



LA **G**INECOLOGIA DEL **T**ERRITORIO  
PERCORSI CLINICI E ORGANIZZATIVI

# Iperglicemia e complicanze materno fetali

Prof. Giorgio Mello





*C.R.R. Gravidanze ad alto rischio*



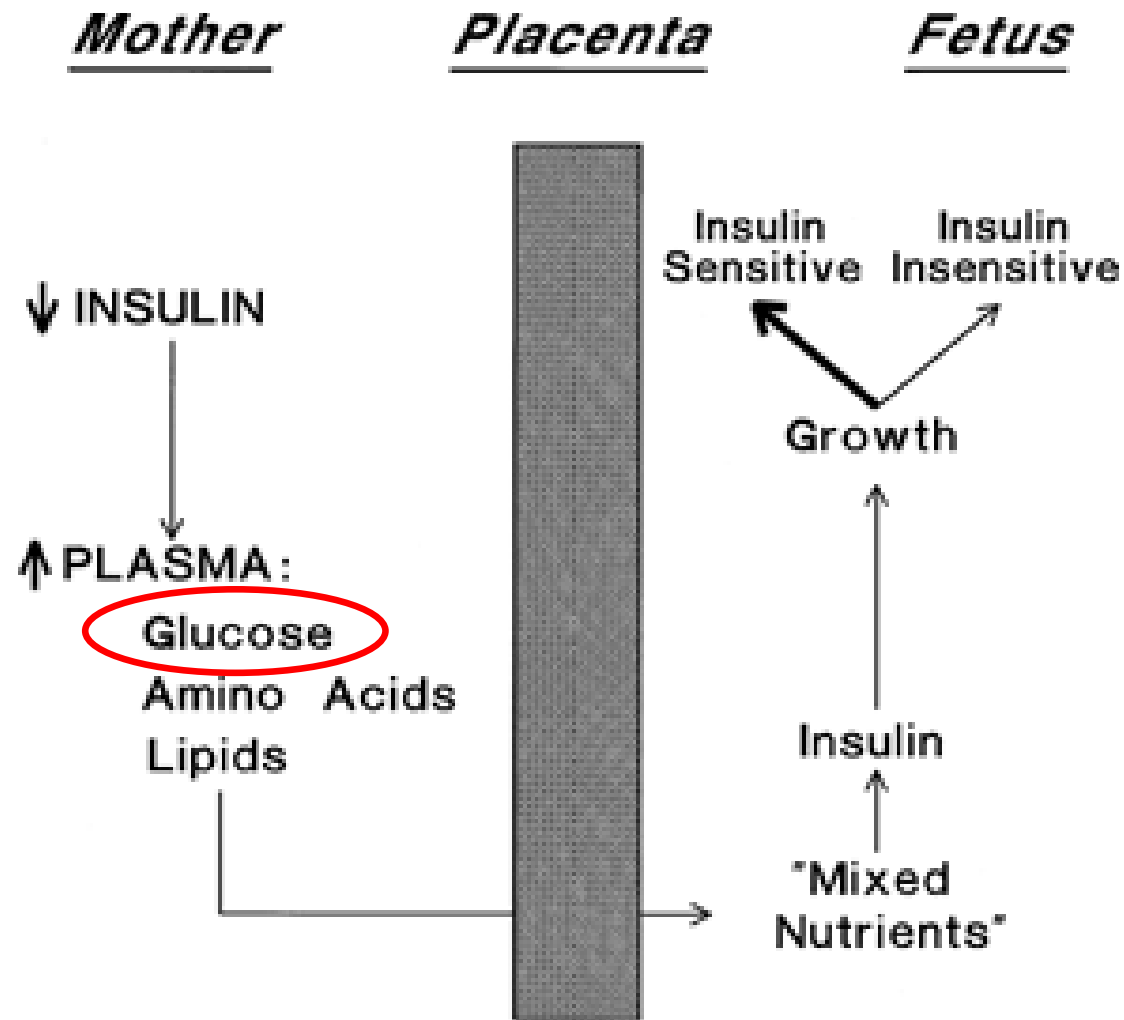
CONGRESSO NAZIONALE A.G.E.O.  
(Associazione Ginecologi Extra Ospedalieri)

11-13 APRILE 20**13**  
Firenze - Teatro Goldoni

# DISORDERS OF GLYCEMIA

Stages Types	Normoglycemia	Hyperglycemia		
	Normal glucose regulation	IGT or IFG	Not insulin requiring	Diabetes mellitus Insulin requiring for control Insulin requiring for survival
Type 1				
Type 2				
Other specific Types				
GDM				

# The "Pedersen hypothesis"



*Pedersen et al. "Blood Sugar in Newborn Infants of Diabetic Mothers" Acta Endocrinol 1954*

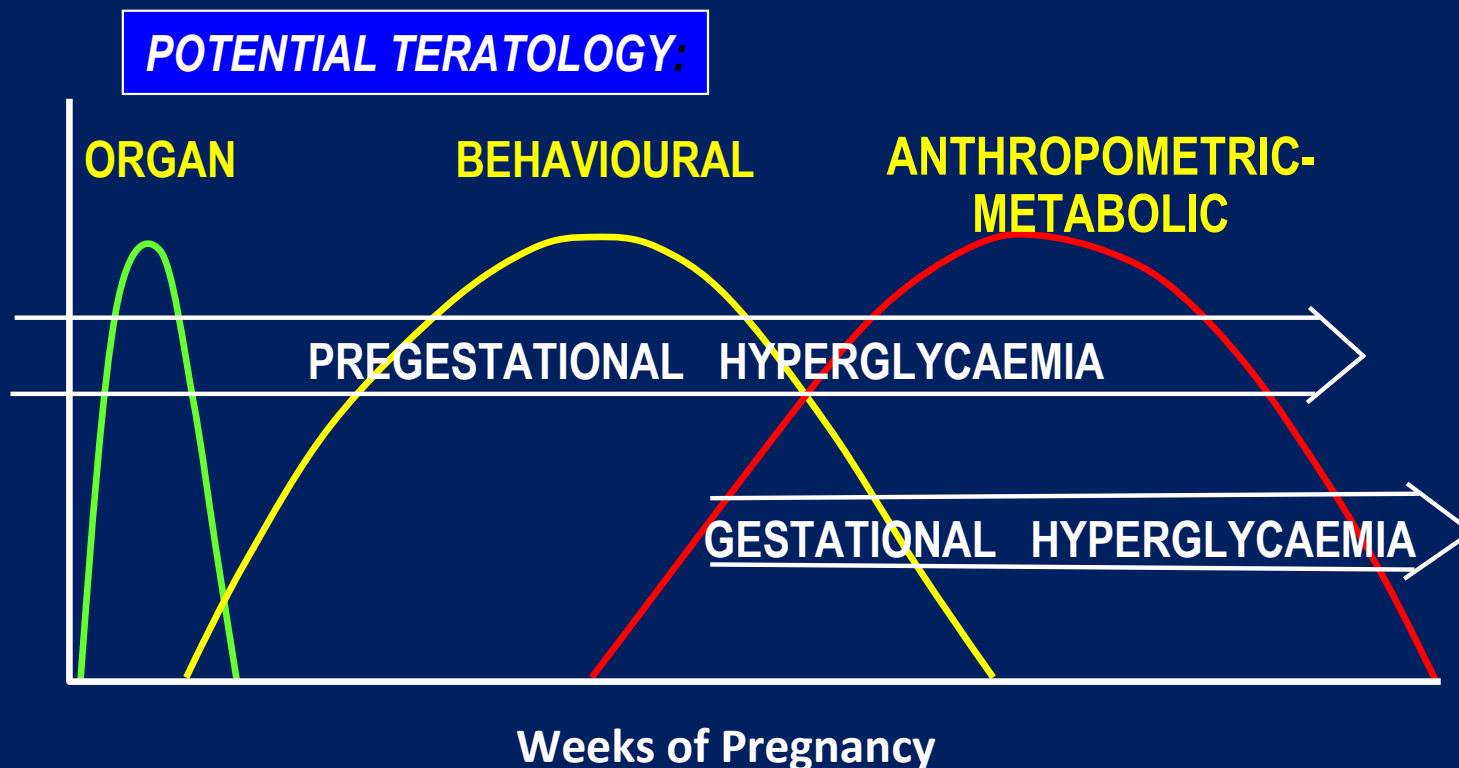


Maternal metabolic disorders of gluco-homeostasis, ranging from slightly impaired glucose tolerance to overt diabetes, since they provide an excess of substrates, are able to provoke an increased stimulation of the fetal  $\beta$ -cell with consequent hyperinsulinemia, which is in turn responsible for fetal hypersomatism as seen clinically at birth from a higher incidence of macrosomia

*P. E. Polani, 1973*

## Banting Lecture 1980 Of Pregnancy and Progeny

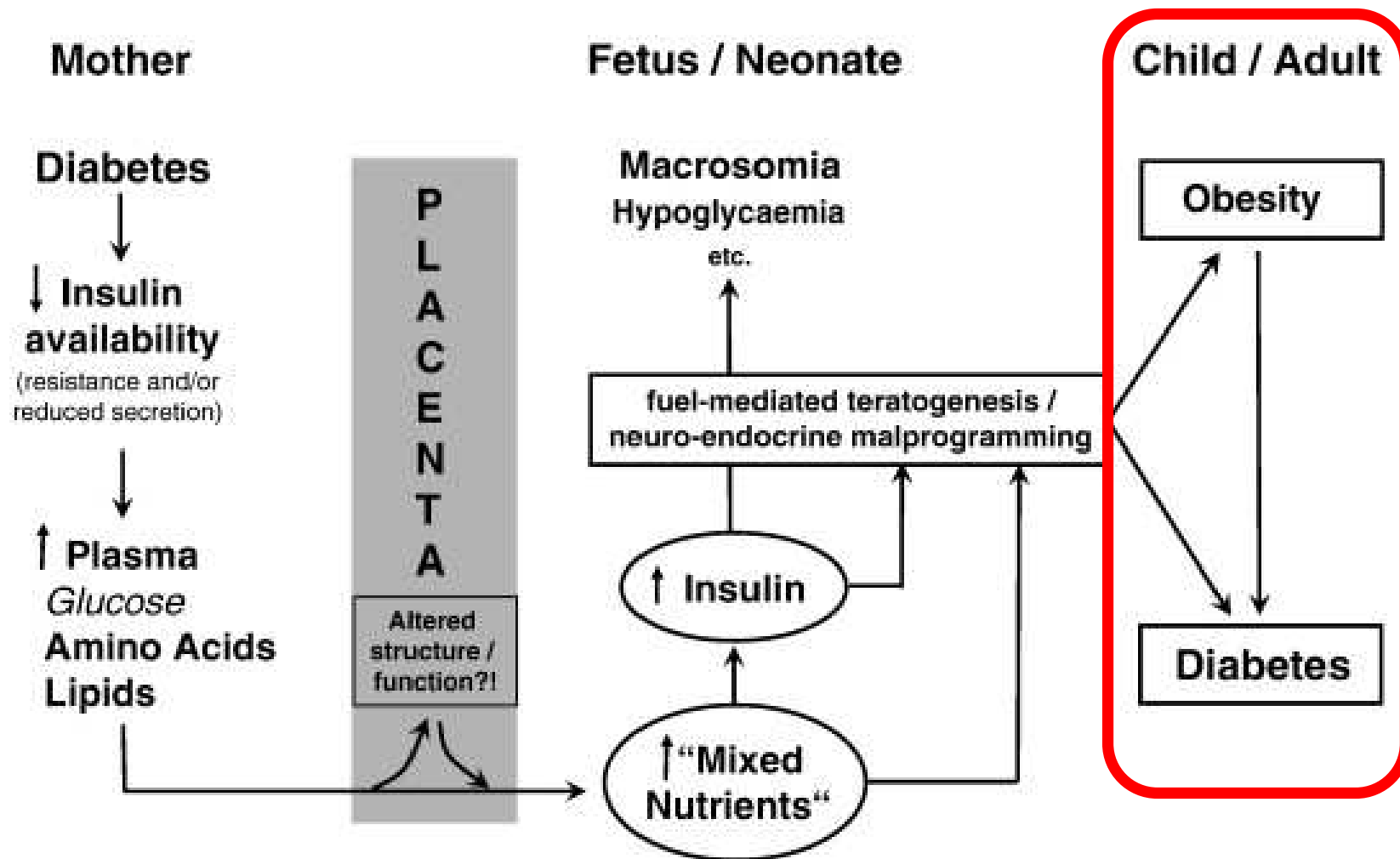
Potential long-range effects upon the fetus of altered interactions in maternal fuels during pregnancy. **Fuel-mediated teratogenesis** as the basis for long-range anatomic and functional changes.



*Norbert Fienkel, 1980 (modified)*

# The Pedersen/Freinkel hypothesis,

supplemented by the "perinatal programming" hypothesis,  
on "fuel-mediated functional teratogenesis"



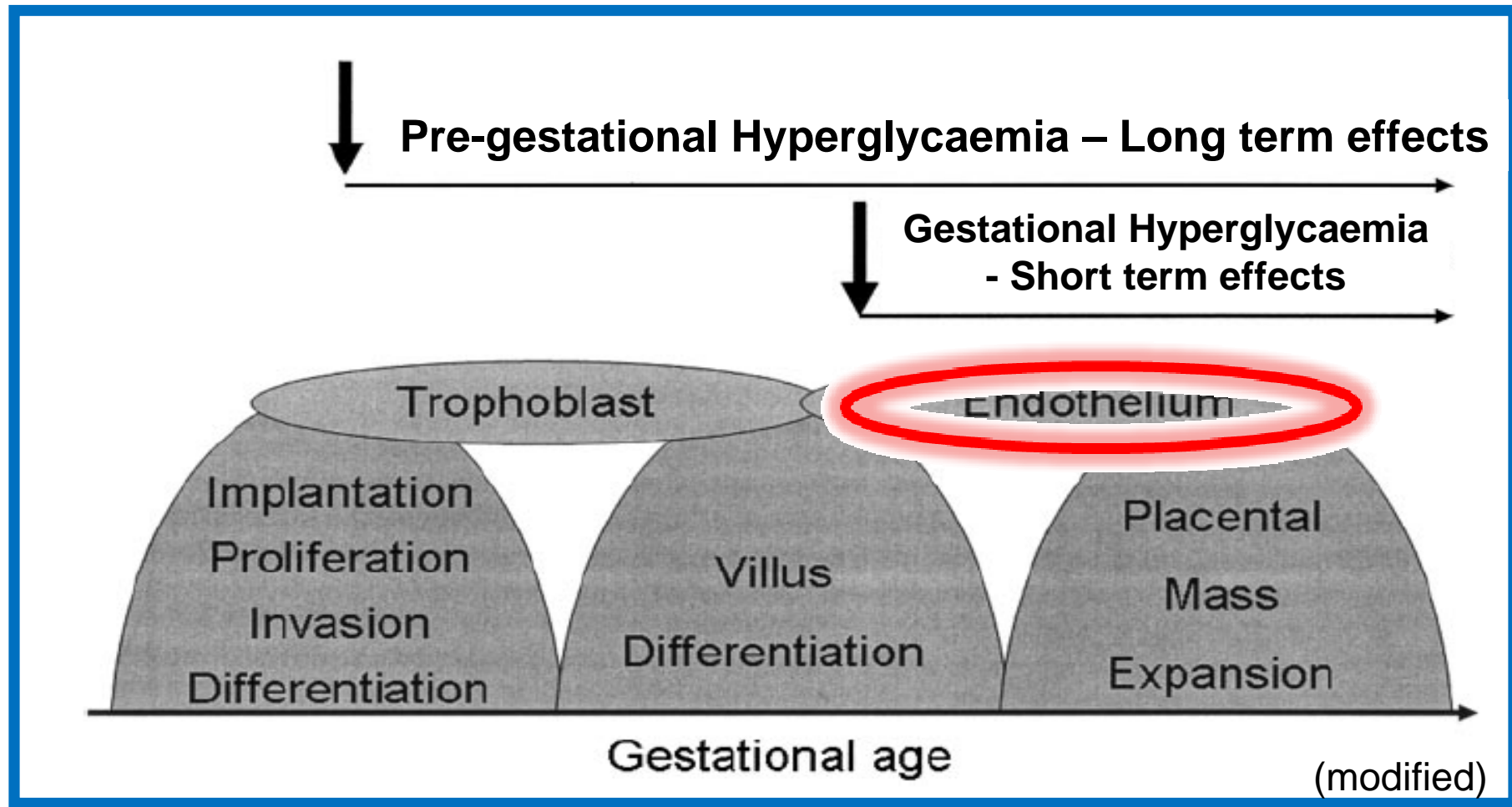
*Pedersen et al. "Blood Sugar in Newborn Infants of Diabetic Mothers" Acta Endocrinol 1954*

*Freinkel N. "Of pregnancy and progeny. Banting lecture 1980. Diabetes 1980*

*Dorner G. et al. "Perinatal hyperinsulinism as possible predisposing factor for diabetes mellitus, obesity and enhanced cardiovascular risk in later life." Horm Metab Res 1994*



# Hyperglycaemia and placental damage



*Any insult of the diabetic environment early in pregnancy will alter the placenta in a period critical for later development and, hence, have long-term effects unless counteracted by adaptive responses. Diabetic insults at later stages in gestation such as in GDM will only have short-term effects predominantly on placental function*

# Hyperglycemia and placental damage

Placenta

Fetus

direct

effects

indirect

Inflammatory status

Endotelial damage

Gene expression

Glycogen ↑

Hypercapillarization

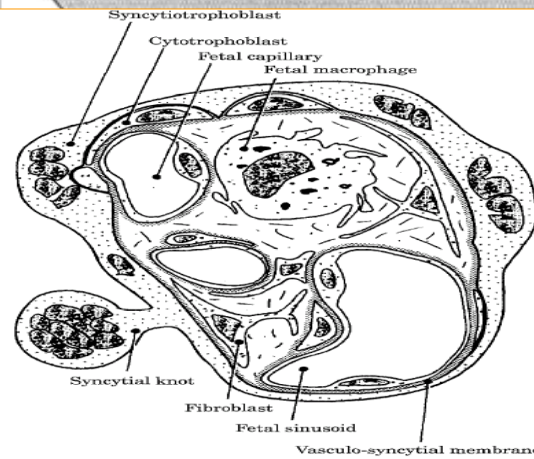
Villous immaturity

Placentomegaly

Substrate metabolism ↑

Oxygen demand ↑

INSULIN

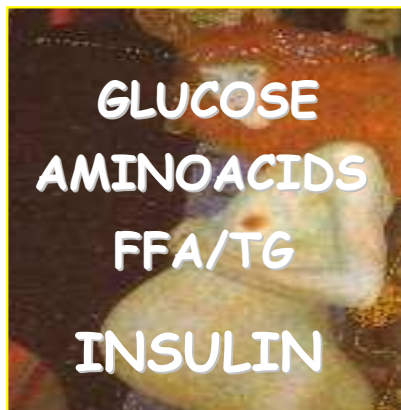


*Fetal insulin will have direct effects on placental alterations in gene expression and structure. In addition, indirect effects mediated by increased oxygen demand can be regarded as adaptive feedback to maintain fetal oxygen supply.*

Thickening of the basement membrane of the chorionic villi in diabetic pregnancies decreasing oxygen transfer.



**MATERNAL  
HYPERGLICEMIA  
/EXCESS OF  
NUTRIENTS**



**FETAL SUBSTRATE  
TRANSFER**



**NEONATAL  
METABOLIC  
COMPLICATIONS**

❖NEONATAL HYPOGLICEMIA  
❖R.D.S.  
❖MIOCARDIOPATHY

**FETAL  
HYPERINSULINEMIA**

**FETAL SUBSTRATE  
UPTAKE**

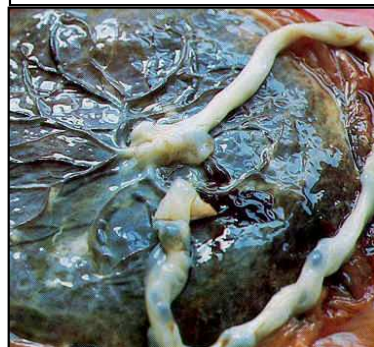
**FETAL HYPOXIA  
AND ACIDOSIS**

**MACROSOMIA**



**CESAREAN SECTION  
SHOULDER DISTOCIA**

**PLACENTAL  
DAMAGE**



**STILLBIRTH**

**ERITROPOIESIS**

**POLICITEMIA**

❖RISK DEEP VESSEL THROMBOSIS  
❖BLOOD HYPERVISCOSITY

**HYPERBILIRUBINEMIA**

# UN PO' DI STORIA...

I CRITERI CHE PER PIÙ DI 40 ANNI SONO STATI UTILIZZATI PER LA DIAGNOSI DI DIABETE GESTAZIONALE:

- ✓ Sono stati scelti per identificare donne ad alto rischio di sviluppare diabete dopo la gravidanza
- ✓ Sono stati ripresi dai criteri per la diagnosi di diabete al di fuori della gravidanza



*NON AVEVANO COME SCOPO PRIMARIO  
DI IDENTIFICARE GRAVIDANZE A  
RISCHIO DI OUTCOME PERINATALE  
AVVERSO*

plasma venoso glucosio mg/dl	OGTT 100 gr
0'	105
1h	190
2h	165
3h	145

plasma venoso glucosio mg/dl	OGTT 75 gr
0'	≥126
2h	>200

1964

ACOG

NDDP

1982

OMS

1998

O'Sullivan

1978

1979

Carpenter

1985

IV Workshop

sangue venoso glucosio mg/dl	OGTT 100 gr
0'	90
1h	165
2h	145
3h	125

plasma venoso glucosio mg/dl	OGTT 100 gr
0'	95
1h	180
2h	155
3h	140

plasma venoso mg/ml	OGTT 100gr	OGTT 75gr
0'	95	95
1h	180	180
2h	155	155
3h	140	=

1964

*45 anni senza  
consensus*

2009

*We may be asking the **wrong question** with the **wrong tool** to identify pregnant women at risk for complications.*

*If the outcome variable is the health of the fetus and neonate, it is time to reassess the question and ask:*

***"WHAT TEST BEST IDENTIFIES  
GLUCOSE TOXICITY  
FOR THE FETUS?"***



*The* NEW ENGLAND  
JOURNAL *of* MEDICINE

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Hyperglycemia and Adverse Pregnancy Outcomes

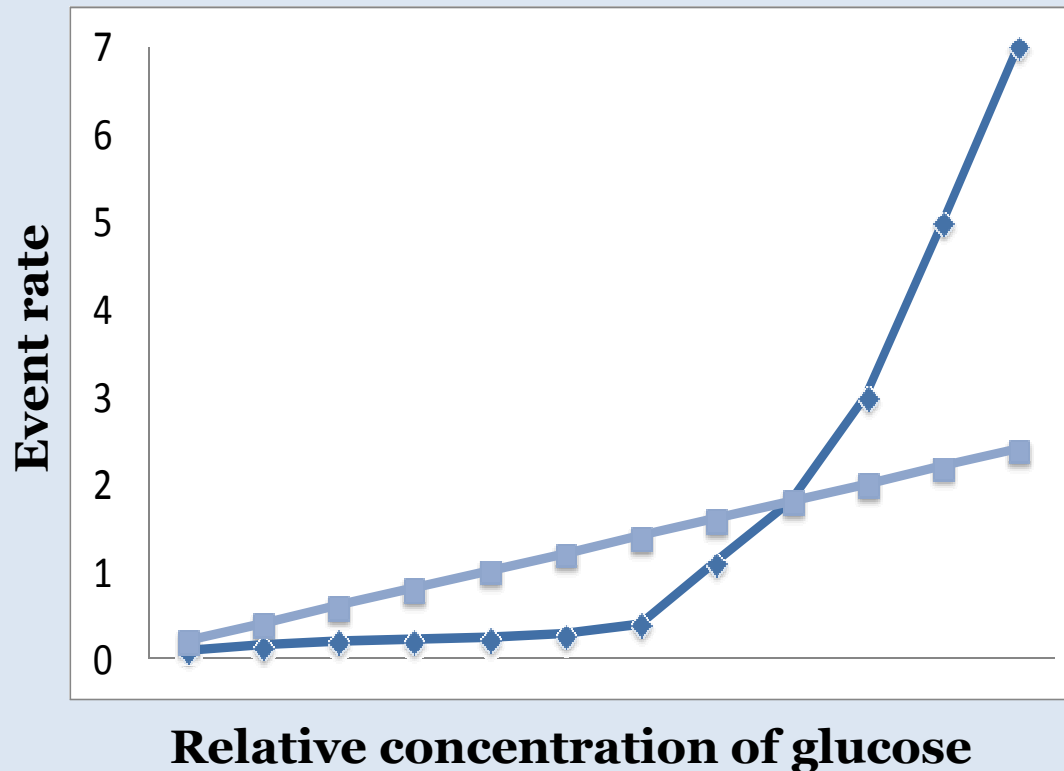
The HAPO Study Cooperative Research Group\*



## Correlazione fra *glicemia materna* e:

- Frequenza parti cesarei
- Frequenza macrosomia
- Iperinsulinemia fetale
- “Obesità” neonatale (spessore delle pliche)
- Ipoglicemia neonatale
- Altre morbidità

## *HAPO STUDY ENDPOINTS*



■ SOGLIA VS CONTINUUM  
■ SE CONTINUUM,  
DEFINIZIONE DI CUT OFF

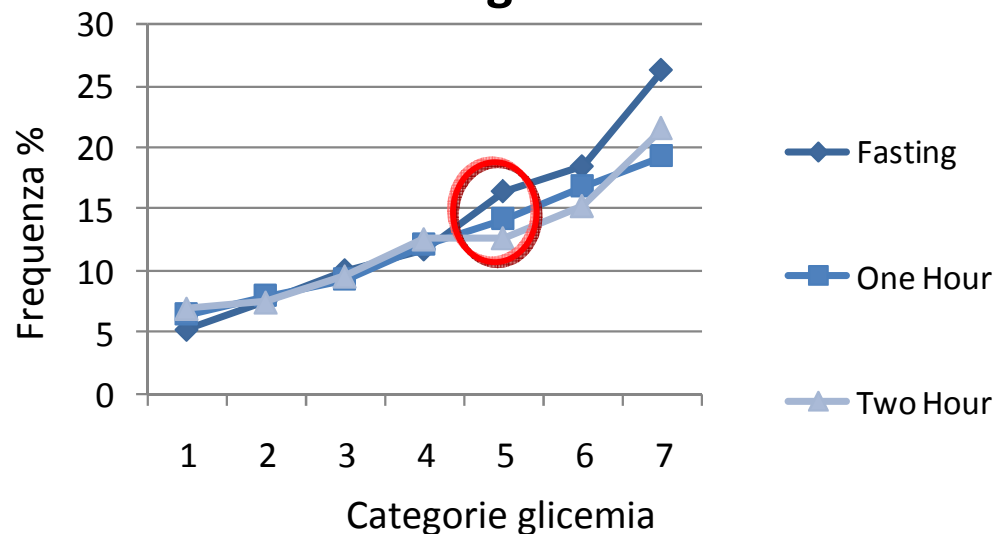


# Categorie di concentrazione di glucosio

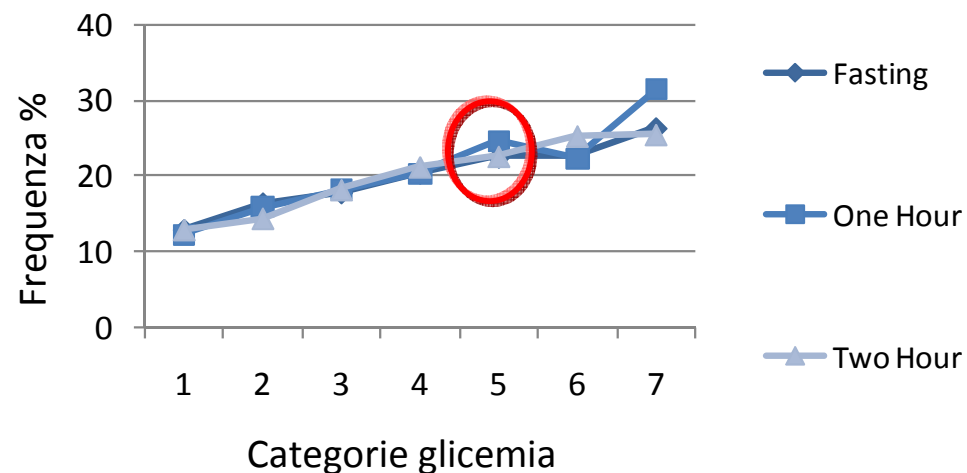
	Digiuno		1h		2h	
	mg/dl	mmol/l	mg/dl	mmol/l	mg/dl	mmol/l
1	<75	<4.2	<110	<6.2	<88	<4.9
2	75-79	4.2-4.4	110-129	6.2-7.2	88-103	4.9-5.8
3	80-84	4.5-4.7	130-149	7.3-8.3	104-123	5.9-6.8
4	85-89	4.8-4.9	150-169	8.4-9.4	124-141	6.9-7.8
5	90-94	5.0-5.2	170-199	9.5-10.5	142-159	7.9-8.8
6	95-99	5.3-5.5	199-218	10.6-11.6	160-177	8.9-9.8
7	≥100	≥5.5	≥219	≥11.7	≥178	≥9.9

# OUTCOME e CATEGORIE GLICEMICHE

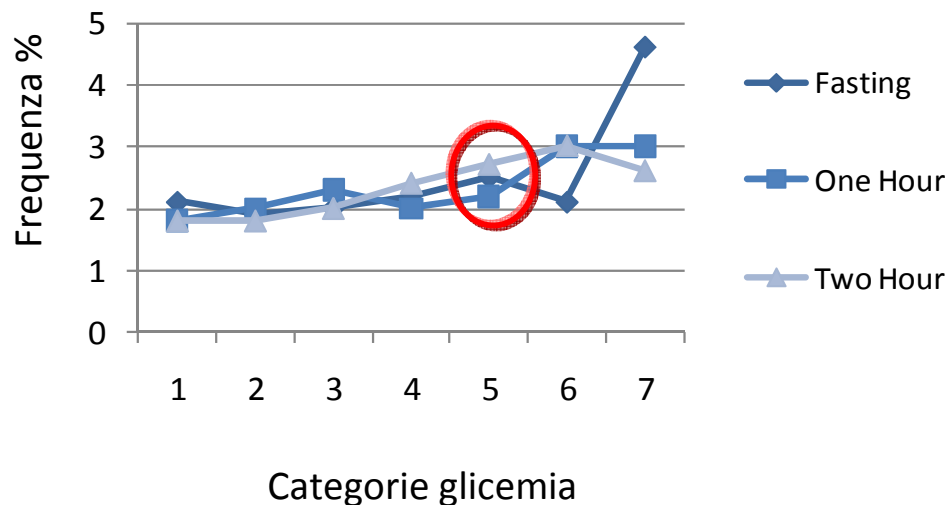
## Birth Weight > 90th Percentile



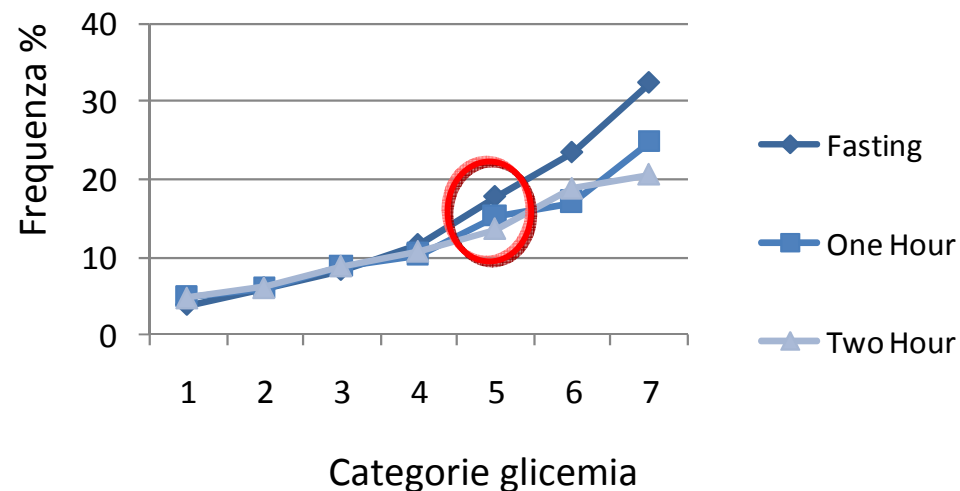
## Primary C-Section



## Clinical Hypoglycemia

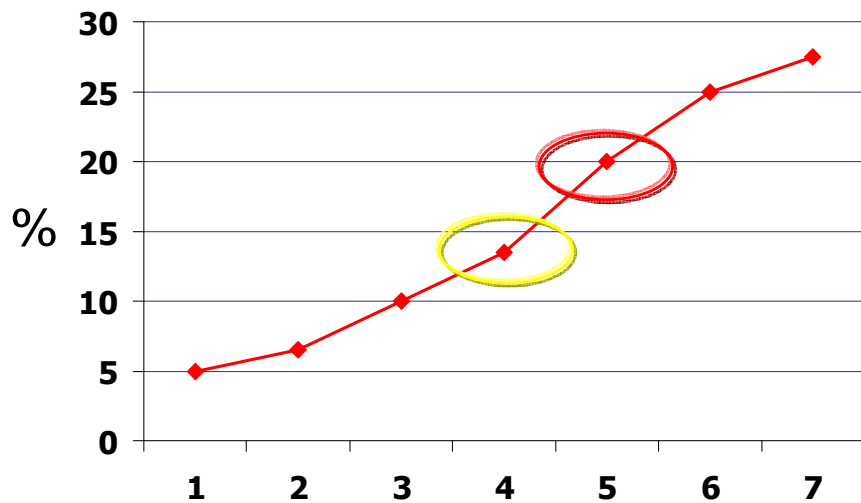


## Cord C-Peptide >90th Percentile

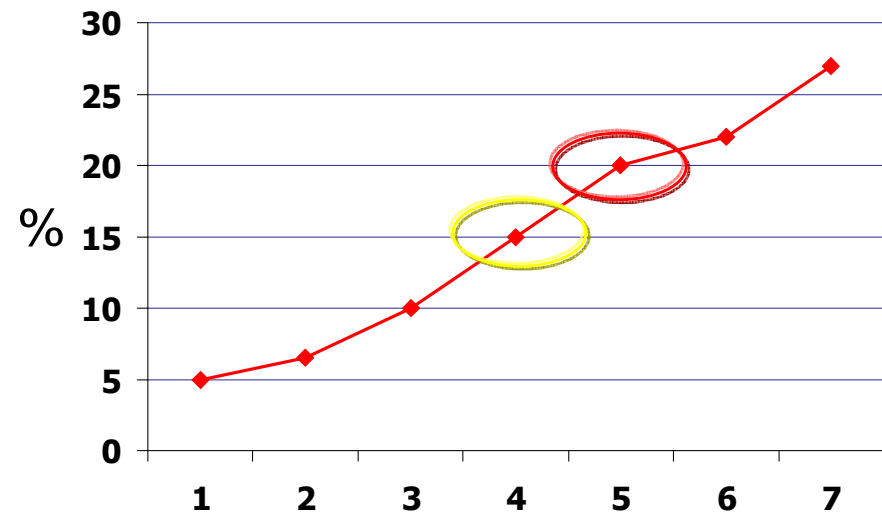


# C-peptide Categori and neonatal features

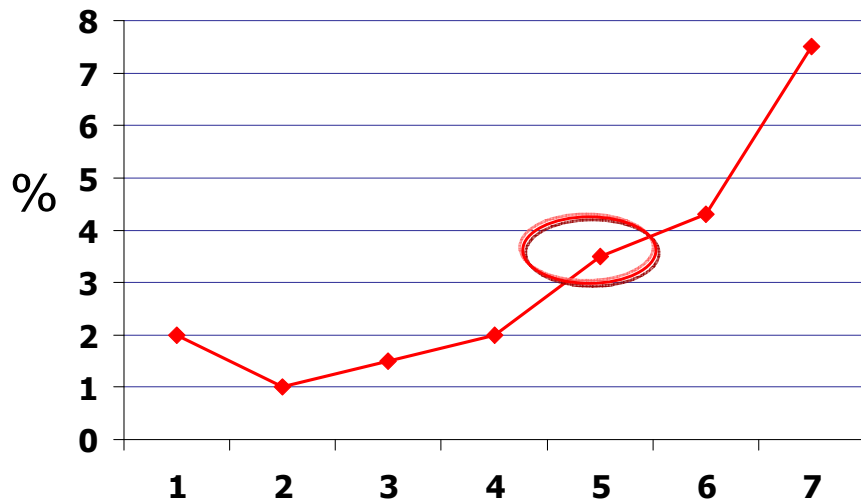
Weight > 90<sup>th</sup> percentile



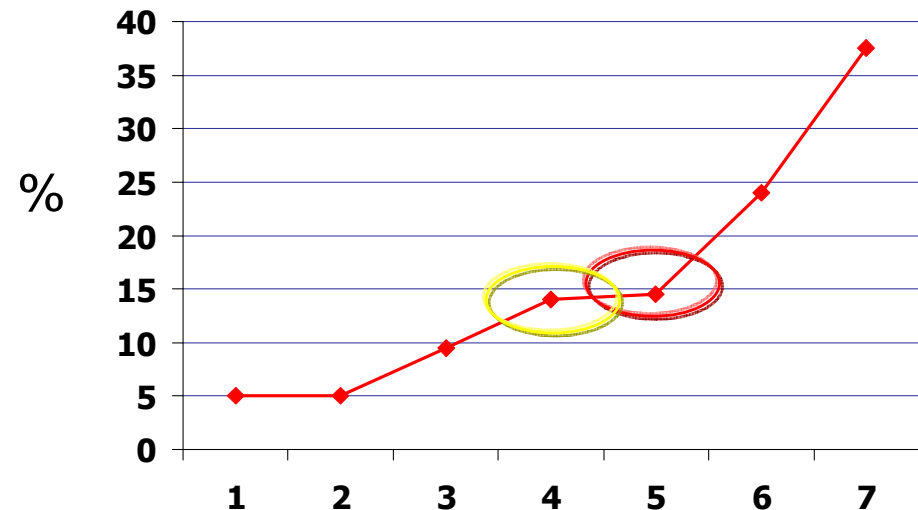
Skin-thickness > 90<sup>th</sup> percentile



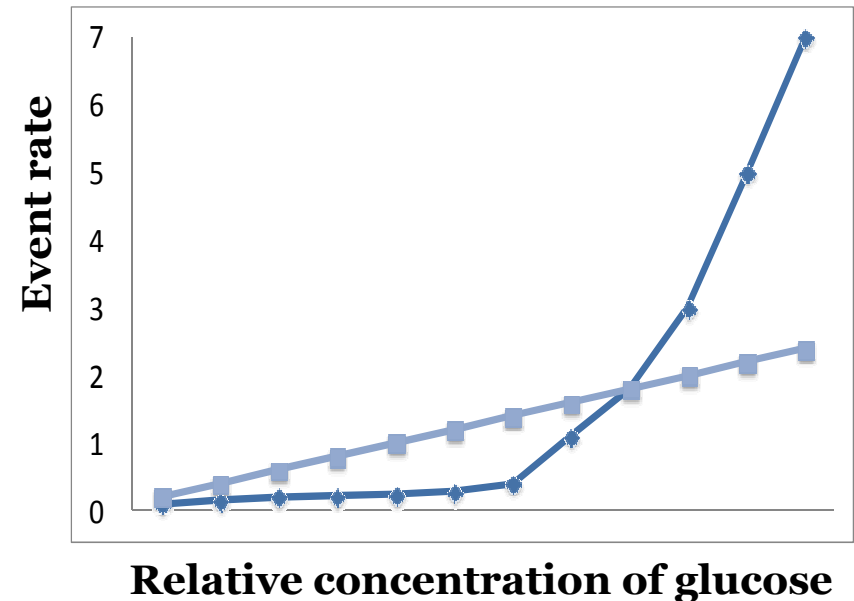
Clinical neonatal hypoglycaemia



Biochem. neonatal hypoglycaemia



Because associations were continuous with no obvious thresholds at which risks increased, it was concluded that a consensus was required to translate these results into clinical practice.



committee of “experts” to resolve issues

IADPSG CONSENSUS PANEL, 2008





# Categorie di concentrazione di glucosio

	Digiuno		1h		2h	
	mg/dl	mmol/l	mg/dl	mmol/l	mg/dl	mmol/l
1	<75	<4.2	<110	<6.2	<88	<4.9
2	75-79	4.2-4.4	110-129	6.2-7.2	88-103	4.9-5.8
3	80-84	4.5-4.7	130-149	7.3-8.3	104-123	5.9-6.8
4	85-89	4.8-4.9	150-169	8.4-9.4	124-141	6.9-7.8
5	90-94	5.0-5.2	170-199	9.5-10.5	142-159	7.9-8.8
6	95-99	5.3-5.5	199-218	10.6-11.6	160-177	8.9-9.8
7	≥100	≥5.5	≥219	≥11.7	≥178	≥9.9

### Panel Members

Boyd Metzger, Chair  
Steve Gabbe, Co-Chair  
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Bill Callaghan  
Pat Catalano  
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Dana Dabelea  
Peter Damm  
Alberto de Leiva  
Alan Dyer  
Lucinda England  
Cathy Fagen  
Denice Feig  
Assiamira Ferrara  
Judith Fradkin  
Patti Geil  
Gilman Grave  
David Hadden  
Teresa Hillier  
Yuji Hiramatsu  
Moshe Hod  
Ghislaine Houde  
Maribeth Inturrisi  
Hak Chul Jang  
Lois Jovanovic  
Alexandra Kautzky-Willer

**24-28 SETTIMANE**

**OGTT 75 g**

**Plasma Glucose Concentrations at Specified OR**

Glucose	Odds Ratio		
mg/dl*	1.5	1.75	2.0
FPG	90	92	95
1-Hr PG	167	180	191
2-Hr PG	142	153	162

**Diagnosi di DIABETE GESTAZIONALE**  
**se uno o più valori sono al di sopra**

**\*Mean of threshold values for : birthweight, cord serum C-peptide,  
% body fat >90<sup>th</sup> percentile**

**IADPSG Consensus Panel, Diab Care 2010**

### Panel Members

Sue Kirkman  
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**Annunziata Lapolla**  
Julia Lowe  
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Catherine Spong  
Takashi Sugiyama  
Elisabeth Trimble  
Surenda Varma  
Huixia Yang  
Ichiro Yasuhi

# Frequencies of Outcomes: Glucose Values $<$ or $\geq$ Threshold

<b>Outcome</b>	<b>% All Values <math>&lt;</math> Threshold</b>	<b>% Any <math>\geq</math> 92/180/153</b>
<b>Birthweight <math>&gt;90^{\text{th}}</math> percentile</b>	<b>8.3</b>	<b>16.2</b>
<b>Cord C-peptide <math>&gt;90^{\text{th}}</math> percentile</b>	<b>6.7</b>	<b>17.5</b>
<b>% Body fat <math>&gt;90^{\text{th}}</math> percentile</b>	<b>8.5</b>	<b>16.6</b>
<b>Preeclampsia</b>	<b>4.5</b>	<b>9.1</b>
<b>Preterm birth (<math>&lt;37</math> weeks)</b>	<b>6.4</b>	<b>9.4</b>
<b>Shoulder dystocia/birth injury</b>	<b>1.3</b>	<b>1.8</b>
<b>Primary Cesarean section</b>	<b>16.8</b>	<b>24.4</b>

# Potenziale **applicazione** della glicemia a digiuno dell'HAP0

Glicemia a digiuno			BW>90° percentile	
Range	n.	%	n.	%
>=90	2784	11.9	491	17.6
80-89	8941	38.3	945	10.6
<80	11591	49.7	785	6.8

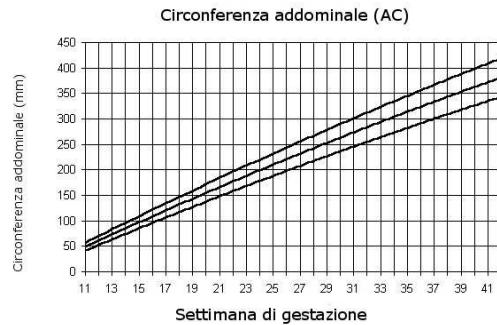
88%

17,4%



# SEGNI INDIRETTI DI "FETAL OVERGROWTH"

**CA > 75° PERCENTILE**



**POLIDRAMNIOS**



**ECCESSIVO  
AUMENTO PONDERALE**

Linee Guida IOM 2009



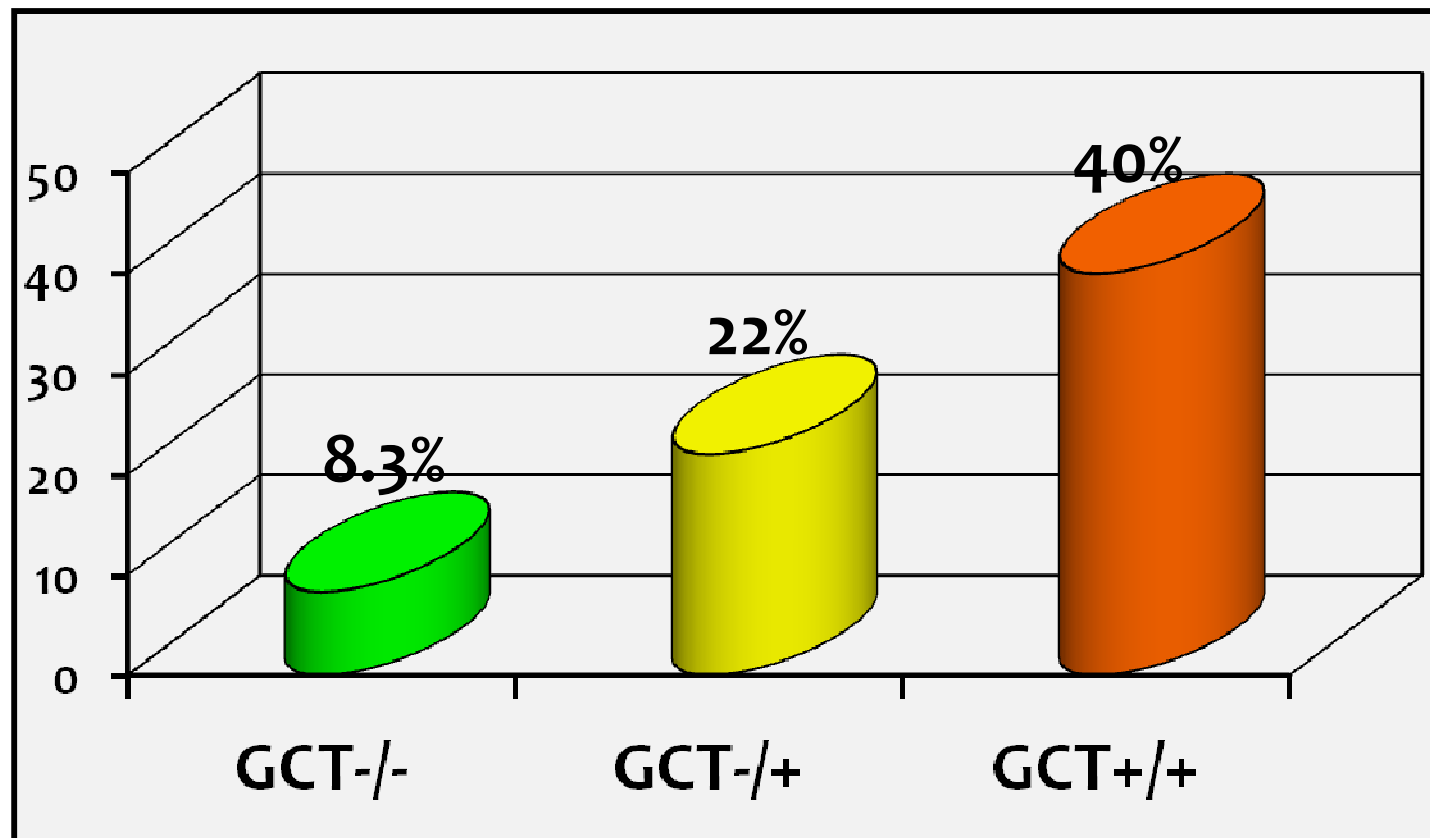
**INCREMENTO SINFISI-FONDO  
> 4 cm ogni 4 settimane**



# Anthropometric characteristics of full-term infants: effects of varying degrees of “normal” glucose metabolism

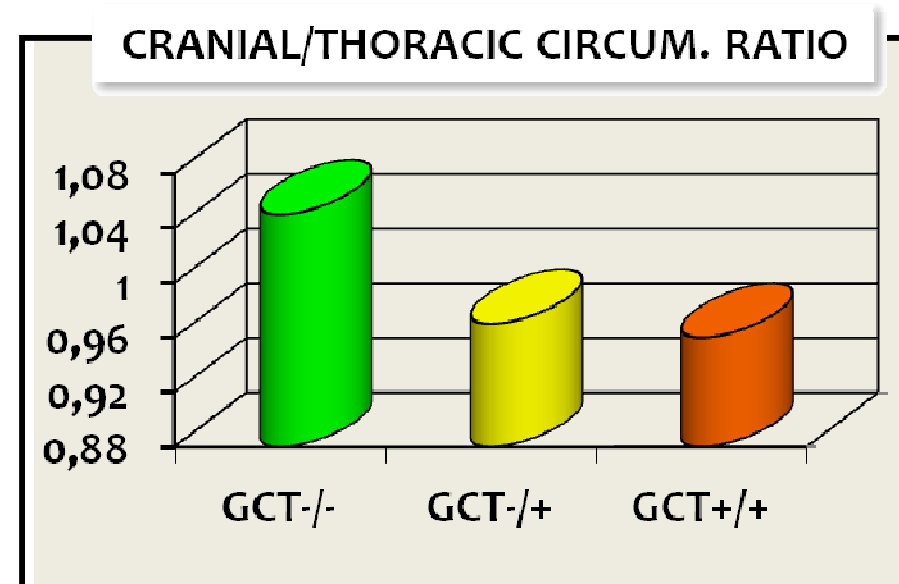
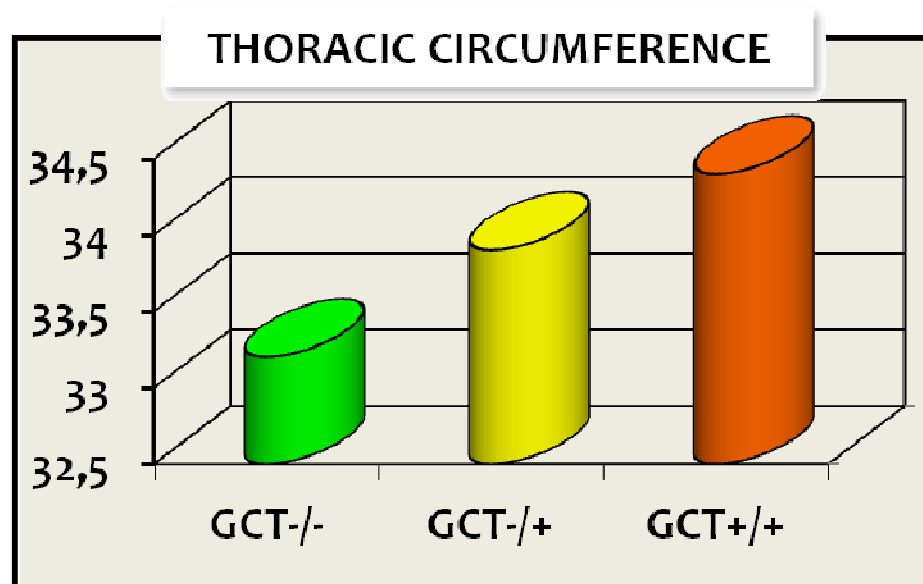
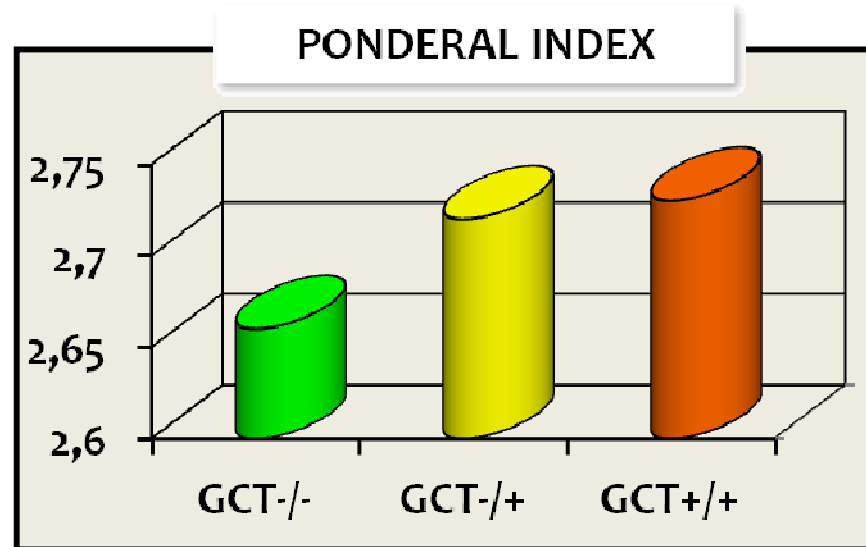
Giorgio Mello<sup>1</sup>, Elena Parretti<sup>1</sup>, Federico Mecacci<sup>1</sup>, Roberto Lucchetti<sup>1</sup>,  
Domenico Cianciulli<sup>2</sup>, Corrado Lagazio<sup>3</sup>, Monica Pratesi<sup>3</sup>, and  
Gianfranco Scarselli<sup>1</sup>

## LGA INFANTS

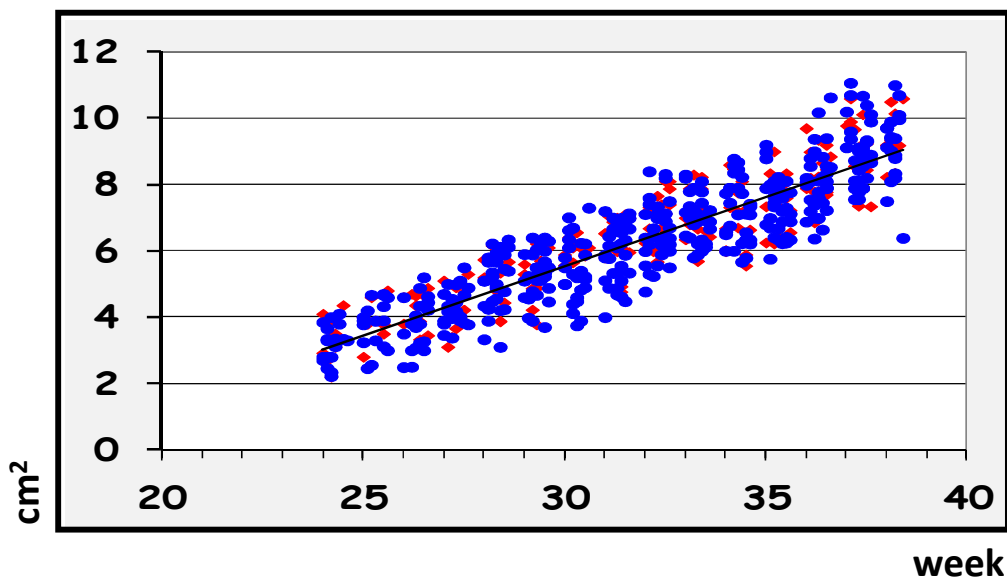


# Anthropometric characteristics of full-term infants: effects of varying degrees of “normal” glucose metabolism

## NEONATAL BODY PROPORTIONS, AGA INFANTS

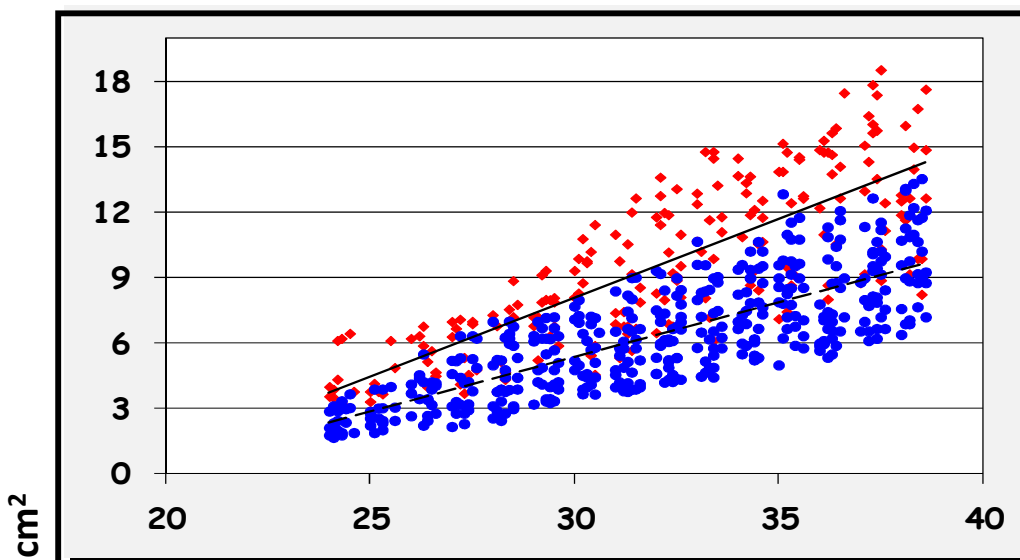


## LEAN BODY MASS MID-THIGH CENTRAL AREA



	$r^2$	$\Delta r^2$
Gestational age	0.60	-
(Gestational age) <sup>2</sup>	0.73	0.13
Neonatal sex	0.78	0.05

## FAT BODY MASS MID-THIGH SUBCUTANEOUS AREA



	$r^2$	$\Delta r^2$
Group	0.45	-
(Gestational age) <sup>2</sup>	0.49	0.04
1-hr post prandial glycemia	0.61	0.05
Pre-pregnancy BMI	0.64	0.03

**Group 1 GCT +**   **Group 2 GCT -**   week

## 739 MOTHERS WITH NEGATIVE SCREENING TEST FOR GDM

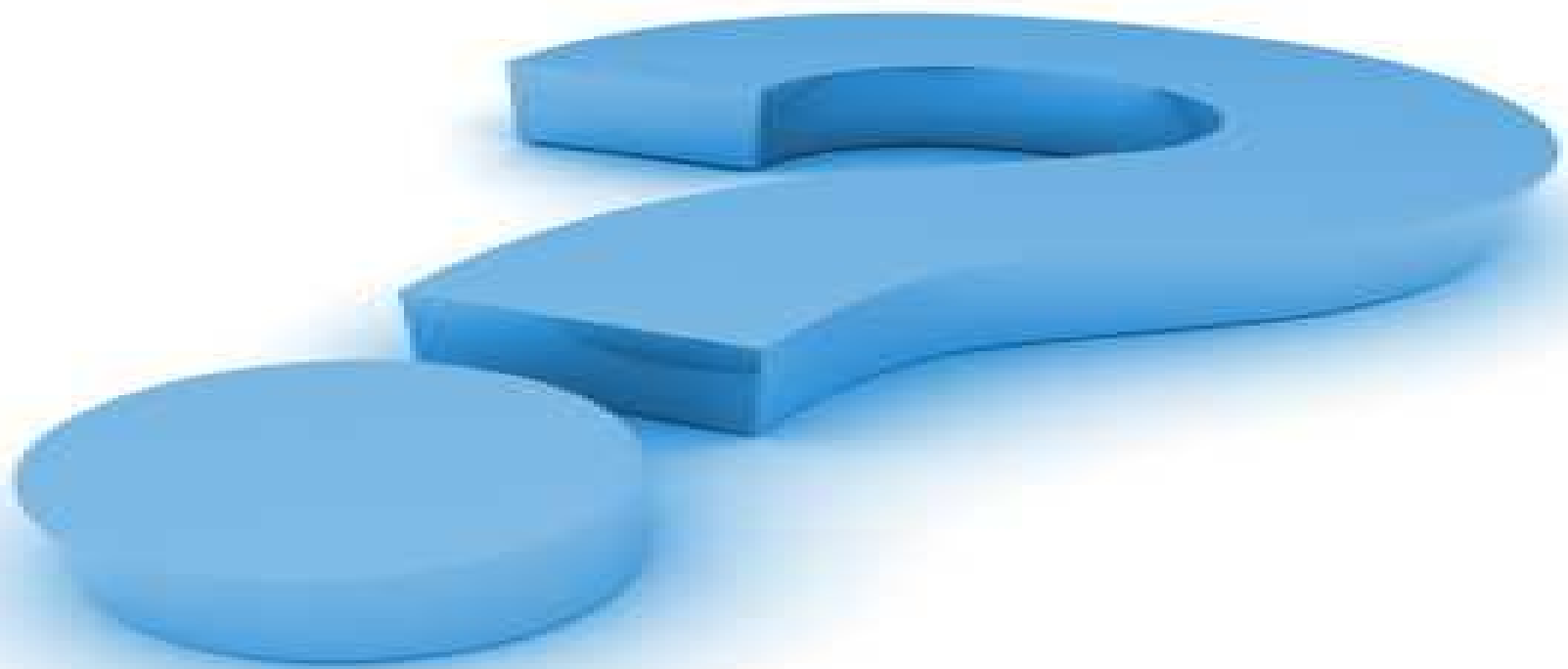
followed by Careggi University Hospital, Florence (January 2011-October 2012)

MATERNAL AND FETAL OUTCOMES	FPG $\geq$ 92 mg/dl (177)	FPG $\leq$ 92 mg/dl (562)	Statistical significance
PREGRAVIDIC BMI	21.24 $\pm$ 0.43	26.74 $\pm$ 8.18	n.s.
G.A. at birth	39.7 $\pm$ 0.7	39.2 $\pm$ 0.21	n.s.
AGA	82/111 (73.88%)	284/363 (78.24%)	n.s.
SGA	12/111 (10.81%)	54/363 (14.87%)	n.s.
<b>LGA</b>	<b>17/111 (15.32%)</b>	<b>25/363 (6.89%)</b>	<b>P=0.01</b>
PI $\geq$ 2.85	30/111 (27.02%)	95/363 (26.17%)	n.s.
<b>Birth weight <math>\geq</math> 4000 g</b>	<b>14/111 (12.61%)</b>	<b>20/363 (5.5%)</b>	<b>P=0.01</b>
Birthweight $\geq$ 4500 g	2/111 (1.8%)	2/363 (0.55%)	n.s.

M NEONATAL OUTCOME	FPG $\geq$ 92 mg/dl PI $\geq$ 2.85	FPG < 92 mg/dl PI $\geq$ 2.85	<i>p</i>
AGA	17/111	76/363	n.s.
<b>LGA</b>	<b>12/111 (10,8%)</b>	<b>11/363 (3,0%)</b>	<b>P=0.002</b>

*Mello G., Mecacci F., Nardini C. et al. : Personal data*

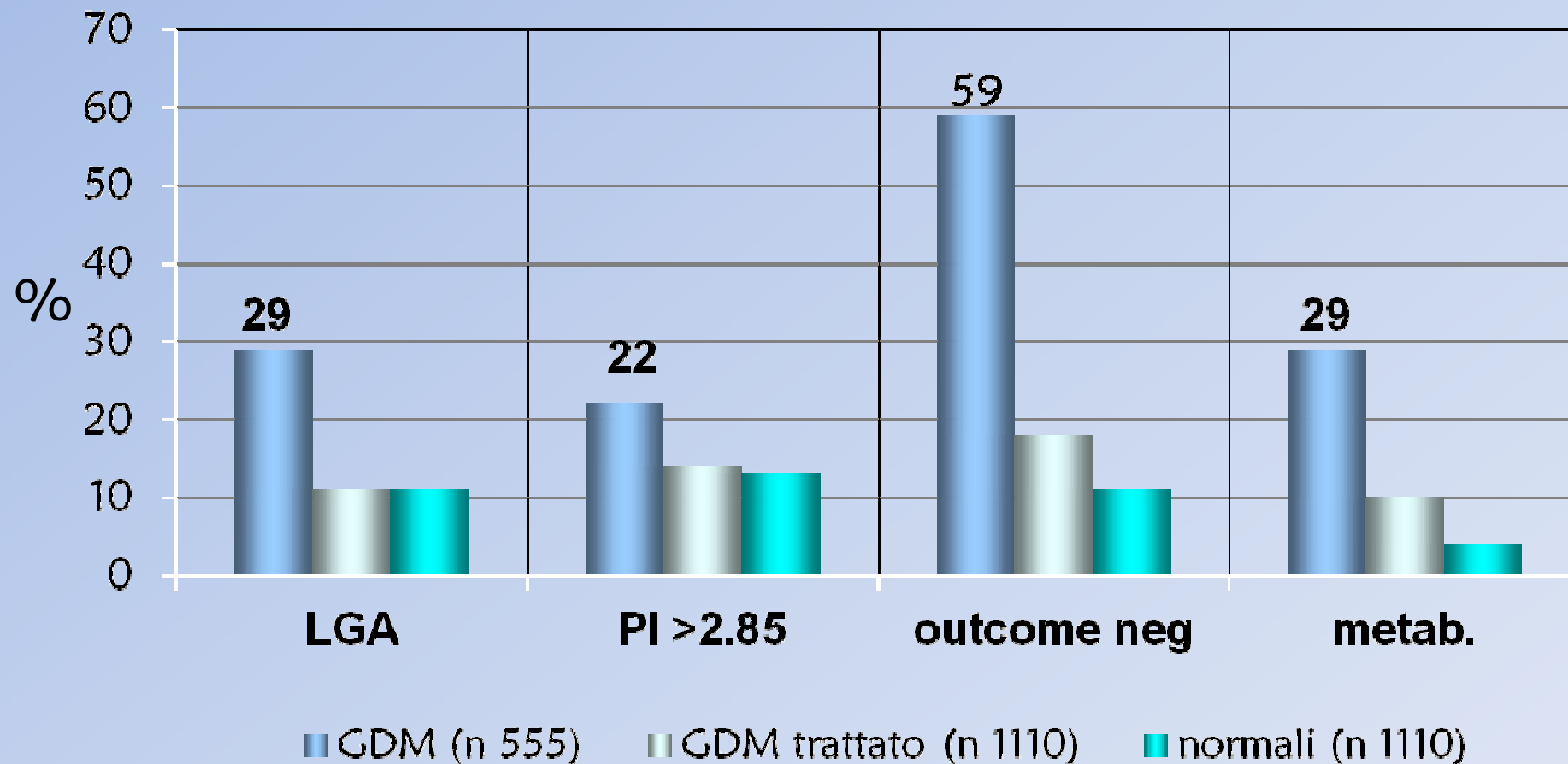
...ed allora...



...che fare...

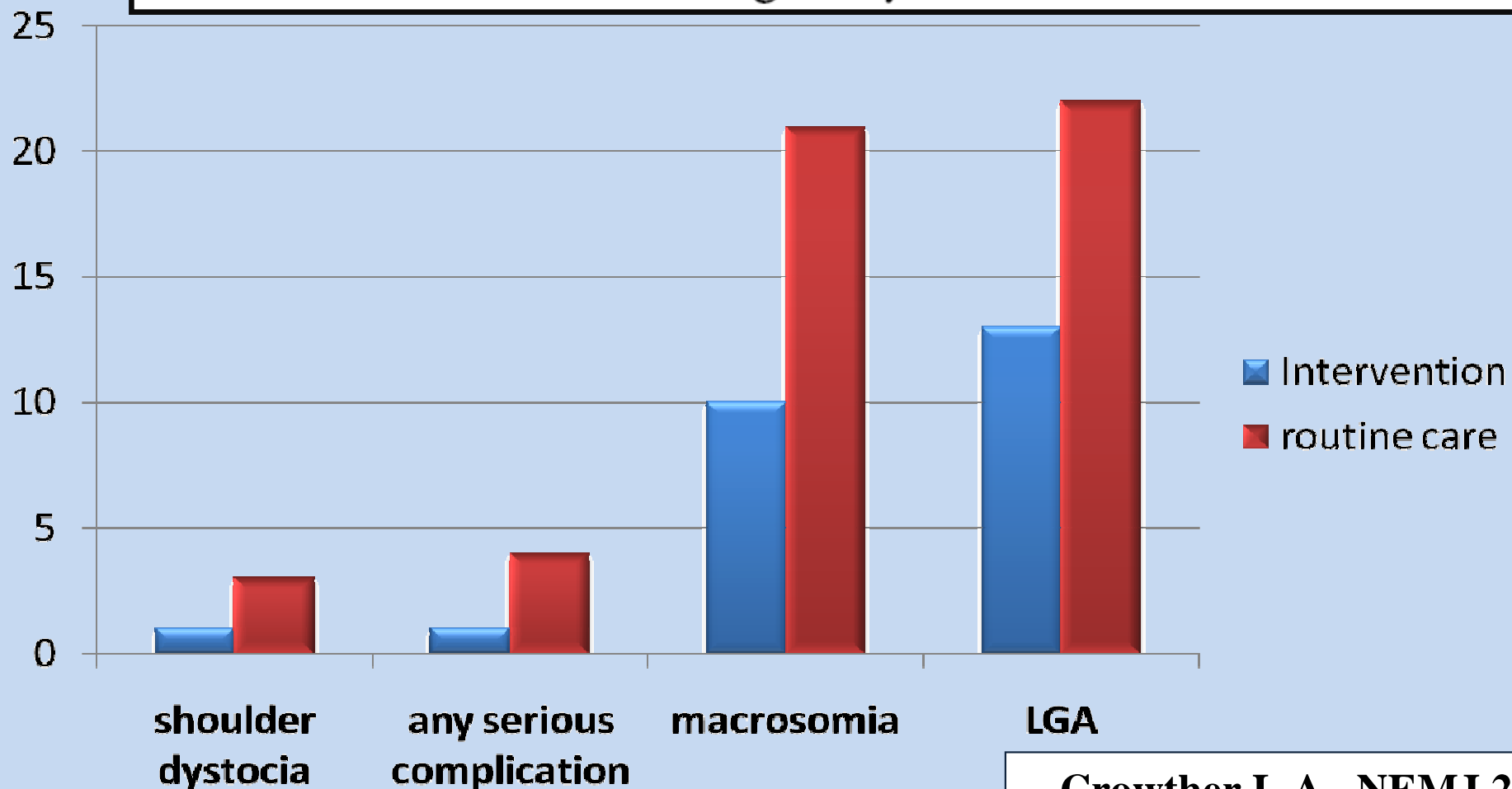


# DIABETE GESTAZIONALE: CONSEGUENZE DEL NON TRATTAMENTO



# *The* NEW ENGLAND JOURNAL *of* MEDICINE

## Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes



Crowther L.A. NEMJ 2005

# IMPORTANZA DEL TRATTAMENTO

## Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes

*The NEW ENGLAND JOURNAL of MEDICINE*

	ROUTINE CARE (N = 510)	INTERVENTION (N = 490)	P
<b>BIRTH WEIGHT</b>	3482 $\pm$ 660	3335 $\pm$ 551	< .001
<b>LGA</b>	22%	13%	< .001
<b>MACROSOMIA</b>	21%	10%	< .001
<b>PREECLAMPSIA</b>	18%	12%	0.02
<b>SGA</b>	7%	7%	ns

Crowther L.A., et al. NEJM 352:2477-86, 2005

# IMPORTANZA DEL TRATTAMENTO

The NEW ENGLAND JOURNAL of MEDICINE

## A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes

**Table 4. Maternal Outcomes.\***

Outcome Variable	Treatment Group (N=476)	Control Group (N=455)	Relative Risk (97% CI)	P Value
Induction of labor — no. (%)	130 (27.3)	122 (26.8)	1.02 (0.81–1.29)	0.86
Cesarean delivery — no. (%)	128 (26.9)	154 (33.8)	0.79 (0.64–0.99)	0.02
Shoulder dystocia — no. (%)	7 (1.5)	18 (4.0)	0.37 (0.14–0.97)	0.02
Preeclampsia — no. (%)	12 (2.5)	25 (5.5)	0.46 (0.22–0.97)	0.02
Preeclampsia or gestational hypertension — no. (%)	41 (8.6)	62 (13.6)	0.63 (0.42–0.96)	0.01
Body-mass index at delivery†	31.3±5.2	32.3±5.2		<0.001
Weight gain — kg‡	2.8±4.5	5.0±3.3		<0.001

Mark B. Landon, N ENGL J MED 361;14 OCTOBER 1, 2009

# Treatment of Mild GDM Reduces Adverse Outcome

NEONATAL OUTCOME	NICHD RCT		P
	Not treated	Treated	
BW >90 <sup>TH</sup> PERCENTILE	14.5	7.1	<0.001
C-PEPTIDE >95 <sup>TH</sup> PERCENTILE	22.8	17.7	0.07
NICU ADMISSION	11.6	9.0	0.19
SHOULDER DYSTOCIA	4.0	1.5	0.02

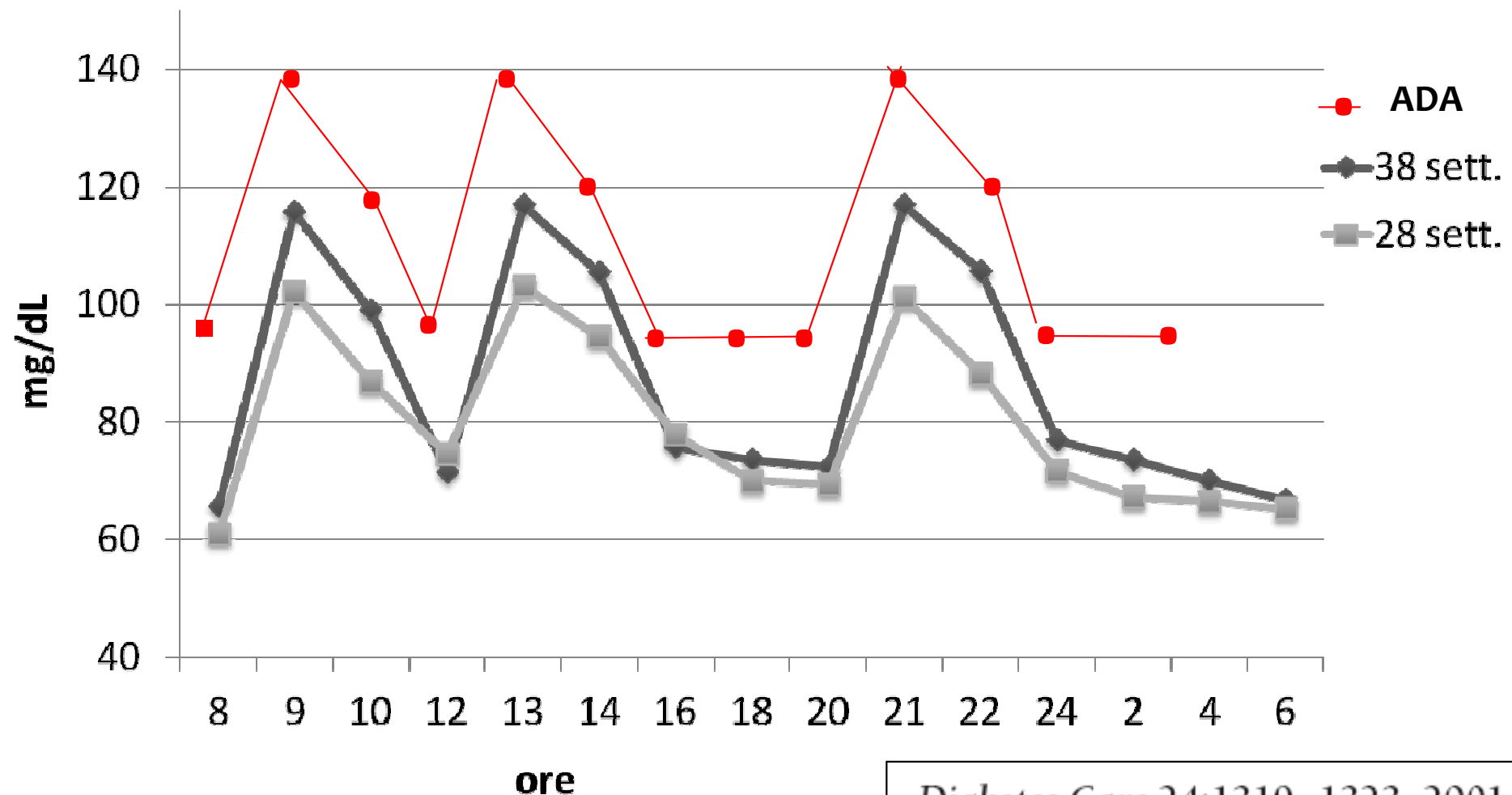
*Landon MB et al. NEJM 2009,361:1339-48*

## WHAT DOES “EUGLYCEMIA” MEAN FOR THE FLORENTINE GROUP?

# Third-Trimester Maternal Glucose Levels From Diurnal Profiles in Nondiabetic Pregnancies

ELENA PARRETTI, MD  
FEDERICO MECACCI, MD  
MARTA PAPINI, MD  
RICCARDO CIONI, MD, MSC

LUCIA CARIGNANI, MD  
MARCELLA MIGNOSA, MD  
PASQUALE LA TORRE, MD  
GIORGIO MELLO, MD

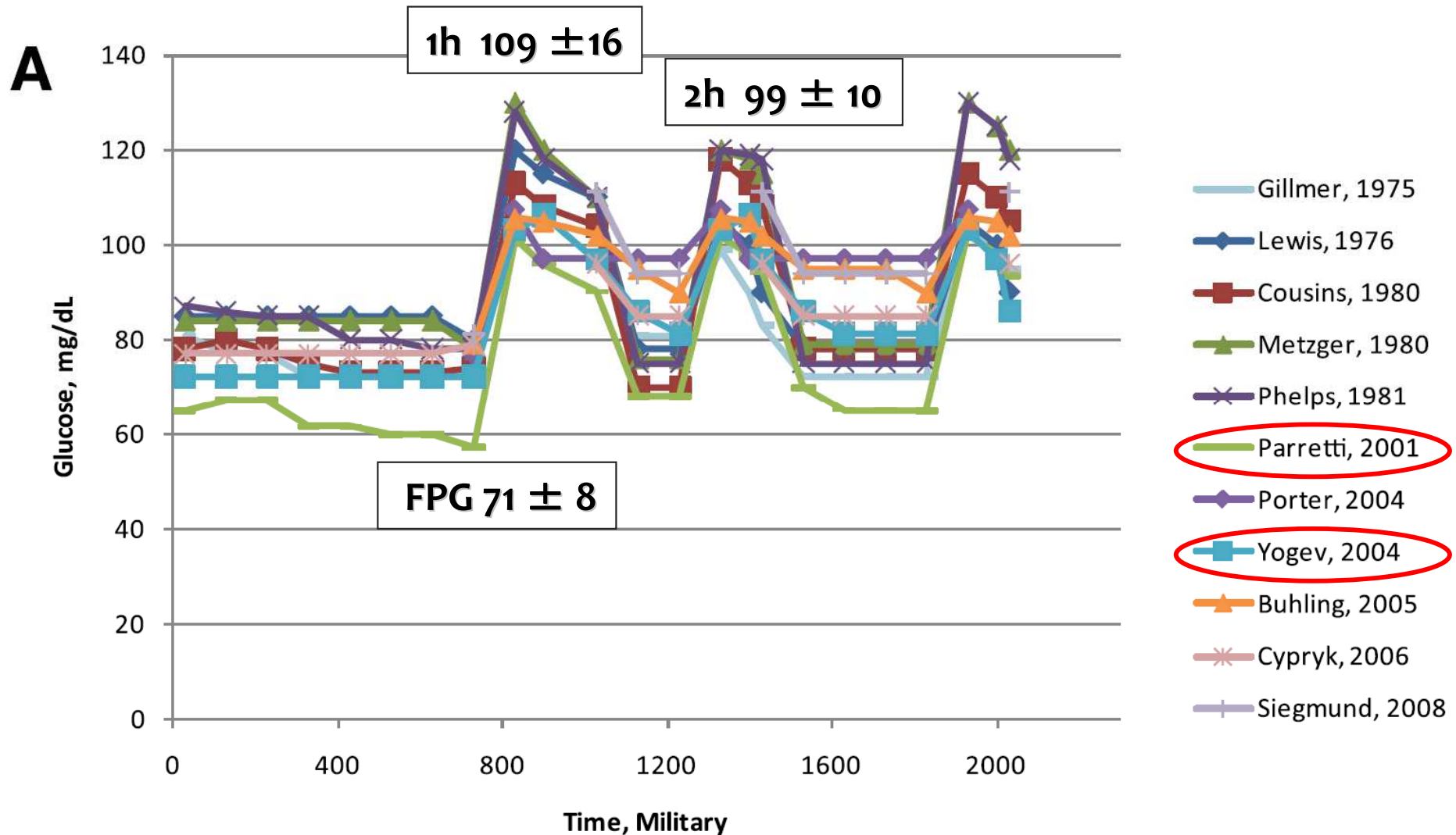


*Diabetes Care* 24:1319–1323, 2001



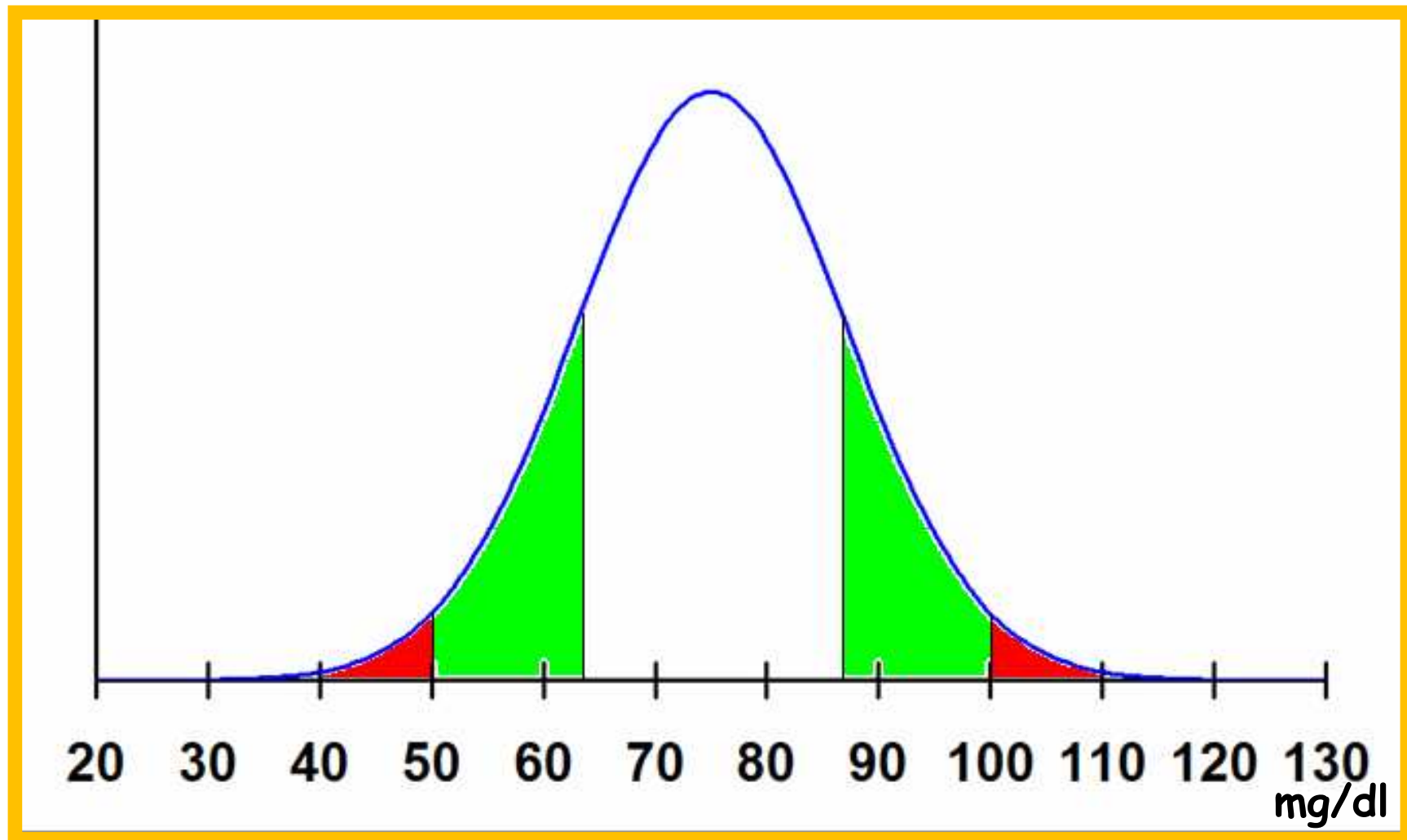
# What does “euglycemia” mean for the Florentine group?

*Patterns of glycemia in normal pregnancy*

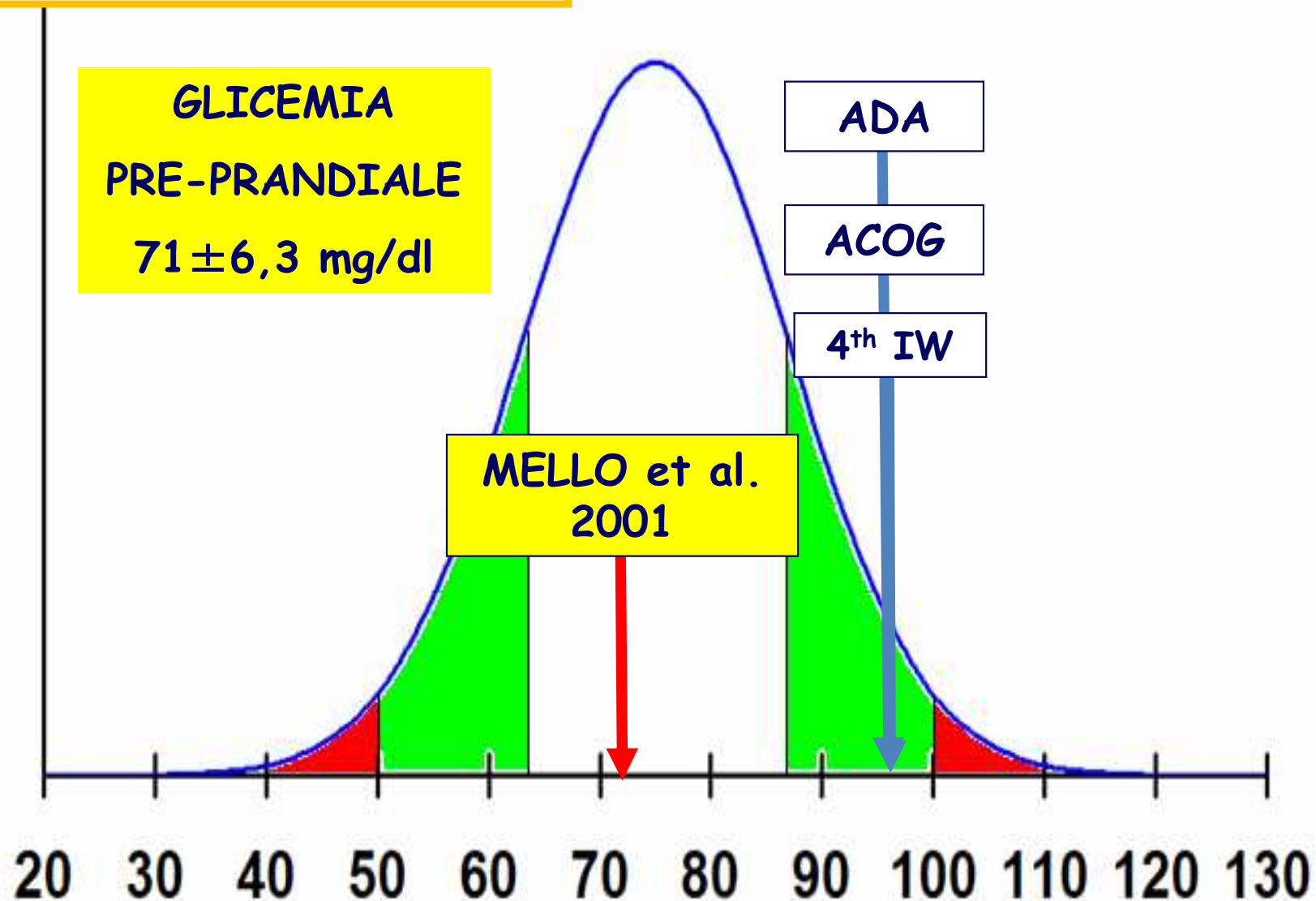


# What is Normal?

## Statistical Evaluation of CGMS Data



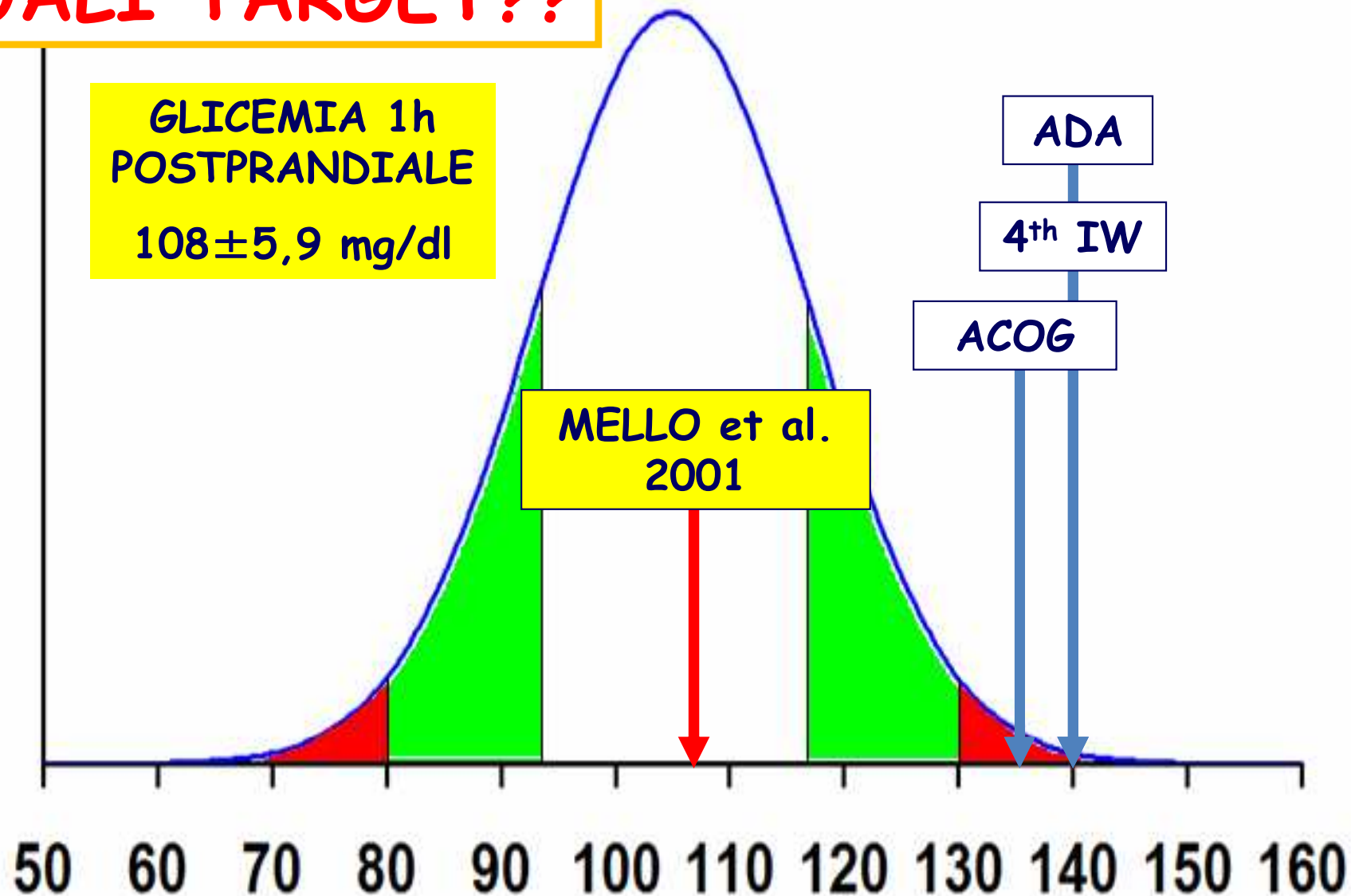
# QUALI TARGET??



**Third-Trimester Maternal Glucose Levels  
From Diurnal Profiles in Nondiabetic  
Pregnancies**

*Diabetes Care* 24:1319–1323, 2001

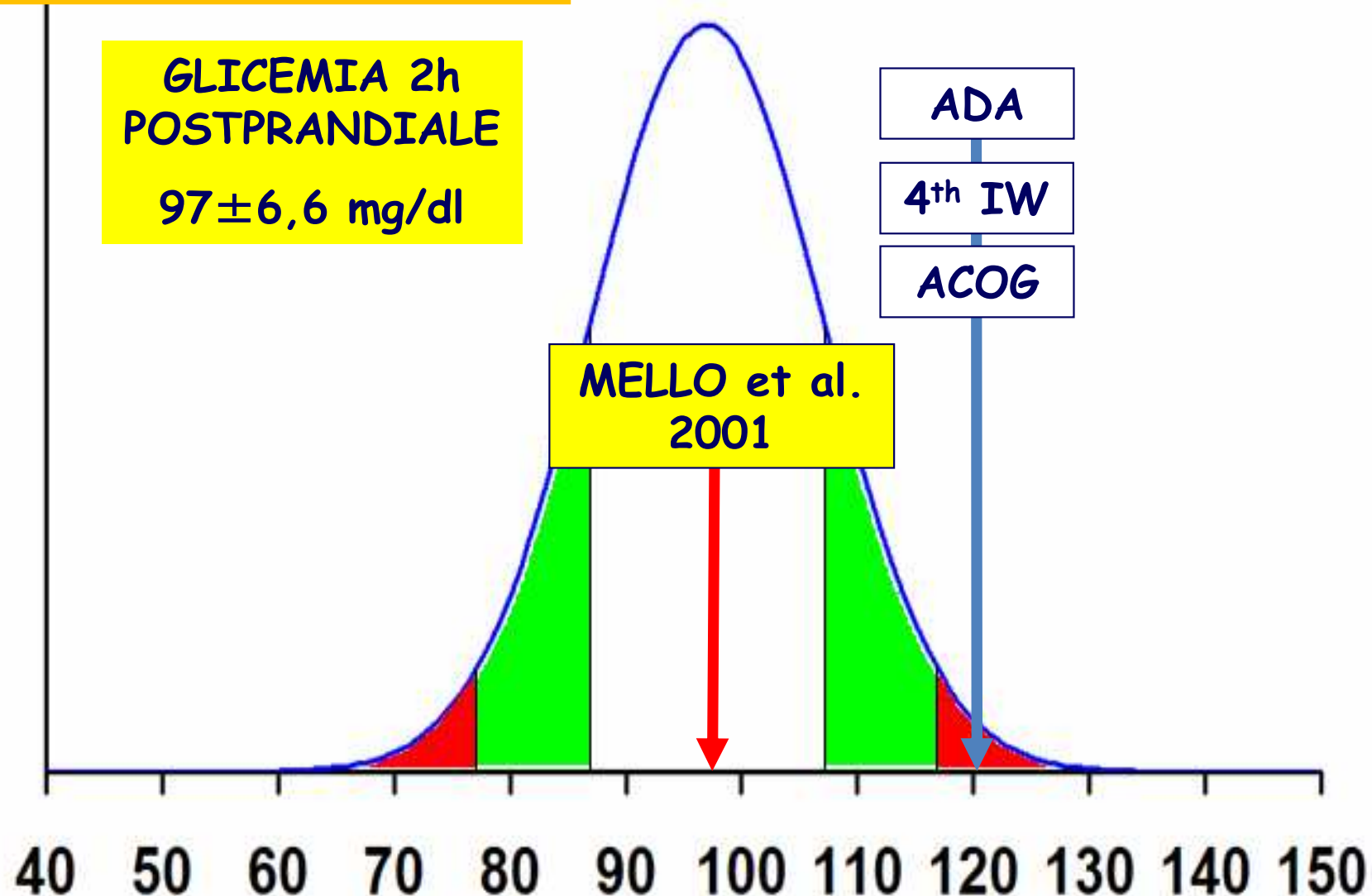
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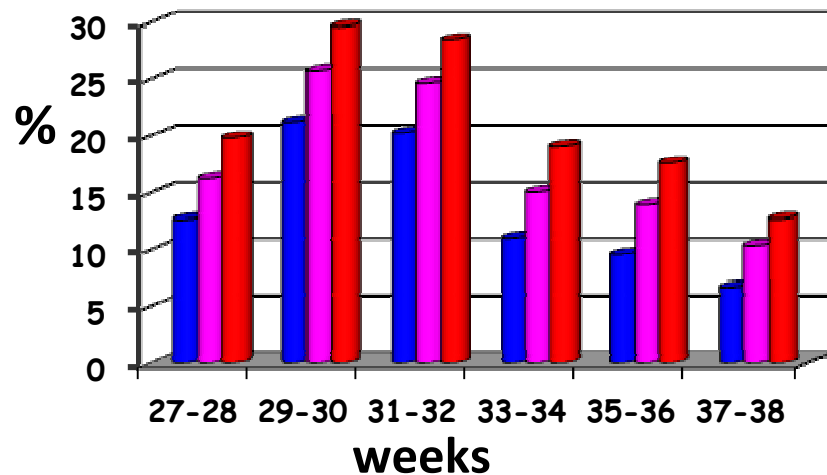
# Post prandial glucose excursion in non-diabetic pregnancies

181 pregnant women with normal glucose tolerance

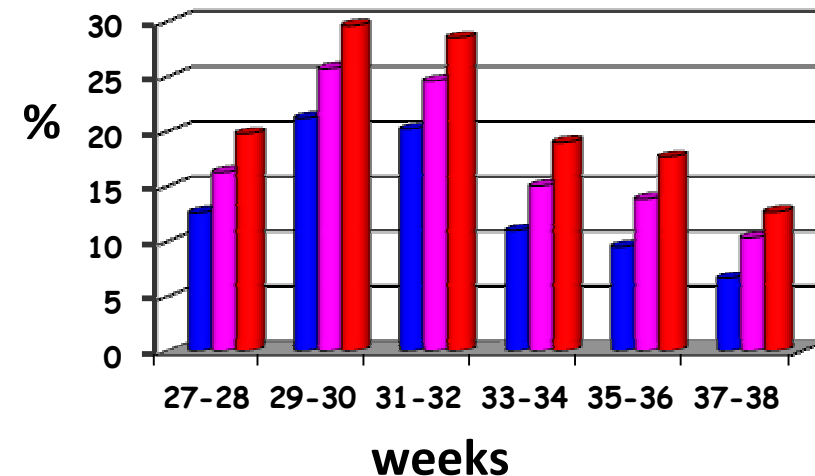
	No of cases	1h-pp glucose excursion (mg/dl)	Daily glucose (mg/dl)
Group 1	48	$\leq 15$	$81,9 \pm 5.5$
Group 2	79	$>15 \leq 30$	$84,1 \pm 6.1$
Group 3	54	$>30 \leq 45$	$85,6 \pm 6.4$

## Growth rates of fetal fat body mass

Anterior abdominal wall thickness



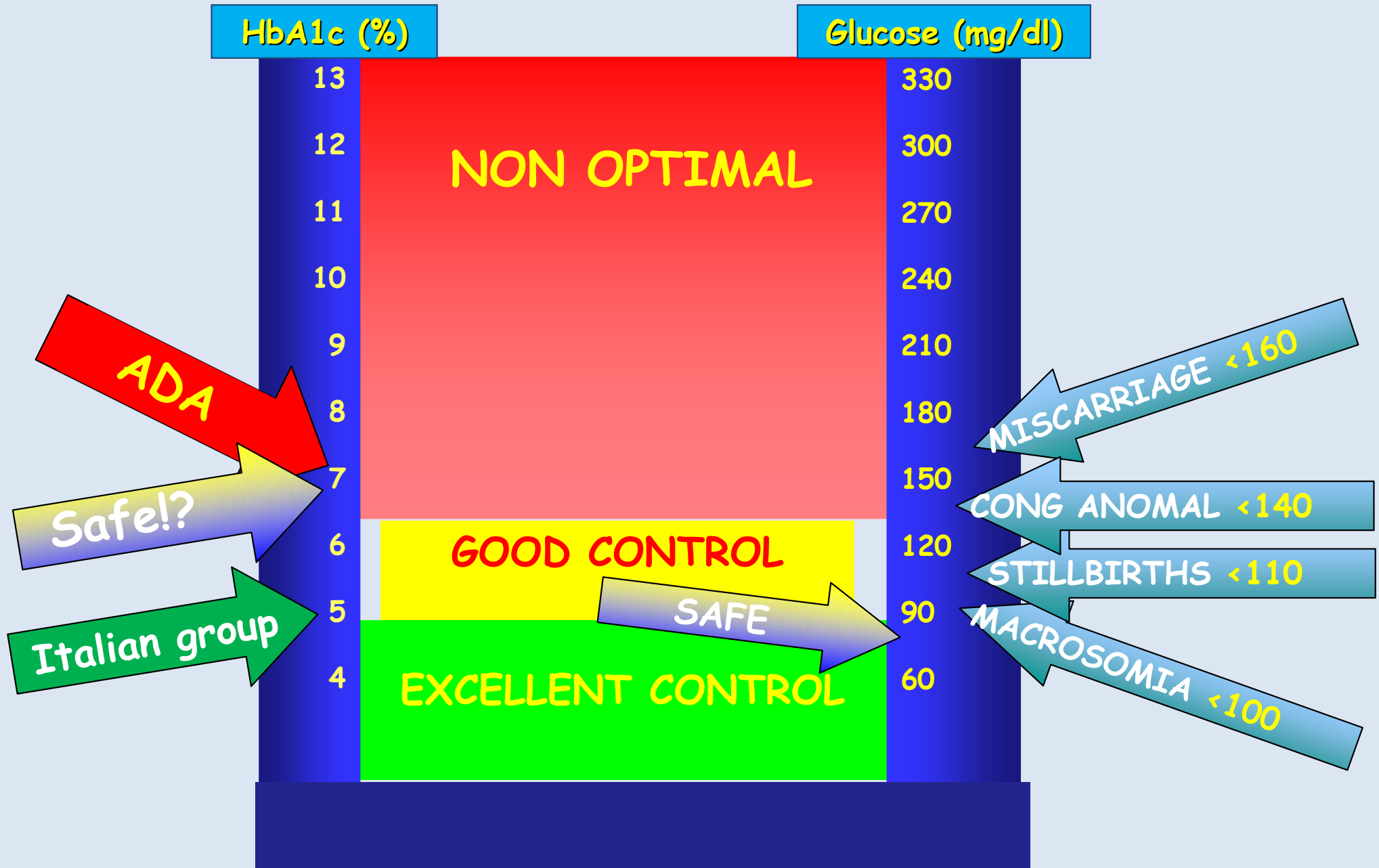
Mid-thigh subcutaneous area



Repeated measures of ANOVA  $p < .0028$  Group differences **GROUP 1** vs **GROUP 2** vs **GROUP 3**

# GLYCEMIC THRESHOLDS FOR PREVENTION OF DIABETIC FETOPATHY COMPLICATIONS

O.Langer, *Diab Rev* 1996





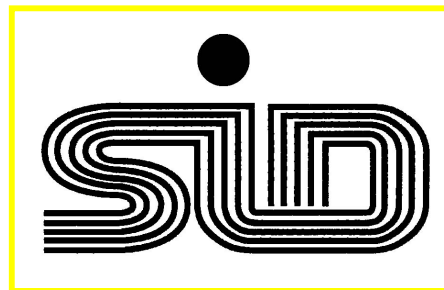
# Screening e diagnosi di GDM

La mancanza di uniformità internazionale, riguardo l'approccio all'accertamento e alla diagnosi di GDM, ha sempre rappresentato un grande ostacolo



The International Association  
of the Diabetes and Pregnancy Study Groups [IADPSG]

Recommendations on the Diagnosis and Classification of  
Hyperglycemia in Pregnancy



The image shows the cover of a "Libretto - ricettario da utilizzarsi nell'ambito del Servizio Sanitario Nazionale" (Libretto - prescription book to be used within the National Health Service). The cover is light blue with a dark blue border. It features a large blue bow graphic. Below the bow, there are fields for "codice fiscale assistito" (assisted fiscal code) and "codice regionale assistito" (assisted regional code), each followed by a series of empty boxes for digits. At the bottom, there are fields for "cognome" (surname) and "nome" (name).

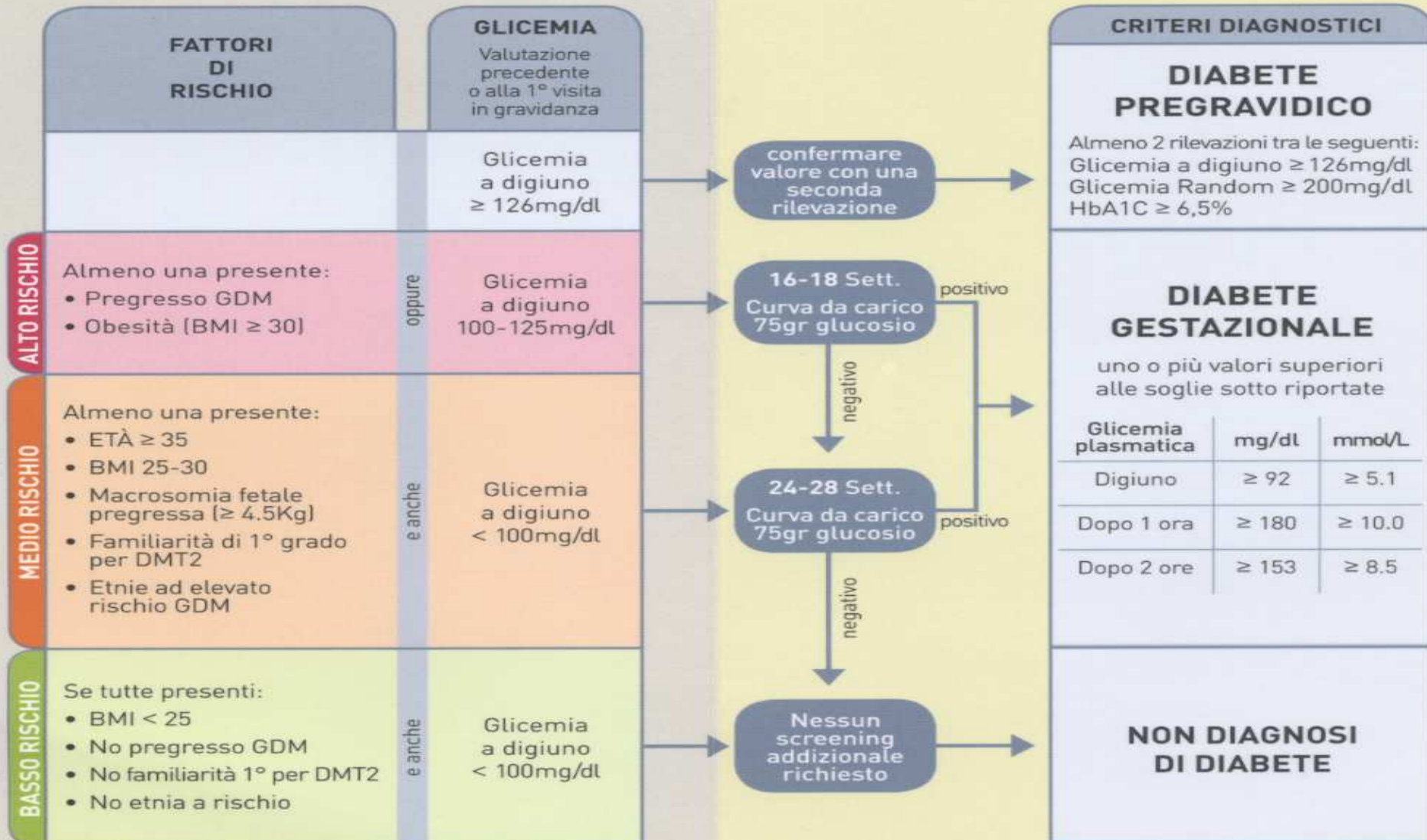
# Raccomandazioni per lo screening e la diagnosi del GDM

AMD-SID, SNLG-ISS, CeVEAS

Aggiornamento 06.07.2011

## Screening sulla base di Fattori di Rischio e Glicemia

## Diagnosi



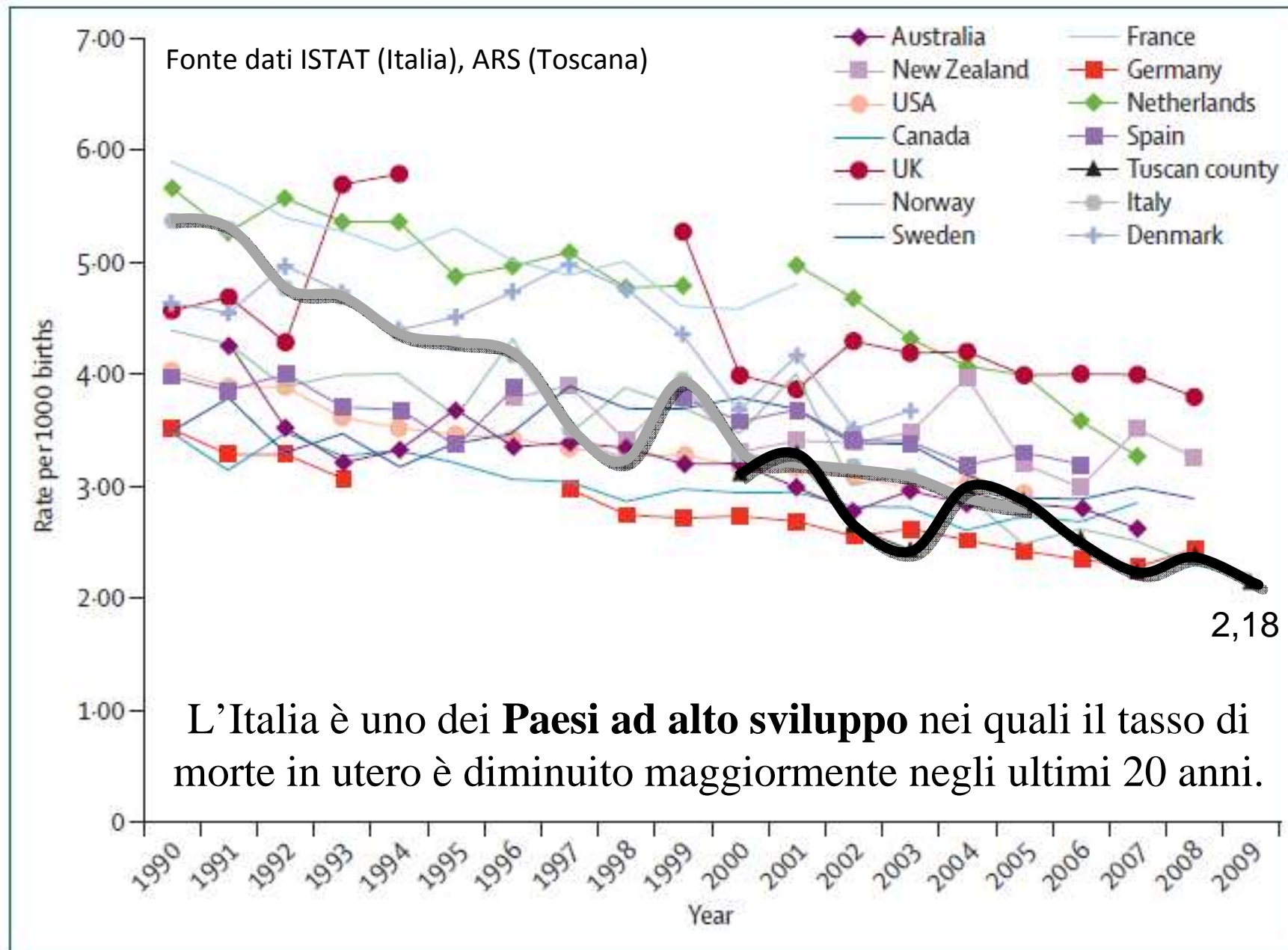


Figure 2: Trends in stillbirth rates at 28 weeks' or more gestation in selected high-income countries, 1990-2008



*To do  
we have to  
caring*

**TIMING**

**ASS**

**NORM**  
repro

**PRE**

to evaluate maternal conditions that can interfere with fetal growth

**MAMMA MIA!!!**

*born"  
d the roots  
a tree*

**GRAZIE PER L'ATTENZIONE**



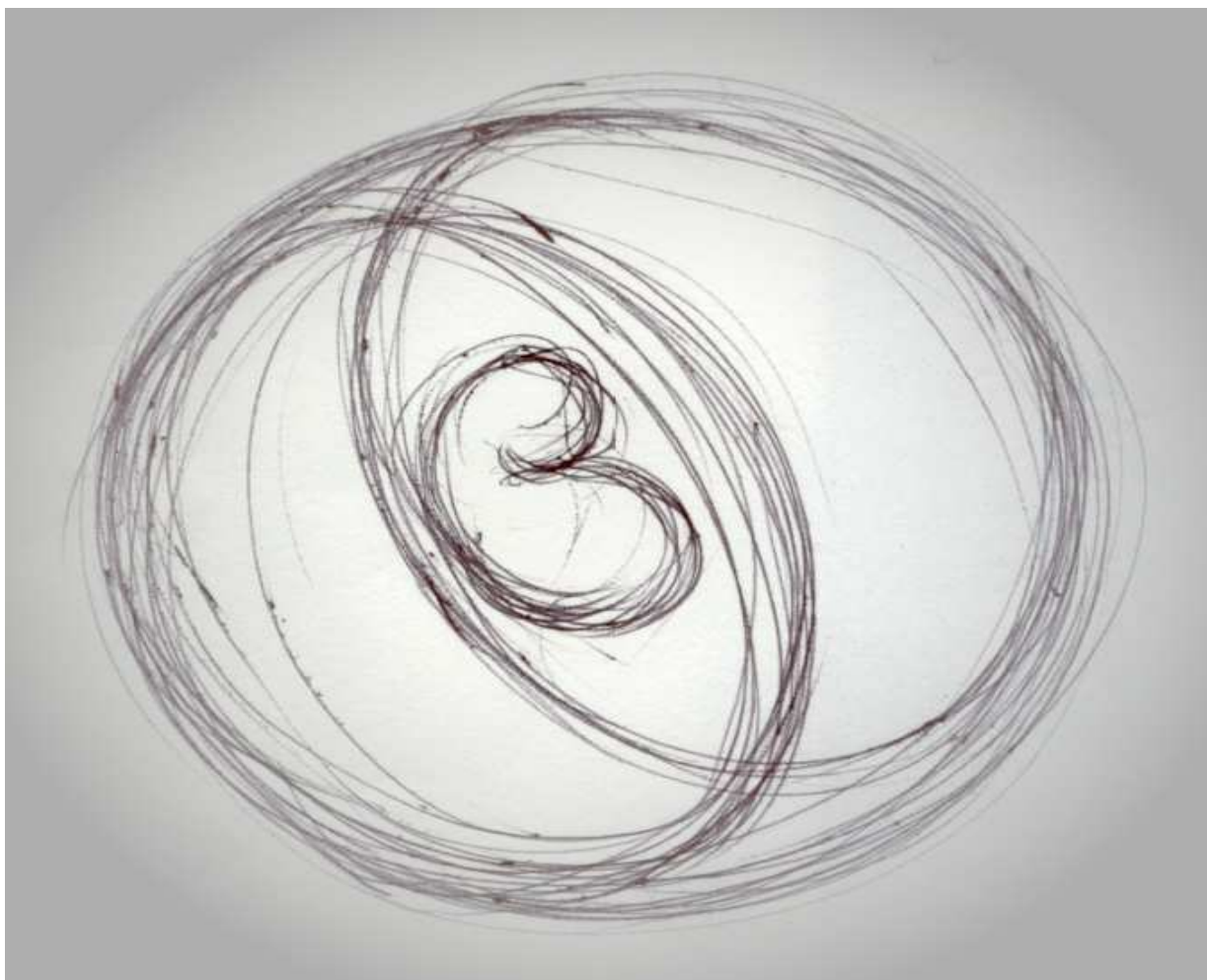


**Un grazie speciale a  
tutto il gruppo**



**Careggi University Hospital, Prenatal  
Medicine-High Risk Pregnancy Unit, Florence  
[mellog@unifi.it](mailto:mellog@unifi.it)**





**GRAZIE PER  
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- FINE



# Gravidanza fisiologica



Alla *Prima visita* valutazione della glicemia plasmatica per identificare la presenza di ***diabete preesistente alla gravidanza***:

- *glicemia a digiuno  $\geq 126$  mg/dL (7,00 mmol/l)*
- *glicemia random  $\geq 200$  mg/dL (11,1 mmol/l)*
- *HbA1c  $\geq 6,5\%$*

*E' necessario che i risultati siano confermati in un secondo prelievo.*



# Gravidanza fisiologica



## ***Curva da carico con 75 g di glucosio (OGTT 75 g)***

a 16-18 settimane e/o a 24-28 settimane in base a fattori di rischio definiti:

- a **16-18 settimane** di età gestazionale, alle pazienti con almeno una delle seguenti condizioni:
  - *Diabete gestazionale in una gravidanza precedente*
  - *Indice di massa corporeo (BMI) pregravidico  $\geq 30$*
  - *Riscontro, precedentemente o all'inizio della gravidanza, di valori di glicemia plasmatica compresi fra 100 e 125 mg/dL ( 5,6-6,9 mmol/L)*

Se la prima determinazione è risultata normale la curva deve essere ripetuta a 24-28 settimane



# Gravidanza fisiologica



- a **24-28 settimane** di età gestazionale, alle pazienti con almeno una delle seguenti condizioni:

- *Età  $\geq 35$  anni*
- *Indice di massa corporea pregravidico  $\geq 25$*
- *Macrosomia fetale in una gravidanza precedente (  $\geq 4,5$  Kg)*
- *Diabete gestazionale in una gravidanza precedente anche se con determinazione normale a 16-18 settimane*
- *Anamnesi familiare di diabete (parente di primo grado con diabete di Tipo 2)*
- *Famiglia originaria di aree ad alta prevalenza di diabete: Asia Meridionale (India, Pakistan, Bangladesh), Caraibi ( per la popolazione di origine africana), Medio Oriente ( Arabia Saudita, Egitto, Giordania, Siria, Omar, Kuwait, Libano).*

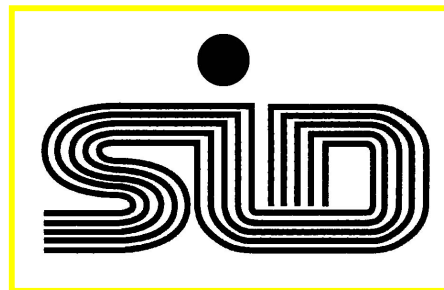
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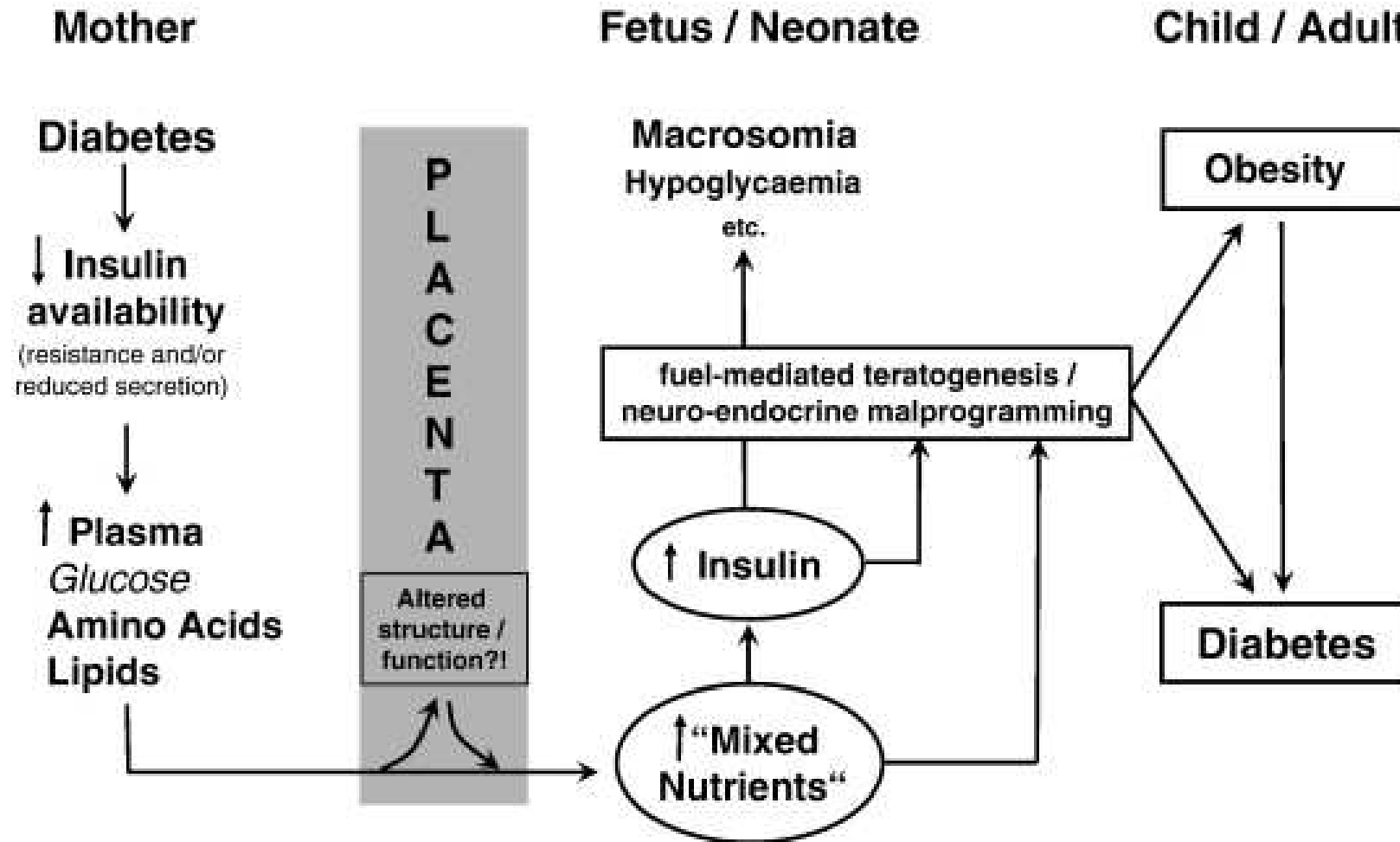


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# The “modified Pedersen hypothesis”



*Pedersen et al. "Blood Sugar in Newborn Infants of Diabetic Mothers" Acta Endocrinol 1954*

# DIABETE GESTAZIONALE

## DEFINIZIONE

*Intolleranza ai carboidrati di vario grado e severità, con inizio o primo riconoscimento durante la gravidanza*

IV International Workshop Conference on GDM, 1997  
Diabetes Care ,1998