GIAN CARLO DI RENZO

PROFESSOR

General Secretary of International Federation

of Gynecology and Obstetrics (FIGO)

University of Perugia

Director of Reproductive Health Center

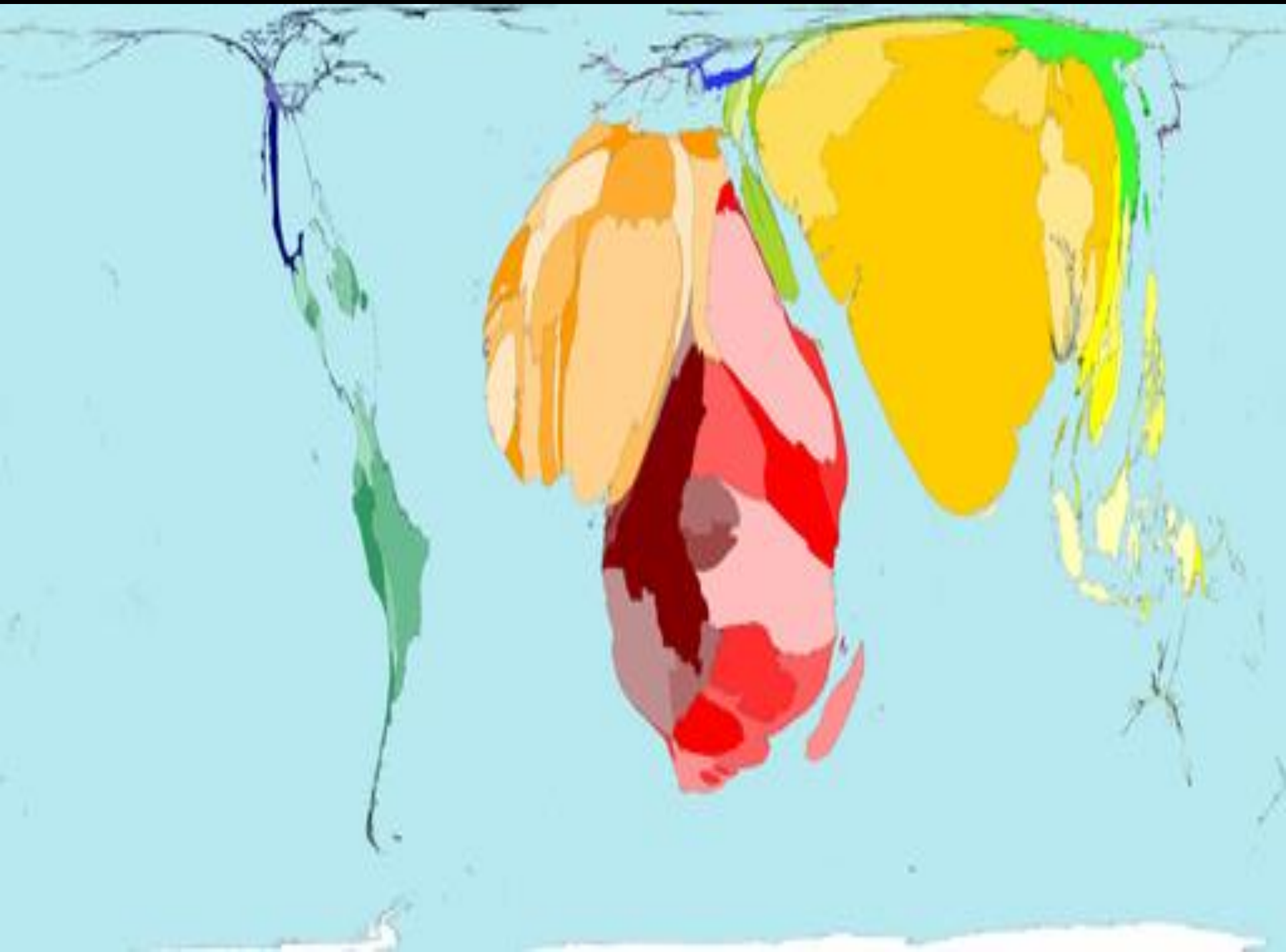
VIETNAM - FRANCE - ASIA - PACIFIC
CONFERENCE ON OBSTETRICS AND GYNECOLOGY
Ho Chi Minh City, May 19th - 20th, 2016

16th

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Good Clinical Practice Advice

G C DI RENZO, MD, PhD, FRCOG, FACOG, FICOG
HON GENERAL SECRETARY FIGO



INEQUITIES

International Federation of Gynecology and Obstetrics

FIGO Mission

- The International Federation of Gynecology and Obstetrics (FIGO) is a unique organization, being the only international professional body that brings together 130 obstetrical and gynecological associations from all over the world.

- FIGO is dedicated to the improvement of women's health and rights and to the reduction of disparities in health care available to women and newborns as well as to advancing the science and practice of obstetrics and gynecology. The organization pursues its mission through advocacy, programmatic activities, capacity strengthening of member associations and education and training.

Working Group on Best Practice in Maternal-Fetal Medicine

Chair: G C Di Renzo

Expert members:
E Fonseca, Brasil
E Gratacos, Spain
S Hassan, USA
M Kurtser, Russia
F Malone, Ireland
S Nambiar, Malaysia
M Sierra, Mexico
K Nicolaides, UK
H Yang, China

Expert members ex officio:
CN Purandare, FIGO
M Hod, EAPM
C Hanson, SM Committee
GH Visser, SM Committee
L Cabero, CBET Committee
V Berghella, SMFM
Y Ville, ISUOG
M Hanson, DOHaD
PP Mastroiacovo, Clearinghouse
JL Simpson, March of Dimes
D Bloomer, GLOWM

Working Group on the Challenges of Labour and Delivery

Chair: R Romero

Expert members:
D Farine, Canada
MT Gervasi, Italy
J M. Robson, Ireland
T Duan, China
S Rosales, Mexico
T Kimura, Japan
L Yeo, Korea-USA

Expert members ex officio:
C N Purandare, FIGO
G C Di Renzo, FIGO
M Stark, NESA
GH Visser, SM Committee
E Castelazo , CBET Committee
C Lees, RCOG
A Conde' Agudelo, NIH NICHD
D Bloomer, GLOWM

International Federation of Gynecology and Obstetrics
March of Dimes
Working Group on Preterm Birth Prevention

Chairs: J L Simpson
G C Di Renzo

Expert members:
Ernesto Castelazo
Mary D'Alton
Eduardo Fonseca
Chris Howson
Bo Jacobsson
James Martin
Jane Norman
T Y Leung

Expert members ex officio:
CN Purandare, FIGO
J Howse, March of Dimes
G Visser, SM Committee
D Bloomer, GLOWM
Jim Larson BCG
David Ferrero, BCG

International Federation of Gynecology and Obstetrics
GDM initiative

Chair: M Hod

Expert members:
Mukesh Agarwal
Blami Dao
Gian Carlo Di Renzo
Hema Divakar
Eran Hadar
Anil Kapur

Expert members ex officio:
CN Purandare, FIGO
GH Visser, SM Committee
D Ayres do Campo, SM Comm
L Cabero, CBET Committee
D Bloomer, GLOWM
R Fabienke, Novo Nordisk

Best practice advice

- ***Folic acid supplementation***
- ***Prediction and prevention of preterm birth***
- ***Non invasive prenatal diagnosis and testing***

Best practice advice

- *Thyroid diseases in pregnancy*
- *MgSO4 use in obstetrics*
- *Appropriate use of ultrasound in pregnancy*
- *Hyperglycemia and pregnancy*

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Preconceptional folic acid for the prevention of NTD

FIGO Recommendation Statement

Methods: a systematic review of the evidence on folic acid supplementation in women of childbearing age published, including review and peer-reviewed papers, government publications, and statements from others societies was used to develop a new clinical practice guideline for the International Federation of Gynecology and Obstetrics.

Objective: to provide information regarding the use of folic acid for the prevention of NTD, and also standardize strategies in the primary prevention of NTD providing an adequate orientation according to scientific bases for all childbearing women.

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Results

- Folic acid supplementation has been proven to be effective in the reduction of NTD.
- However, take into account that nearly 50% of pregnancies are unplanned, and about 5-20% of all pregnant women start folic acid before pregnancy.

- **the recommendation for preconceptional folic acid supplementation has to achieve both health workers and childbearing women.**

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Scientific evidence: Folic acid deficience and NTD

- Several RCT has demonstrated that periconceptional Folic Acid reduces the incidence or the recurrence .
- The folate concentration in the red cell is lower in women who has a fetus with NTD.

Reduction 72-85% on the prevalence

MRC – Vitamins study research group. Lancet, 1991; 338:131-7
Berry et al. N Engl J Med, 1999; 341: 1485-90.

FIGO

International Federation of Gynecology and Obstetrics Working Group on Best Practice on Maternal-Fetal Medicine

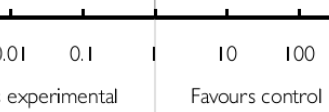
Supplementation with folic acid versus no treatment/other micronutrients/placebo for NTD

Study or subgroup	Folic acid n/N	treat/other MN/placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Czeizel 1994	0/2104	6/2052		14.4 %	0.08 [0.00, 1.33]
ICMR 2000	4/137	10/142		21.4 %	0.41 [0.13, 1.29]
Kirke 1992	0/172	4/192		9.3 %	0.12 [0.01, 2.29]
Laurence 1981	2/60	4/51		9.4 %	0.43 [0.08, 2.23]
MRC 1991	6/593	21/602		45.5 %	0.29 [0.12, 0.71]
Total (95% CI)	**3066**	**3039**		**100.0 %**	**0.28 [0.15, 0.52]**

Total events: 12 (Folic acid), 45 (No treat/other MN/placebo)

Heterogeneity: $Chi^2 = 1.79$, df = 4 (P = 0.77); $I^2 = 0.0\%$

Test for overall effect: Z = 4.05 (P = 0.000051)



Reduction of 72%

This review of five RCT, involving 6105 women (1949 with a Hx of a pregnancy affected by a NTD and 4156 with no Hx of NTDs), confirms that folic acid prevents the first and second time occurrence of NTDs.

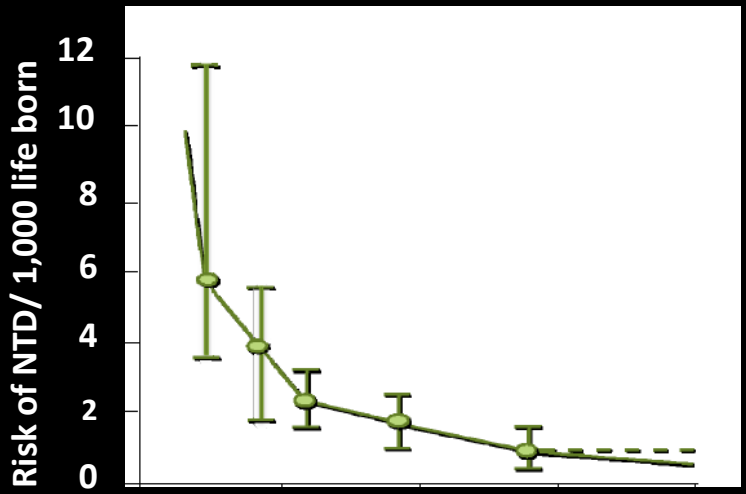
International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Scientific evidence: Folic acid deficience and NTD

- Several RCT has demonstrated that periconceptional Folic Acid reduces the incidence or the recurrence.
- The folate concentration in the red cell is lower in women who has a fetus with NTD.

Lower folate
the higher the NTD risk



Daly et al. JAMA, 1995; 274: 1698-702.

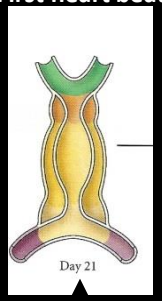
International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

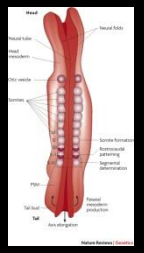
When

Before conception,
since a fertility control method is stopped
up to the end of the first trimester

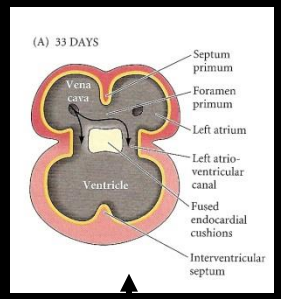
First heart beat

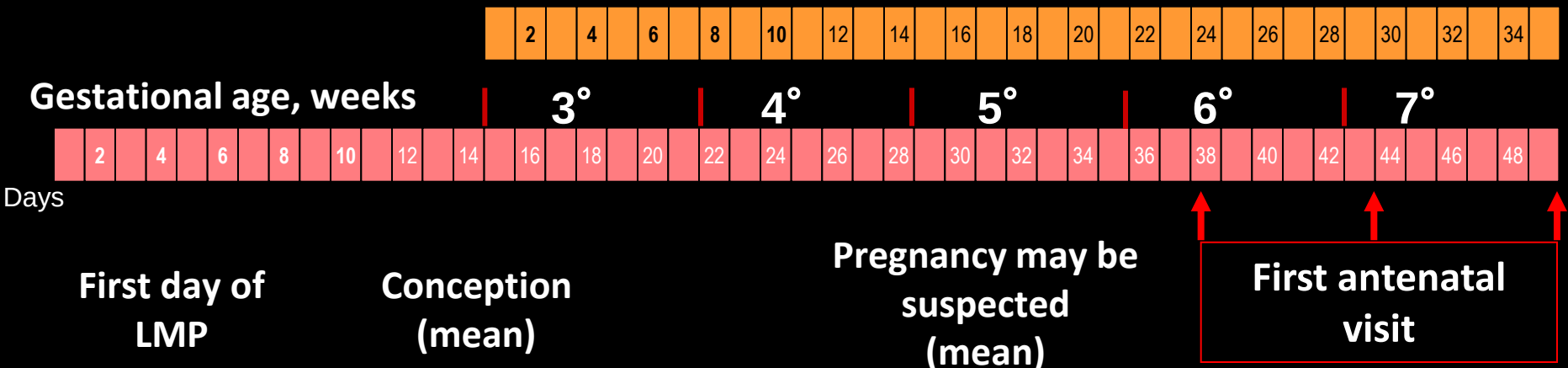


Neural tube closes



4-chamber





First day of LMP

Conception (mean)

Pregnancy may be suspected (mean)

First antenatal visit

- Up to 50% of pregnancies are unplanned,
- About 5-20% of all pregnant women start folic acid before pregnancy.

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Folic Acid in the strategy for NTD

- Nutritional guidance and food fortification
- Periconceptional supplementation
- Folic acid in association with pills

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

RDA (Recommended Dietary Allowance) for folate: 400µg daily

Nutritional guidance

- Natural form: folate
- Daily intake: 200µg
- Absortion of 50%: 100µg

Food fortification

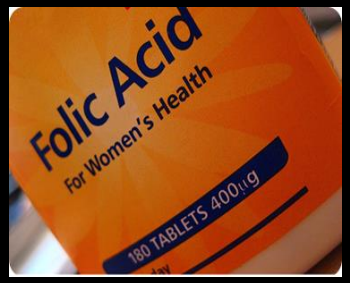
- Synthetic form: Folic Acid
- Fortification: 100 g of flour have 150µg folic acid
- 14 to 19% of women take lower than they needed.

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Fortification of flour with folic acid for the NTDs prevention

EE USP ENFERMAGEM



Prevalence of NTDs

- N=3.666.911 live birth
- Prior: 1.069 (0.57 per %°)
- After: 647 (0.37 per %°)

- Spina bifida 0.52 (0.45-0.59)
- Anencephaly 0.72 (0.67-0.91)
- Encephalocele 1.01 (0.76-1.36)

Global Reduction 35%

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

First:	RECOMMENDATION FOR LOW RISK POPULATION

All women who plans to become pregnant or all women at childbearing age without contraceptive method and who does not present risk factors for NTD utilize **400 micrograms (0.4mg)** of synthetic folic acid, beginning at least 30 days before the conception and to continue daily supplements throughout the first trimester of pregnancy.

Expert panels suggest that supplemental intake in this population should range from 400 µg to 800 µg, no more.

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Second: **RECOMMENDATION FOR INCREASING THE INTAKE OF FA**

All women in the reproductive age group should be advised about the benefits of folic acid supplementation during wellness visits (birth control renewal, Pap testing, yearly examination), especially if pregnancy is contemplated.

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Third:	RECOMMENDATION FOR HIGH RISK POPULATION

Women who have NTD-affected previous pregnancyshould be advised that synthetic folic acid supplementation at a dose of **4,000 mcg per day (4.0 mg)** is recommended. It should start at least 30 days before the conception and to continue daily supplements throughout the first trimester of pregnancy.

In this group, it would be important; if possible, preconception genetic counseling with a physician specialized in medical genetics.

FIGO

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Moderately High Intake of Folic Acid Has a Negative Impact on Mouse Embryonic Development

Methods: Pregnant mice with or without a deficiency in MTHFR were fed a control diet (recommended FA intake of 2 mg/kg diet for rodents) or an FA-supplemented diet (FASD; 10-fold higher than the recommended intake [20 mg/kg diet]). At E14.5, mice were examined for embryonic loss and growth retardation, and hearts were assessed for defects and for ventricular wall thickness.

Results: Higher doses of FA was associated with embryonic loss, embryonic delays, higher incidence of ventricular septal defects, and thinner left and right ventricular walls, compared to mothers fed control diet.

(a)Mikael, LG et al. **Birth Defects Research,** 2013: 97:47-52.

(b) Pickell, L et al. **Birth Defects Research,** 2011: 91:8-19

FIGO

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

JAMA Pediatrics
Formerly *Archives of Pediatrics & Adolescent Medicine*

Advanced Search

Home | Current Issue | All Issues | Online First | Collections | CME | Multimedia | Quizzes | For Authors | Subscribe

AIM: To examine the association between the use of high dosages of FA supplements during pregnancy and child neuropsychological development after the first year of life.

RESULTS: 57.3% did not reach the recommended dosages of FA supplements (400 µg/d); 25.2% women took **>1000 µg/d of FA** supplements and 3.5% consuming **>5000 µg/d**.

- Children whose mothers used FA supplement dosages **>1000 µg/d** during pregnancy had a **statistically significantly lower mean psychomotor scale score** than children whose mothers used a recommended dosage of FA supplements (400-1000 µg/d).
- Increased risk of delayed psychomotor development (psychomotor scale score <85) was also evident among children whose mothers took FA supplement dosages **>5000 µg/d**, although the association was not statistically significant (OR = 1.59; 95% CI, 0.82-3.08).

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Additional guidance

Pregnant women taking a multivitamin with folic acid supplement should be advised not to take more than 1 daily dose of vitamin supplement, as indicated on the product label.

Considering the high frequency of unplanned pregnancies worldwide, the international Federation of Gynecology and Obstetrics encourages all efforts of public agencies worldwide towards the development of more comprehensive programs to fortify food with synthetic folic acid and more vigilance in monitoring these programs.

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Cervical length and Progesterone for the Prediction and Prevention of Preterm Birth

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

Objective: To develop a clinical practice recommendation for the International Federation of Gynecology and Obstetrics regarding the screening and prevention of preterm birth.

Methods: A systematic review of the published evidence on preterm birth prevention with the use of vaginal progesterone and progestogens, including review and peer-reviewed papers, government publications, and society statements was conducted.

1. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. N Engl J Med 2007;357:462-69;
2. Hassan SS, Romero R, Vidyadhari D, et al. Ultrasound Obstet Gynecol 2011;38:18-31;
3. Romero R, Nicolaides K, Conde-Agudelo A, et al. Am J Obstet Gynecol 2012;206:124 e1-19
4. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Am J Obstet Gynecol 2003;188:419-24;
5. Maher MA, Abdelaziz A, Ellaithy M, Bazeed MF. Acta Obstet Gynecol Scand 2013;92:215-22.
6. Cahill AG, Odibo AO, Caughey AB, et al. Am J Obstet Gynecol 2010;202:548 e1-8.
7. Werner EF, Han CS, Pettker CM, et al. Ultrasound Obstet Gynecol 2011;38:32-37.
8. Miller ES, Grobman WA. Am J Obstet Gynecol. 2013 Dec;209(6):546.e1-6.
9. Campbell S. Ultrasound Obstet Gynecol 2011;38:1-9.
10. Berghella V. Obstet Gynecol Surv 2012;67:653-8.
11. Combs CA. Am J Obstet Gynecol 2012;206:101-3.

FIGO

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice

International Journal of Gynecology and Obstetrics xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

www.figo.org

FIGO COMMITTEE REPORT

Best practice in maternal–fetal medicine☆

FIGO Working Group on Best Practice in Maternal–Fetal Medicine [1]

Gian Carlo Di Renzo (Chair), S Arulkumaran, E Fonseca, S Hassan, M Kurtzer, M Leis, N Malhotra, P Mastroiacovo, K Nicolaides, M Hod, Y Ville, L Cabero, C Hanson, J Simpson, H Yang

International Journal of Gynecology and Obstetrics: 128(2015)80-82

Cervical length screening and progesterone for the prevention of preterm birth

- Sonographic Cervical length screening in all women 19 – 23 6/7 weeks using transvaginal ultrasound
- Women with a cervical length ≤ 25 mm should be treated with daily vaginal progesterone for the prevention of preterm birth and neonatal morbidity
- Progesterone formulation – 200 mg (pm) or 90 mg (am) daily
- Universal cervical length screening and vaginal progesterone is a cost-effective model for the prevention of preterm birth
- In cases in which a transvaginal ultrasound is not available, other methods to assess cervical length can be considered

International Journal of Gynecology and Obstetrics: 128(2015)80-82

Screening for chromosomal abnormalities and non invasive prenatal diagnosis and testing

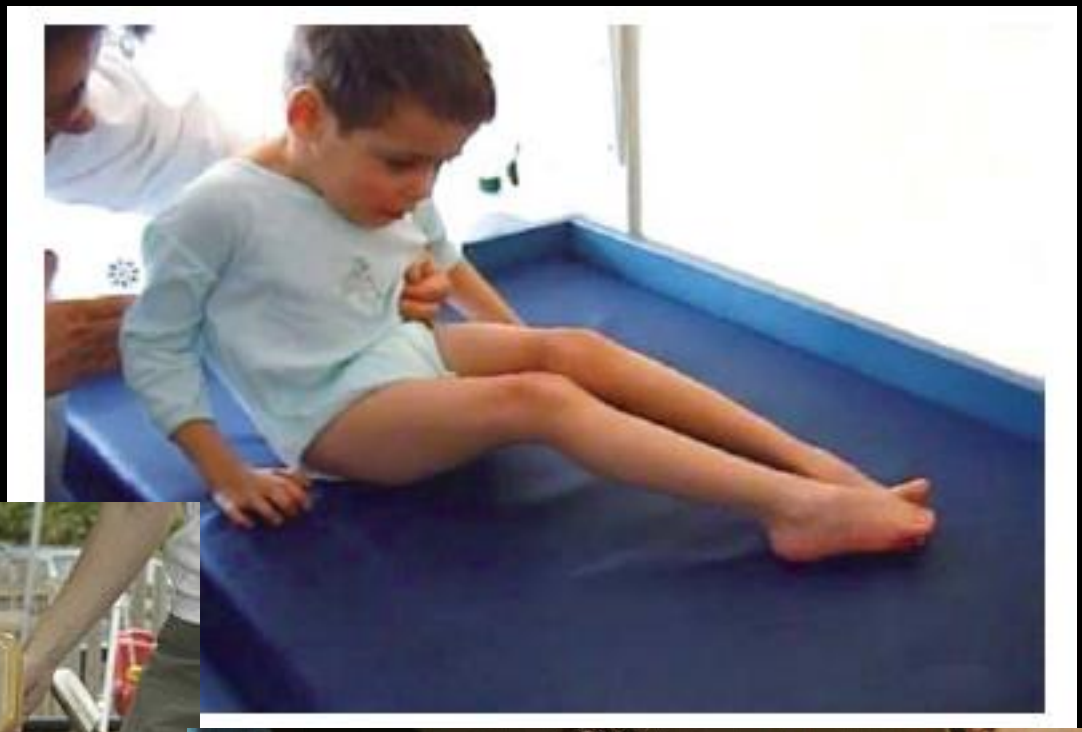
- Maternal age has a low performance as a screening for fetal chromosomal abnormalities with a DR of 30-50% for FPR of 5-20%. Therefore, invasive testing for diagnosis of fetal aneuploidies should not be carried out by taking into account only maternal age.
- First-line screening for trisomies 21, 18 and 13 should be achieved by the combined test, which takes into account maternal age, fetal nuchal translucency (NT) thickness, fetal heart rate (FHR) and maternal serum free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A). The combined risk test has a DR of 90% for trisomy 21 and 95% for trisomies 18 and 13, at FPR of about 5%.

- The combined test could be improved by assessing additional ultrasonographic markers, including the fetal nasal bone and Doppler assessment of the fetal ductus venosus flow and tricuspid flow. If all those markers are included the DR is increased to more than 95% and the FPR decreased to less than 3%.
- Screening by analysis of cfDNA in maternal blood has a DR of 99% for trisomy 21, 97% for trisomy 18 and 92% of trisomy 13, at a total FPR of 0.4%.

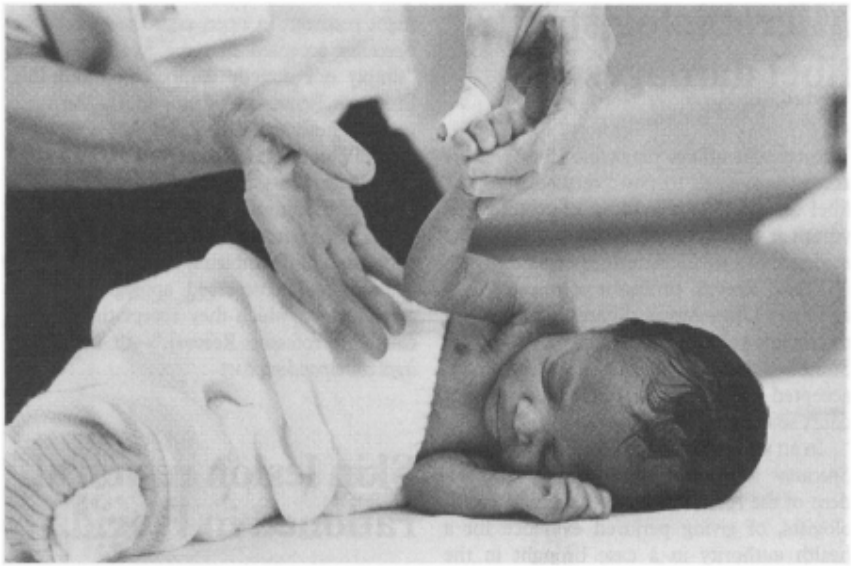
- Clinical implementation of cfDNA testing should preferably be in a contingent strategy based on the results of first-line screening by the combined test at 11-13 weeks' gestation. In this case, we recommend the strategy below:
  - Combined test risk over 1 in 100: the patients can be offered the options of cfDNA testing or invasive testing.
  - Combined test risk between 1 in 101 and 1 in 2,500: the patients can be offered the option of cfDNA testing
  - Combined test risk lower than 1 in 2,500: there is no need for further testing.

PRETERM BIRTH and CEREBRAL PALSY

- HOW BIG IS THE PROBLEM?
- CP 2-2.5 per 1000 LB
- Prematurity,LBW
- 30% attributed to prematurity



Prenatal magnesium sulphate cuts risk of cerebral palsy



SAM TANNER

Very low birthweight babies are at risk of cerebral palsy

Giving magnesium sulphate during pregnancy to women at risk of delivering very low birth weight babies reduces the risk of the offspring developing cerebral palsy and mental retardation, according to a study published this week.

American researchers followed up developmental outcome in over 500 very low birth weight babies (less than 1500 g) born in the metropolitan area of Atlanta who survived infancy. Infant mortality was also investigated in an additional group of 1097 very low birth weight babies born in Georgia over a two year period (*JAMA* 1996;**276**:1805-10).

Hospital medical records were checked to see if mothers had been given magnesium sulphate before delivery. Dr Diana Schendel, from the division of birth defects and developmental disabilities at the Centers for Disease Control and Prevention in Atlanta, reported: "Only one of the magnesium sulphate exposed children had cerebral palsy, corresponding to a 90% lower prevalence compared to those not exposed. Two had mental retardation, giving a 70% risk reduction." Reassuringly, magnesium sulphate was not found to increase the risk of mortality in exposed children.

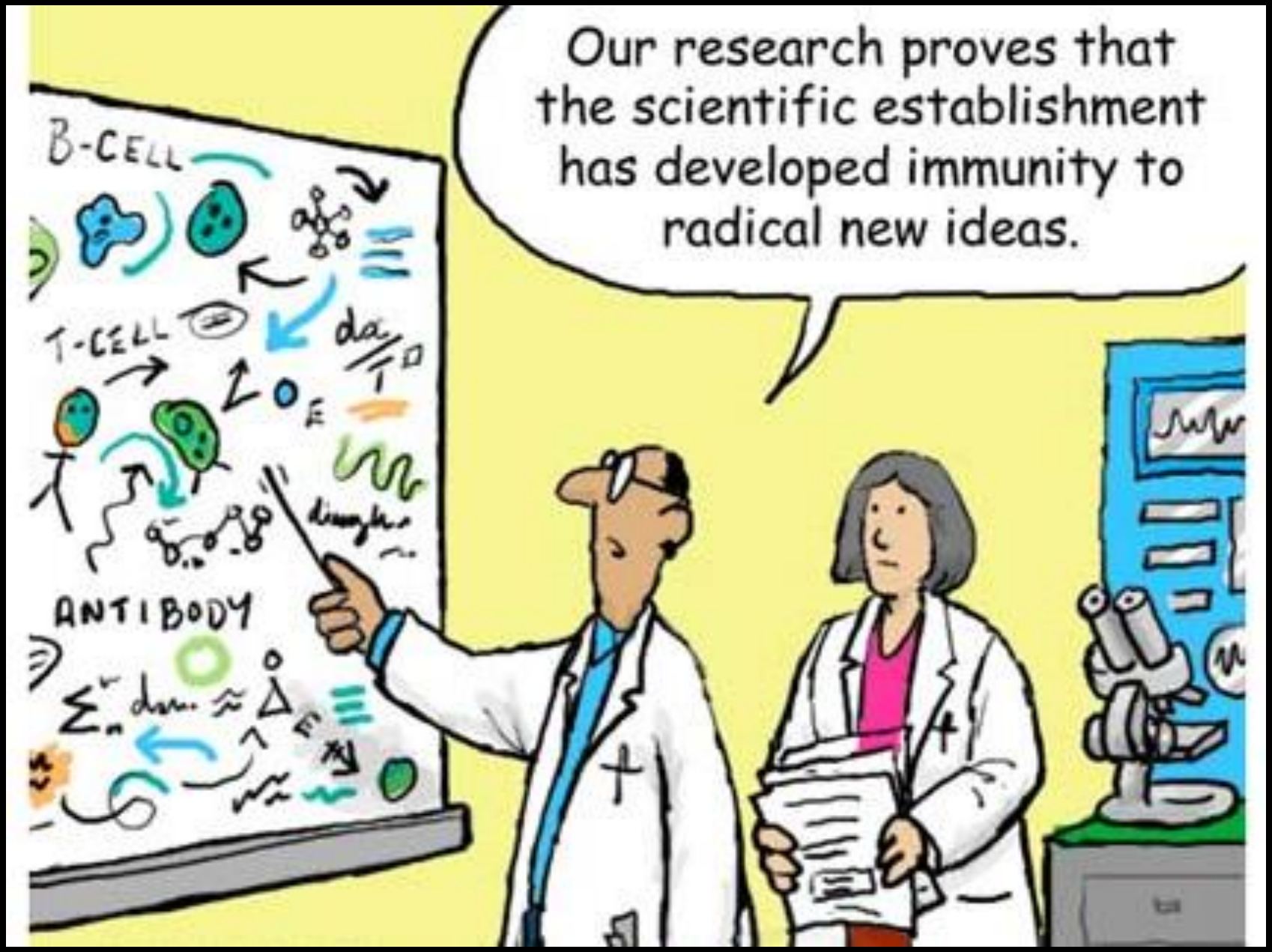
The authors state: "The possible public health benefit conferred by a protective effect of prenatal magnesium sulphate exposure

infants were exposed prenatally to magnesium sulphate, with 52% of mothers having pre-eclampsia or eclampsia.

In an editorial accompanying the Atlanta study, Dr Karin Nelson from the neuroepidemiology branch of the National Institutes of Health reports that several randomised trials are now under way in the United States. An international randomised trial in which magnesium sulphate is given to term babies with perinatal asphyxia is also about to restart in several countries, including the United Kingdom, after having been halted because babies were inadvertently given too high a dose of the drug.

reported their research in *Nature Medicine* (1996:**2**:1382-5). They caused severe stress in a group of mice by forcing them to swim for eight minutes and then injected them with pyridostigmine. The drug was found in the brain cells in the mice in the experimental group but not in those in a comparable control group. After this surprising finding, the researchers tested other substances, including dyes, and these too entered the brain in stressed animals.

The brain is unique among organs in that, due to an elaborate membrane structure, few chemicals have been known to pass into it from the blood. Pyridostigmine, an


Our research proves that the scientific establishment has developed immunity to radical new ideas.
B-CELL
T-CELL
ANTIBODY

1995

- Nelson and Grether
- BW < 1500g
- 150,000 children up to age 3
- $MgSO_4$ exposed vs non exposed
- 7% vs 36% CP (OR 0.14, 95% CI 0.05-0.51)

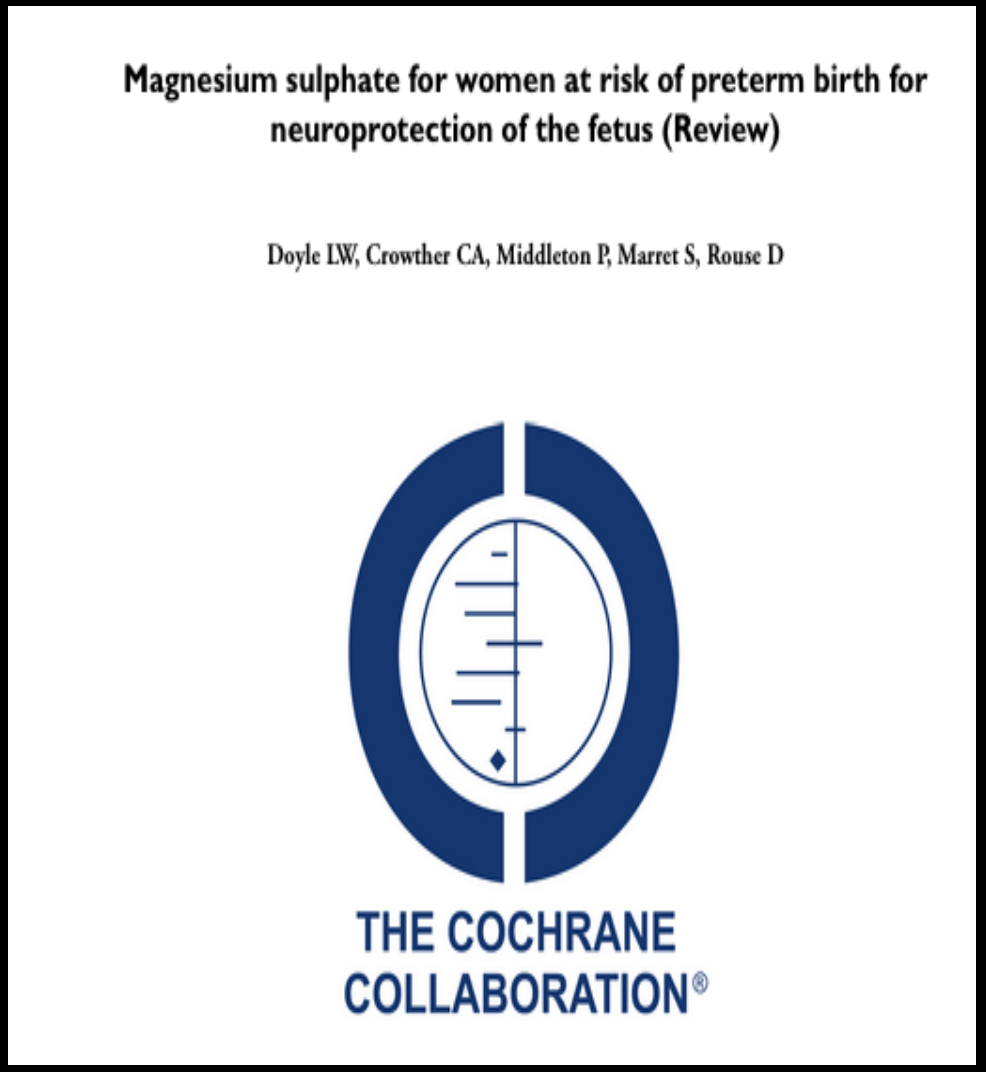
- Animal studies followed
- Human trials started

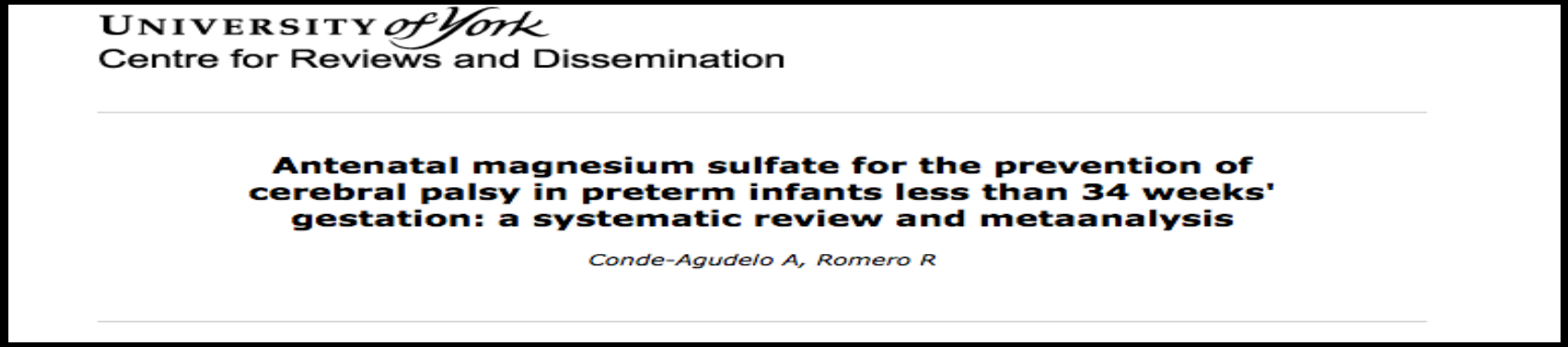
RCTS

TRIAL	Sample size	Gestational age	Trial Intent	Outcomes studied
ACTOMgSO4 2003	1062	< 30 weeks	Neuro protection	Mortality, CP, both
PREMAG 2007	573	< 33 weeks	Neuro protection	Mortality, US cranial abn
BEAMS 2008	2241	< 32 weeks	Neuro protection	Mortality by 1 yr,mod to severe CP at >2yrs
MAGPIE 2002	10,141 (2895)		Preclampsia	Disability at 18 mths
MagNET 2002	149	24-33 weeks	PTL or PPROM	Adverse outcomes (mortality, IVH,PVL,CP)

Meta analysis

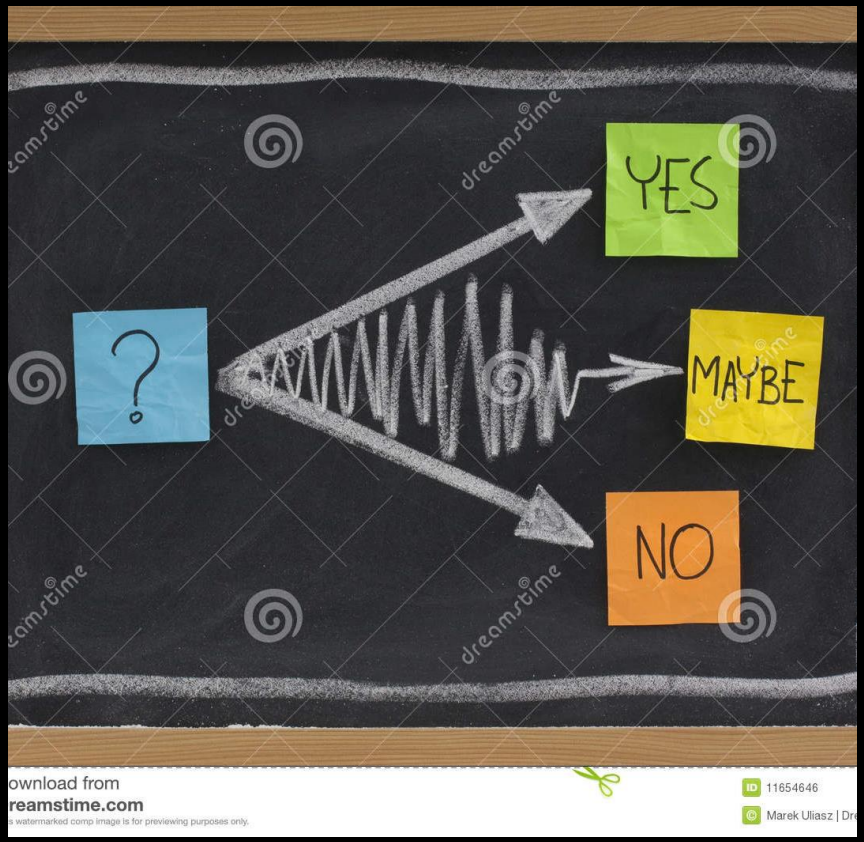
- 2009
- 5 RCTs, 6145 babies
- CP RR 0.68 (5)
- GMD RR 0.61 (4)
- No significant paed mortality, neurologic impairment, mat complications
- NNT 63





- No difference for primary outcome of death or CP
- Combined death and CP RR 0.85 (3)
- CP any severity RR 0.70 (5) mod – severe RR 0.60
- Similar when results for under 30 weeks
- NNT 52
- No effect on mortality

WHY THE HESITATION ?



- We are not convinced
- Trial sequential analysis
- Reluctance to change practice
- Ignorance
- Resource limitations
- Too many unanswered questions?

DOSAGES?

- Still no consensus

- 5 trials- 5 regimens
- Suggestion of increased mortality with higher dosage used for tocolysis
- Similar benefit from lower dosages

No consensus

REGIMENS?

Obstet Gynecol. 2014 Oct;124(4):749-55. doi: 10.1097/AOG.0000000000000467.

Association of duration of neuroprotective magnesium sulfate infusion with neonatal and maternal outcomes.

McPherson JA[1], Rouse DJ, Grobman WA, Palatnik A, Stamilio DM.

BJOG. 2014 Apr;121(5):595-603. doi: 10.1111/1471-0528.12535. Epub 2014 Jan 6.

Maternal adverse effects with different loading infusion rates of antenatal magnesium sulphate for preterm fetal neuroprotection: the IRIS randomised trial.

Bain ES[1], Middleton PF, Yelland LN, Ashwood PJ, Crowther CA.

Reasonable to use the lower dosage 4g bolus followed by 1-2 g /hour up to 24 hours

GESTATION?

Table 4a. Subgroup analyses by gestational age at randomization: neuroprotective trials only[35–38]

	RR (95% CI)		NNT to prevent harm		
Weeks	Death or CP	CP	Death or CP	CP	Trials, n, infants, n
<34	0.85 (0.74 to 0.98)	0.71 (0.55 to 0.91)	43	53	5 trials, 6145 infants
<32	0.86 (0.74 to 1.00)	0.68 (0.52 to 0.91)	43	50	3 trials, 3981 infants
<30*	0.87 (0.74 to 1.03)	0.69 (0.48 to 0.99)	36	53†	3 trials, 2475 infants
<28*	0.95 (0.74 to 1.22)	0.45 (0.23 to 0.87)	91	30	1 trial, 938 infants

* Includes the <28 week subgroup of Rouse et al.[38] which had women as the denominator.

† Inclusion of only the Crowther et al.[35] trial and exclusion of the BEAM data (Rouse et al.[38]) give an NNT of 24.

NNT increases with gestation

Table 4b. Subgroup analyses by gestational age at randomization: all trials[26,35-38,41]

	RR (95% CI)		NNT to prevent harm		
Weeks	Death or CP	CP	Death or CP	CP	Trials, n, infants, n
<34	0.94 (0.78 to 1.12)	0.68 (0.54 to 0.87)	105	63	5 trials, 6145 infants
<32	0.95 (0.76 to 1.18)	0.69 (0.52 to 0.91)	71	56	3 trials, 3981 infants
<30*	0.97 (0.78 to 1.21)	0.70 (0.49 to 0.99)	71	56†	3 trials, 2475 infants
<28*	0.95 (0.74 to 1.22)	0.45 (0.23 to 0.87)	91	30	1 trial, 938 infants

* Includes the <28 week subgroup of Rouse et al.,[38] which had women as the denominator.

This also includes the <30 week subgroup data provided by the MAGPIE trial.

† In the Cochrane review,[34] the <30 week subgroup did not include the BEAM trial data for <28 week[38] and the NNT was 50.

GESTATION

- **What about > 34 weeks? Or > 37 weeks?**

- **Reasonable to use where it affords the greatest benefit without potentially overexposing women at later gestations**

STUDY PROTOCOL Open Access

Magnesium sulphate at 30 to 34 weeks' gestational age: neuroprotection trial (MAGENTA) - study protocol

Caroline A Crowther[1,2*], Philippa F Middleton[1], Dominic Wilkinson[1], Pat Ashwood[1], Ross Haslam[2,3] and for the MAGENTA Study Group

Recommendations from FIGO MFM Working Group

1. ***For imminent preterm birth*** **which is either active labor diagnosed with or without rupture of membranes or elective delivery for maternal or fetal concerns, *antenatal magnesium sulphate should be considered for fetal neuroprotection*.**
2. **Although there is controversy about the upper gestational age*, antenatal magnesium sulphate should be considered from viability until 31 week + 6 days gestation.***
3. ***Magnesium sulphate should be discontinued*** **if delivery is no longer imminent or after a maximum of 24 hours of therapy.**

Recommendations from FIGO MFM Working Group

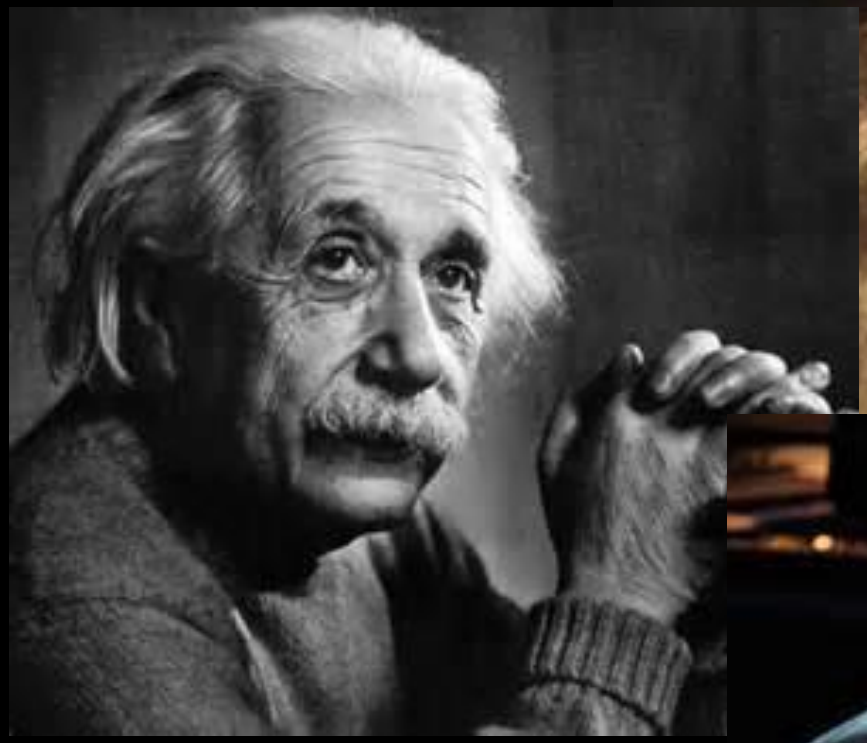
- **Magnesium sulphate should be administered as a *4g loading dose over 30 minutes*, ideally 4-6 hours before delivery followed by an infusion *of 1g/hour until delivery* occurs. However there still may be benefit if given less than 4 hours prior to delivery.**
- **There is insufficient evidence for use of a repeat course of antenatal magnesium sulphate for fetal neuroprotection.**
- **Delivery should not be delayed in order to administer antenatal magnesium sulphate if there are maternal or fetal indications for emergency delivery.**

RECOMMENDATIONS

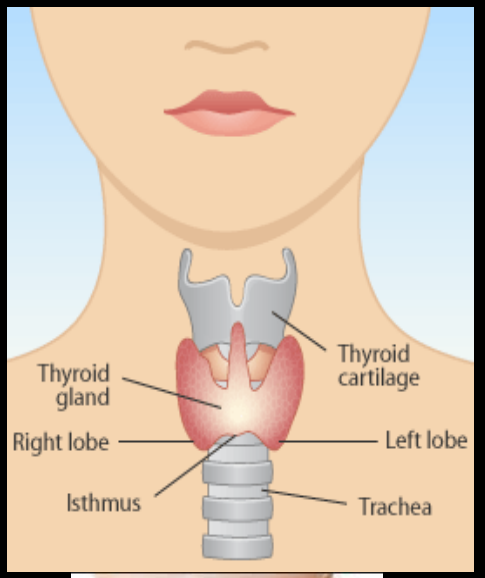
- **When magnesium sulphate is given for fetal neuroprotection, maternity care providers should use *existing protocols to monitor women for signs of toxicity as those used in cases of pre eclampsia/eclampsia.***
-
- **Neonatologists should be alerted to assess neonates for hypotonia and/or apnea as therapy with magnesium sulphate has the potential to cause hypocalcemia.**

CONCLUSION

CONCLUSION



Thyroid Gland



One of the largest endocrine gland

2 inch long, Butterfly shaped gland

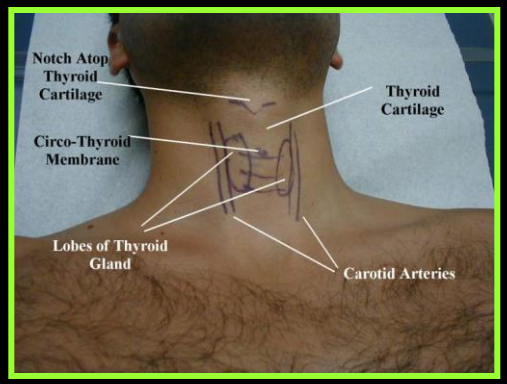
Located front of the neck, below the larynx

It has two lobes (Right & Left)

Average weight 25-30g in adults (slightly more in women)

The thyroid makes two thyroid hormones

- **Thyroxine (T4)**
- **Triiodothyronine (T3)**

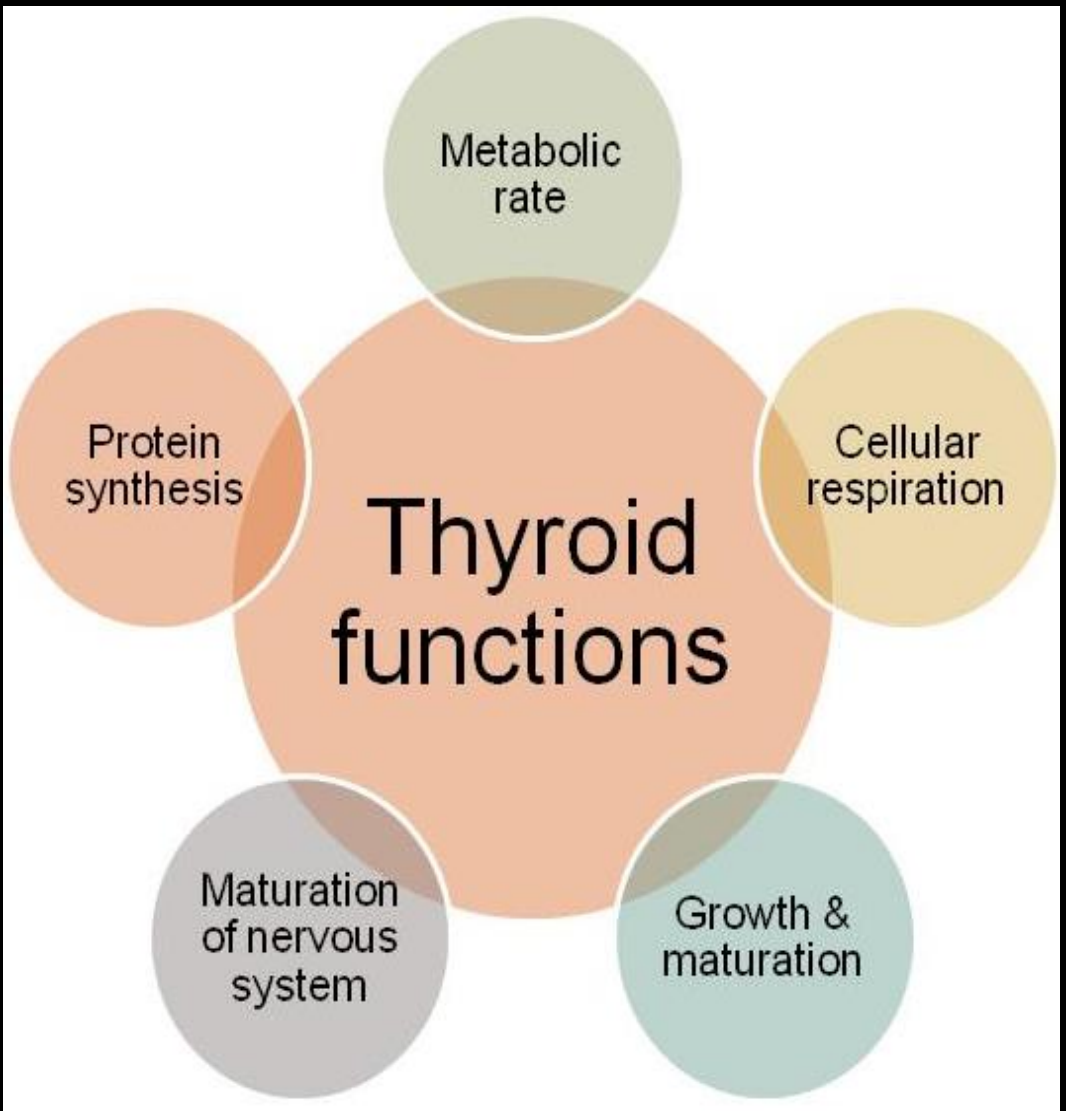


International Journal of Health Sciences & Research.2013;3(5):29

Thyroid Gland Functions

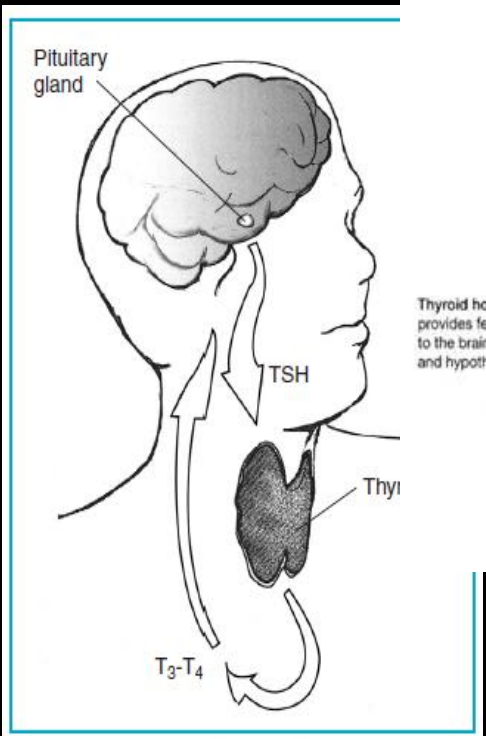
One of the largest endocrine gland The thyroid makes two thyroid hormones

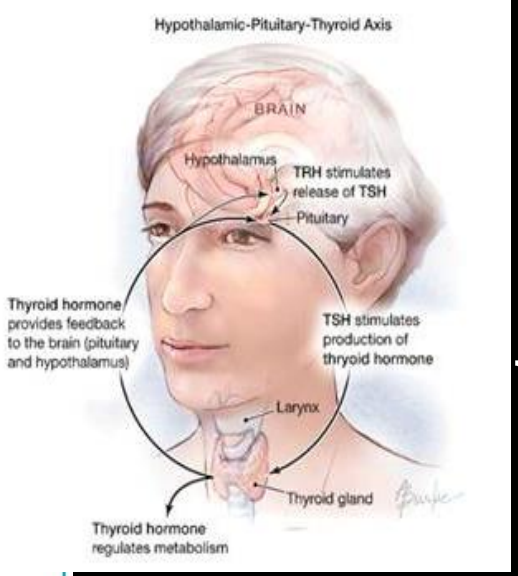
- **Thyroxine (T4)**
- **Triiodothyronine (T3)**

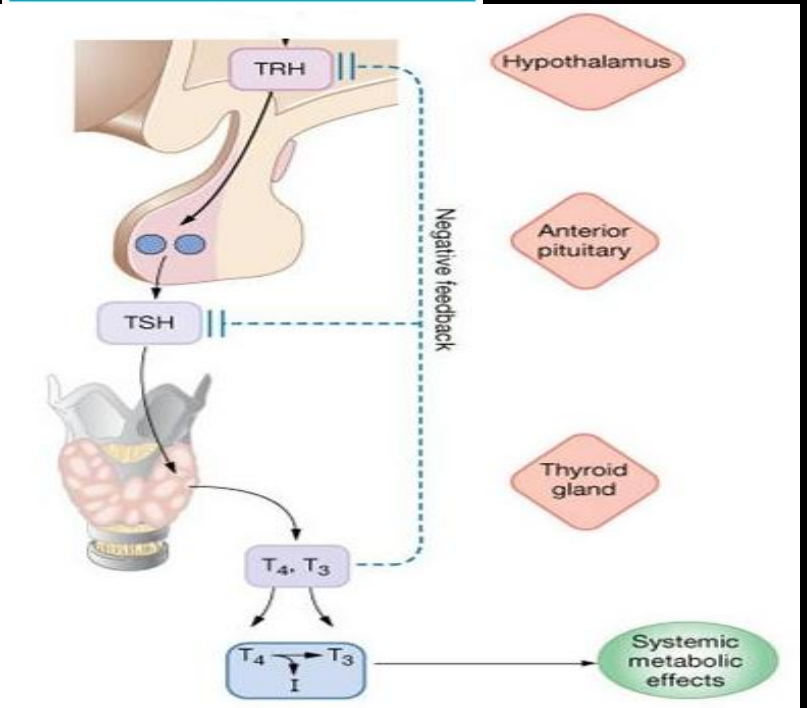


MOST OF FUNCTION DUE TO T3

Growth & development
Increasing rate of metabolism
Increase metabolic rate in CVS → blood flow
Regulating cerebral conducion in cns
Sleep
Lipid metabolism







Points to be remembered....

When thyroid hormone levels in the blood are low, the pituitary releases more TSH.
(↓ T4 & T3 ---↑ TSH)

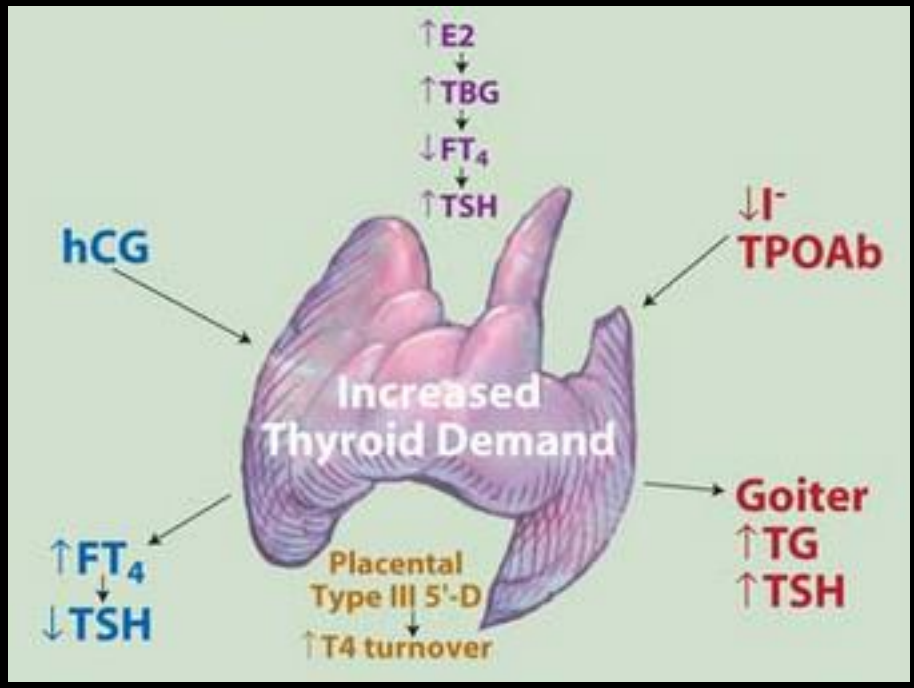
When thyroid hormone (T4, T3) levels are high, the pituitary decreases TSH production.
(↑ T4 & T3 --- ↓ TSH)

Increased TSH levels indicates.....
Pituitary gland working extra hard to maintain normal circulating thyroid hormones !

Early Pregnancy

Serum Thyrotropin level decreases

Weak TSH effect of HCG
'Spill over'
Increase in free Thyroxine



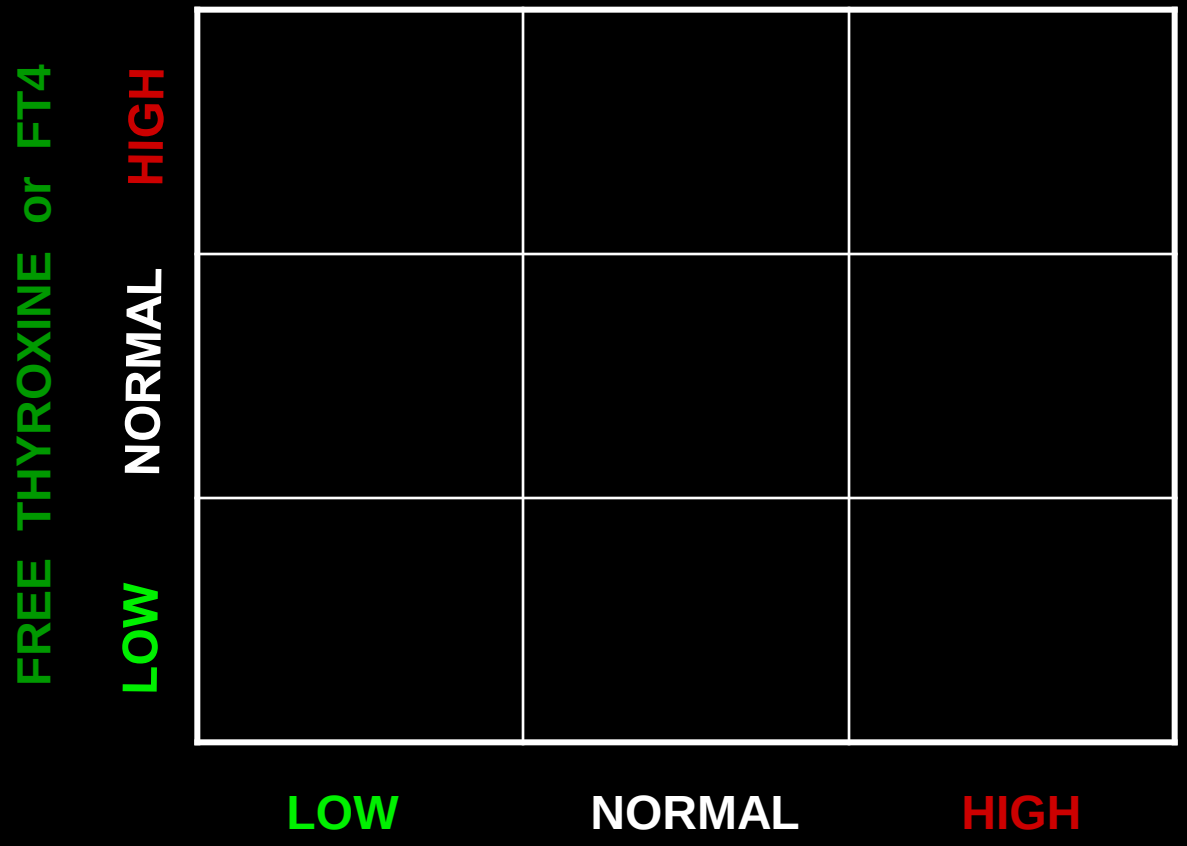
1.Lazarus JH. *British Medical Bulletin.* 2010;1-12.
2.Galofre JC. *J Womens Health (Larchmt).* 2009;18(11):1847-185
3.Thyroid disease and pregnancy. American Thyroid Association website

The Nine Square Game

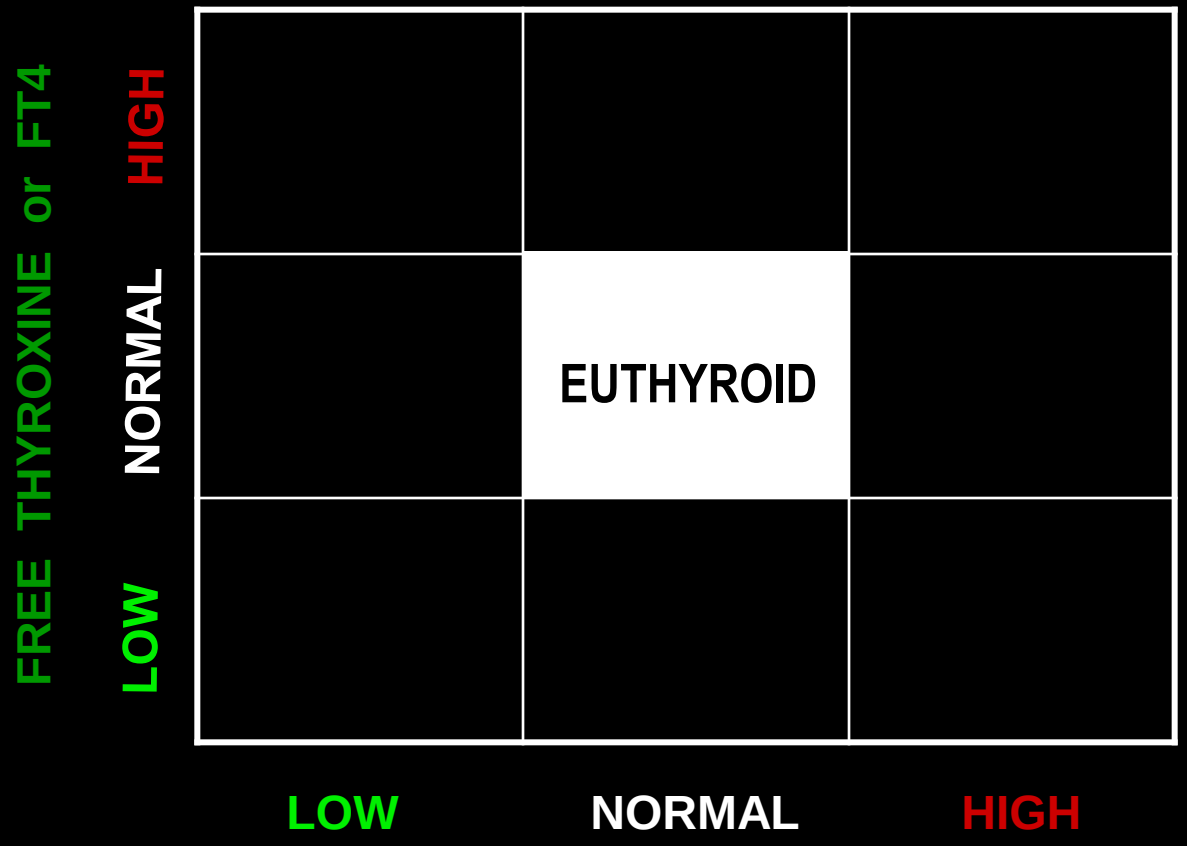
To evaluate our Thyroid patient

As per the AACE and ITS Guidelines

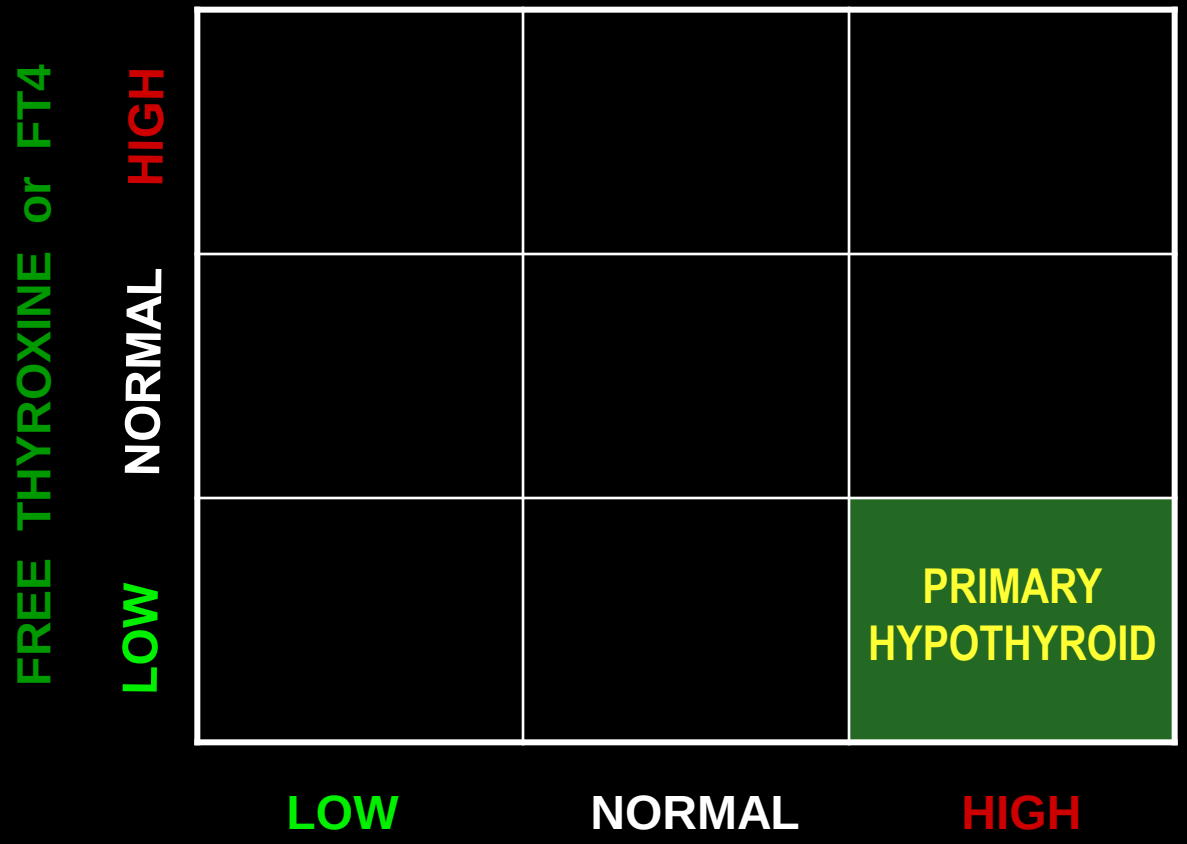
BASIC THYROID EVALUATION



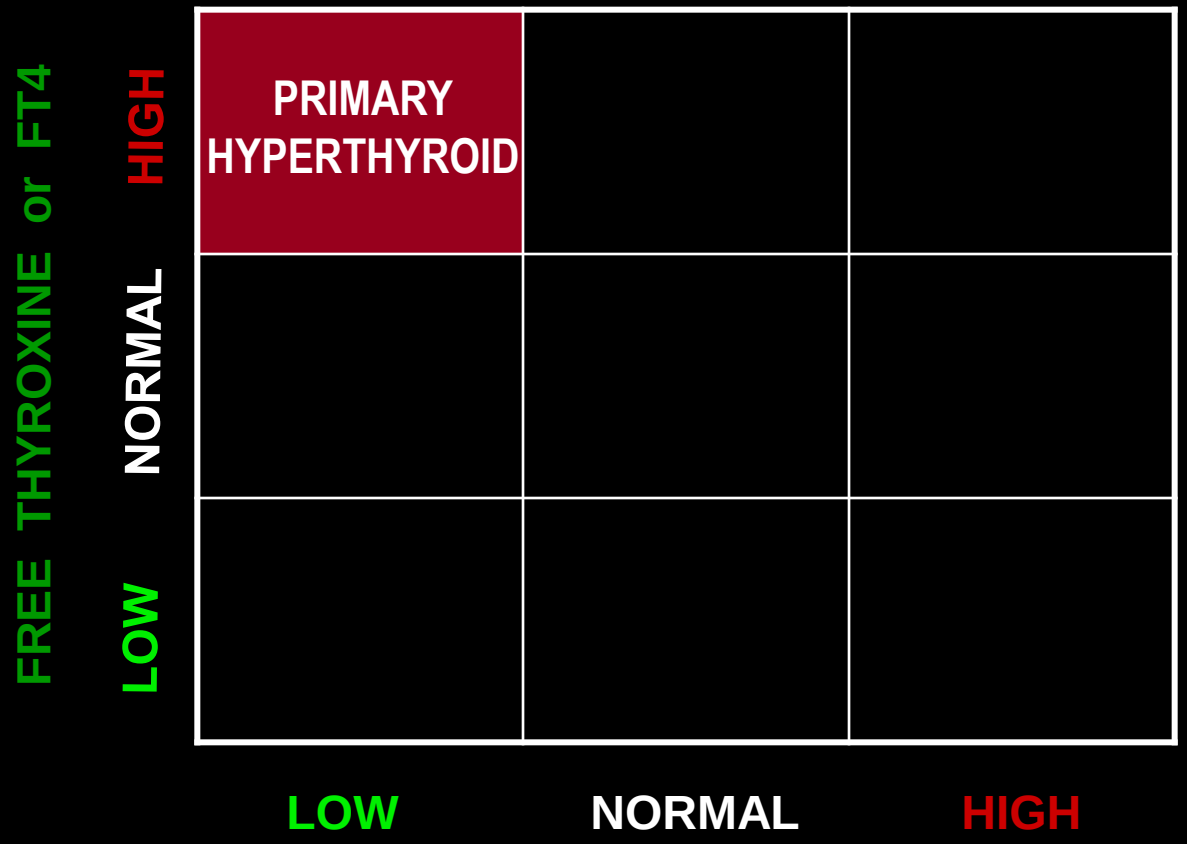
BASIC THYROID EVALUATION



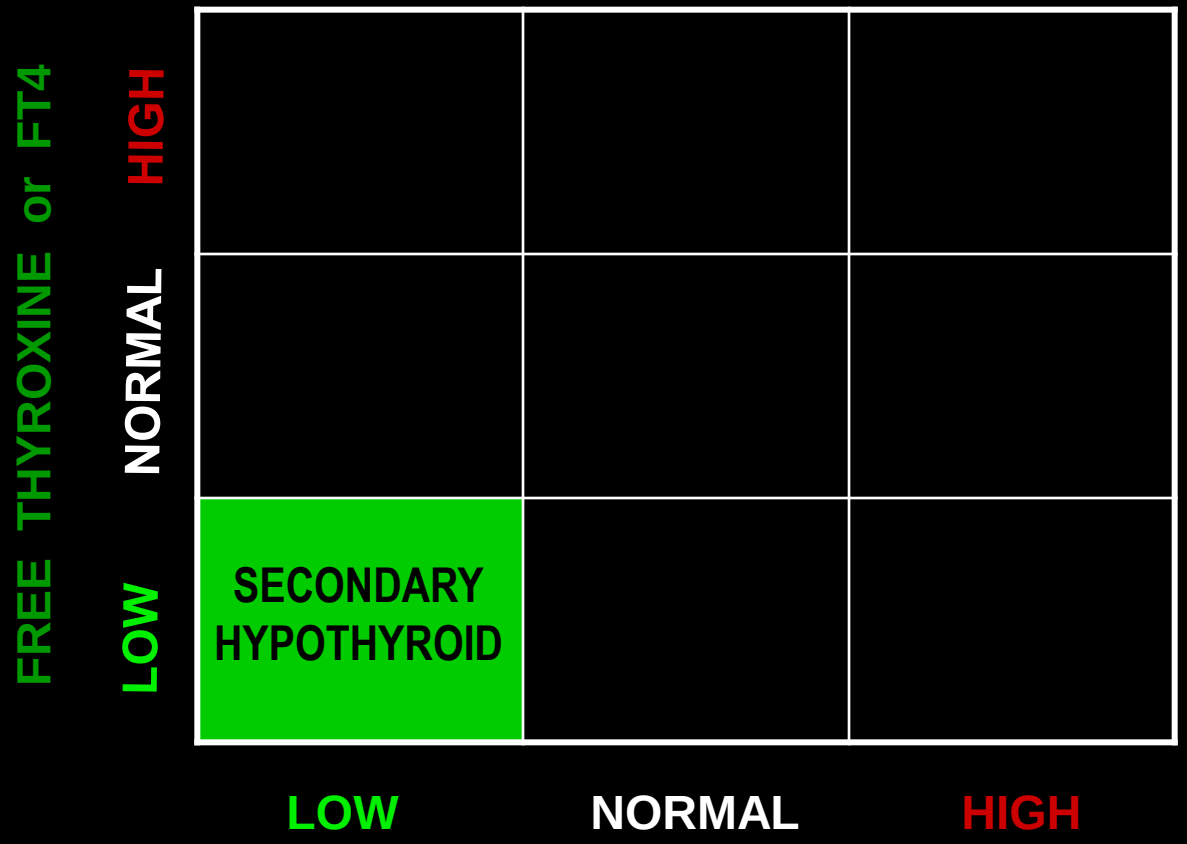
BASIC THYROID EVALUATION



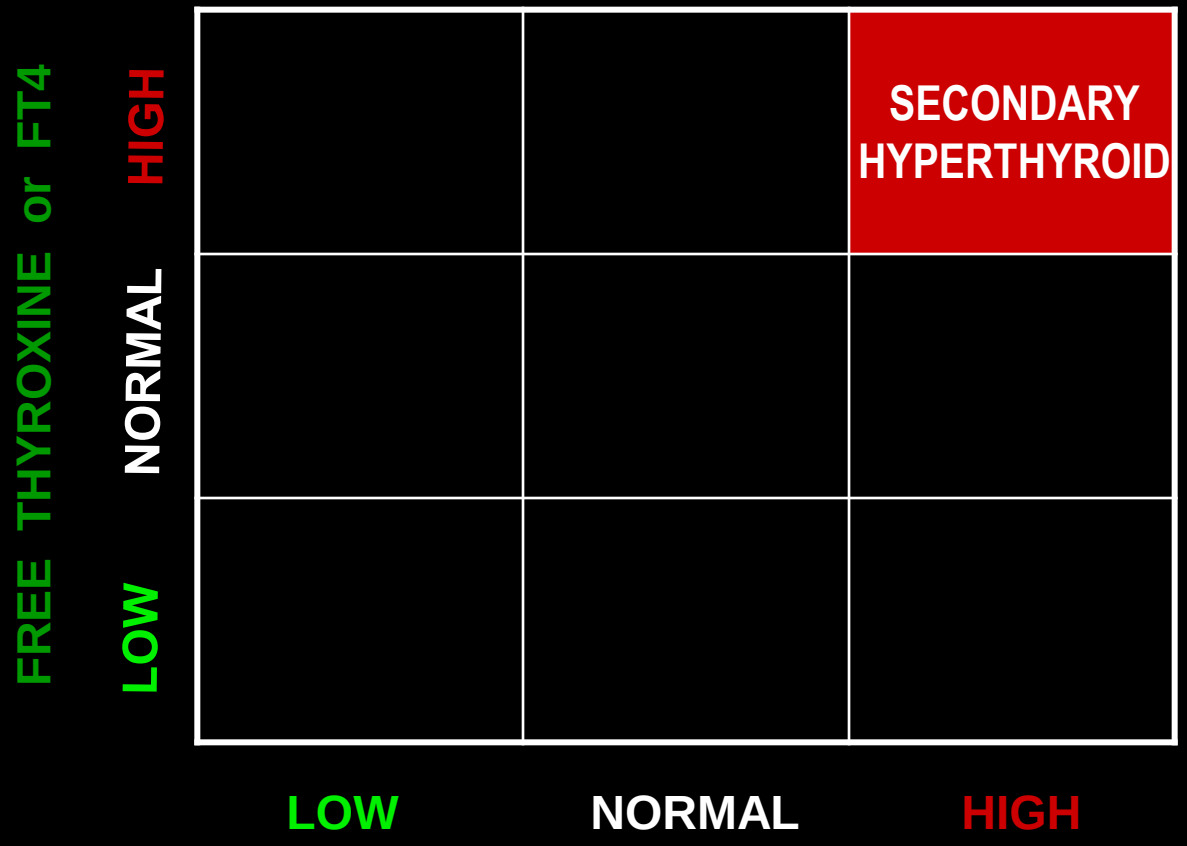
BASIC THYROID EVALUATION



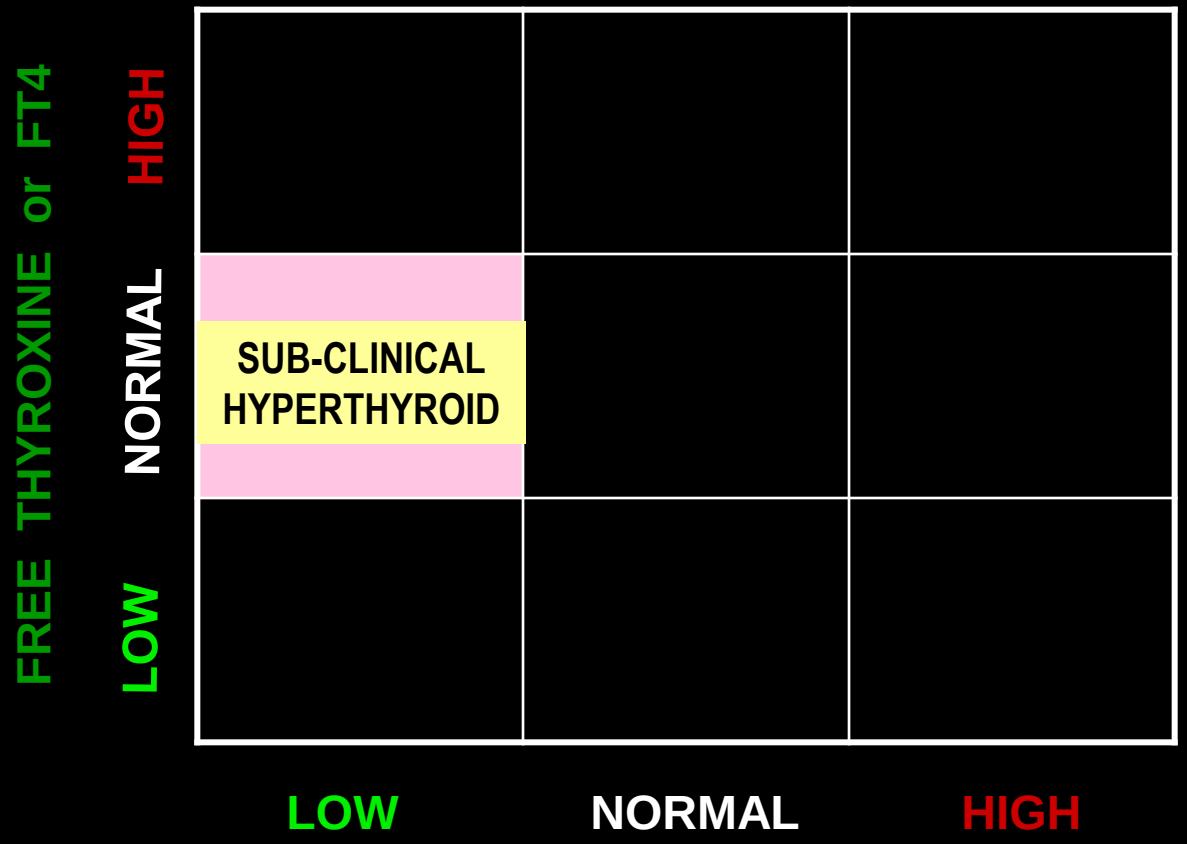
BASIC THYROID EVALUATION



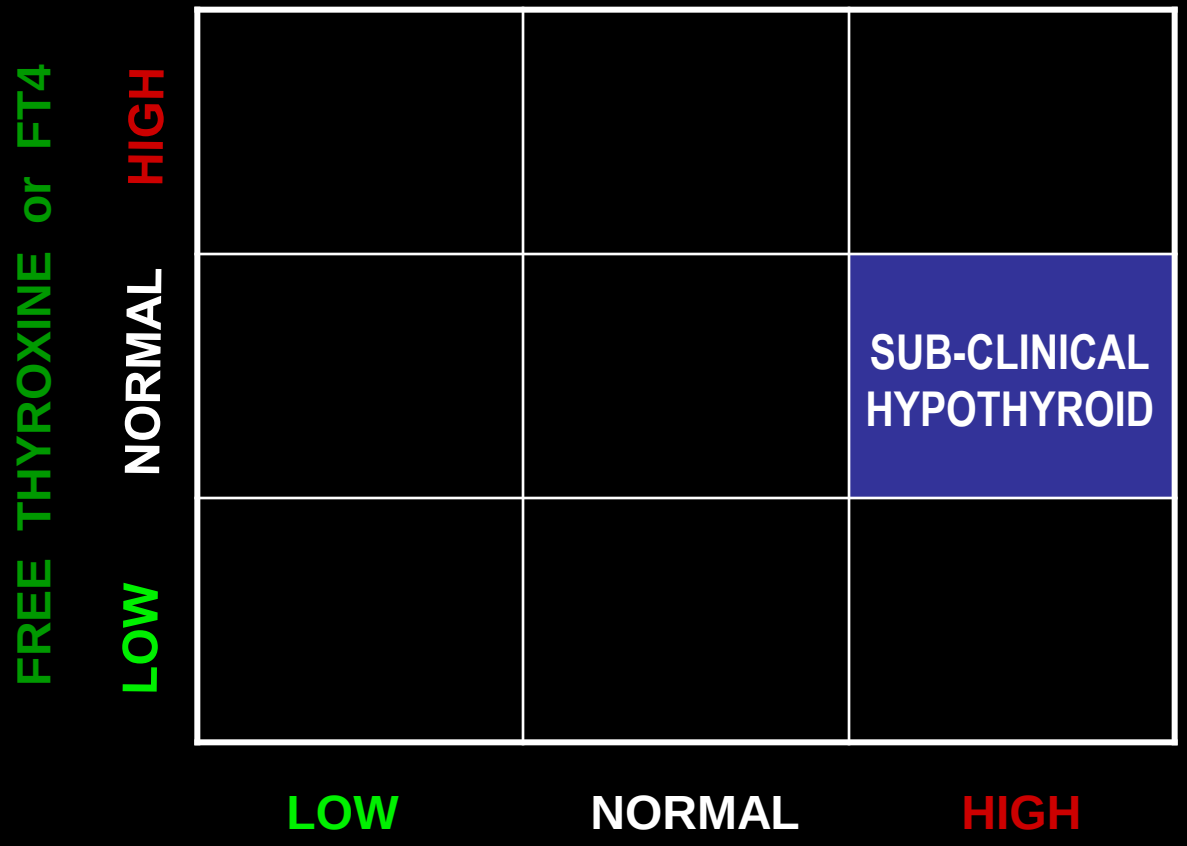
BASIC THYROID EVALUATION



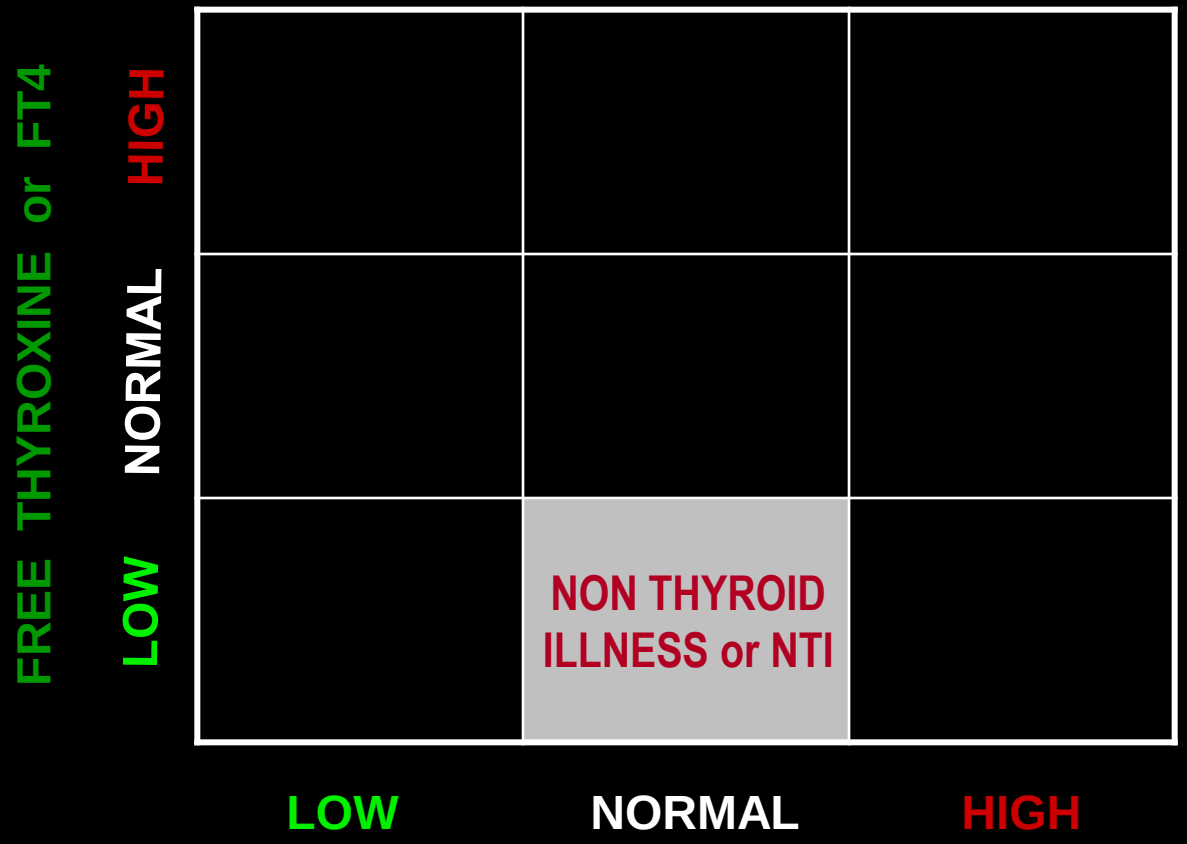
BASIC THYROID EVALUATION



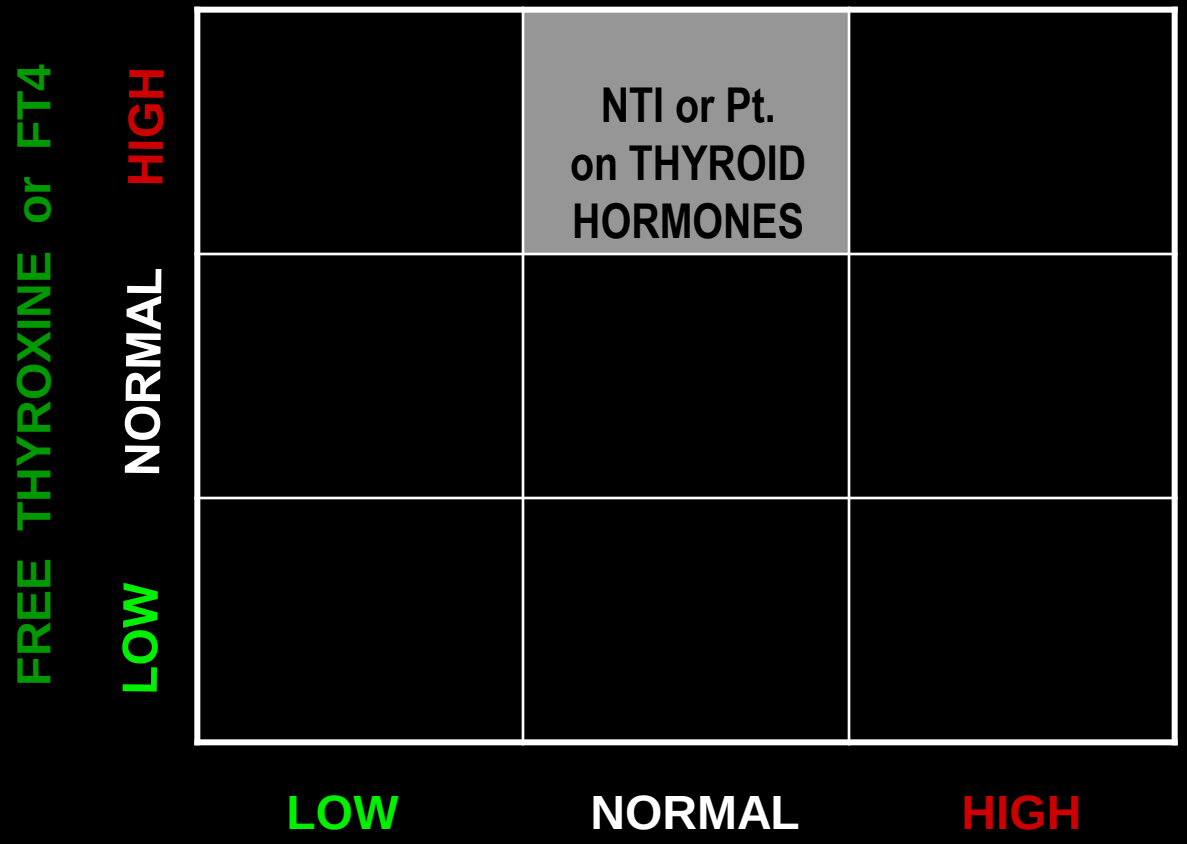
BASIC THYROID EVALUATION



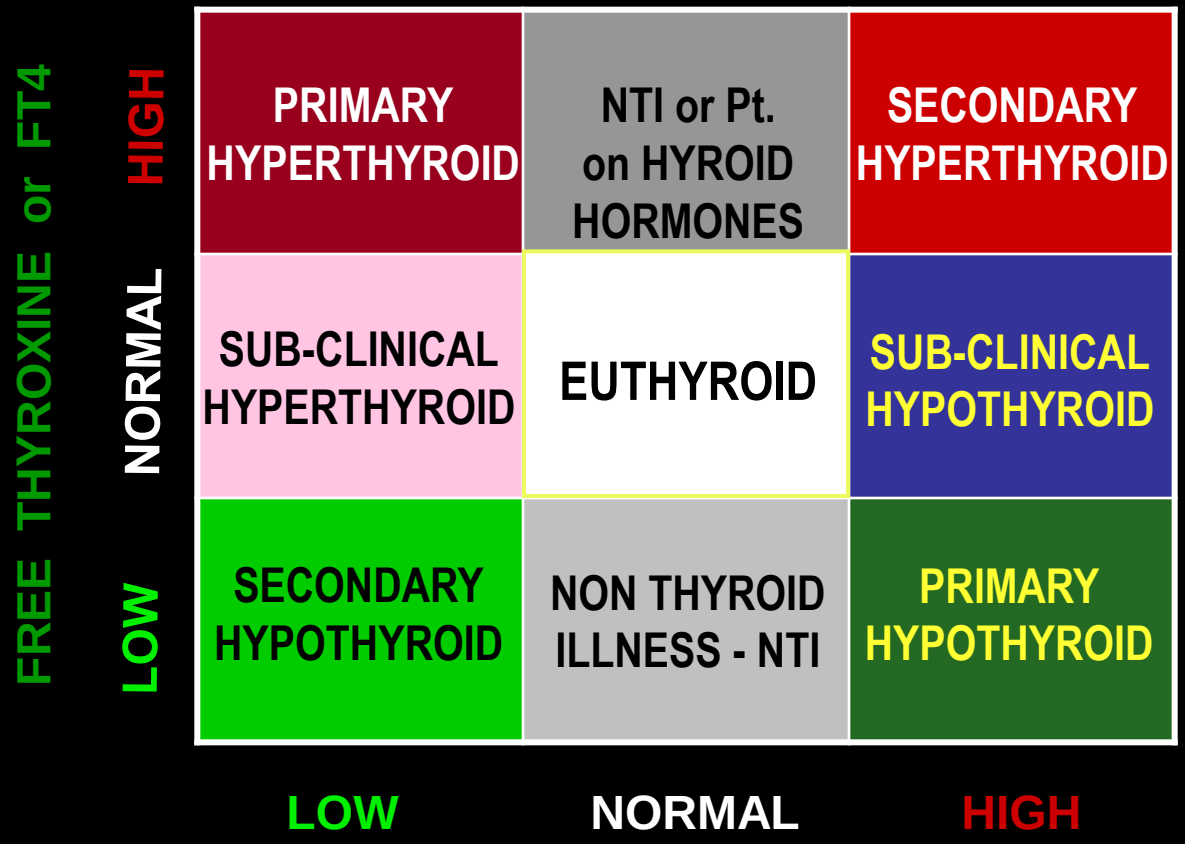
BASIC THYROID EVALUATION



BASIC THYROID EVALUATION



BASIC THYROID EVALUATION

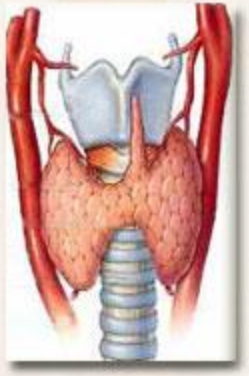


THYROID HORMONES

TEST	REFERENCE RANGE
TSH	Normal Range 0.3 - 4.0 mU/L
Free T_4	Normal Range 0.7-2.1 ng/dL

TSH upper limit has been revised to 2.5 mU/L

Thyroid Disorder



HYPERTHYROIDISM	HYPOTHYROIDISM
SOLITARY NODULE /GOITRE	POSTPARTUM THYROIDITIS

Thyroid disease is the second most common cause of endocrine dysfunction in women of child bearing age.

Hypothyroidism is more common during pregnancy than hyperthyroidism.

What if the mom's thyroid doesn't work? ~2% of all pregnancies

	Subclinical Hypothyroidism	Overt
Spo		%
Pre		%
Abr		%
Stil		%
Anemia[2,3]	0-2%	0-31%
Postpartum hemorrhage[2,3,4]	0-17%	0-19%
Preterm birth[2,3,7,8]	0-9%	20-31%

"Maternal hypothyroidism is associated with increased rate of pregnancy complications, and the risk is greatest in overt hypothyroidism compared to subclinical hypothyroidism."

LaFranchi, Thyroid 2005

HYPOTHYROIDISM

Overt- 2-3 preg / 1000

Commonest – Hashimoto Thyroiditis

Increased TSH
Decreased T4

Other:

Endemic Iodine defic

Ablative radioiodine therapy

thyroidectomy

Increased TSH
Normal T4

Subclinical hypothyroidism – 2-3% of pregnant women

Elevated TSH normal T4

Screening and Treatment - controversial

International Journal of Health Sciences & Research.2013;3(5):29

Complications of Hypothyroidism in Pregnancy

Complications	Maternal	Fetal
Effect of hypothyroidism on general health	Anemia Congestive heart failure Antepartum depression	
Complications during the course of gestation	Eclampsia Preeclampsia Gestational hypertension Placental abruption	Growth restriction Increased perinatal mortality
Complications during delivery	Increased chances of cesarean section, preterm delivery	Miscarriage
Long-term complications	Postpartum depression Postpartum hypertension Lactation problems	Impaired neuropsychointellectual development

Indications for Screening of Pregnant Women for Thyroid Disease

- Evidence substantiating the benefits of universal screening of thyroid dysfunction not adequate
- Endocrine Society of Clinical practice guidelines – 2007 and Indian Thyroid Guidelines – 2011 recommend screening of pregnant women if they have
  - History of thyroid abnormalities
  - Family history of thyroid abnormalities
  - Goiter
  - Thyroid autoantibodies
  - Symptoms, signs, or biochemical markers suggestive of thyroid disease
  - Type 1 diabetes
  - Other autoimmune disorders
  - Infertility
  - Previous head or neck irradiation
  - History of miscarriage or preterm delivery

Sub-clinical Hypothyroidism causes Pregnancy Complications !

Sub-clinical Hypothyroidism is common during pregnancy.

Production of thyroid hormones requirement increases by ~**50%** during pregnancy.

Pregnant women with Sub-clinical Hypothyroidism have an increased risk of pregnancy complications like.....

- Pre-eclampsia, Preterm Birth, Low Birth Weight,
- Placental abruption, Recurrent Miscarriage, &
- Perinatal Mortality
- Intellectual impairment during childhood

CONCLUSION: Maintain a normal serum TSH is essential during pregnancy

Hyperthyroidism

Complicates 1 in 1000 to 2000 pregnancies

Overwhelming cause in pregnancy

Grave's Disease (95%)

Autoimmune organ specific disease

Usually associated with thyroid stimulating antibodies

Late first / early second trimester

3rd generation thyrotropin assay

0.002mU/L analytical sensitivity

SUBCLINICAL HYPERTHYROIDISM

abnormally low TSH

Normal thyroxine level

Anti-thyroid Drugs Used During Pregnancy

Propylthiouracil	Methimazole
Commonly used in the first trimester of pregnancy or in patients who are suffering from a thyroid storm or are allergic to methimazole	Methimazole has been used as an alternative to propylthiouracil for patients with hyperthyroidism who cannot tolerate propylthiouracil
Can be harmful to the liver in children and adults	Once-daily regimen and fewer major side effects may be considered more advantageous than propylthiouracil
Mothers with Graves' disease treated with propylthiouracil have a risk of developing fetal hypothyroidism	Mothers with Graves' disease treated with methimazole also have a risk of developing fetal hypothyroidism
Widely used in North America	Widely used in Europe, South America, and Asia

5-10% of pregnancies
Occurs 3-4 mths postpartum
Autoimmune
3 fold increase in type 1 diabetic

Phases:
Hyperthyroidism
Hypothyroidism
Full recovery
E IV ; R – C; Ref-69
POST NATAL DEPRESSION

POST PARTUM THYROIDITIS

Symptomatic treatment
E IIa ; R – B; Ref-71

Annual thyroid function test
E IV ; R – C; Ref-69

CONCLUSIONS
Pearls for Practice

Thyroid dysfunction

Hypothyroidism

- T4 essential for early fetal development
- Little T4 crosses placenta after 1st trim
- Adequate treatment – good outcome

Hyperthyroidism

- Careful D/D at early weeks
- Untreated- poor preg. Outcome
- drugs cross placenta: lowest optimal dosage
- Cord blood - Thyroid function

Postpartum Thyroiditis

- Occurs 3-4 mths postpartum
- Autoimmune disorder
- Phases of hyper-hypo-recovery
- Annual thyroid function tests

Thyroid nodule & Cancer

- Defer preg. For 1 year after trt. With radioactive iodine
- Nodule identified beyond 20 weeks- biopsy after delivery
- Large goitre – anesthetic complications

FIGO recommends the following:

- Screening for thyroid function is recommended in the first trimester particularly in countries with a deficient iodine diet and in symptomatic patients
- TSH is the superior method for screening. Free T4 and TPO Ab testing are not recommended for screening. The best reliable tests for TSH are by C.I.A or 3rd generation R.I.A (Radio Immuno Assay). Notably normal thyroid test values change in pregnancy

- Treatment for hypothyroidism is recommended when TSH levels are >2.5 and >3,0 IU/L during the first and second/third trimesters respectively. The only replacement therapy is L-thyroxine. The starting does of L-thyroxine are presented in fig. 4. Instead treating subclinical hypothyroidism, in the presence of negative thyroid auto-antibodies, is still debatable. Importantly, women on L-thyroxine before pregnancy should increase their dosage by 30-50% when they first recognize the pregnant state.

- Treatment of Hyperthyroidism due to Grave's disease is by anti thyroid drugs (Propylthiouracil (PTU) or Carbimazole/Methimazole (MMI)). It is not recommended to change drugs during pregnancy Symptomatic (fig-1) treatment with beta- blockers for short term may be needed.

- Primary, prevention of hypothyroidism is by a healthy diet and Iodised fortified salt (especially in iodine deficient areas).

- If the patient has a thyroid nodule she should be evaluated and treated during pregnancy. The first steps are perfomance of a thyroid ultrasonogram and a fine needle aspiration (FNA) as needed. Surgery should be preferably deferred to the postpartum period.

Follow up and postpartum TSH evaluation and reduction of L-thyroxine dose to pre- pregnant levels in patients with hypothyroidism.

FIGO opinion on:

Reproductive Health Impacts of Exposure to Toxic Environmental Chemicals

Toxic chemicals in global commerce are harming our ability to reproduce, negatively affecting pregnancies and causing numerous other long-term reproductive and developmental health problems. The science linking exposure to harm is robust

Global exposure to toxic chemicals in commerce is ubiquitous; however some populations are more vulnerable to exposure and/or to adverse health impacts than others

Preventing exposures is a critical opportunity for reproductive health professionals to improve patient and population health

FIGO joins ACOG, ASRM and RCOG in calling for timely action to prevent exposure to toxic chemicals through intervening on the patient, health care institutional and policy level

www.figo.org

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

SPECIAL COMMUNICATION

International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals☆

Gian Carlo Di Renzo [a], Jeanne A. Conry [b], Jennifer Blake [c], Mark S. DeFrancesco [b], Nathaniel DeNicola [b], James N. Martin Jr. [b], Kelly A. McCue [b], David Richmond [d], Abid Shah [d], Patrice Sutton [e], Tracey J. Woodruff [e,*], Sheryl Ziemin van der Poel [f], Linda C. Giudice [g]

[a] International Federation of Gynecology and Obstetrics, London, UK
[b] American College of Obstetricians and Gynecologists, Washington, DC, USA
[c] Society of Obstetricians and Gynaecologists of Canada, Ottawa, ON, Canada
[d] Royal College of Obstetricians and Gynaecologists, London, UK
[e] Program on Reproductive Health and the Environment, University of California, San Francisco, San Francisco, CA, USA
[f] World Health Organization, Geneva, Switzerland
[g] American Society for Reproductive Medicine, Birmingham, AL, USA

This seminal paper was published and distributed to 7000 participants at the FIGO Conference. It is a available for free down load.

FIGO's response to the scientific opinion paper

Given accumulating evidence of adverse health impacts related to toxic chemicals, including the potential for inter-generational harm, FIGO has wisely proposed a series of recommendations

FIGO proposes physicians, midwives, and other reproductive health professionals advocate for policies to reduce the burden of unsafe chemicals on patients and communities

Recommendations accepted by the General Assembly of FIGO in 2015

1. Advocate for policies to prevent exposure to toxic enviromental chemicals.
2. Work to ensure a healthy food system for all.
3. Make environmental health part of health care.
4. Champion environmental justice

These recommendations were proposed by Professor Linda Giudice – Chair of the FIGO working group on envirnment and health and were unanimously accepted by the FIGO General Assembly

FIGO's working group on Environmental toxins and Reproductive Health

- Explore ways and means of implementing recommendations by working with National Societies
- Scientific sessions organised in National and Regional meetings to increase awareness
- Explore the possibility of working with National Governments, like minded organisations and partners (donors) to make environmental toxins and reproductive health as a Government priority
- Identify country specific issues (e.g. chemical factories discharhing chemicals in an irresponsible way) and work with Government and partners to identify solutions
- Sensitise the public and make them aware of the harms and make them own the responsibility to resolve issues
- Innovate – identify new ways of reducing environmental toxins
- Develop an accounting mechanism; monitor the impact made by the introduction of Interventions

FIGO initiative on GDM

Educational tools

Develop protocols and guidelines for standards of care

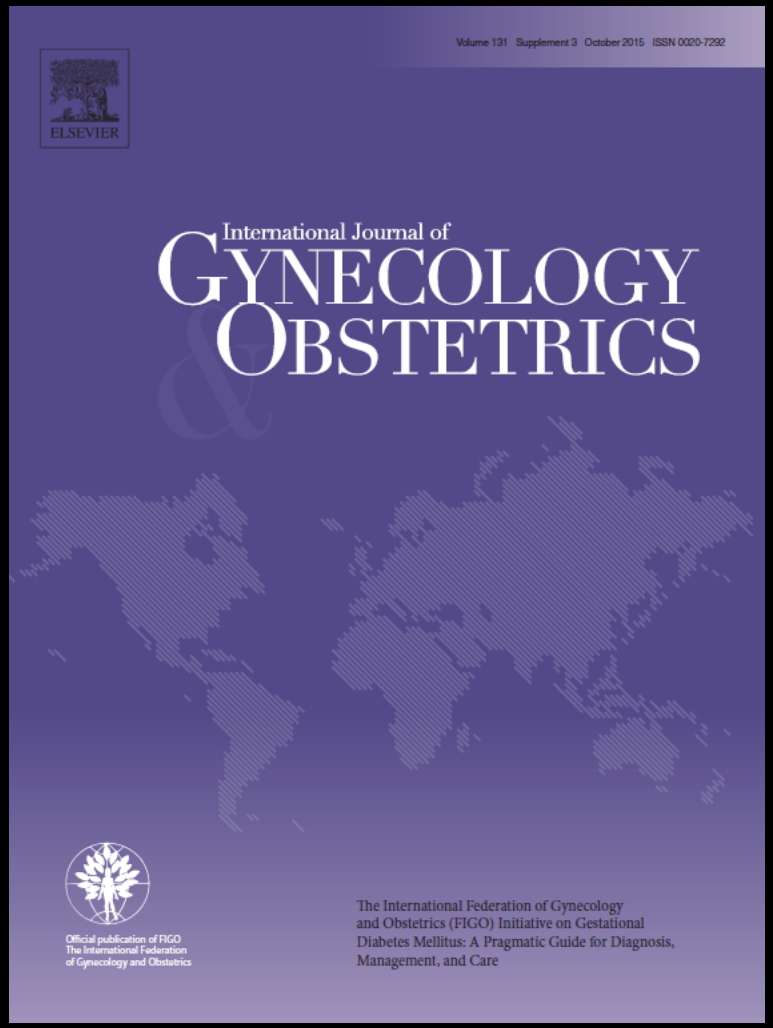
To address the issue of diabetes and pregnancy based on available resources – fully resourced, medium resourced, low resource or resource challenged countries and regions.

- **Publish these protocols and standards as a supplement to IJGO.**
- **Develop role and resource based training materials**
  to support regional and country chapters of FIGO for capacity development to support implementation of these standards of care.
- **Develop tools to assist regional and country chapters of FIGO**
  to advocate for universal screening of all pregnant women for diabetes and for additional resources to promote and integrate diabetes and NCD prevention within existing MCH programs.

FIGO

International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice
Hyperglycemia in pregnancy



International Journal of Gynecology and Obstetrics 131 S3 (2015) S173–S211

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

www.figo.org

The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care*

Moshe Hod [a], Anil Kapur [b], David A. Sacks [c], Eran Hadar [d,e], Mukesh Agarwal [f], Gian Carlo Di Renzo [g], Luis Cabero Roura [h], Harold David McIntyre [i], Jessica L. Morris [j,*], Hema Divakar [k]

[a] Division of Maternal Fetal Medicine, Rabin Medical Center, Tel Aviv University, Petah Tikva, Israel
[b] World Diabetes Foundation, Gentofte, Denmark
[c] Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA
[d] Helen Schneider Hospital for Women, Rabin Medical Center, Petah Tikva, Israel
[e] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[f] Department of Pathology, UAE University, Al Ain, United Arab Emirates
[g] Centre of Perinatal and Reproductive Medicine, Department of Obstetrics and Gynecology, University of Perugia, Perugia, Italy
[h] Maternal Fetal Medicine Unit, Vall d'Hebron University Hospital, Barcelona, Spain
[i] University of Queensland Mater Clinical School, Brisbane, Australia
[j] International Federation of Gynecology and Obstetrics, London, UK
[k] Divakar's Specialty Hospital, Bangalore, India

Contributors

In addition to the authors, the following people provided important contributions during the creation of the document. Thanks go to international experts: Tao Duan, Huixia Yang, Andre Van Assche, Umberto Simeoni, Tahir Mahmood, Biodun Olagbuji, Eugene Sobngwi, Maicon Falavigna, Rodolfo Martinez, Carlos Ortega, Susana Salzberg, Jorge Alvariñas, Gloria Lopez Steward, Silvia Lapertosa, Roberto Estrade, Cristina Faingold, Silvia Garcia, Argyro Syngelaki, Stephen Colagiuri, Yoel Toledano, Mark Hanson, and Blami Dao. Special thanks, for FIGO guidance and coordination, go to President Sabaratnam Arulkumaran, President Elect CN Purandare, Chief Executive Hamid Rushwan, and Chair of the SMNH Committee, William Stones.

The following external groups evaluated the document and support its contents: European Board and College of Obstetrics and Gynaecology (EBCOG), The Society of Obstetricians and Gynaecologists of Canada (SOGC), Chinese Society of Perinatal Medicine, Diabetic Pregnancy Study Group (DPSG), African Federation of Obstetrics and Gynaecology (AFOG), South Asian Federation of Obstetrics and Gynecology (SAFOG), Australian Diabetes in Pregnancy Society (ADIPS), International Association of Diabetes in Pregnancy Study Groups (IADPSG), European Association of Perinatal Medicine (EAPM), Diabetes in Pregnancy Study Group of India (DIPSI), and the Diabetes in Pregnancy Study Group of Latin America. In addition to the FIGO Executive Board, all relevant FIGO Committees and Working Groups contributed to and supported the document.

Acknowledgments

This project was funded by an unrestricted educational grant from Novo Nordisk.

Conflict of interest

The authors have no conflicts of interest to declare.

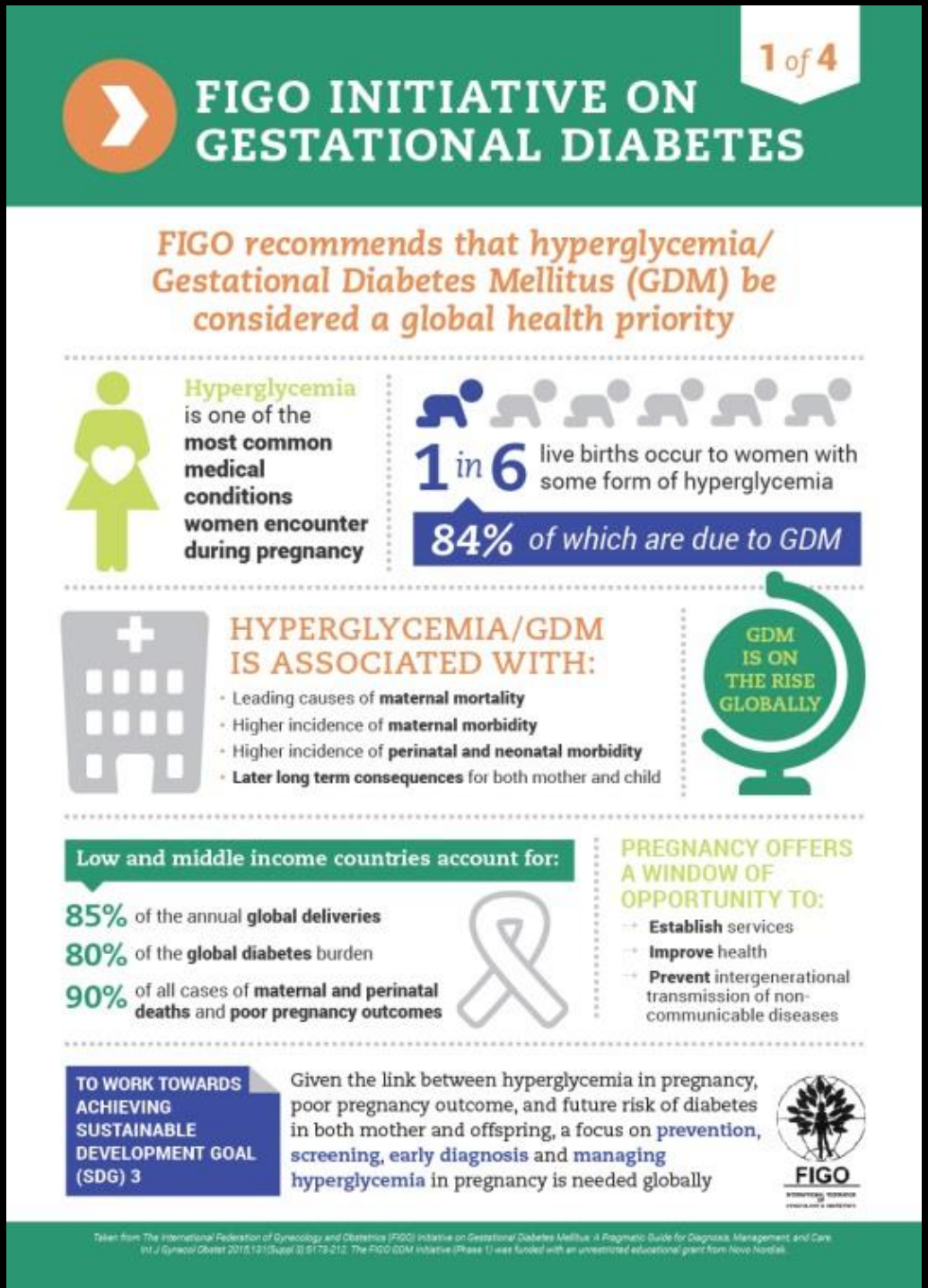
Women queue for gestational diabetes services in Barranquilla, Colombia. Photograph by Jesper Wesley for the World Diabetes Foundation.

* This document was endorsed by the FIGO Executive Board at its annual meeting held on May 30–31, 2015, in Melbourne, Australia

* Corresponding author at FIGO House, Suite 3, Waterloo Court, 10 Theed Street, London, SE1 8ST. Tel.: +44 207 928 1166
E-mail address: JessicaM@figo.org (J.L. Morris).

Infographics

The basics



International Federation of Gynecology and Obstetrics
Working Group on Best Practice on Maternal-Fetal Medicine

Best Practice Advice
Hyperglycemia in pregnancy

- **All pregnant women should be tested for hyperglycemia. Universal testing by all member associations**
- **WHO(2013) and IADPSG(2010) criteria for diagnosis of gestational diabetes must be used**
- **Diagnosis of HDP should be on properly collected venous plasma samples. In developing countries a plasma calibrated hand held gluocometer is acceptable**
- **Management of HDP should be in accordance with available national resources and infrastructure**

Infographics

Diagnosis

Infographics

Management

Infographics

Postpartum

FIGO INITIATIVE ON GESTATIONAL DIABETES

FIGO recommends using the postpartum period for increased engagement to improve health for mother and child

POSTPARTUM AIMS

- Early **DETECTION** of infections
- **SUPPORT** of breastfeeding
- **ADVICE** on pregnancy spacing
- **RETEST** all women with GDM at 6-12 weeks postpartum
- Future blood glucose **TESTS**

The postpartum period is an important platform to **initiate early preventive health** for both the mother and the child who are both at higher risk of:

- **Future Obesity**
- **Metabolic Syndrome**
- **Diabetes**
- **Hypertension**
- **Cardiovascular Disorders**

Both **lifestyle intervention** and **metformin** can be effective in **delaying** or **preventing diabetes** in women with impaired glucose tolerance and a history of GDM

Obstetricians to link with other healthcare providers to support postpartum follow-up through **child vaccination/ regular health visits**

AIMS FOR PRECONCEPTION & INTER-PREGNANCY INTERVALS

Increase acceptance and access to **preconception services**

Universal pre-conception screening for malnutrition, anemia, overweight and obesity, hypertension, diabetes and thyroid dysfunction

FIGO
INTERNATIONAL FEDERATION OF GYNECOLOGY & OBSTETRICS

Taken from The International Federation of Gynecology and Obstetrics (FIGO) Initiative on Gestational Diabetes Mellitus: A Pragmatic Guide for Diagnosis, Management, and Care. Int J Gynecol Obstet 2015;131(Suppl 3):S173-212. The FIGO GDM Initiative (Phase 1) was funded with an unrestricted educational grant from Novo Nordisk.

- **Nutrition and physical activity counselling is a must and continue after birth also**
- **Insulin is added if lifestyle and diet modification does not control Hyperglycemia. Metformin and or glyburide may be used in 2nd and 3rd trimesters. Oral drugs may be first choice in 2nd and 3rd trimester**
- **Postpartum 8 weeks visit counselling and life style modifications for mother and child is necessary**
- **Public health measures to increase awareness and acceptance of preconception counselling should be applied for all women planning pregnancy.**

CONCLUSIONS

FOCUS ON GLOBAL STRATEGIES

- AMELIORATE OUR PROFESSION OVERCOMING THE LIMITS OF NATIONAL SOCIETIES GUIDELINES: THE BEST PRACTICE ADVICE
- GLOBAL STRATEGIES FOR:

PRETERM BIRTH PREVENTION

NON COMMUNICABLE DISEASES

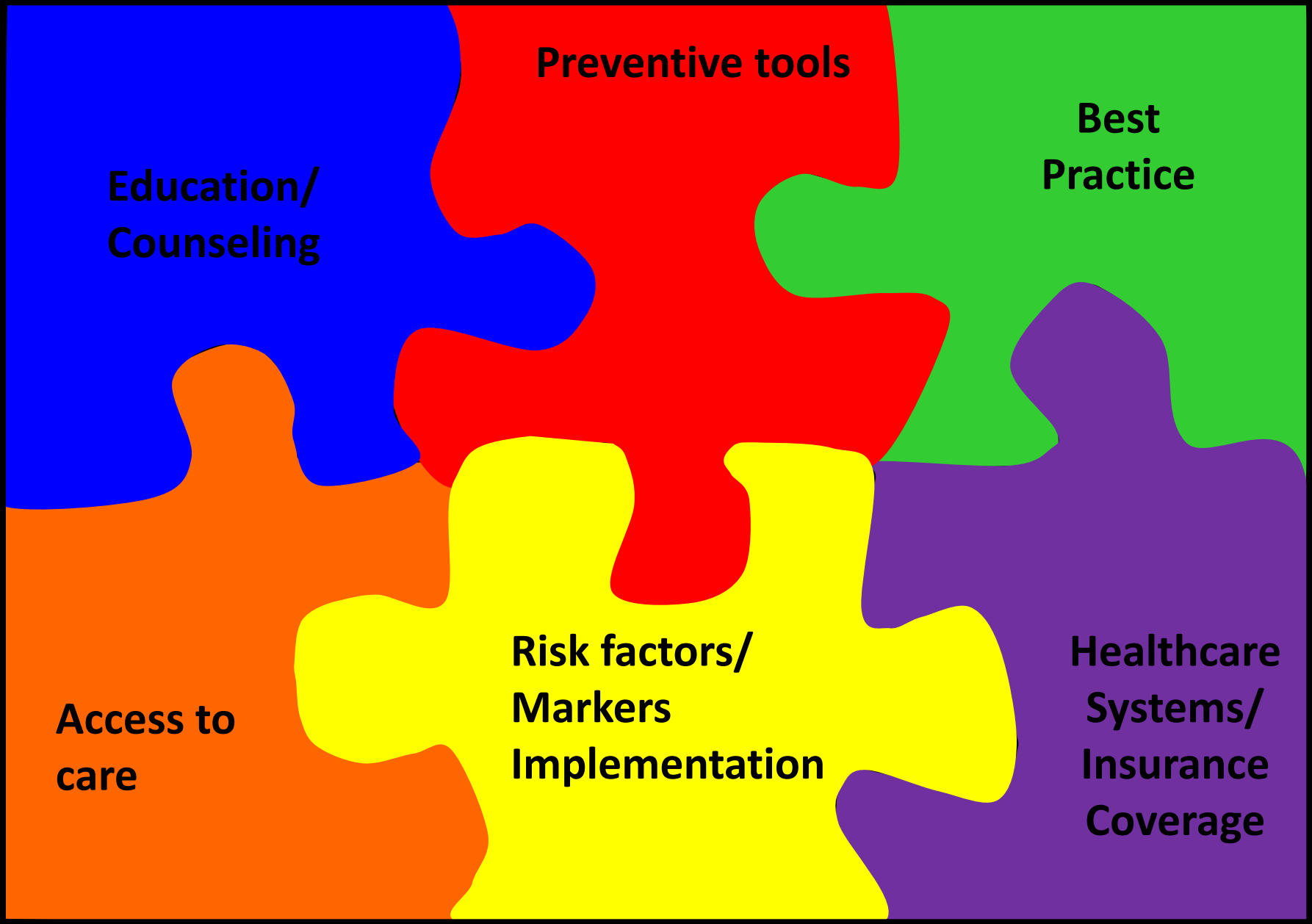
PREVENTING EXPOSURE TO TOXIC CHEMICALS

FIGHTING THE INEQUITY

Gathering data on maternal mortality and maternal health is notoriously difficult.

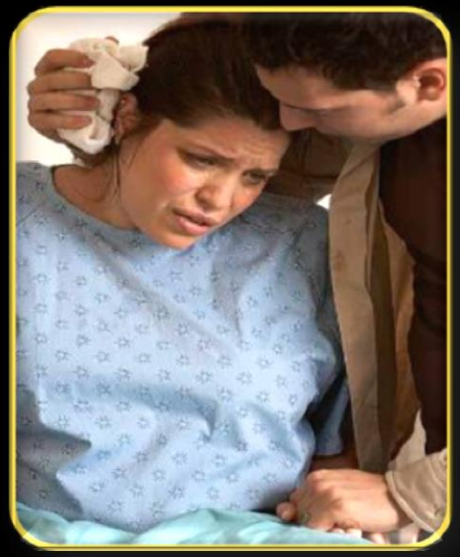
However, one thing is clear from all the statistics: although maternal and perinatal mortality and morbidity is falling globally

the perspectives for women-infants in poor resources countries are much worst than for those in industrialised countries.


Preventive tools
Best Practice
Education/ Counseling
Access to care
Risk factors/ Markers Implementation
Healthcare Systems/ Insurance Coverage

Window of Opportunity

Pregnancy offers a window of opportunity to provide maternal care services to mother and offspring



Reduce traditional maternal and perinatal morbidity and mortality indicators

Address intergenerational prevention of preterm birth and NCDs, such as diabetes, hypertension, cardiovascular disease, and stroke.

On Sept 2015 the UN General Assembly adopted the **"Agenda 2030: Transforming our World"**, with a consensus of the World Government Community - introduced 17 sustainable development goals SDGs**.**

Many of the suggested SDG's have Environmental and Reproductive health embedded in their goals

It is a sheer co-incidence that September 2015 witnessed the 20th anniversary of the Beijing World Conference on Women under the slogan -**“Planet 50-50 by 2030: Set it up for Gender Equality”**.

‘The Agenda 2030; Transforming our world’ or Planet 50-50 by 2030’ i.e. SDGs will not materialise without the contribution of 50% of its population i.e. women - This can be achieved only with gender equality, equal education and employment opportunities + providing sexual reproductive health and rights.

Reproductive Health and Rights will not be complete unless we improve environmental Health

FIGO was not and will not be a passive observer to bring about this required change and will act to make these dreams real for women.


EFCNI
european foundation for
the care of newborn infants


IPPF


GLOWM
Global Library of Women's Medicine


BILL & MELINDA
GATES foundation


March
of Dimes
Saving babies, together


USAID
FROM THE AMERICAN PEOPLE