



TIROIDE E GRAVIDANZA (nutrizione iodica)

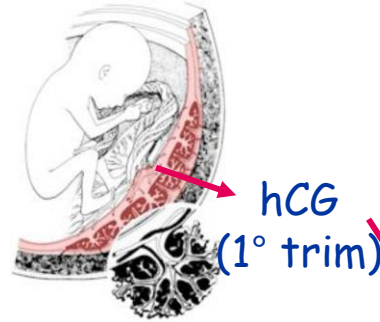
Francesco Trimarchi,

Mariacarla Moleti e Francesco Vermiglio

Dipartimento di Medicina Clinica e Sperimentale Università di Messina



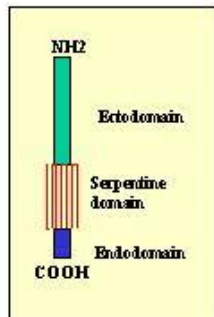
FISIOLOGIA TIROIDEA MATERNA IN GRAVIDANZA



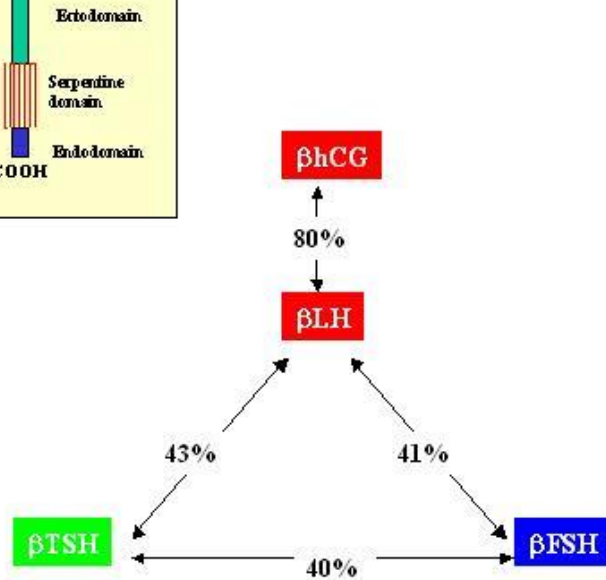
**STIMOLAZIONE
TIROIDEA**



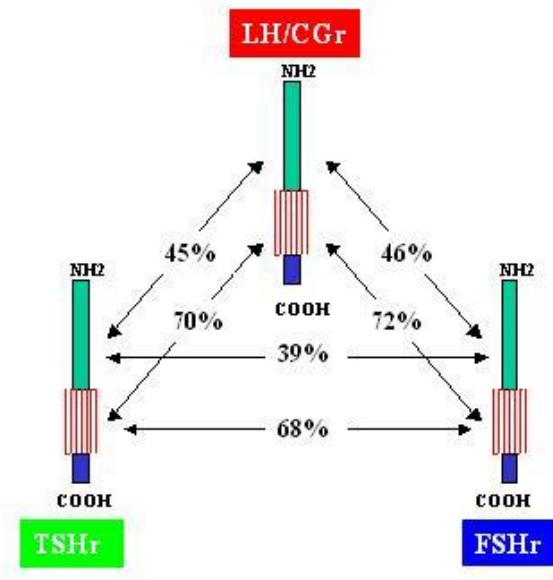
AZIONE TIREOTROPA DELLA GONADOTROPINA CORIONICA



OMOLOGIA STRUTTURALE

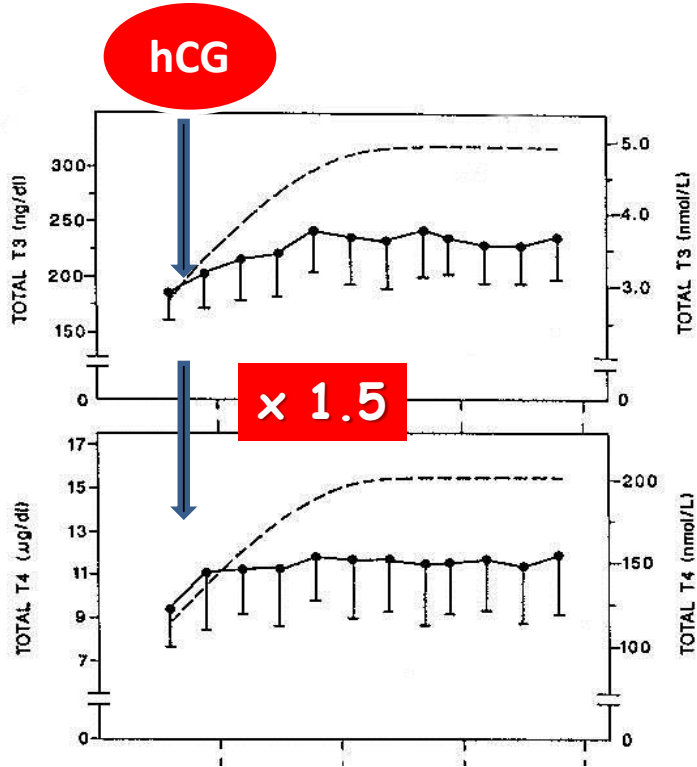


βhCG e βTSH



CGr e $TSHr$

FISIOLOGIA TIROIDEA IN GRAVIDANZA



FISIOLOGIA TIROIDEA MATERNA IN GRAVIDANZA



Elevati livelli
estrogeni

hCG
(1° trim)



↑ livelli sierici TBG

Aumento ormoni tiroidei totali
Relativa riduzione
ormoni tiroidei liberi

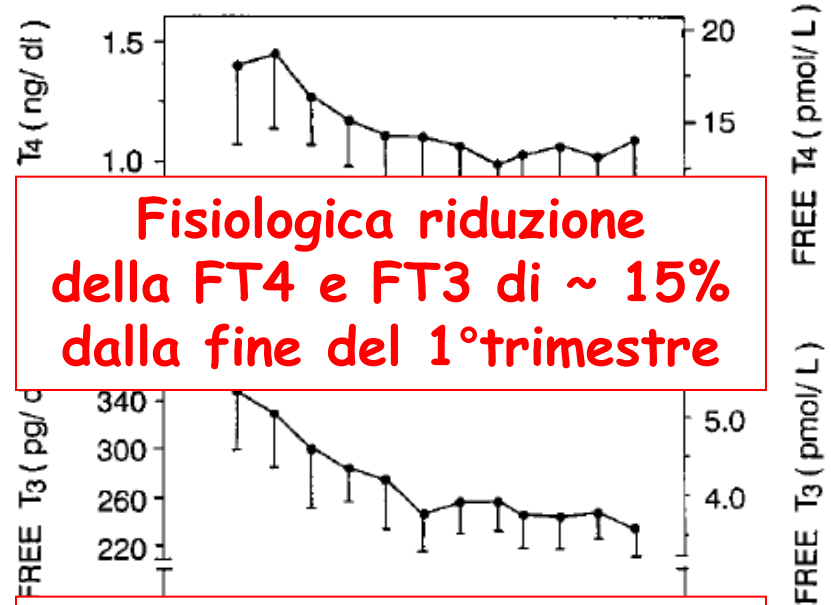
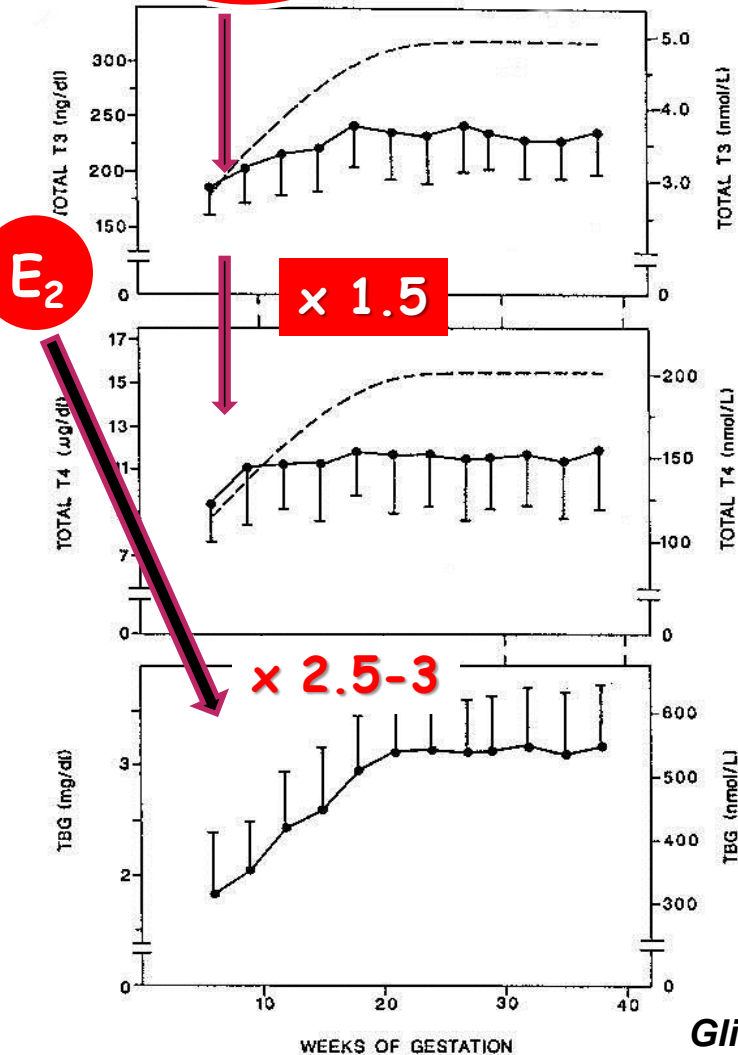
↑ TSH
(2°-3° trim)

**STIMOLAZIONE
TIROIDEA**



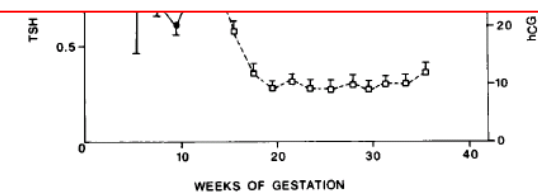
FISIOLOGIA TIROIDEA IN GRAVIDANZA

hCG



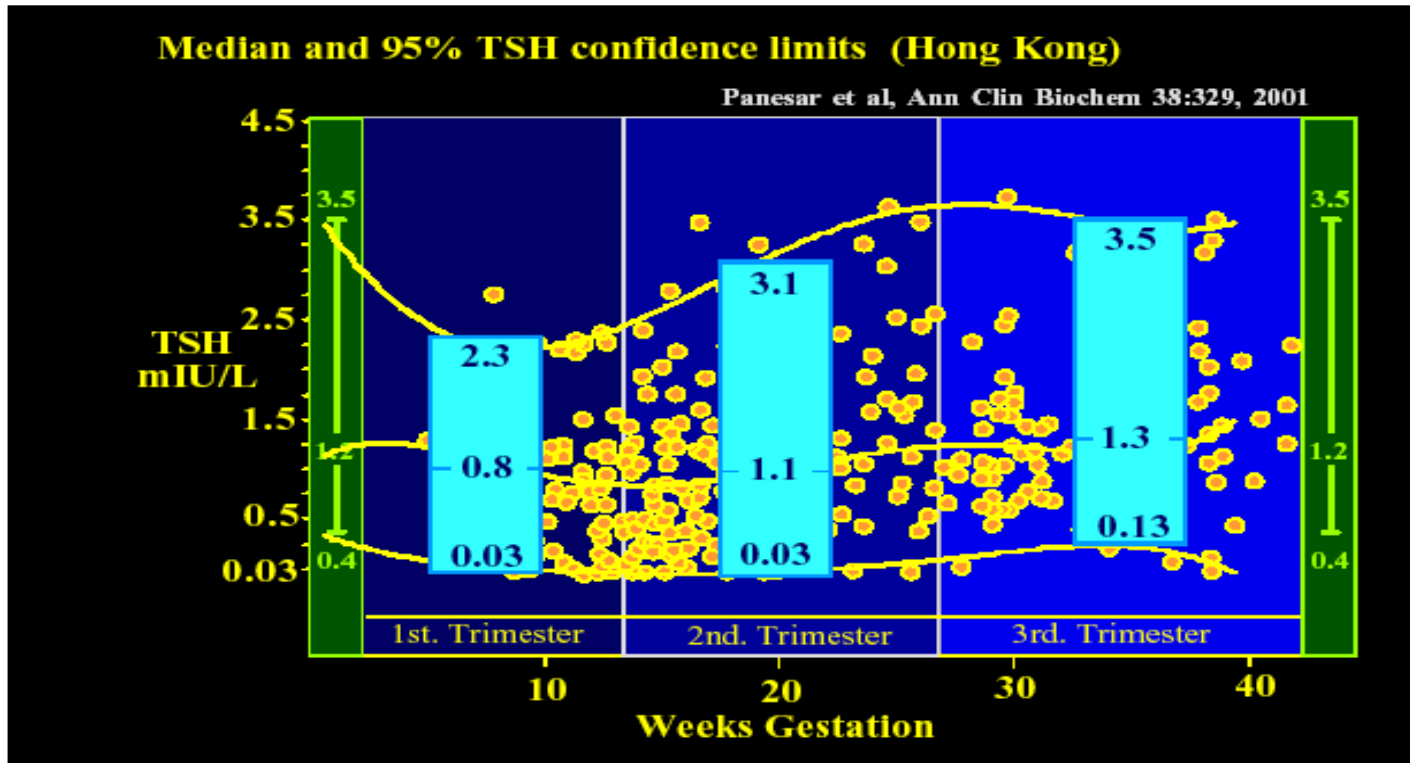
Fisiologica riduzione della FT4 e FT3 di ~ 15% dalla fine del 1°trimestre

Fisiologica riduzione del TSH durante il 1°trimestre e successivo incremento



Glinoe, JCEM 1990

RANGE DI RIFERIMENTO TRIMESTRE-SPECIFICI TSH

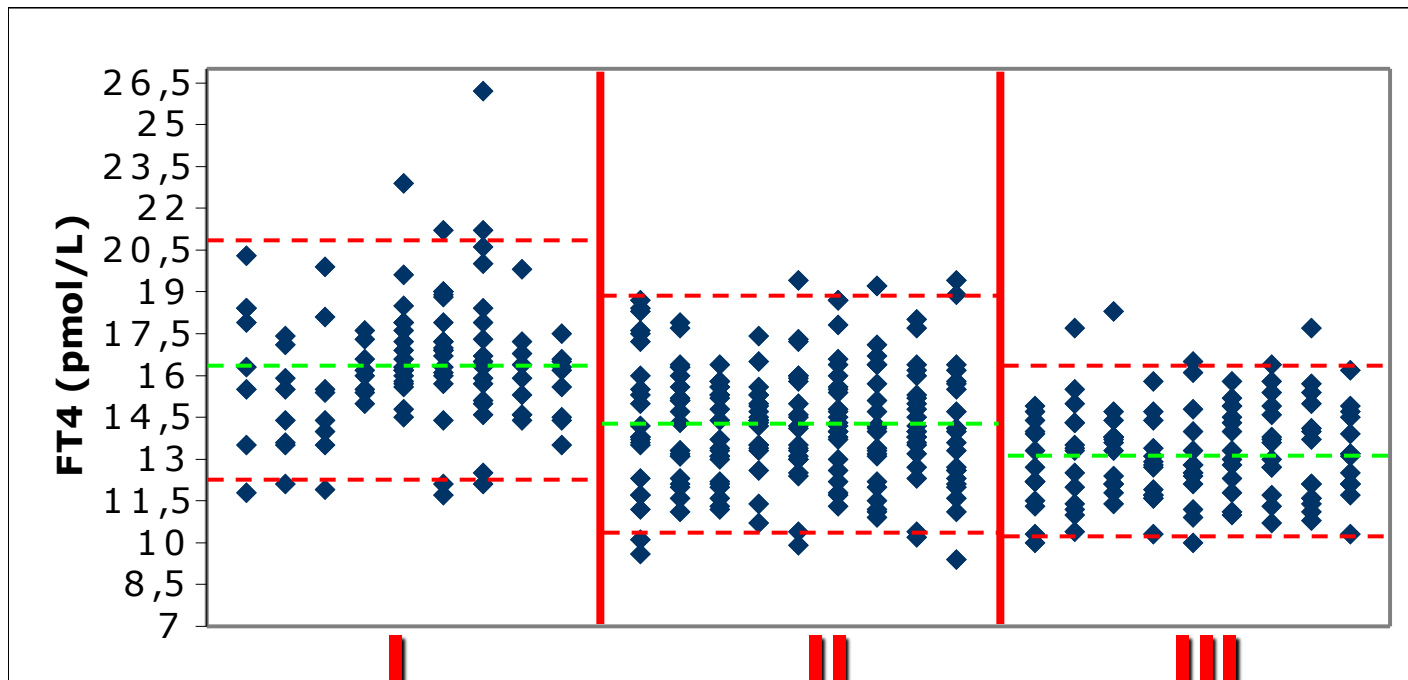


Panesar NS, Li CY, Rogers MS 2001 Reference intervals for thyroid hormones in pregnant Chinese women.

Ann Clin Biochem 38:329–332

RANGE DI RIFERIMENTO TRIMESTRE-SPECIFICI

FT4



12.0-20.8

(M±SD 16.5±2.3;
Median 16.4)

10.4-18.7

(M±SD 14.3±2.1;
Median 14.2)

10.3-16.4

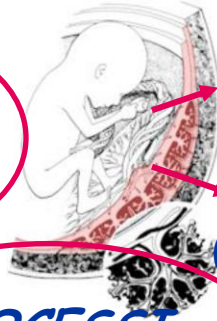
(M±SD 13.2±1.7;
Median 13.1)

FISIOLOGIA TIROIDEA MATERNA IN GRAVIDANZA



↑ RICHIESTE
METABOLICHE
MATERNE

SVILUPPO
SNC
FETALE



Elevati livelli
estrogeni

hCG
(1° trim)

PROCESSI
PLACENTAZIONE

APPORTO T4
UNITA'
FETO-PLACENTARE

↑ 50% T4 (T3)

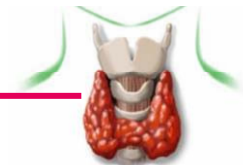


↓ livelli sierici TBG

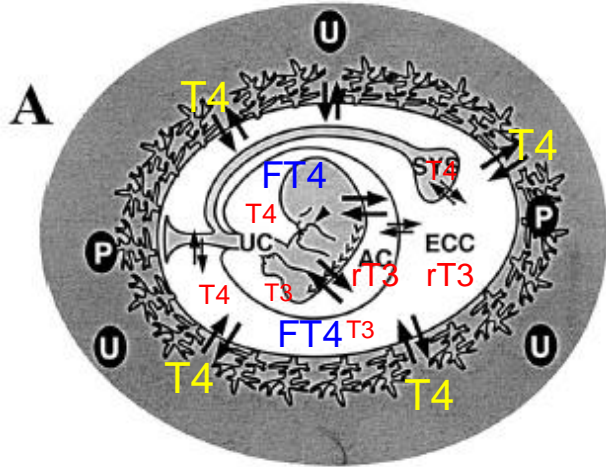
Aumento ormoni tiroidei totali
Relativa riduzione
ormoni tiroidei liberi

↓ TSH
(2°-3° trim)

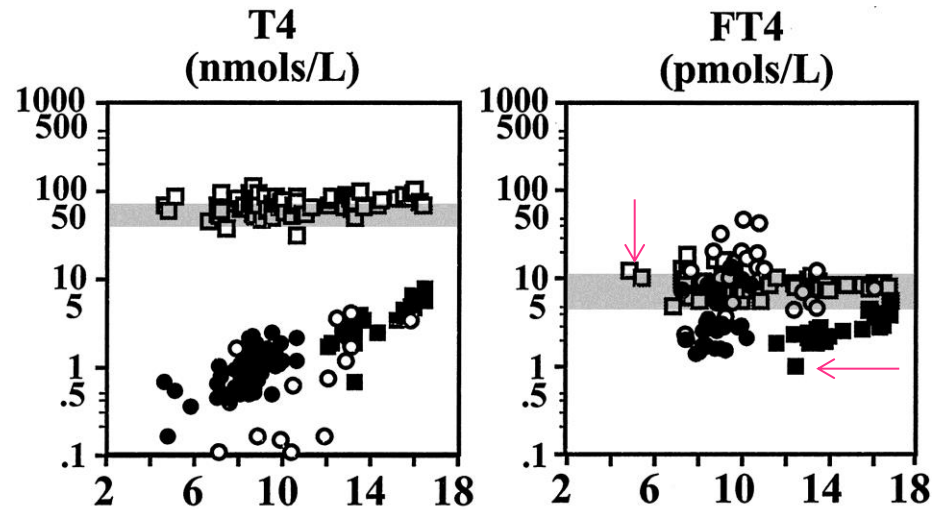
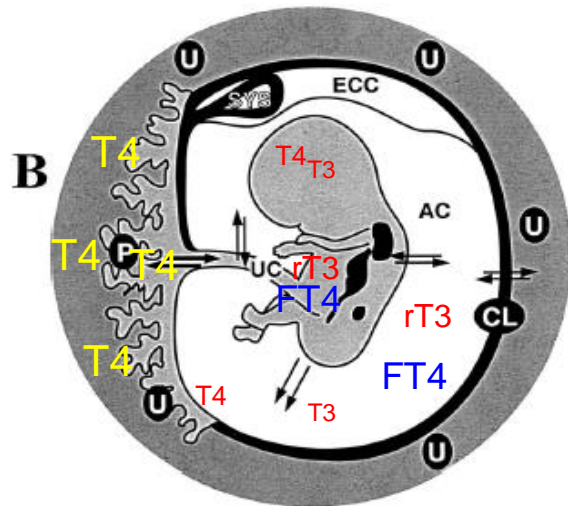
STIMOLAZIONE
TIROIDEA



PASSAGGIO TRANS-PLACENTARE DEGLI ORMONI TIROIDEI MATERNI



[FT4] feto ~ 43% [FT4] madre

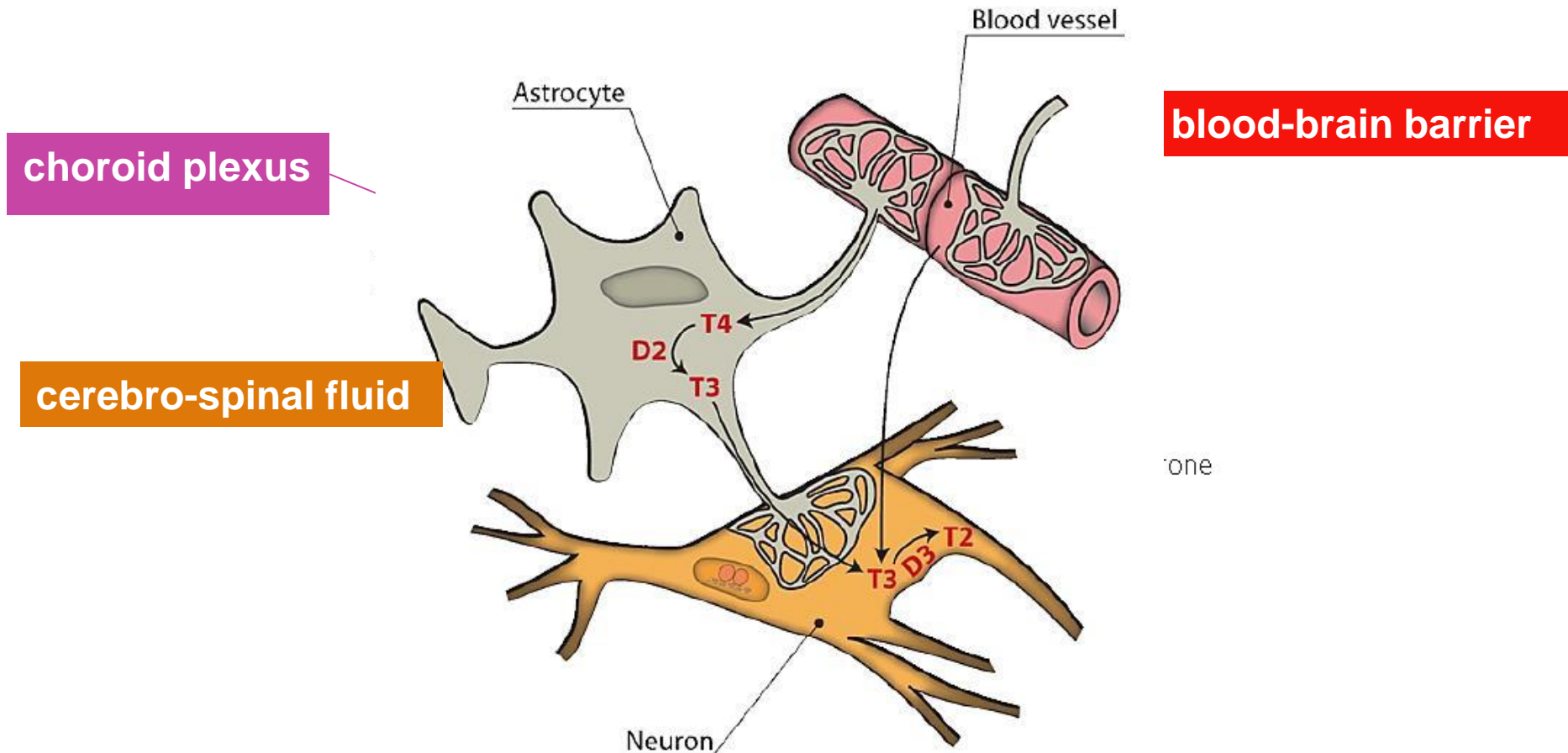


Gestational age in weeks

- Coelomic fluid
- Amniotic fluid
- Fetal blood
- Maternal blood

UNICO STUDIO SU EMBRIONI UMANI
PRIMA DELL'INIZIO PIENA ATTIVITA'
TIROIDEA FETALE

DELIVERY OF THYROID HORMONES TO NEURONES



J Bernal on line 2013

FISIOLOGIA TIROIDEA MATERNA IN GRAVIDANZA



SVILUPPO SNC FETALE



Elevati livelli estrogeni

hCG (1° trim)



↑ livelli sierici TBG

Aumento ormoni tiroidei totali
Relativa riduzione ormoni tiroidei liberi

↓ TSH (2°-3° trim)

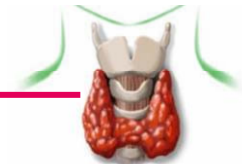
PROCESSI PLACENTAZIONE

APPORTO T4 UNITA' FETO-PLACENTARE

APPORTO IODICO ADEGUATO

INTEGRITA' TIROIDE MATERNA

↑50% T4 (T3)



↑
ME
MATERNE

ONE
TIROIDEA

The Role of Thyroid Hormones in Prenatal and Neonatal Neurological Development—Current Perspectives

February, 1993

SUSAN P. PORTERFIELD AND CHESTER E. HENDRICH

Department of Physiology and Endocrinology, Medical College of Georgia, Augusta, Georgia 30912-3395

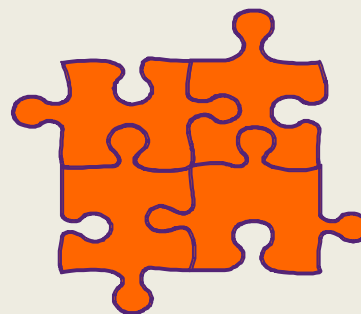
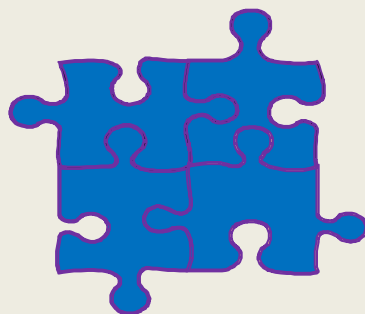
I. Introduction

FOR YEARS thyroid hormones have been known to be important for normal neonatal brain development, and numerous reviews have covered this topic in depth. It now also appears that fetal thyroid hormones play an essential role in fetal brain development. In addition, as some placental transport of thyroid hormones has been shown to occur, it is possible that maternal thyroid hormones might influence fetal brain development.

IODOCARENZA

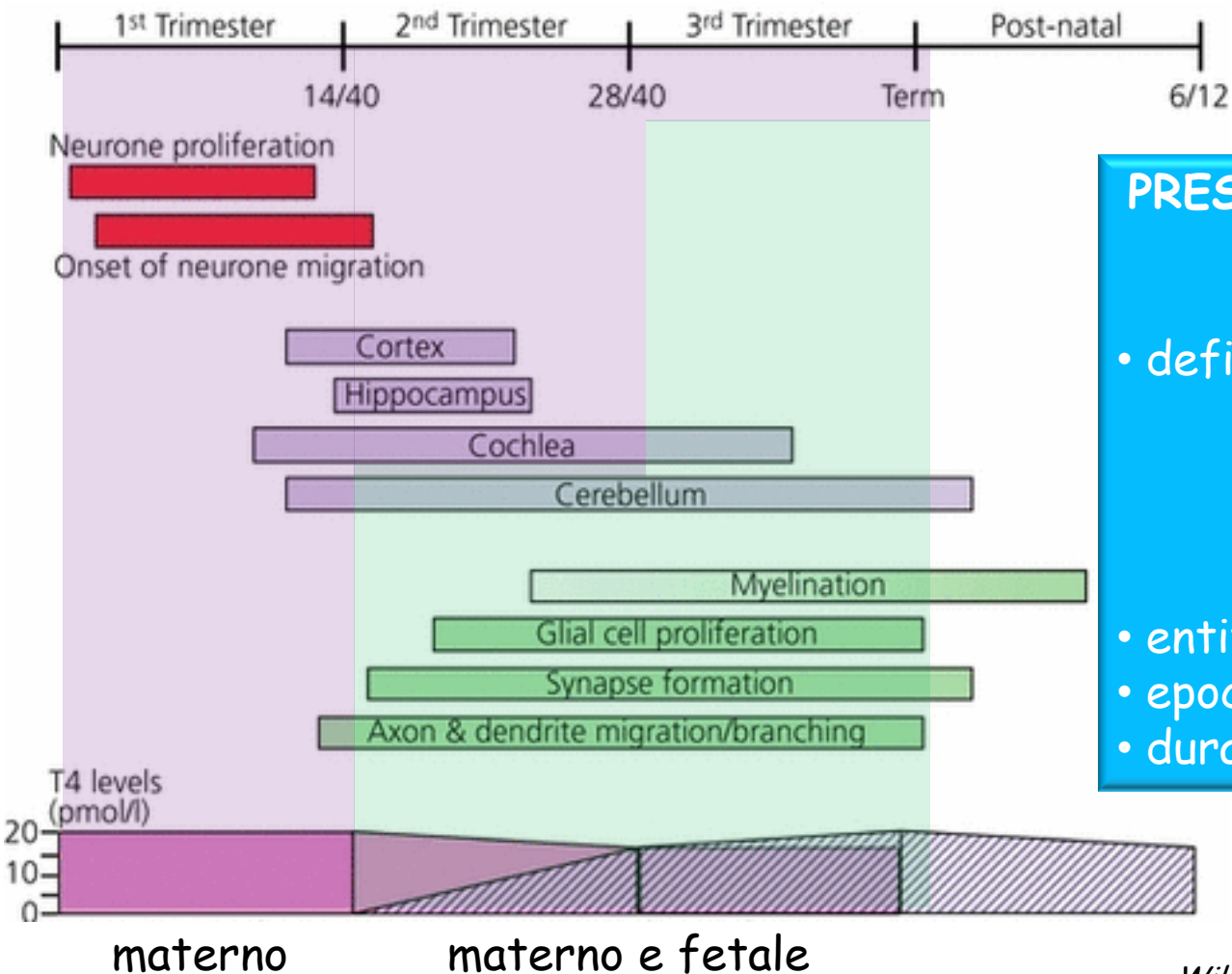


**DEFICIT
FUNZIONE
TIROIDEA
MATERNA**



**DISORDINI
NEURO-PSICO-
INTELLETTIVI
"MINORI"**

SVILUPPO SNC e CONTRIBUTO TIROIDEO MATERNO E FETALE



PRESENTAZIONE CLINICA VARIABILE

in rapporto con

- deficit ormonale
 - materno
 - materno-fetale
 - fetale

- entità deficit
- epoca di comparsa
- durata

IL DEFICIT DI FUNZIONE TIROIDEA MATERNO PRECOCE E
NON CORRETTO È CAUSA DI RIDOTTO QI E DI ALTERAZIONI
DELLE CAPACITÀ COGNITIVE E DI APPRENDIMENTO NEI NATI

dei

controlli

Pop

Alte

cent

Pop

Svilu

24a

Kool

108

signi

Scal

Hen

L'ipo

cogn

IDD NEWSLETTER | AUGUST 2013 | AUTISM | 7

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a entro

score

ssment

rdo

Increased risk of autism in children born to mothers with poor thyroid function

Read more:

Román GC, et al. Association of gestational maternal hypothyroxinemia and increased autism risk. *Ann Neurol.* 2013 Aug 13. [Epub ahead of print]. Sullivan KM. Iodine deficiency as a cause of autism. *J Neurol Sci.* 2009;276(1-2):202.

J Clin Endocrinol Metab. 1990 Feb;70(2):379-84.

Defective neuromotor and cognitive ability in iodine-deficient schoolchildren of an endemic goiter region in Sicily

Vermiglio F, Sidoti M, Finocchiaro MD, Battiato S, Lo Presti VP, Benvenga S, Trimarchi F



719 scolari (6-11 anni) di area iodocarente
(85.2% popolazione scolare)

Bender Visual Motor Gestalt Test (Bender)

processi di strutturazione e di
organizzazione percettivo-motoria

Terman-Merrill Test

capacità intellettuale generale

Valutazione neurologica standard



14% Bender+ e 17% Bender "borderline"
1/3 Bender+ *anche* disordini neurologici minori
QI↓ rispetto ai Bender- e ai controlli
NON ALTERAZIONI FUNZIONE TIROIDEA

ENDEMIC COGNITIVE DEFICIENCY

DISORDINI NEUROPSICOINTELLETTIVI IN NATI DA MADRI RESIDENTI IN AREE LIEVEMENTE O MODERATAMENTE IODOCARENTI

TABLE 1. Neuropsychiatric and intellectual deficits in infants and schoolchildren born to mothers residing in conditions of mild to moderate ID

Region	Tests	Main findings	First author(s), date (Ref.)
Spain	Locally adapted: Bayley, McCarthy, Cattell	Lower psychomotor and mental development	Bleichrodt, 1989 (42)
Italy (Sicily)	Bender-Gestalt	Low perceptual integrative motor ability and neuromuscular and neurosensorial abnormalities	Vermiglio, 1990 (45)
Italy (Tuscany)	Wechsler Raven	Low verbal IQ, perception, and motor and attentive functions	Fenzi, 1990 (43)
Italy (Tuscany)	WISC reaction time	Lower velocity of motor response to visual stimuli	Vitti, 1992 (46), Aghini-Lombardi, 1995 (40)
India	Verbal, pictorial learning tests, tests of motivation	Lower learning capacity	Tiwari, 1996 (44)
Iran	Bender-Gestalt, Raven	Retardation in psychomotor development	Azizi, 1993 (41)

Table modified from Glincoer and Delange (38).

Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries.

Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisà A, Artemisia A, Trimarchi F.

MOTHERS → **Thyroid function monitoring over the 1st half of gestation**

ID mothers
8/16 (50%)
hypo-T4

IS mothers
1/11 (9.1%)
hypo-T4

CHILDREN



Neurobehavioural/
psychomotor
evaluation

9/16
suspicious ADHD at 18-36 mo

1/11
suspicious ADHD



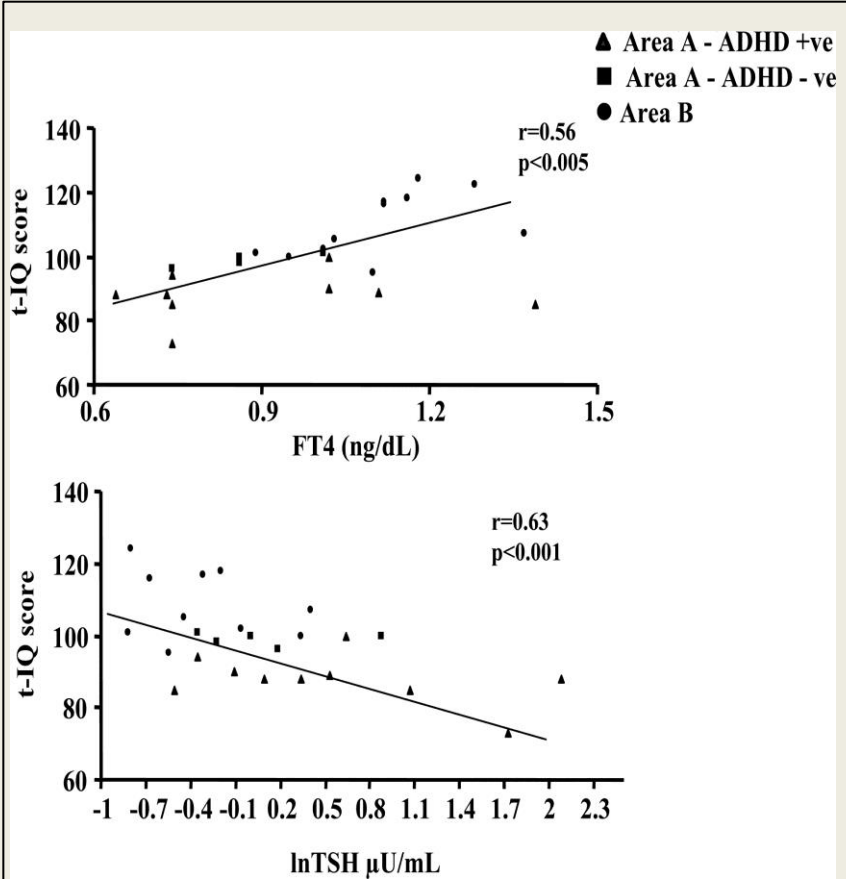
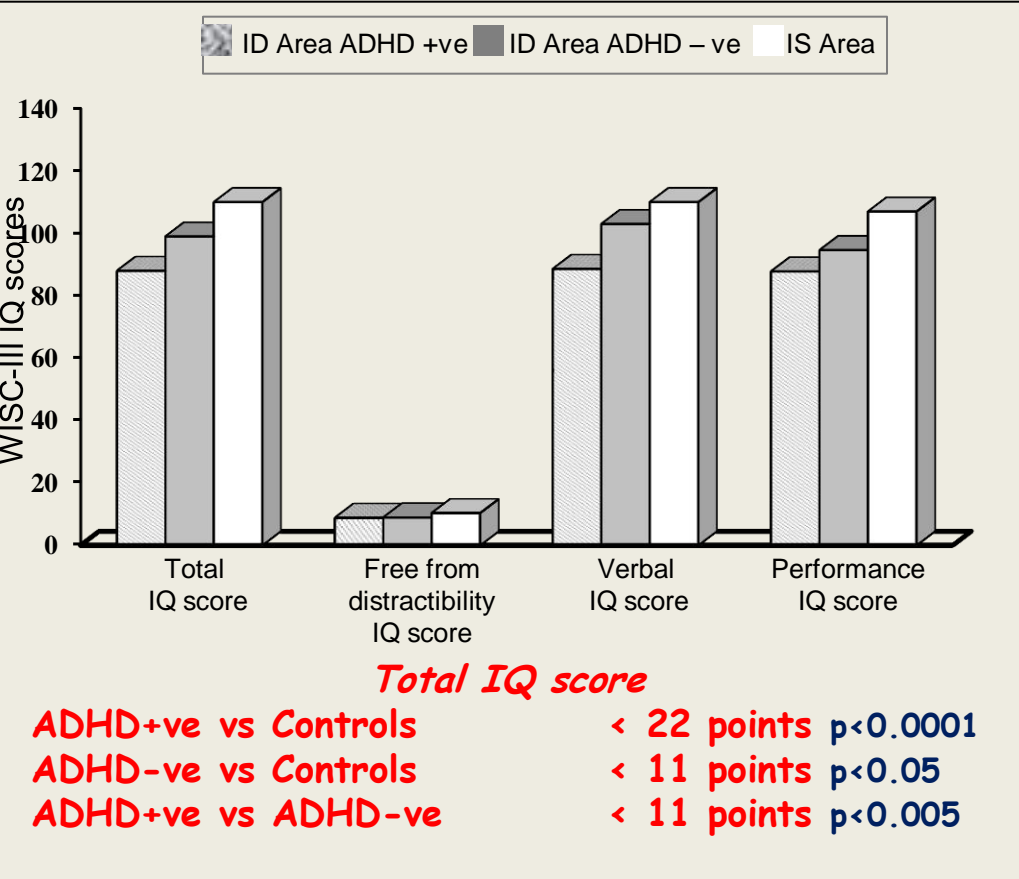
11/16
confirmed ADHD at 8-10 yr

0/11
confirmed ADHD

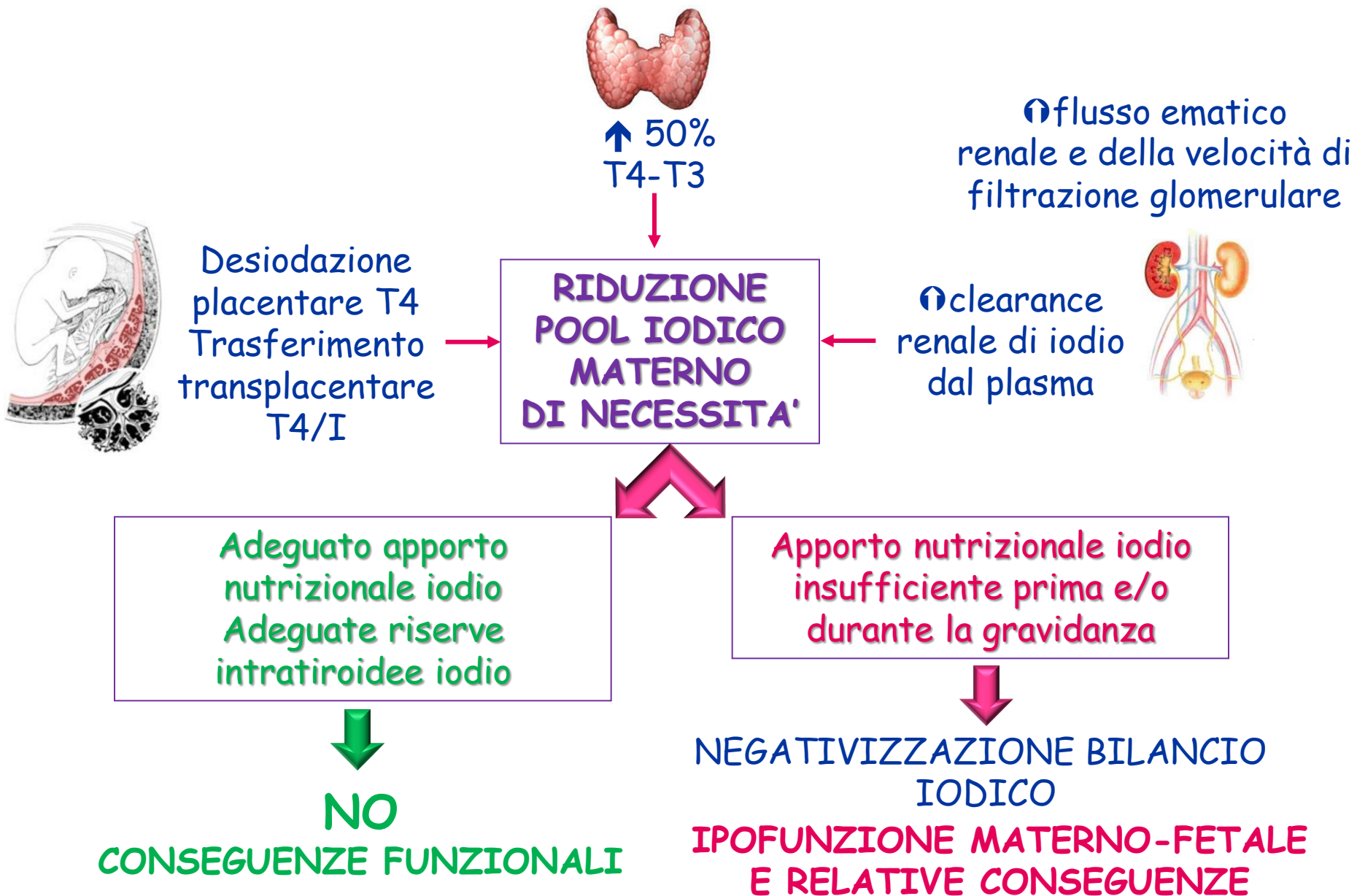
68% in newborns of ID mothers
87.5% in newborns of hypo-T4 mothers

Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries.

Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisà A, Artemisia A, Trimarchi F.

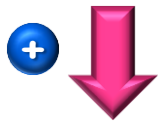


IODIO E GRAVIDANZA

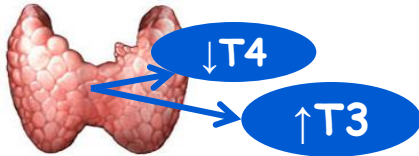


FISIOPATOLOGIA TIROIDEA **MATERNA** IN CARENZA IODICA LIEVE-MODERATA

APPORTO
IODICO
INADEGUATO



**AUTOREGOLAZIONE
TIROIDEA**
TSH-indipendente



Produzione preferenziale T3

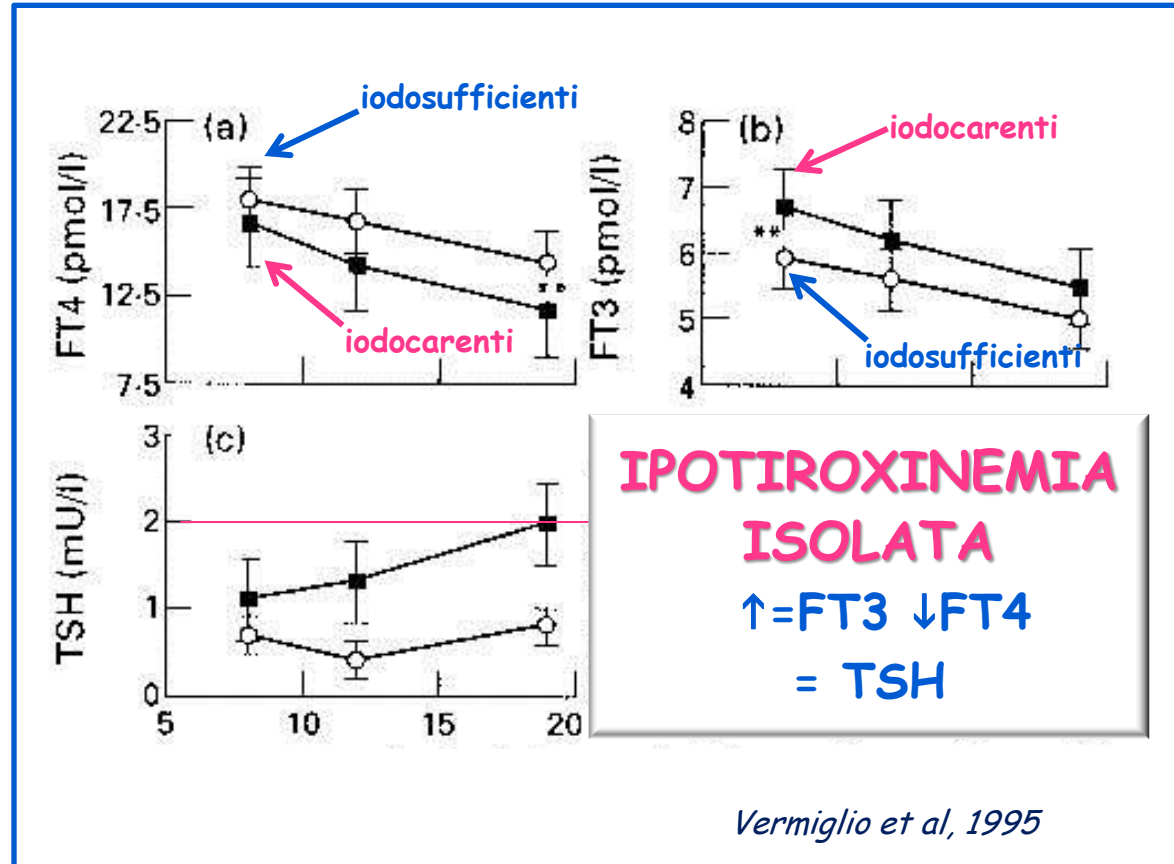
↑ Vascolarizzazione

↑ Flusso ematico

↑ Trapping iodio

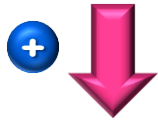
↑ Altezza cellule follicolari

Iperplasia



FISIOPATOLOGIA TIROIDEA MATERNA IN CARENZA IODICA LIEVE-MODERATA

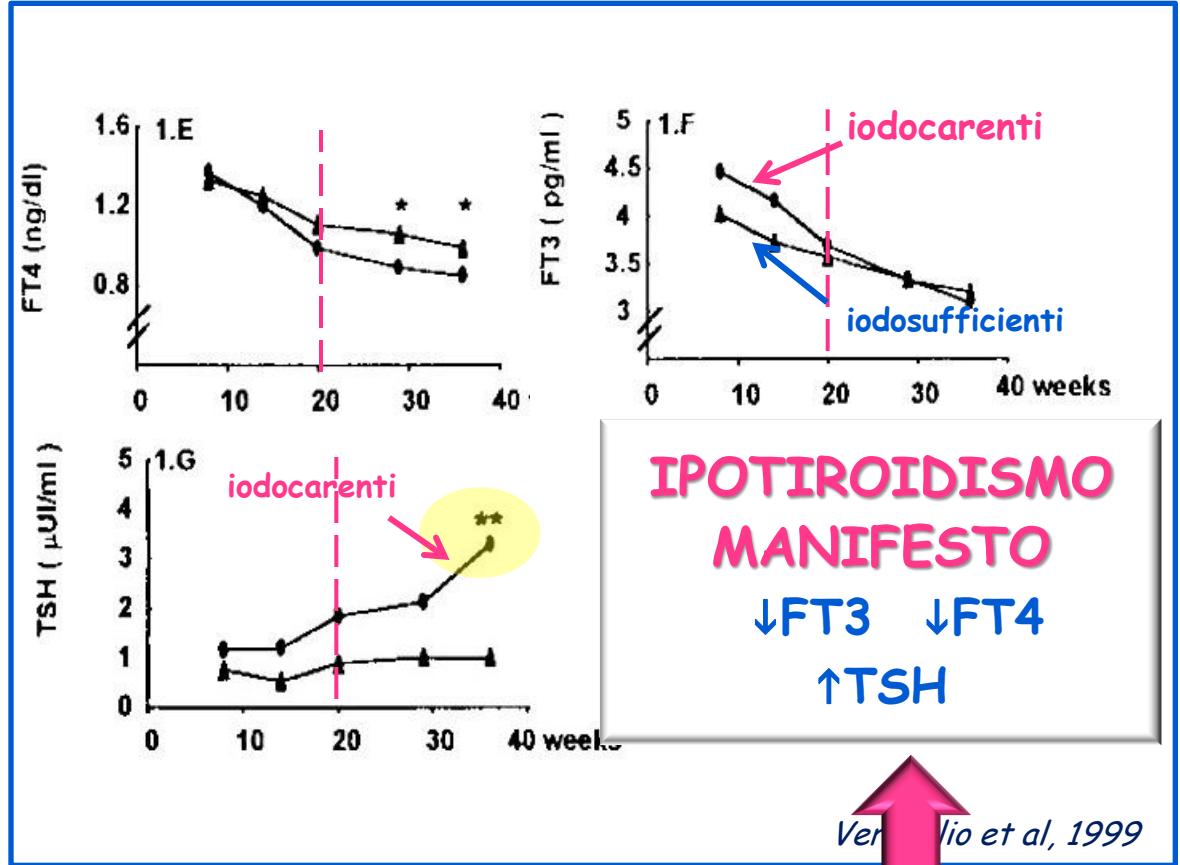
APPORTO IODICO INADEGUATO



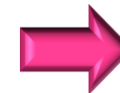
AUTOREGOLAZIONE TIROIDEA TSH-indipendente



IPOTIROXINEMIA ISOLATA



APPORTO IODICO PERSISTENTEMENTE INADEGUATO



PROGRESSIVO ESAURIMENTO SCORTE IODIO

MODIFICAZIONI FUNZIONE TIROIDEA IN GRAVIDANZA E NUTRIZIONE IODICA

BRUSSELS

North Eastern SICILY



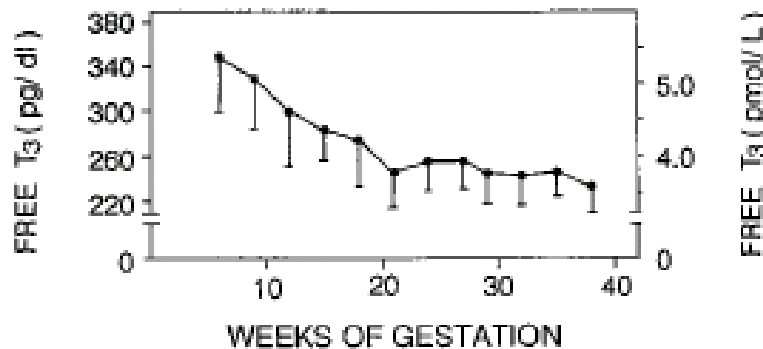
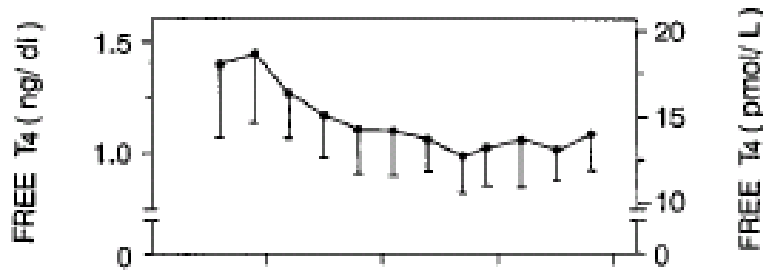
median UIE 91 $\mu\text{g/L}$

Marginally IS area
~ 20% FT4 reduction

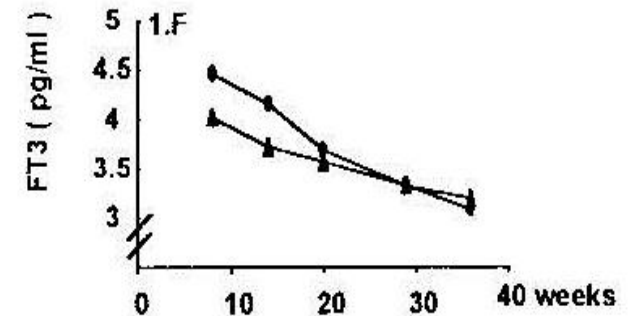
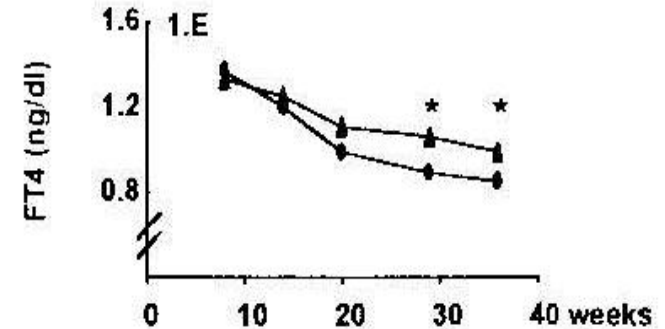


median UIE 46 $\mu\text{g/L}$

Moderately ID area
~ 37% FT4 reduction



Glinoer, et al, 1990



Vermiglio et al, 1999

RECOMMENDED IODINE INTAKE DURING PREGNANCY OVER THE YEARS

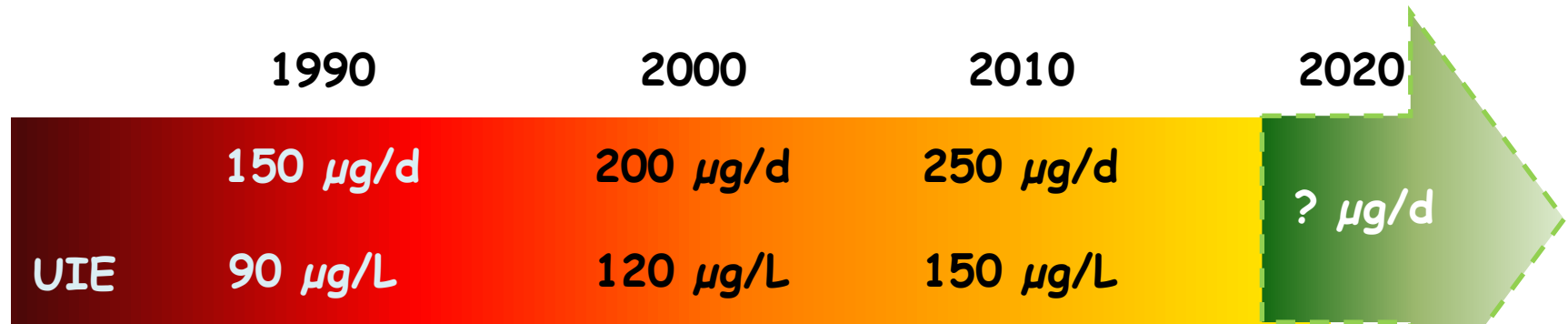


TABLE 1. Recommendations for iodine intake ($\mu\text{g}/\text{d}$) by age or population group

Age or population group	IOM		Age or population group	WHO RNI
	EAR	AI or RDA		
Infants 0–12 months		110–130	Children 0–5 yr	90
Children 1–8 yr	65	90	Children 6–12 yr	120
Children 9–13 yr	73	120		
Adults ≥ 14 yr	95	150	Adults > 12 yr	150
Pregnancy	160	220	Pregnancy	250
Lactation	200	290	Lactation	250

Zimmermann M, 2009

DA CRETINISMO ENDEMICO A ADHD

CRETINISMO
ENDEMICO

NUTRIZIONE
IODICA

DISORDINI
PSICO-NEUROLOGICI MINORI



CRETINISMO
MIXEDEMATOSO



CRETINISMO
MISTO



CRETINISMO
NEUROLOGICO



DEFICIT
COGNITIVO
ENDEMICO



ADHD

Circa 1900

ca 1945

1950

1978

1995

Iodine prophylaxis using iodized salt and risk of maternal thyroid failure in conditions of mild iodine deficiency.

Moleti M, Lo Presti VP, Campolo MC, Mattina F, Galletti M, Mandolino M, Violi MA, Giorgianni G, De Domenico D, Trimarchi F, Vermiglio F.

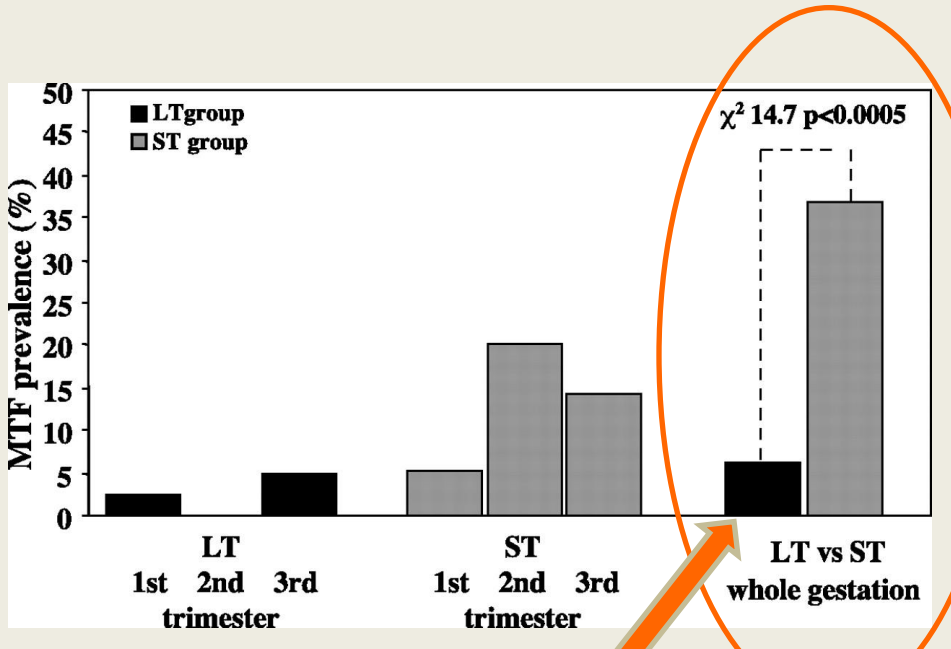
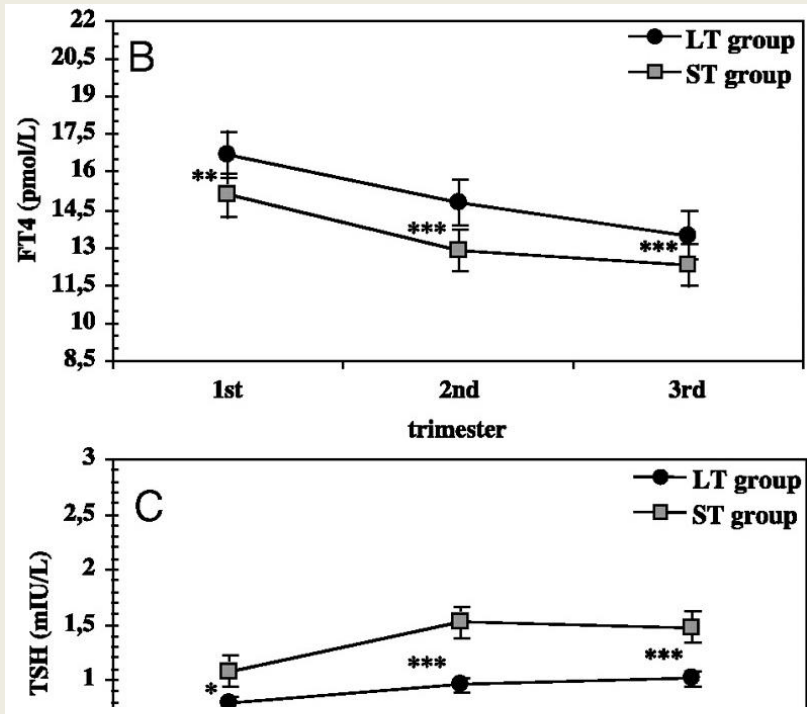


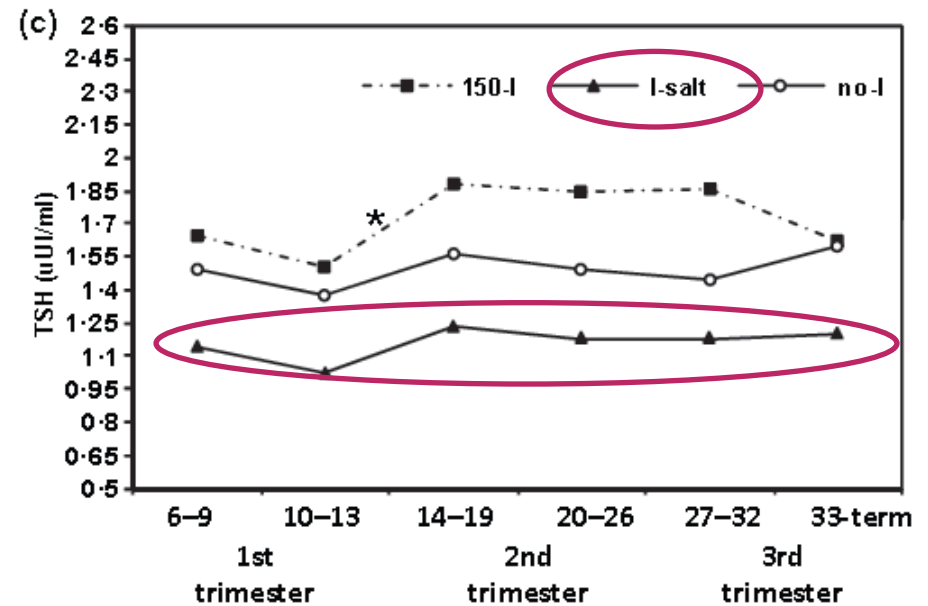
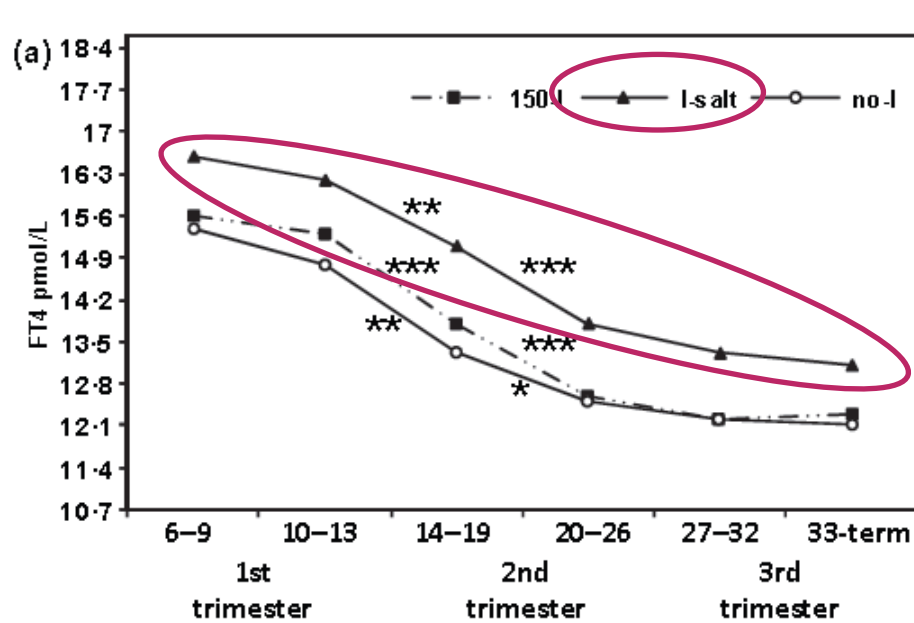
TABLE 1. Epidemiological and biochemical features of both LT and ST women at enrollment (6–9 wk of gestation)

Group	Age range (mean ± SD)	Parity = 0 % (n)	Parity ≥ 1 % (n)	Tg, ng/ml (mean ± SD)	UIE, μg/liter (median)	Estimated iodine intake (μg/d) ^a
LT (n = 62)	17–35(28.4 ± 4.9)	29 (18)	71 (44)	10.2 ± 9.2	115	190
ST (n = 38)	17–36(26.9 ± 4.8)	31.6 (12)	68.4 (26)	24.1 ± 19.3	63	105

ORIGINAL ARTICLE

Maternal thyroid function in different conditions of iodine nutrition in pregnant women exposed to mild-moderate iodine deficiency: an observational study

Mariacarla Moleti*, Beatrice Di Bella*, Grazia Giorgianni†, Alfredo Mancuso‡, Antonio De Vivo‡, Angela Alibrandi§, Francesco Trimarchi* and Francesco Vermiglio*



The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

FEBRUARY 9, 2012

VOL. 366 NO. 6

Antenatal Thyroid Screening and Childhood
Cognitive Function

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Arthur B. Parkes, Ph.D., Mohammed Joomun, M.Sc., and Nicholas J. Wald, F.R.S.

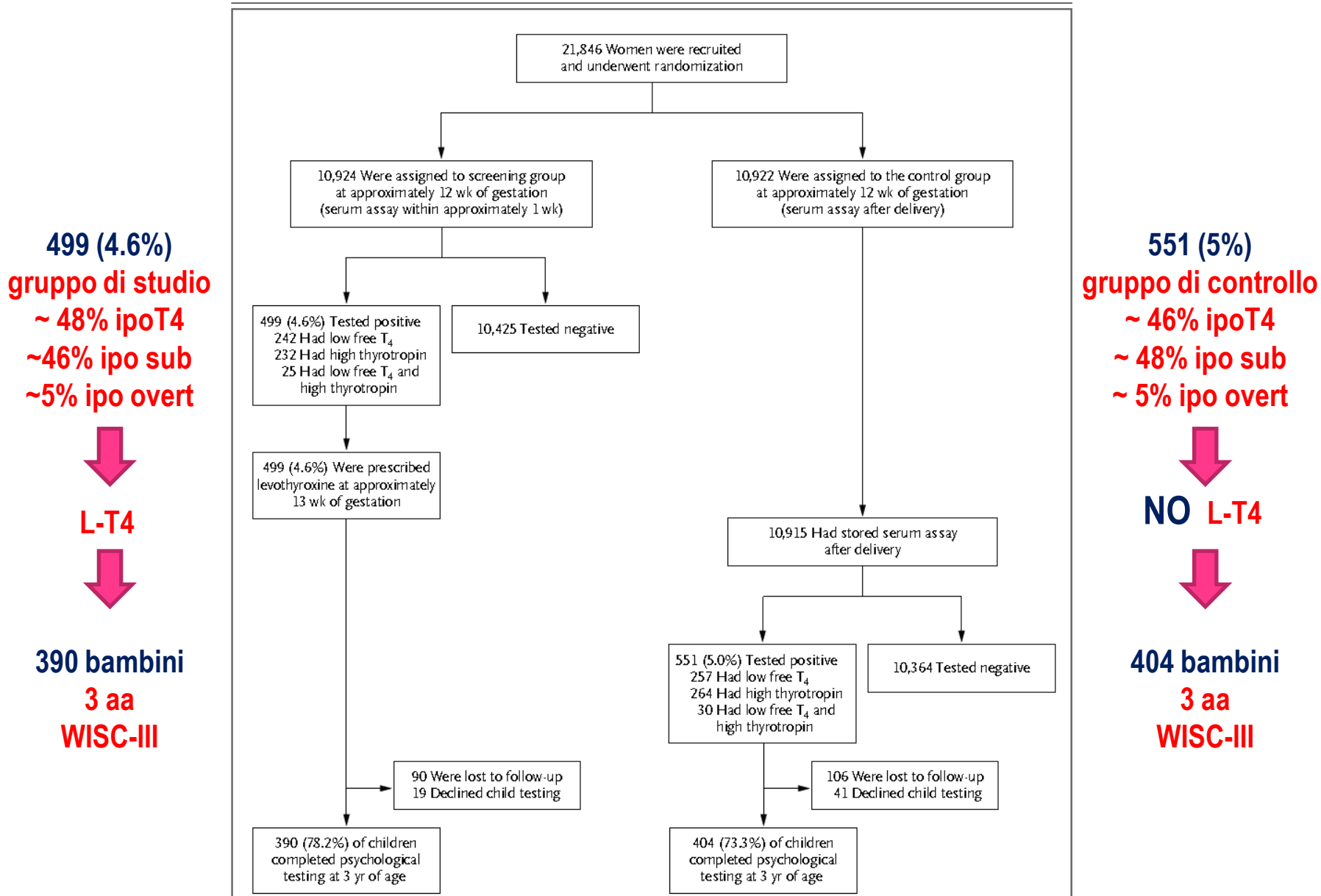


Figure 1. Randomization and Follow-up of the Study Participants.

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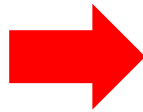
499 (4.6%)
gruppo di studio
~ 48% ipoT4
~46% ipo sub
~5% ipo overt



L-T4



390 bambini
3 aa
WISC-III



media
t-QI
99.2

p NS

media
t-QI
100



551 (5%)
gruppo di controllo
~ 46% ipoT4
~ 48% ipo sub
~ 5% ipo overt



NO L-T4



404 bambini
3 aa
WISC-III

IQ < 85 pt
12.1%

p NS

IQ < 85 pt
14.1%

CONCLUSIONS

Antenatal screening (at a median gestational age of 12 weeks 3 days) and maternal treatment for hypothyroidism did not result in improved cognitive function in children at 3 years of age.



The Debate over Thyroid-Function Screening in Pregnancy

Gregory A. Brent, M.D.

MAJOR BIASES

1. INCLUSION OF WOMEN WITH MILD HYPOTHYROIDISM
2. L-T4 STARTED AT A MEDIAN GESTATIONAL AGE OF 13+3 WKS (TOO LATE?)
3. RELATIVE CRUDENESS OF IQ TESTING AT 3 YRS OF AGE

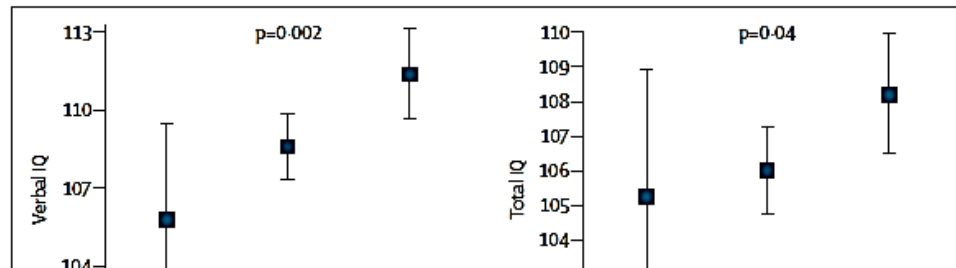
OTHER BIASES

1. NO CONTROL GROUP (CHILDREN BORN TO MOTHERS WITH NORMAL FT4 AT EARLY GESTATION)
2. MODERATELY IODINE DEFICIENT WOMEN (AND FETUSES)

Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC)

Sarah C Bath, Colin D Steer, Jean Golding, Pauline Emmett, Margaret P Rayman

www.thelancet.com Published online May 22, 2013 [http://dx.doi.org/10.1016/S0140-6736\(13\)60436-5](http://dx.doi.org/10.1016/S0140-6736(13)60436-5)



Our study is the first to show an association between mild-to-moderate maternal iodine deficiency in UK pregnant women and impaired cognitive outcomes in their children at ages 8–9 years. Iodine deficiency in pregnant women in the UK should be treated as an important public health issue that needs attention.

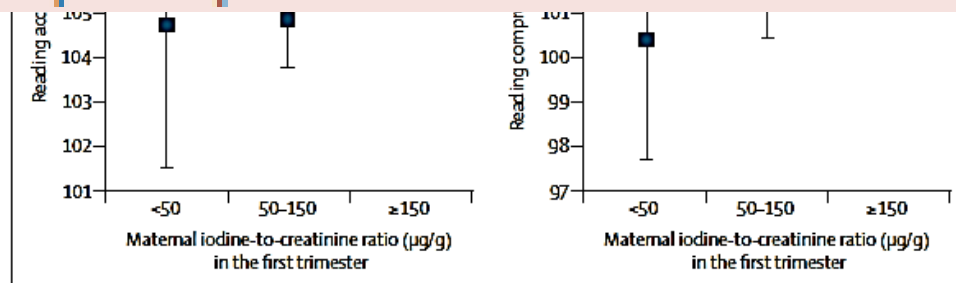


Figure: Means (95% CIs) for child cognitive outcomes according to maternal iodine status in the first trimester. Values are adjusted for the effect of confounders (model three). Child verbal and total IQ were assessed at age 8 years and reading accuracy and comprehension at age 9 years. IQ=intelligence quotient.

Maternal Hypothyroxinemia in Early Pregnancy Predicts Reduced Performance in Reaction Time Tests in 5- to 6-Year-Old Offspring

Martijn J. J. Finken, Manon van Eijsden, Eva M. Loomans, Tanja G. M. Vrijkotte, and Joost Rotteveel

Results: Maternal hypothyroxinemia (ie, maternal free T4 in the lowest 10% of distribution) was associated with a 41.3 (95% confidence interval, 20.3–62.4) ms slower response speed in a simple reaction time task. In this test, it was also associated with a decreased stability in response speed. The relations found persisted after adjustment for family background and perinatal conditions. The effect of hypothyroxinemia on these outcomes was dependent on its interaction with TSH level.

Conclusions: Lower maternal free T4 concentration at the end of the first trimester predicted slower response speed and decreased stability in response speed in offspring at 5 to 6 years of age.
(*J Clin Endocrinol Metab* 98: 1417–1426, 2013)

Maternal Thyroxine and Fetal Brain Development: The Latest Chapter, a Look Back, and Considerations for the Future

James E. Haddow



ETA 2013

LEIDEN The Netherlands

THYROID FUNCTION MONITORING AND TSH LEVELS IN PREGNANT INDIVIDUALS ON LEVOTHYROXINE FOR PRIMARY HYPOTHYROIDISM IN THE UK

Taylor PN¹, Minassian C², Iqbal A³, Rehman A⁴, Thomas SL², Okosieme O¹, Lazarus J¹, Dayan CM¹

Conclusions: Almost 50% of women of child-bearing age on levothyroxine have thyroid function that is not optimal for pregnancy and many go on to have suboptimal thyroid function throughout pregnancy. Given that many UK pregnancies are unplanned there may also be benefits in “tighter” control of thyroid function in younger women.

UK

EFFECTS OF IODINE SUPPLEMENTATION ON PREGNANCY AND ON THE OFFSPRING

Mamenko M¹, Belykh N¹, Valiyev O², Mimyaylo N³, Kovalenko N⁴

Conclusions: Insufficient iodine supplementation leads to the gestational hypothyroxinemia, maternal and infant’s thyroid dysfunction, high frequency of neonatal hyperthyrotropinemia.

UKRAINE

IODINE SUPPLEMENTATION DURING PREGNANCY AND OFFSPRING NEUROCOGNITIVE DEVELOPMENT AT 2 YEARS OF AGE IN AN AREA OF MILD IODINE DEFICIENCY

Brucker-Davis F¹, Chauliac F², Panaia-Ferrari P³, Fenichel P¹, Hieronimus S¹

Conclusions: This study should allow us to precise the potential benefit of iodine supplementation on neurocognitive development of children born to mildly iodine-deficient healthy women.

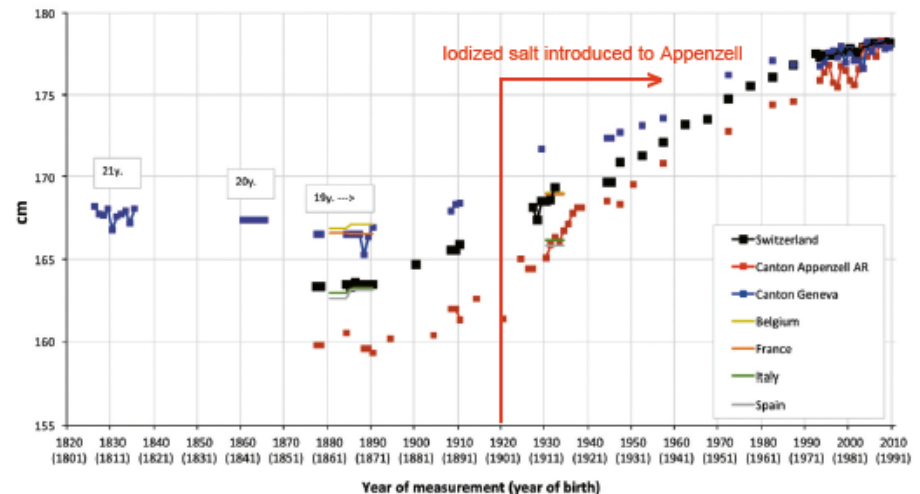
FRANCE

Introduction of iodized salt in the 1920's linked to increased IQ and growth in the U.S. and Switzerland



Using information about average scores of recruits the authors infer that for the one quarter of the population most deficient in iodine this intervention raised IQ by approximately 10 points.

Figure 4: Published average height (cm) of 19 years-old conscripts in Switzerland and in the cantons Geneva and Appenzell Ausserhoden, complete conscription years



WHY MORE IODINE IN PREGNANCY?

**MATERNAL
TH SYNTHESIS
+ 50%**

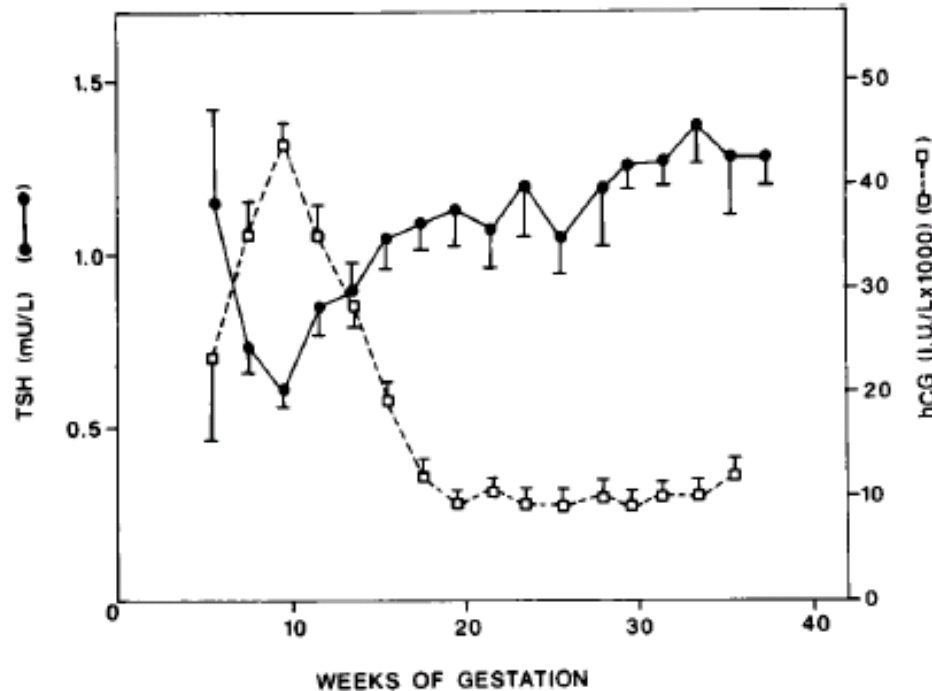
**MATERNAL
IODIDE
POOL**

**FETAL
IODIDE
POOL**

1st trimester
hCG stimulates

2nd-3rd trimester
TSH stimulates

✓ Normal placental
fetal brain development

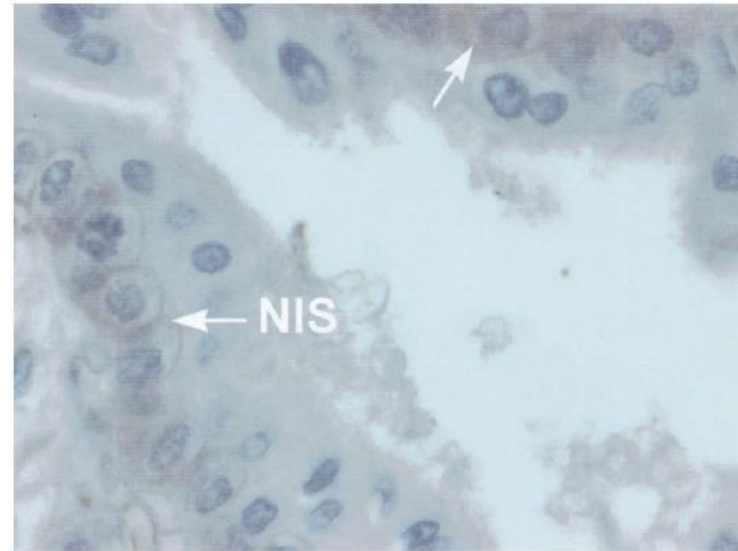
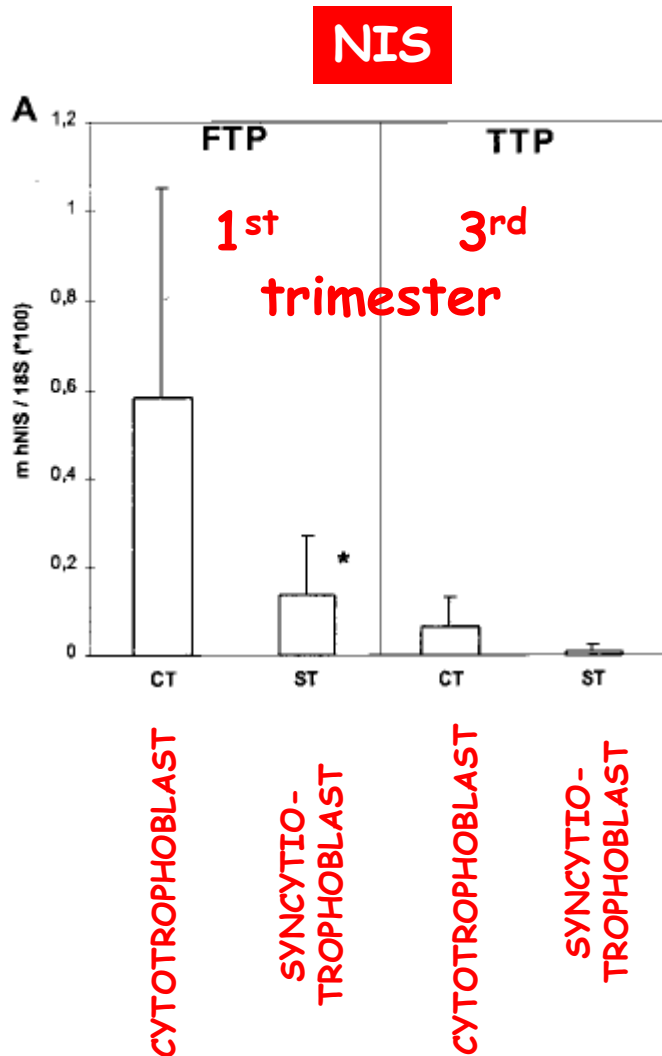


**FETAL
TH SYNTHESIS
(6 wks)**

growth and
development

Expression of Na⁺/I⁻ Symporter and Pendred Syndrome Genes in Trophoblast Cells*

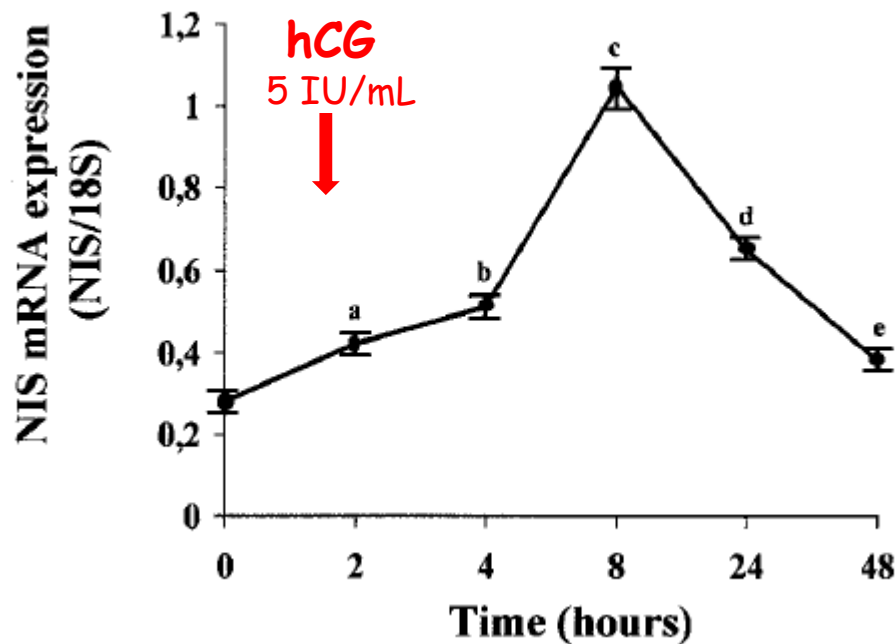
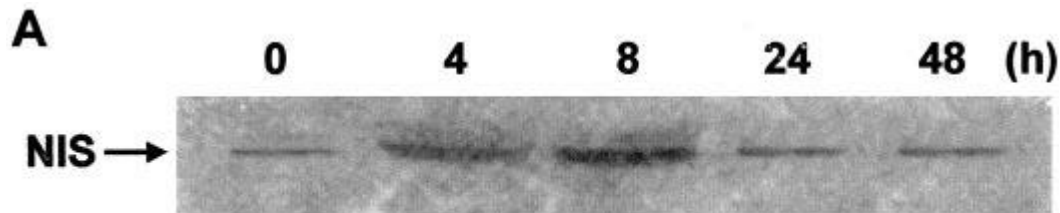
JEAN-MICHEL BIDART, LUDOVIC LACROIX, DANIELLE EVAIN-BRION, BERNARD CAILLOU, VLADIMIR LAZAR, RENÉ FRYDMAN, DOMINIQUE BELLET, SEBASTIANO FILETTI, AND MARTIN SCHLUMBERGER



NIS gene is expressed in the placenta, with a preferential expression in cytotrophoblast cells and at early pregnancy

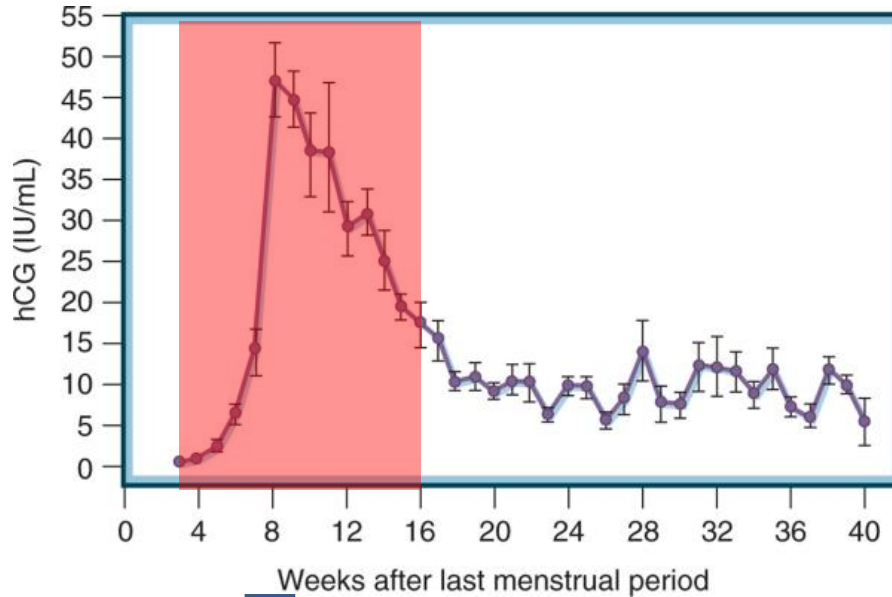
Regulation by Human Chorionic Gonadotropin of Sodium/Iodide Symporter Gene Expression in the JAr Human Choriocarcinoma Cell Line

FRANCO ARTURI, LUDOVIC LACROIX, IVAN PRESTA, DANIELA SCARPELLI, BERNARD CAILLOU, MARTIN SCHLUMBERGER, DIEGO RUSSO, JEAN-MICHEL BIDART, AND SEBASTIANO FILETTI



hCG significantly increases NIS expression at both mRNA and protein level

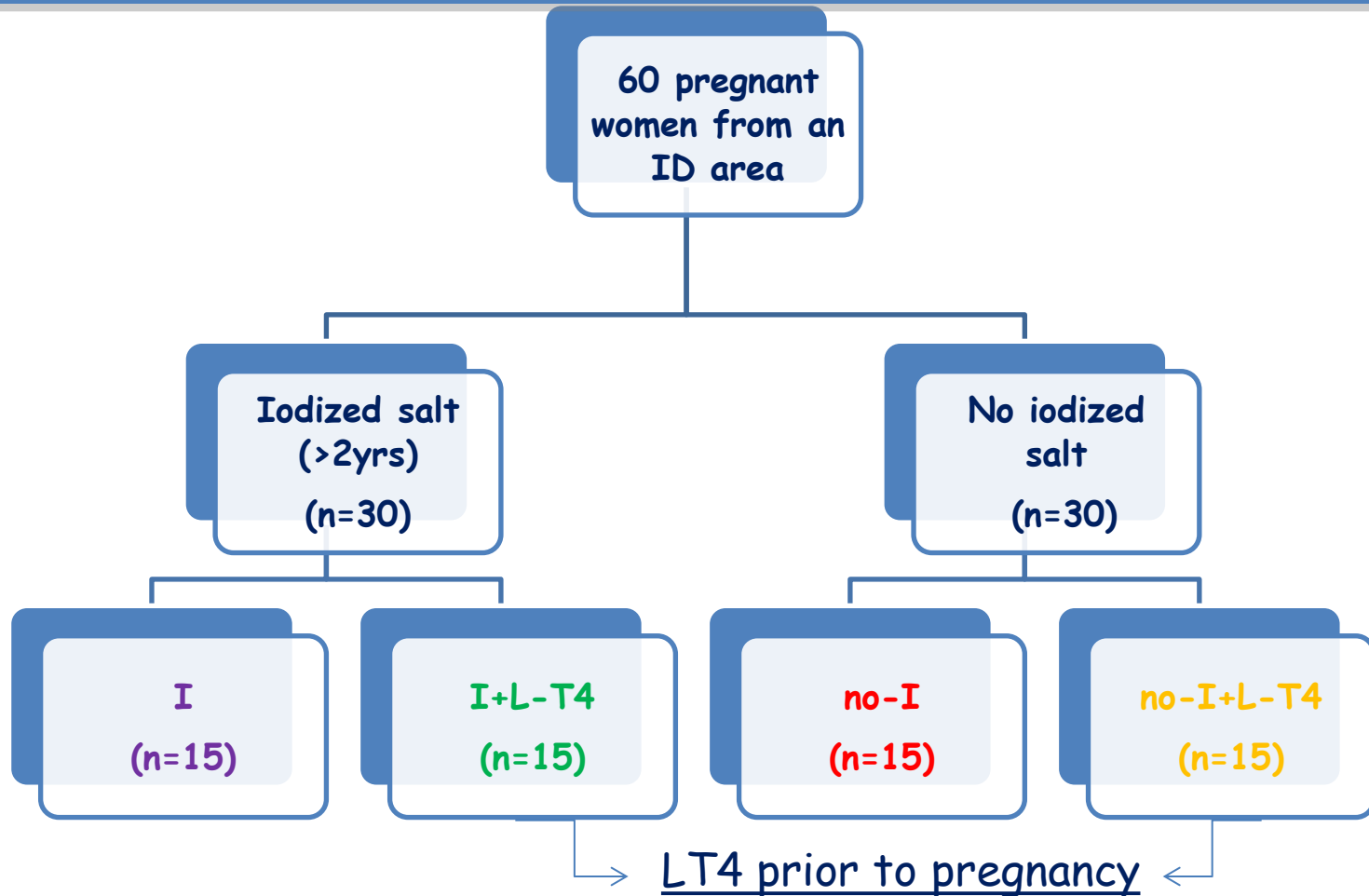
hCG AS THE EARLY GESTATION *KEY HORMONE*



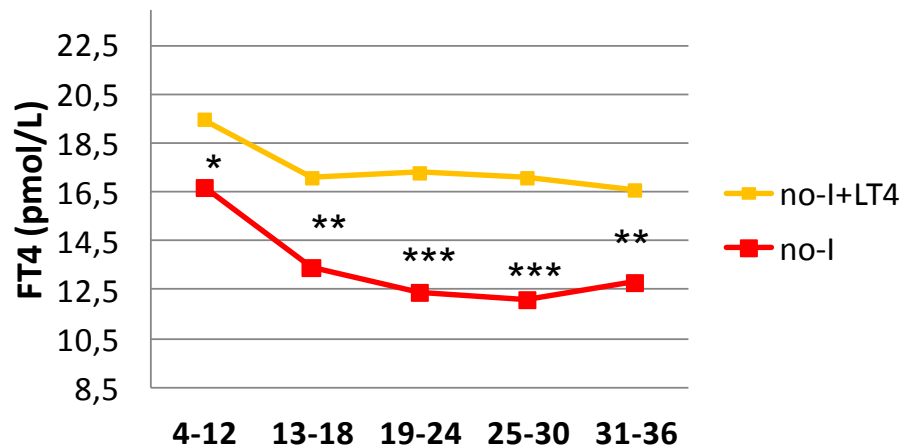
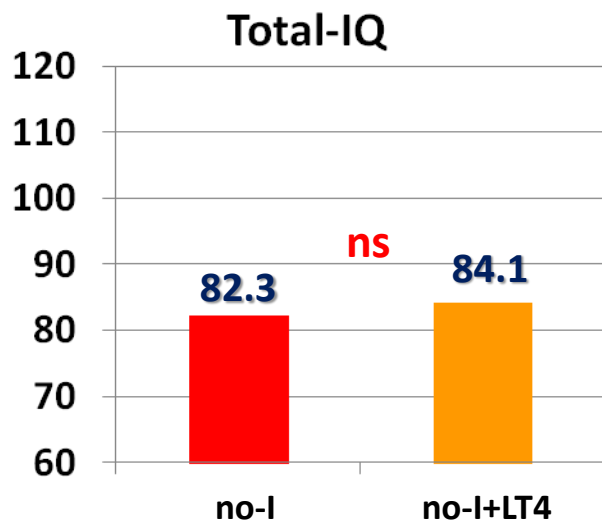
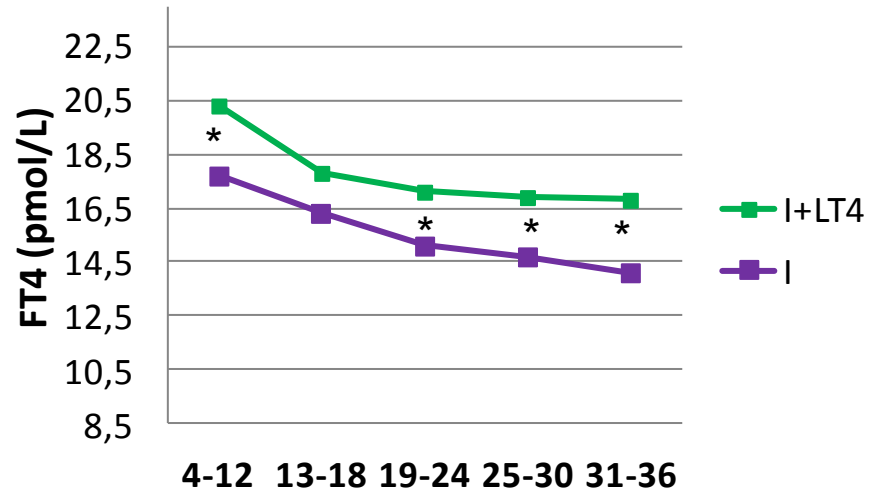
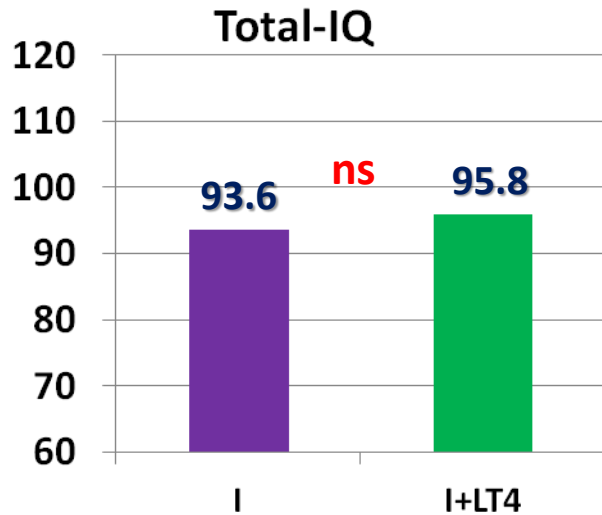
Very early
feto-placental
iodide storage(?)

FETAL EUTHYROIDISM

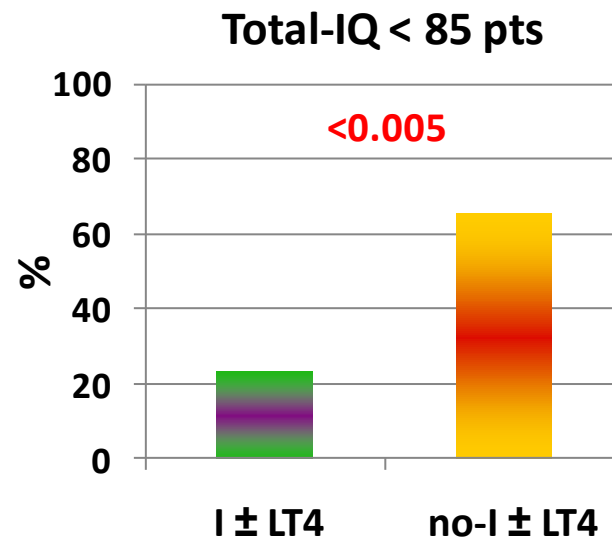
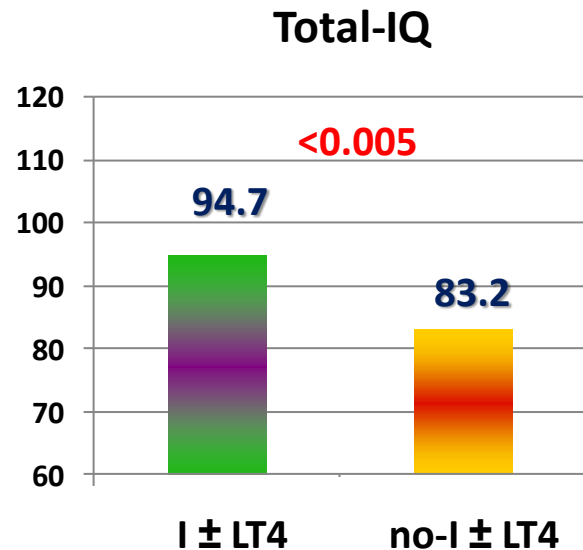
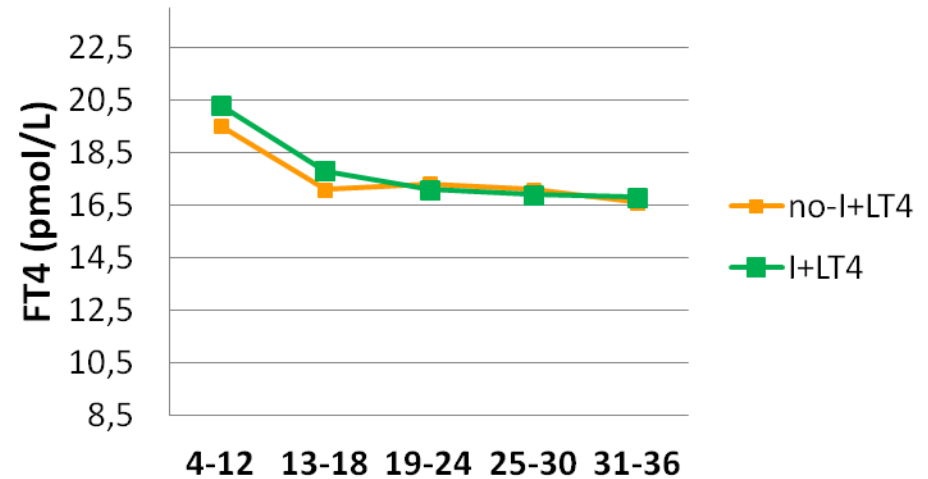
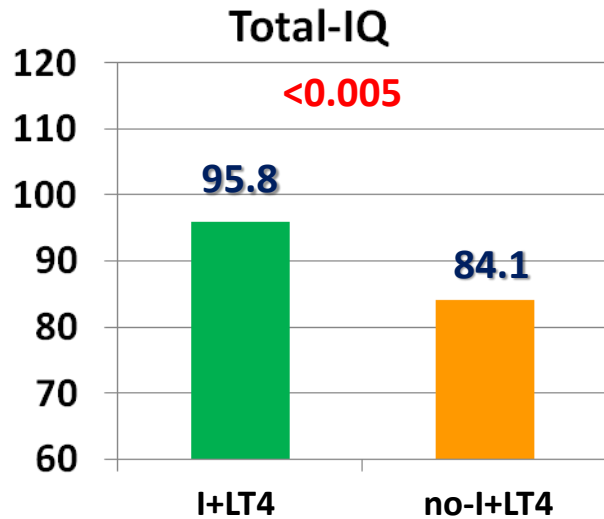
IODINE PROPHYLAXIS AND NEURO-INTELLECTUAL DEVELOPMENT



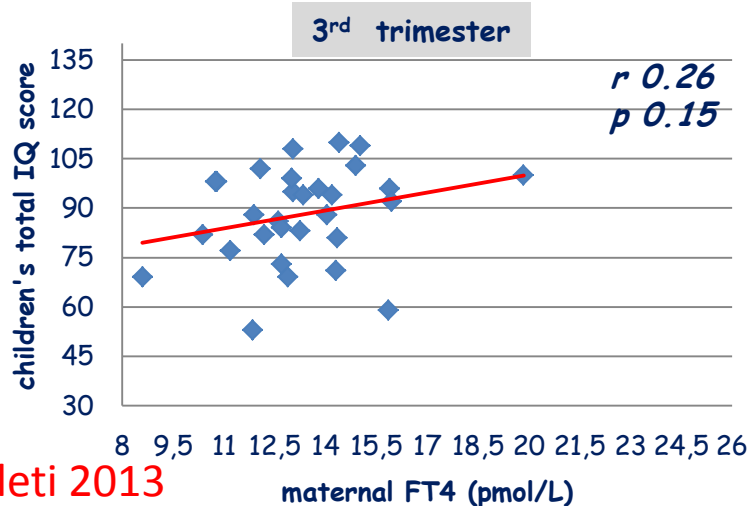
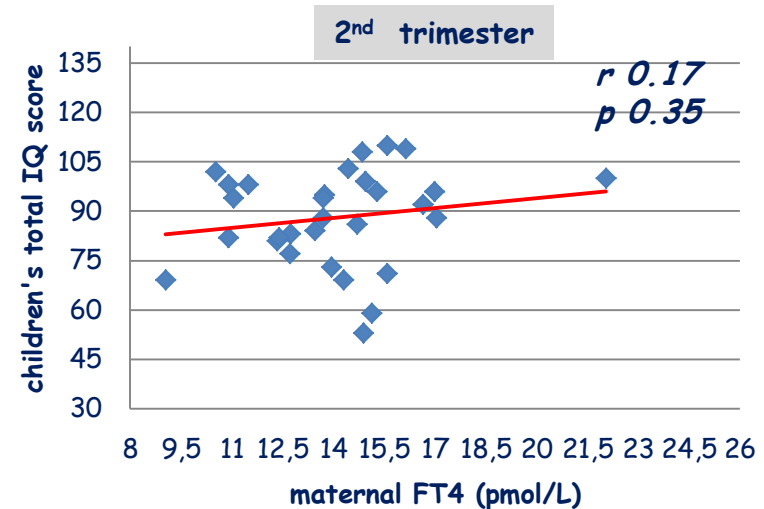
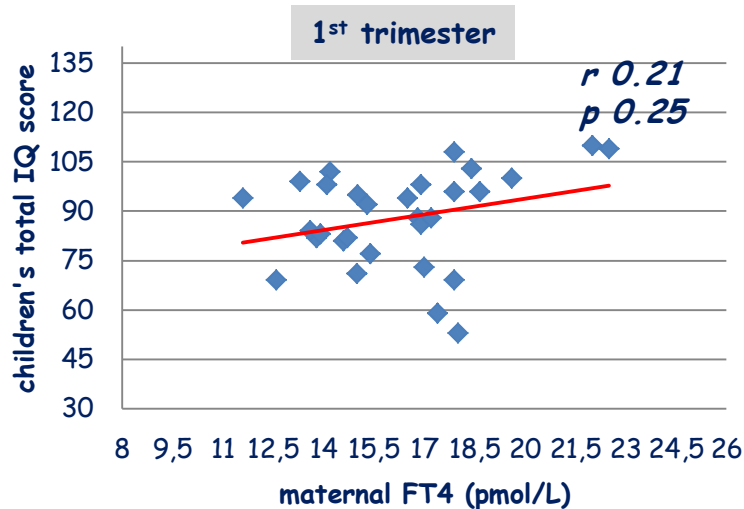
IODINE PROPYLAXIS AND NEURO-INTELLECTUAL DEVELOPMENT



IODINE PROPHYLAXIS AND NEURO-INTELLECTUAL DEVELOPMENT



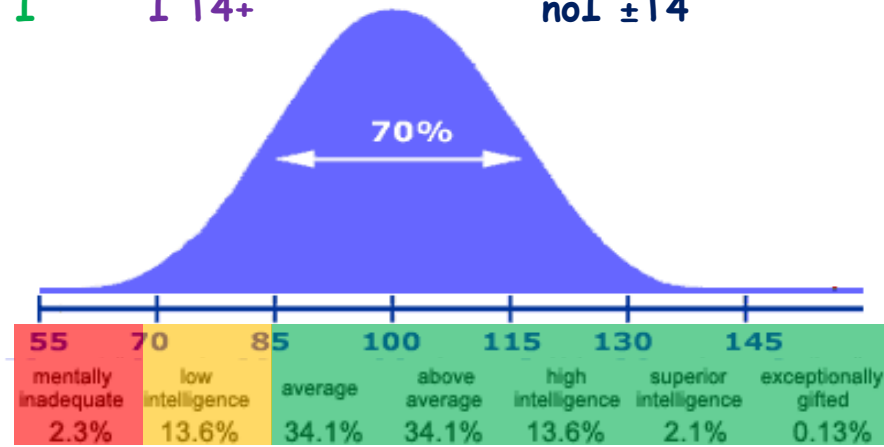
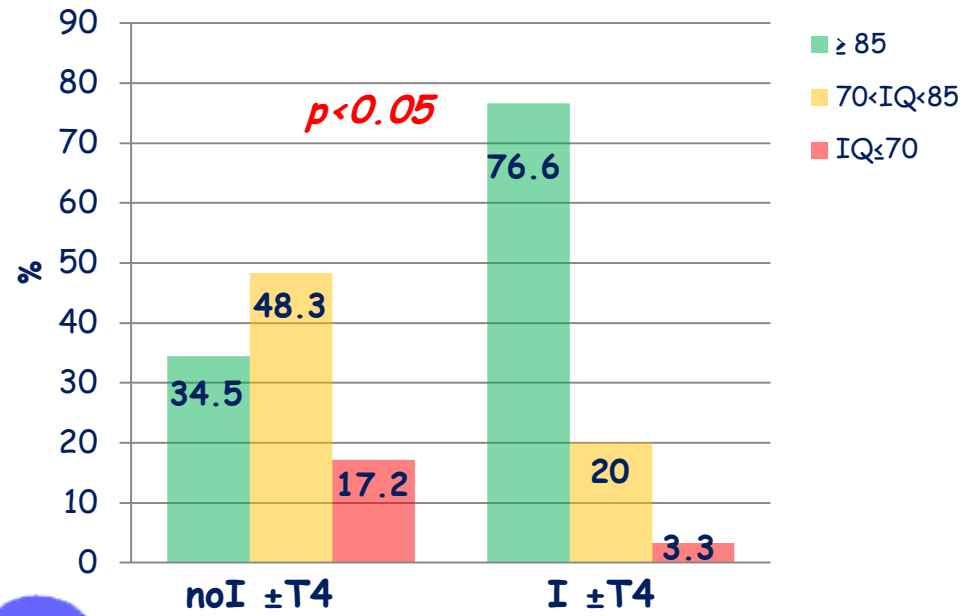
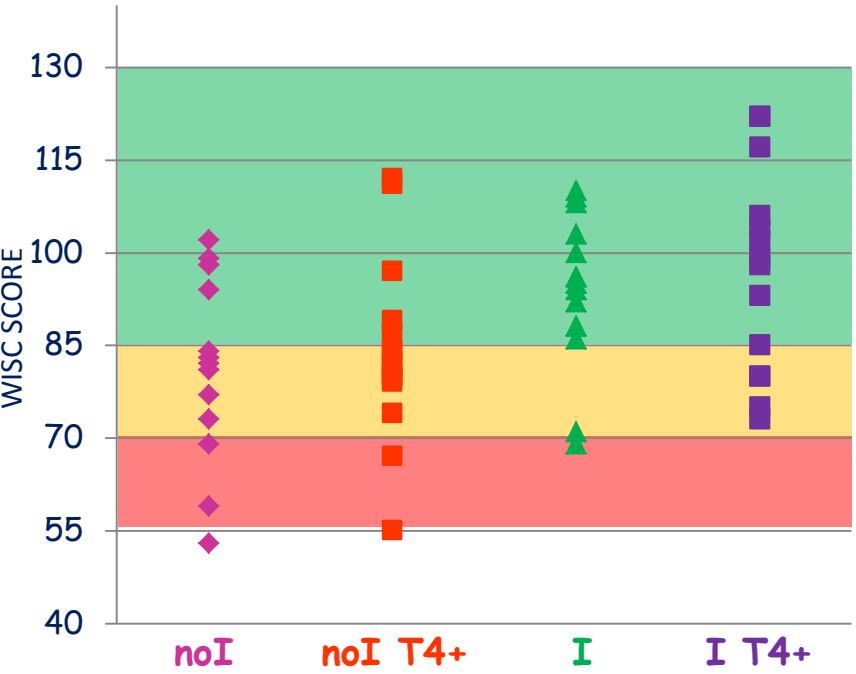
tIQ and maternal FT4 in children born to I- supplemented (I+) and unsupplemented (noI-) mothers



NO relationship
between
serum maternal FT4 levels
throughout gestation and
total IQ

of children born to noI and I+ women

Total IQ: individual data



Mild iodine deficiency in pregnancy in Europe and its consequences for cognitive and psychomotor development of children: A review

Caroline Trumpff^{a,b,*}, Jean De Schepper^c, Jean Tafforeau^a, Herman Van Oyen^a, Johan Vanderfaeillie^d, Stefanie Vandevijvere^a

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.de/jtemb

2013

In iodine sufficient or mildly iodine deficient areas, iodine deficiency during pregnancy frequently appears in case the maternal thyroid gland cannot meet the demand for increasing production of thyroid hormones (TH) and its effect may be damaging for the neurodevelopment of the foetus. MID during pregnancy may lead to supplementation from the first trimester until the end of pregnancy may decrease the risk of cognitive and psychomotor developmental delay in the offspring. Finally, some studies suggest that iodine

Monitoring and effects of iodine deficiency in pregnancy: still an unsolved problem?

EN Pearce

Iodine is required for the production of thyroid hormone. Thyroid hormone affects many metabolic processes in the body, including maturation of the central nervous system. In early pregnancy, the fetus is dependent on maternal thyroid hormone for normal brain development. If iodine deficiency leads to inadequate production of thyroid hormone during pregnancy, irreversible brain damage can result in the fetus. Therefore, achieving adequate iodine nutrition during pregnancy is an important public health objective. Although there have been tremendous gains over the last several decades in our understanding of the effects of iodine deficiency in pregnancy and how to combat them, a number of questions remain about how best to monitor the iodine status of pregnant populations, the effects of mild to moderate iodine deficiency on maternal and child outcomes, the safe upper limit of daily iodine intake in pregnant women and the risks and benefits of iodine supplementation for mildly iodine-deficient pregnant women.

CHE FARE?

- Integrazione iodica in gravidanza
- Screening donne a rischio (+ carenza iodica)
- Monitoraggio funzione tiroidea in gravidanza
- Correzione ipotiroxinemia gravidica

- Profilassi iodica universale
- Profilassi iodica preconcepimento

Conclusions: This study provides preliminary evidence that even mild iodine deficiency during pregnancy can have long-term adverse impacts on fetal neurocognition that are not ameliorated by iodine sufficiency during childhood. (*J Clin Endocrinol Metab* 98: 1954–1962, 2013)