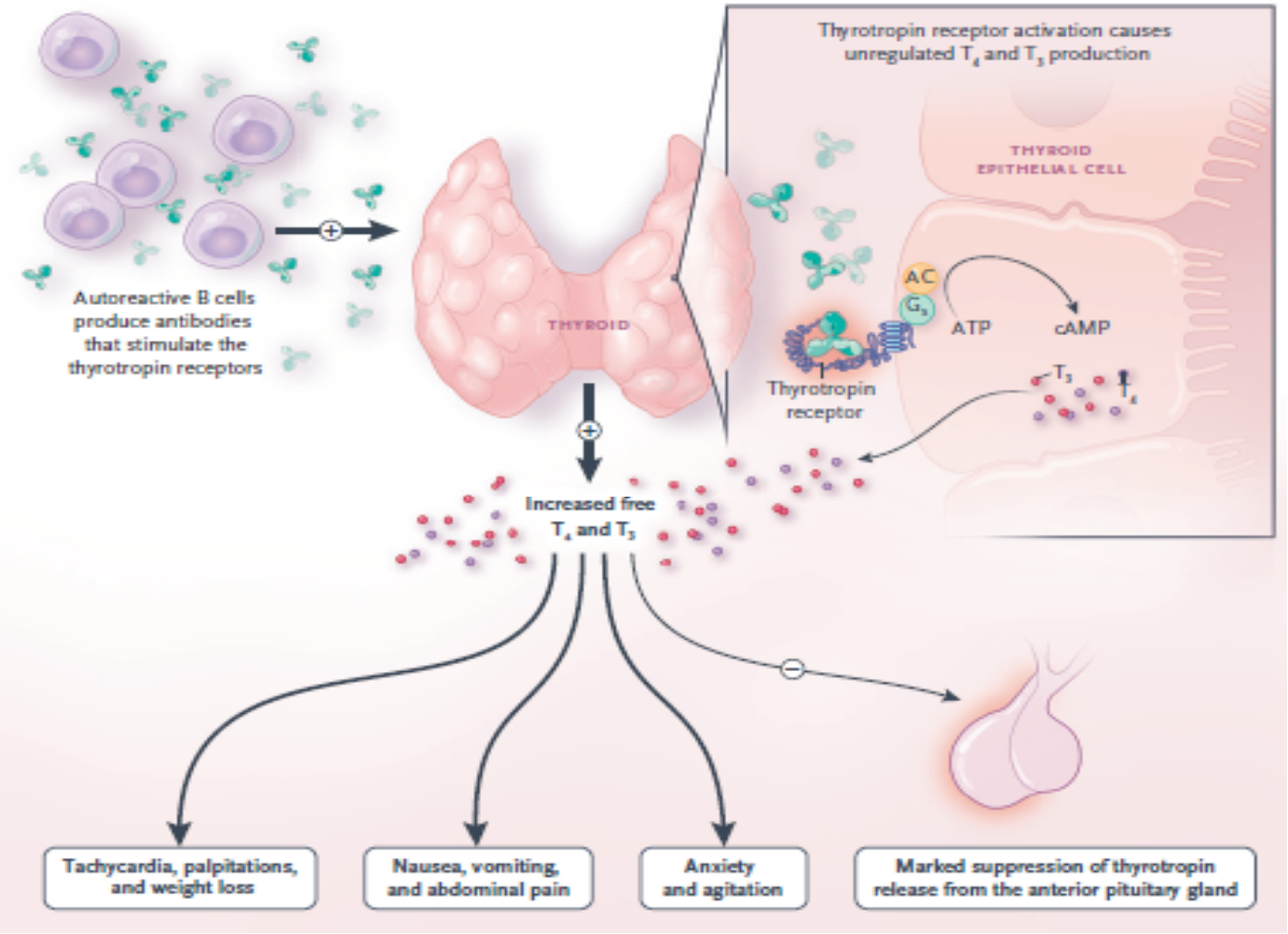
1. To advocate ablative therapy before attempting conception
2. Change MMI to PTU before planning for pregnancy
3. Early detection of pregnancy (<5 wk) and change to PTU
4. Early detection of pregnancy, withdraw ATD and weekly TFT's

Recommendation 46

The decision to stop medication should take into account the disease history, goiter size, duration of therapy, results of recent thyroid function tests, TRAb measurement, and other clinical factors.

2017 ATA Guidelines, Thyroid

Production of Thyroid-Stimulating Immunoglobulin and Clinical Manifestations of Graves' Disease



Chiappa V, et al. N Engl J Med. 2019 Aug 8;381(6):581-582.

TSAb, like TSH, bind primarily to the large amino terminal ectodomain of the TSH-R and activate the cAMP signal transduction pathway leading to stimulation of thyroid hormone production and proliferation of thyrocytes.

TSH receptor antibody (TRAb) testing in hyperthyroidism

Early pregnancy: *1) Past hitory of GD treated with radioiodine or surgery*

2) GD patients on ATD treatment

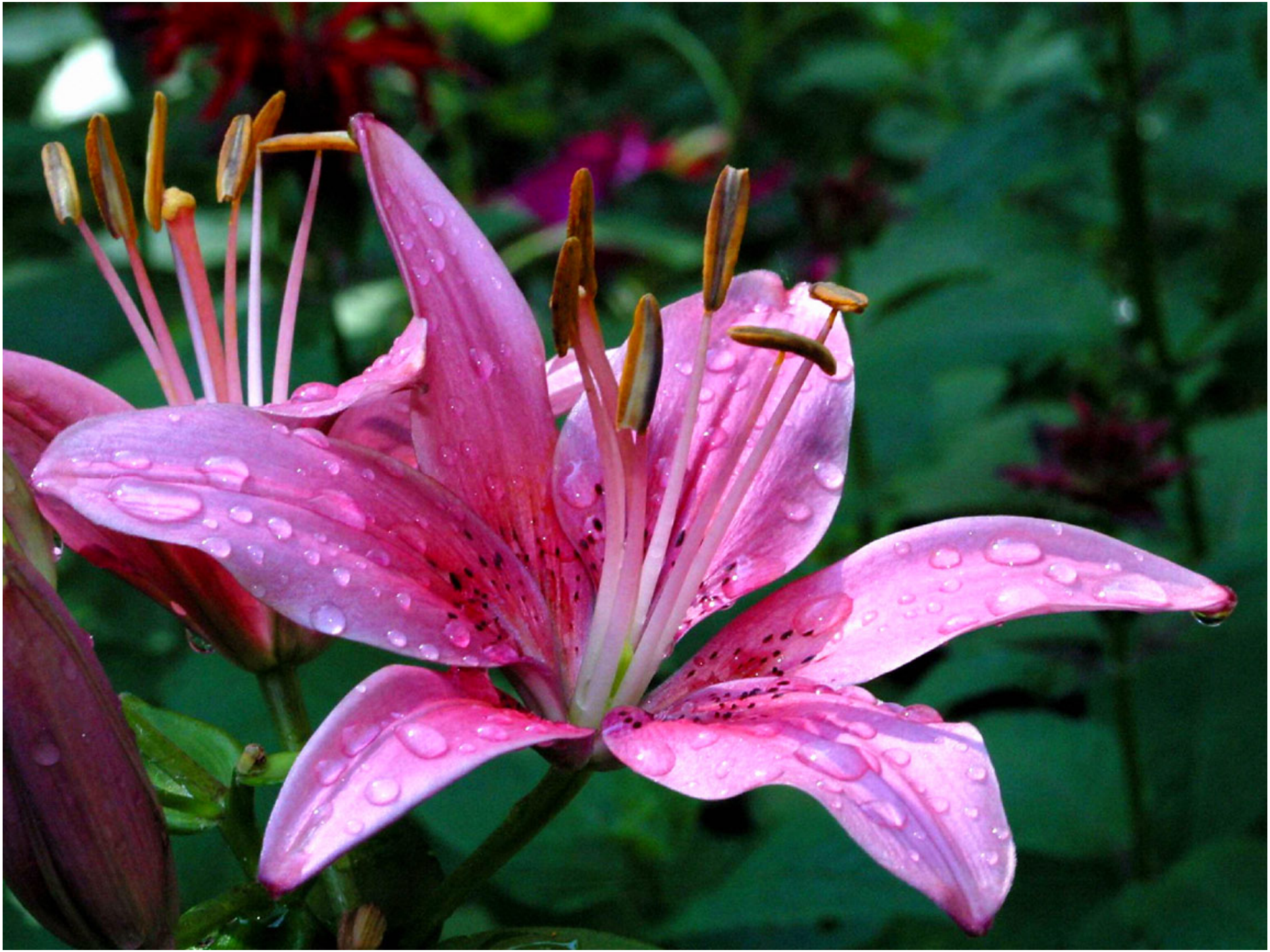
Midpregnancy: *Continupos ATD therapy:*
TRAb at 18-22 WK

Third trimester: *Elveated TRAb at 18-22 wk and GD patients on ATD: TRAb at 30-34 wk*

2017 ATA Guidelines, Thyroid

Conclusion

- **Thyroid dysfunction is rather common during pregnancy and postpartum and influence the health of mother, fetus and infant.**
- **Effective evidence based strategies for both detection and management should be developed for the benefit of both mother and child.**
- **Prompt and appropriate treatment of thyroid disease could dramatically improve the pregnancy outcome and ensure health promotion for mother and infant.**



How much iodine we get from iodized salt?

(numbers in red are daily iodine intake)*

Daily salt intake (gm)	Amount of iodine in table salt		
	20 ppm	30 ppm	40 ppm
2	40	60	80
4	80	120	160
6	120	180	240

* Daily requirement of pregnant women: 200-300 μg/day

Recommendation 6 & 8

Women who are planning pregnancy or currently pregnant, should

supplement their diet with a daily oral supplement that contains 150 µg of iodine in the form of potassium iodide. This is optimally started 3 months in advance of planned pregnancy.

There is no need to initiate iodine supplementation in pregnant women who are being treated for hyperthyroidism or who are taking LT4.

2017 ATA Guidelines, Thyroid

Iodine Supplementation in Pregnancy

Before conception & First trimester:

Folic Acid + Iodine 150 µg

Second and third trimesters:

Multivitamins + Iodine 150 µg

or Folic Acid + Iodine 150 µg