Con il Patrocinio di

ASR ABRUZZO
AGENZIA SANITARIA REGIONALE

IL DIABETE IN GRAVIDANZA

Chieti, 19-20 aprile 2018

DALLA RICERCA ALLA PRATICA CLINICA

Lezioni dalla curva da carico di glucosio: ascoltare, interpretare e predire

Elena Succurro

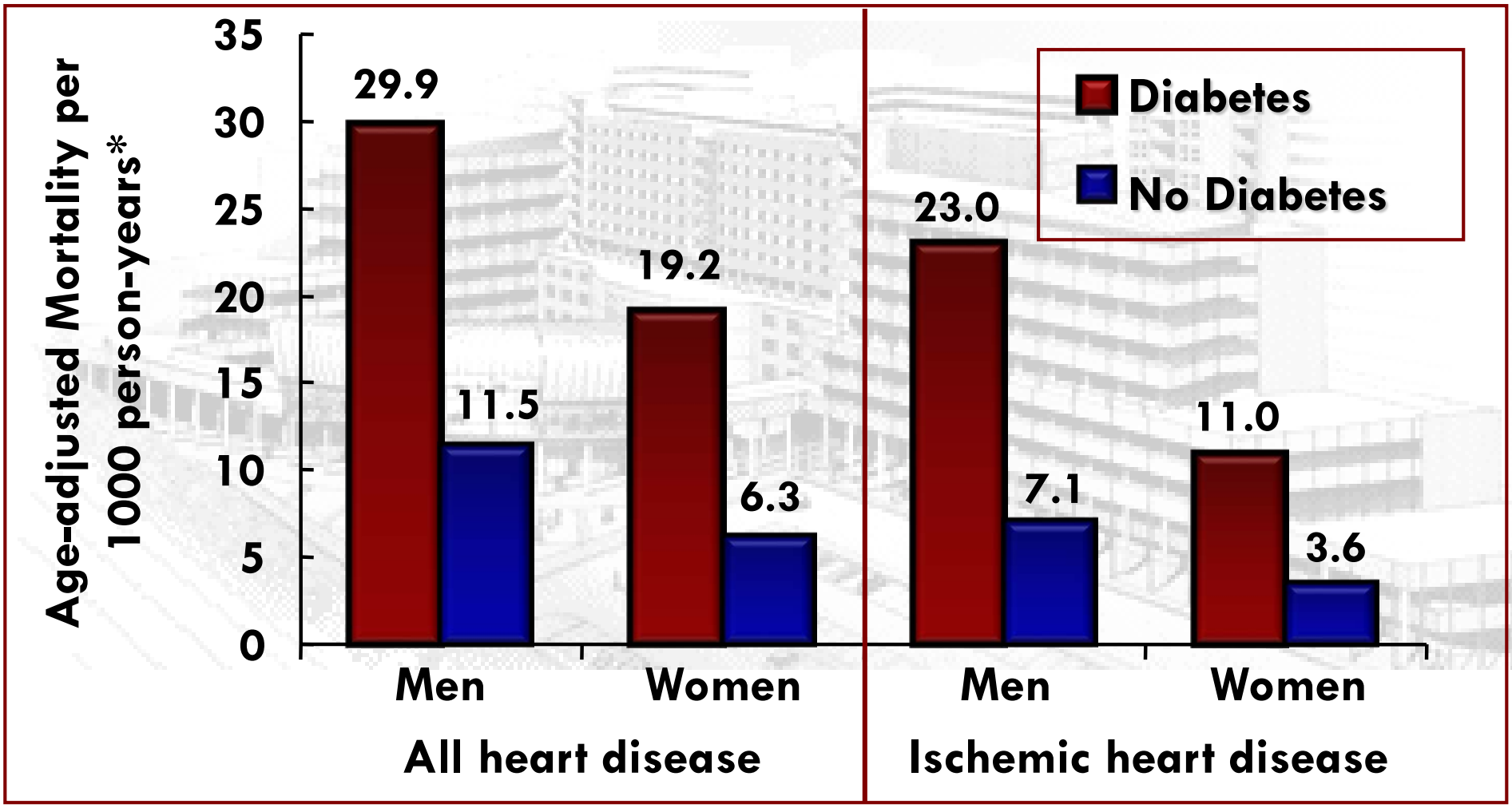
Università degli Studi "Magna Graecia" di Catanzaro

Dipartimento di Scienze Mediche e Chirurgiche

U.O.C. di Medicina Interna

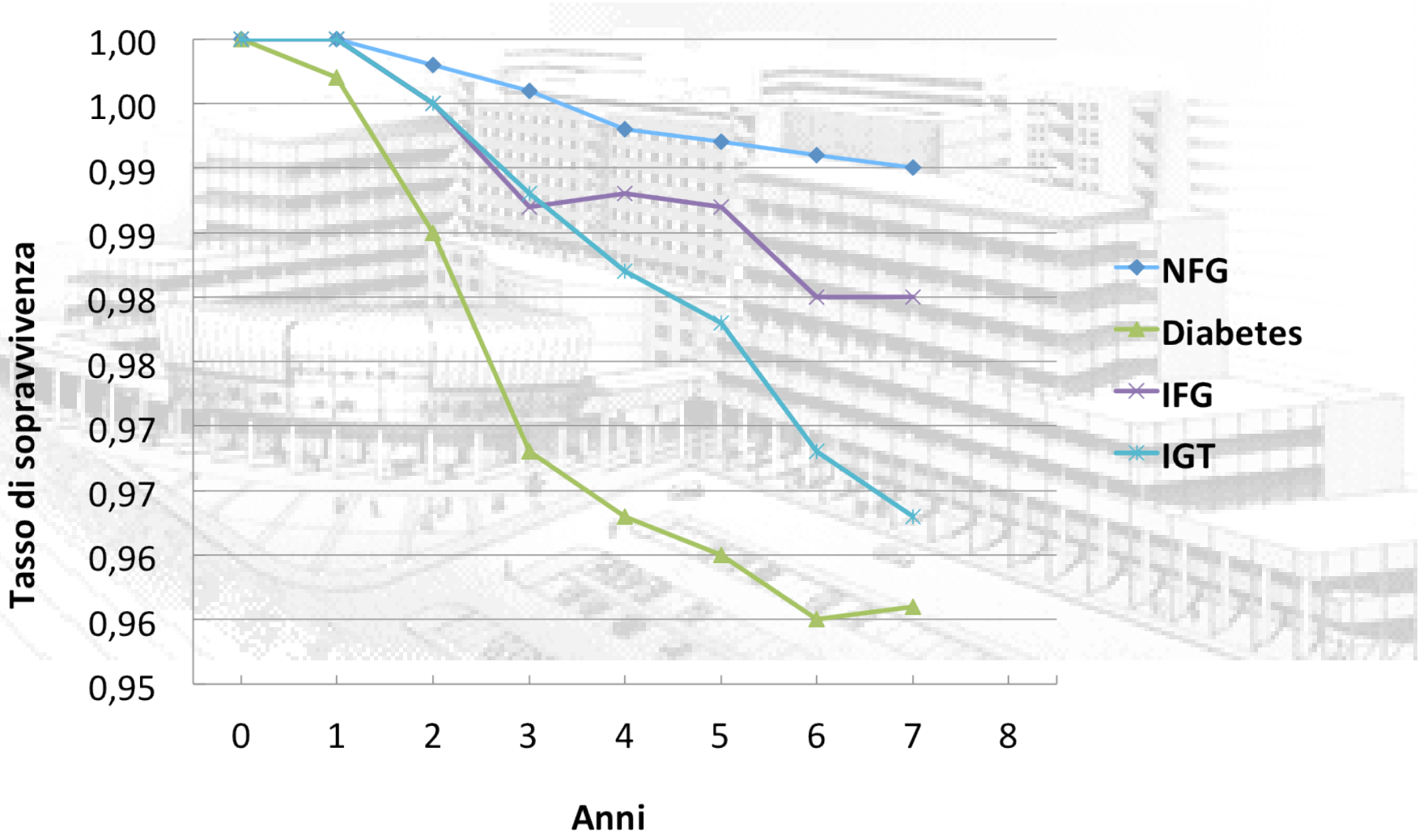


Mortalità cardiovascolare in relazione al diabete negli uomini e nelle donne (NHANES)



Gu K et al. Diabetes Care 21:1138-1145, 1998

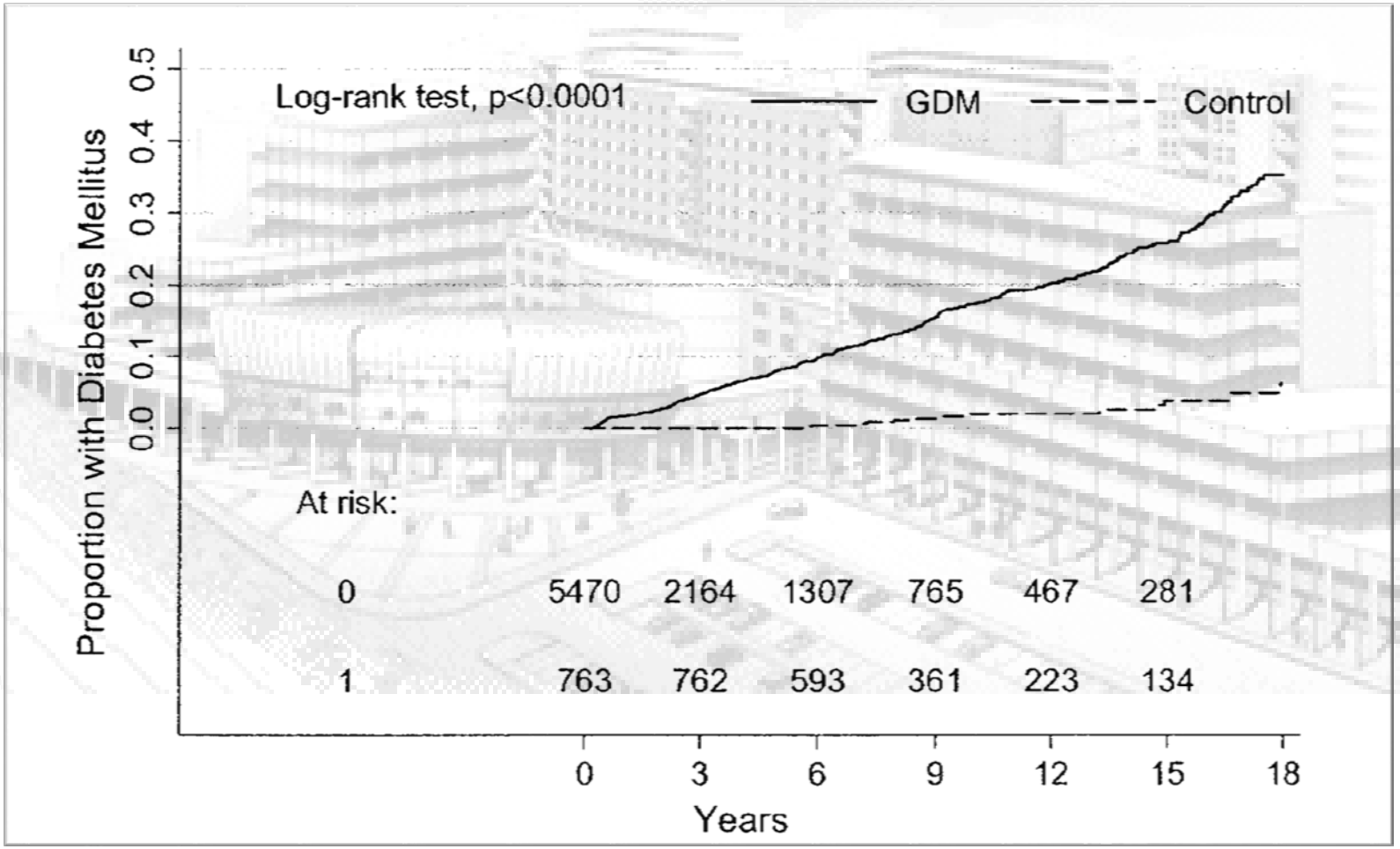
Mortalità cardiovascolare nei diversi stati di tolleranza glucidica (Funagata Study)



Adapted from Tominaga M et al. Diabetes Care, 1999

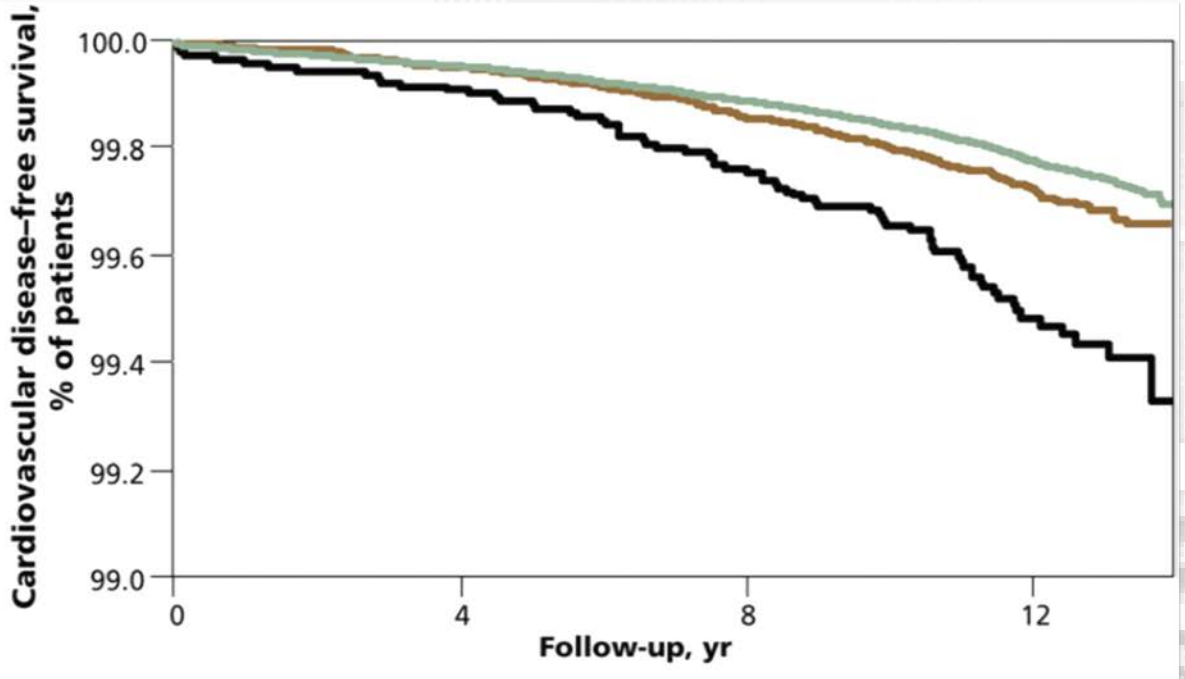
Incidenza di diabete tipo 2 in donne con GDM

Incidenza 5-10% nel post partum
35 %- 60% dopo 15-20 anni



Lee et al Diabetes Care 2007, 30:878–883

Incidenza di CVD in donne con GDM e con iperglicemia alla prima ora durante OGTT

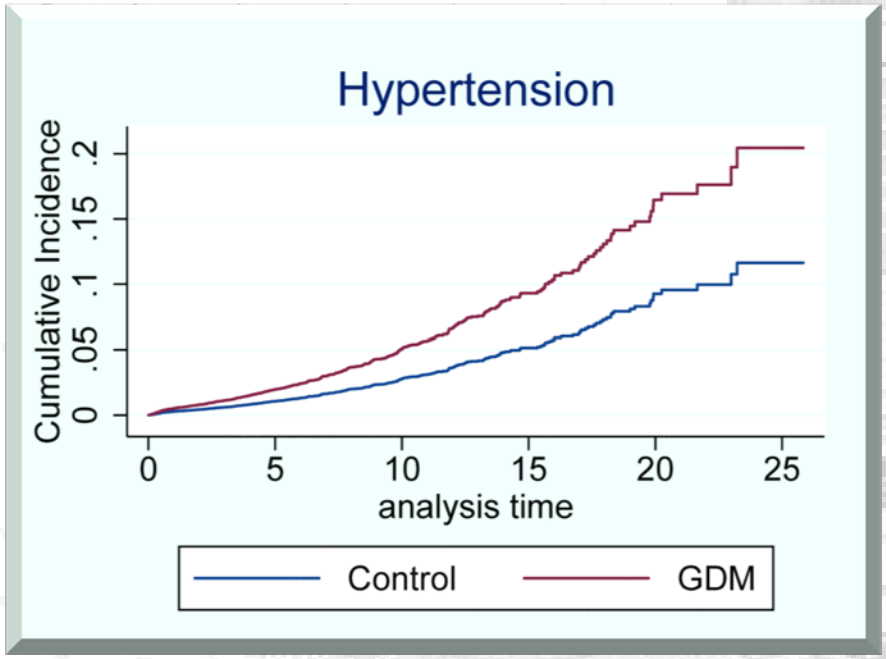


No. at risk

Gestational diabetes	13 888	13 856	13 813	7 670
Received an oral glucose tolerance test	71 831	71 734	71 560	39 555
Did not receive an oral glucose tolerance test	349 977	349 441	348 651	206 382

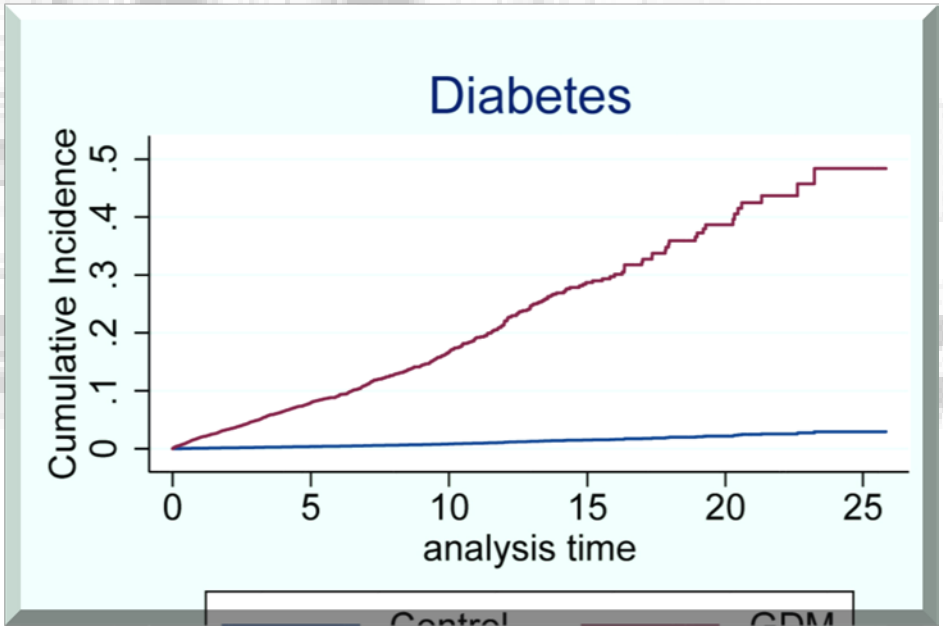
Retnakaran and Shah CMAJ 2009, 181:371– 6.

Aumentata incidenza di malattie cardiovascolari in donne con GDM



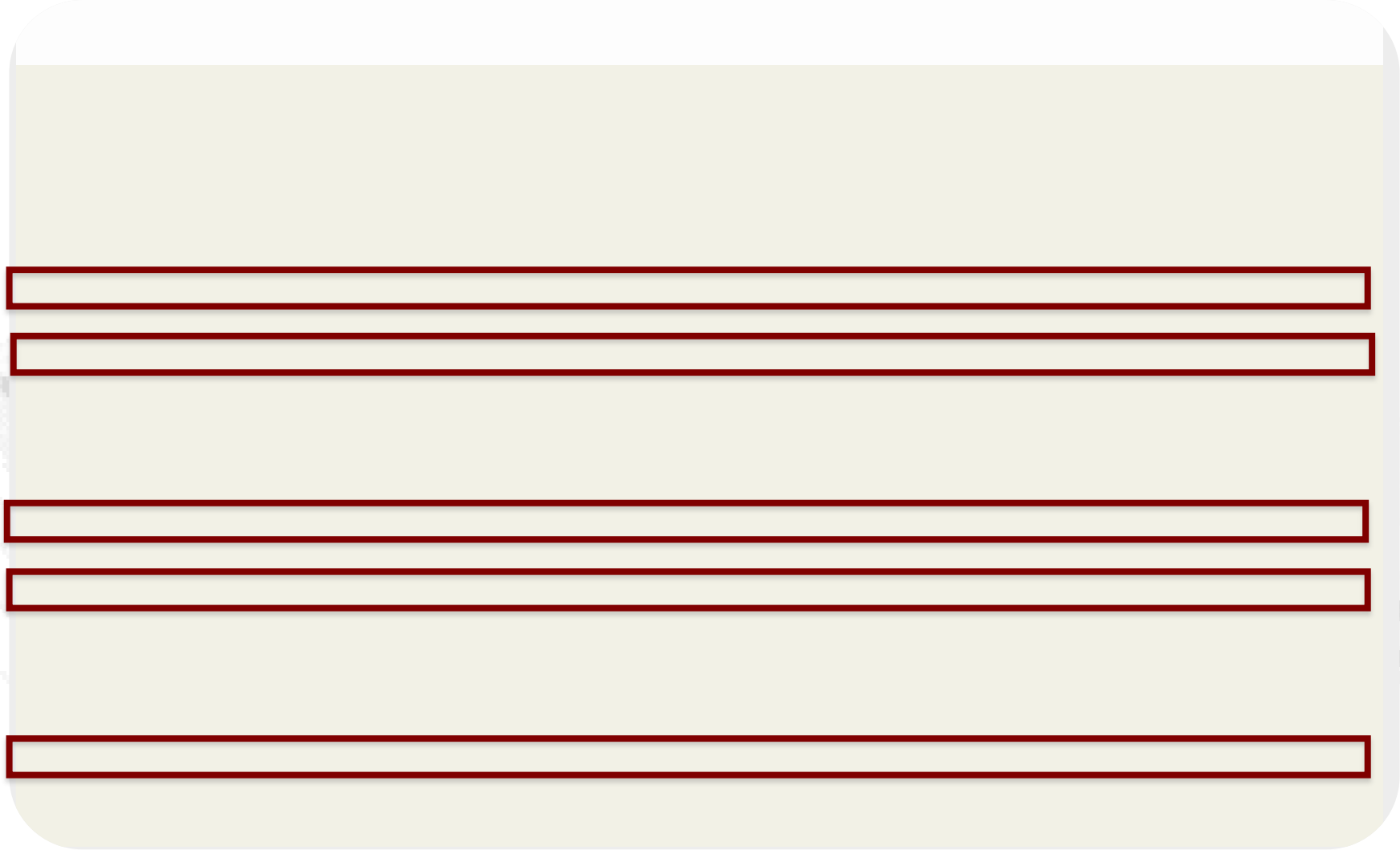
IRR = 1.85; 95% CI 1.59–2.16

IRR= 2.78; 95% CI 1.37–5.66



Daly B et al Plos Medicine 2018

Aumentata incidenza di malattie cardiovascolari in donne con GDM NHS II



Tobias DK et al JAMA Intern Med 2017

Problematiche

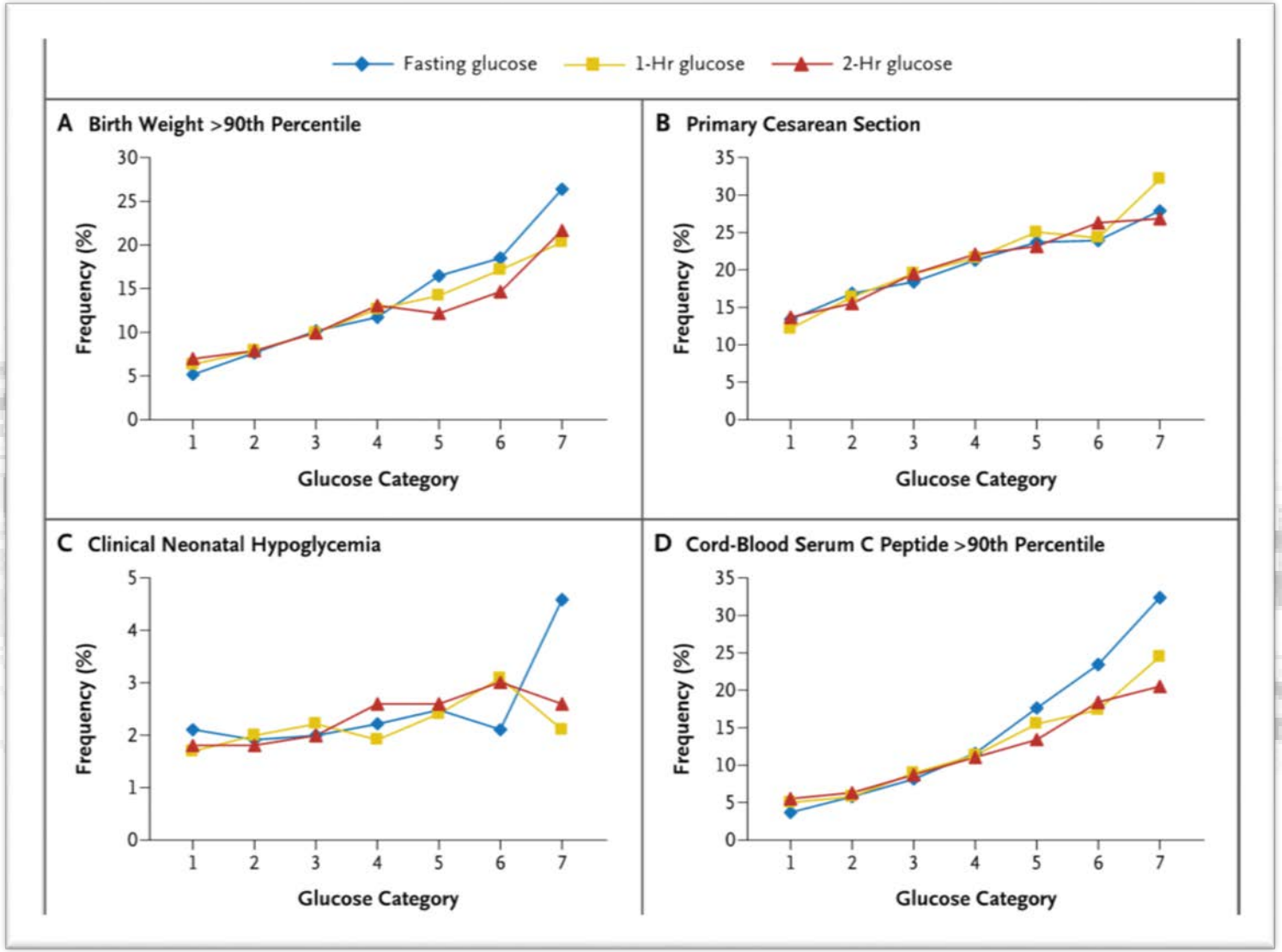


Numerosi studi hanno evidenziato che meno del 50% delle donne con GDM effettua il follow-up.

Obiettivi nel GDM

- ✧ Prevenire gli outcome avversi neonatali e materni
- ✧ Prevenire la comparsa del diabete tipo 2 e ridurre il rischio cardiovascolare
- ✧ Identificare le donne a maggior rischio di outcome avversi e di diabete tipo 2

Correlazione lineare tra Iperglicemia a digiuno e Glicemia 1 h e 2 h durante OGTT e outcome avversi perinatali Hapo Study



HAPO Study Group N Engl J Med 2008;358:1991-2002.

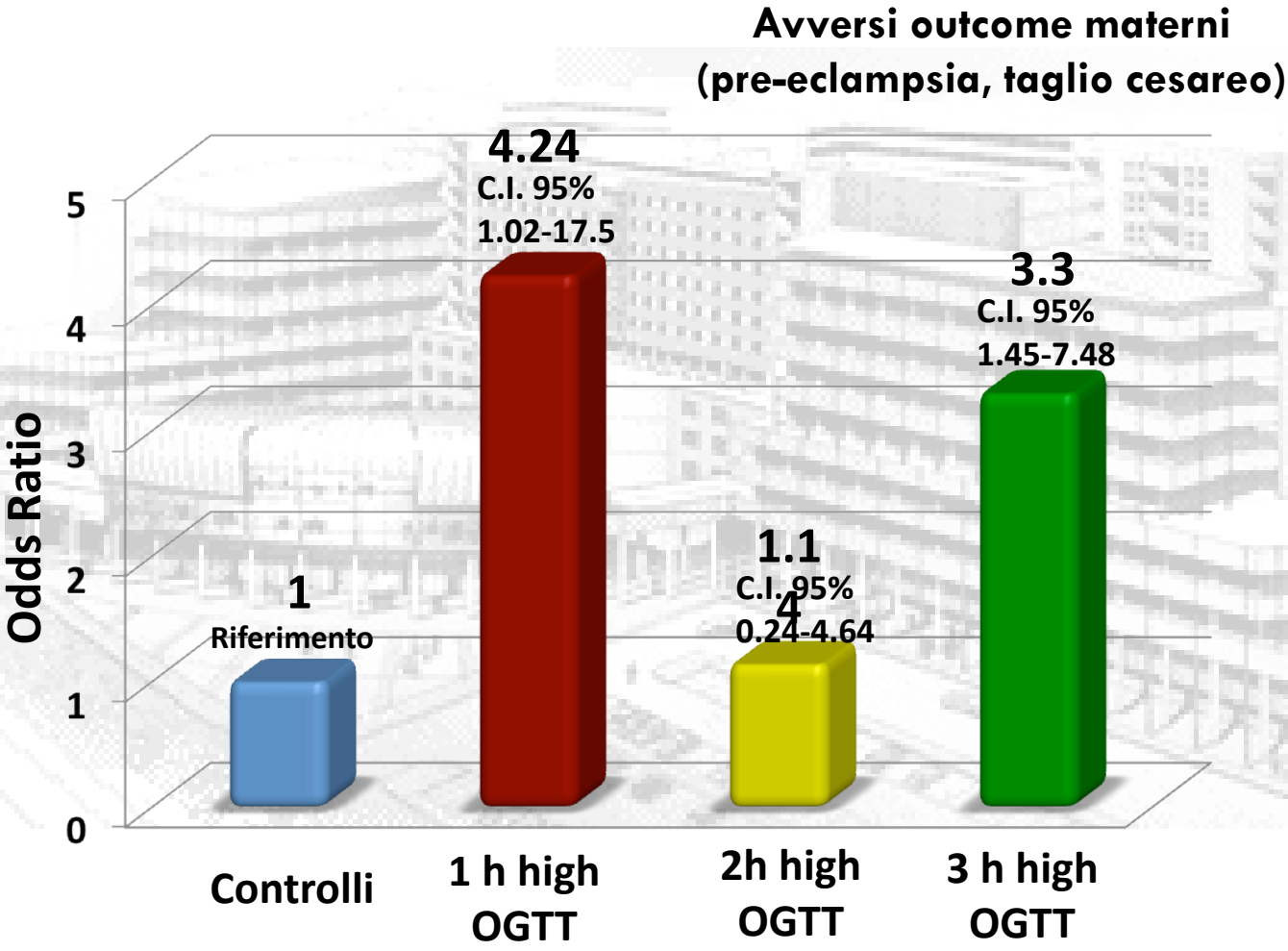
Iperglicemia a digiuno e Glicemia 1 h e 2 h predittori indipendenti di outcome avversi perinatali Hapo Study

Table 3. Adjusted Odds Ratios for Associations between Maternal Glycemia as a Continuous Variable and Primary and Secondary Perinatal Outcomes.*

Outcome	Plasma Glucose Level		
	Fasting	At 1 Hr	At 2 Hr
	odds ratio (95% CI)		
Primary outcome			
Birth weight >90th percentile	1.38 (1.32–1.44)	1.46 (1.39–1.53)	1.38 (1.32–1.44)
Primary cesarean section†	1.11 (1.06–1.15)	1.10 (1.06–1.15)	1.08 (1.03–1.12)
Clinical neonatal hypoglycemia	1.08 (0.98–1.19)‡	1.13 (1.03–1.26)	1.10 (1.00–1.12)
Cord-blood serum C peptide >90th percentile	1.55 (1.47–1.64)	1.46 (1.38–1.54)	1.37 (1.30–1.44)
Secondary outcome			
Premature delivery (before 37 wk)	1.05 (0.99–1.11)	1.18 (1.12–1.25)	1.16 (1.10–1.23)
Shoulder dystocia or birth injury	1.18 (1.04–1.33)	1.23 (1.09–1.38)	1.22 (1.09–1.37)
Intensive neonatal care	0.99 (0.94–1.05)	1.07 (1.02–1.13)	1.09 (1.03–1.14)
Hyperbilirubinemia	1.00 (0.95–1.05)	1.11 (1.05–1.17)	1.08 (1.02–1.13)
Preeclampsia	1.21 (1.13–1.29)	1.28 (1.20–1.37)	1.28 (1.20–1.37)

HAPO Study Group N Engl J Med 2008;358:1991-2002.

Glicemia 1 h e 3 h durante OGTT durante la gravidanza predittori indipendente di avversi outcome materni

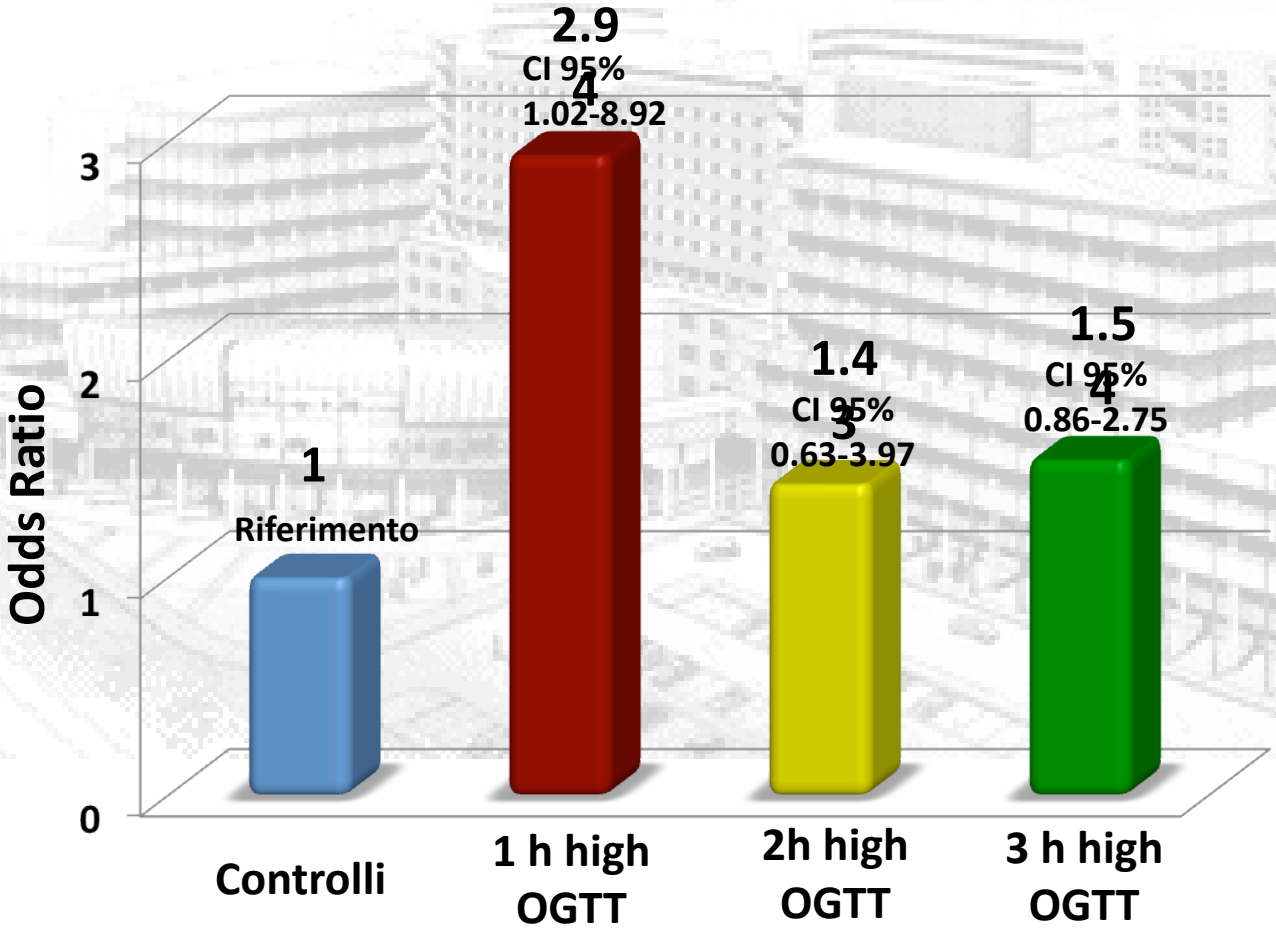


Analisi corretta per parto pre-termine, obesità, BMI > 26 kg/m^2.

Kim HS et al Int J Gynecol Obstet 2002;78:131–138

Glicemia 1 h durante OGTT durante la gravidanza è predittore indipendente di avversi outcome neonatali

Avversi outcome neonatali
(LGA, Apgar Score, Distress Fetale, Ipoglicemia, Morte perinatale, Distress respiratorio, SGA)



Analisi corretta per parto pre-termine, obesità, BMI > 26 kg/m^2.

Kim HS et al Int J Gynecol Obstet 2002;78:131–138

Predittori clinici a lungo termine di diabete tipo 2

GDM 5740
Controlli 783

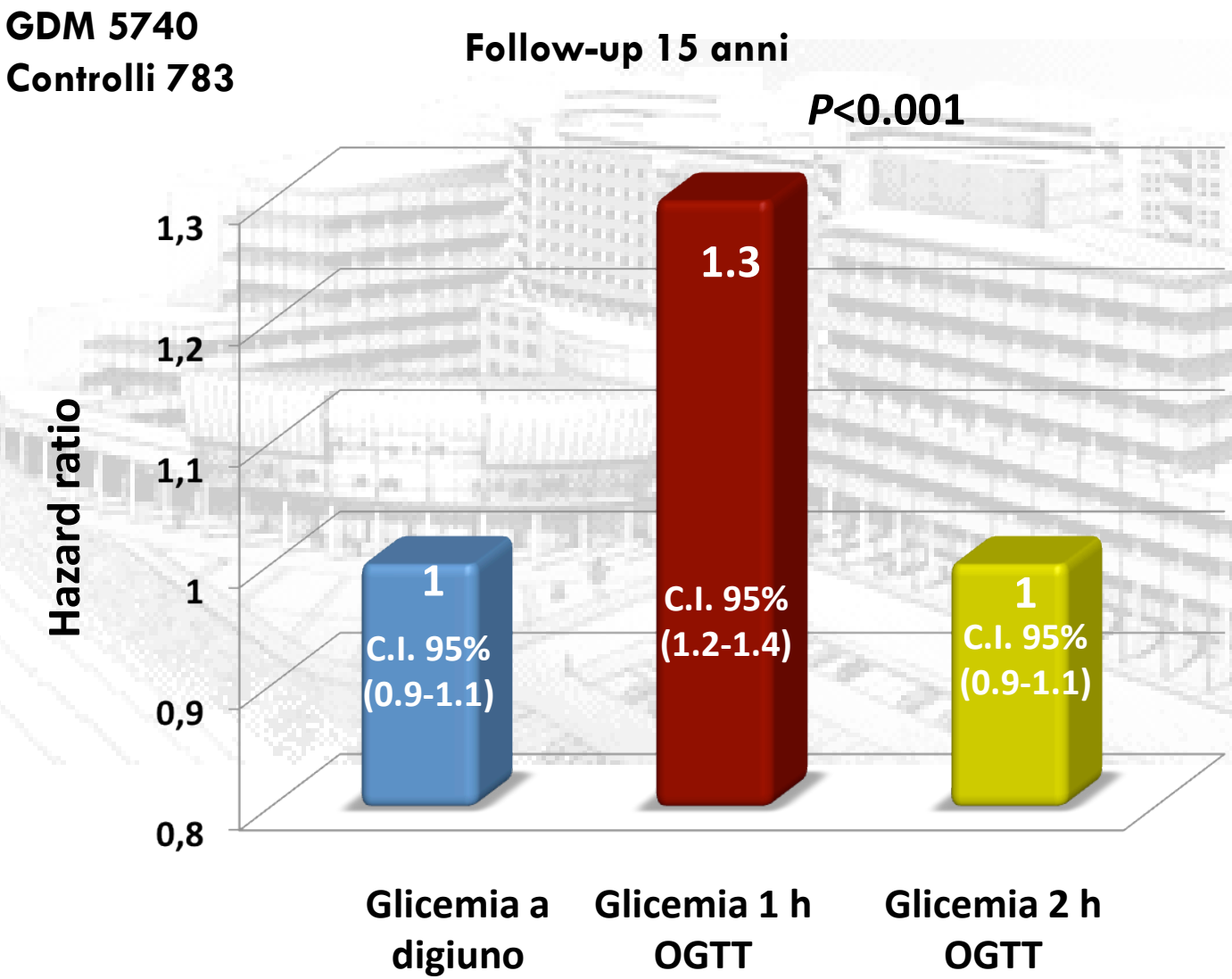
Follow-up 15 anni

Covariate	Imputation	Complete case
n	5,470	3,578
Insulin usage	3.5 (2.6–4.7)	3.4 (2.5–4.7)
Asian race	2.1 (1.7–2.7)	2.4 (1.9–3.2)
FBG (mmol)	1.1 (0.9–1.2)*	1.0 (0.9–1.1)*
1-h blood glucose (mmol)	1.3 (1.21.4)	1.3 (1.2–1.4)
2-h blood glucose (mmol)	1.0 (0.9–1.1)*	1.0 (0.9–1.1)*
BwtGC (per 10-unit increase from mean)	1.05 (1.0–1.1)†	1.03 (1.0–1.1)†
BMI (5-unit increase from BMI = 20 kg/m^2)	1.4 (1.21.6)	1.6 (1.41.8)

All *P* values <0.001, except *$P > 0.10$ and †$P = 0.02$.

Lee et al Diabetes Care 2007, 30:878–883

Glicemia alla prima ora durante OGTT predittore indipendente di diabete tipo 2



Lee et al Diabetes Care 2007, 30:878–883

Glicemia alla prima ora durante OGTT predittore indipendente di diabete tipo 2

women with GD (carbohydrate intolerance of variable severity with onset or first recognition during pregnancy (4)) in whom diabetes mellitus persisted or was diagnosed postpartum in 2,957 pregnancies complicated by GD, a prevalence of 2.0% (95% CI, 1.5-2.6%) of women with GD.

In the analysis of the predictors of postnatal diabetes mellitus the patient with diabetic ketoacidosis at 31 weeks' gestation was not included in the analysis. For the remaining 58 women, the results of univariate analysis are shown in table 1. The significant factors on the analysis were use of insulin in pregnancy, severity (grade) of GD, result of the antenatal GTT, the BMI at the postnatal visit, fetal macrosomia and Asian origin. **Only 2 of 2,037 women (0.1%) with Grade 1 GD had diabetes mellitus at the postnatal visit, compared with 8 of 407 (2.0%) with Grade 2 GD, 18 of 438 (4.1%) with**

DISCUSSION

Other authors have examined the prevalence and predictors of diabetes mellitus diagnosed soon after a pregnancy complicated by gestational diabetes. The first was Mestman et al (5) who found that of 70 women with GD tested within the first year postpartum, none had 'overt diabetes'. Metzger et al (6) found that in an obese population in Chicago, 38% of 113 women with GD developed diabetes within the first postpartum year, with predictors being the severity of GD and age. In a largely Hispanic population in Southern California, Kjos et al (7) reported that the prevalence of diabetes in the first 2 months postpartum after GD was 9%, being more likely with increased severity of GD, increased fasting glucose level in pregnancy and earlier diagnosis of GD. Lam et al (8) in Hong Kong found that of 120 Chinese women with GD who had persistent

Aust. NZ J Ohstet Gynaecol 1997; 37:4:420

Glicemia 1 h durante OGTT predittore indipendenti di ridotta tolleranza al glucosio al follow-up

	B	standard error	p value	odds ratio (95% CI)
PG at 1-hour in 75g OGTT at GDM diagnosis	0.026	0.011	0.020	1.027 (1.004-1.050)
PG at 2-hour 75g OGTT at GDM diagnosis	0.001	0.011	0.906	1.001 (0.980-1.023)
Number of abnormal points in 75g OGTT at GDM diagnosis	0.439	0.429	0.306	1.551 (0.669-3.594)
HbA1c	1.091	0.705	0.121	2.978 (0.749-11.847)
Ketone bodies in urine	0.443	0.182	0.015	1.558 (1.091-2.225)
History of insulin therapy (1: no, 2: yes)	-0.250	0.636	0.694	0.779 (0.224-2.708)

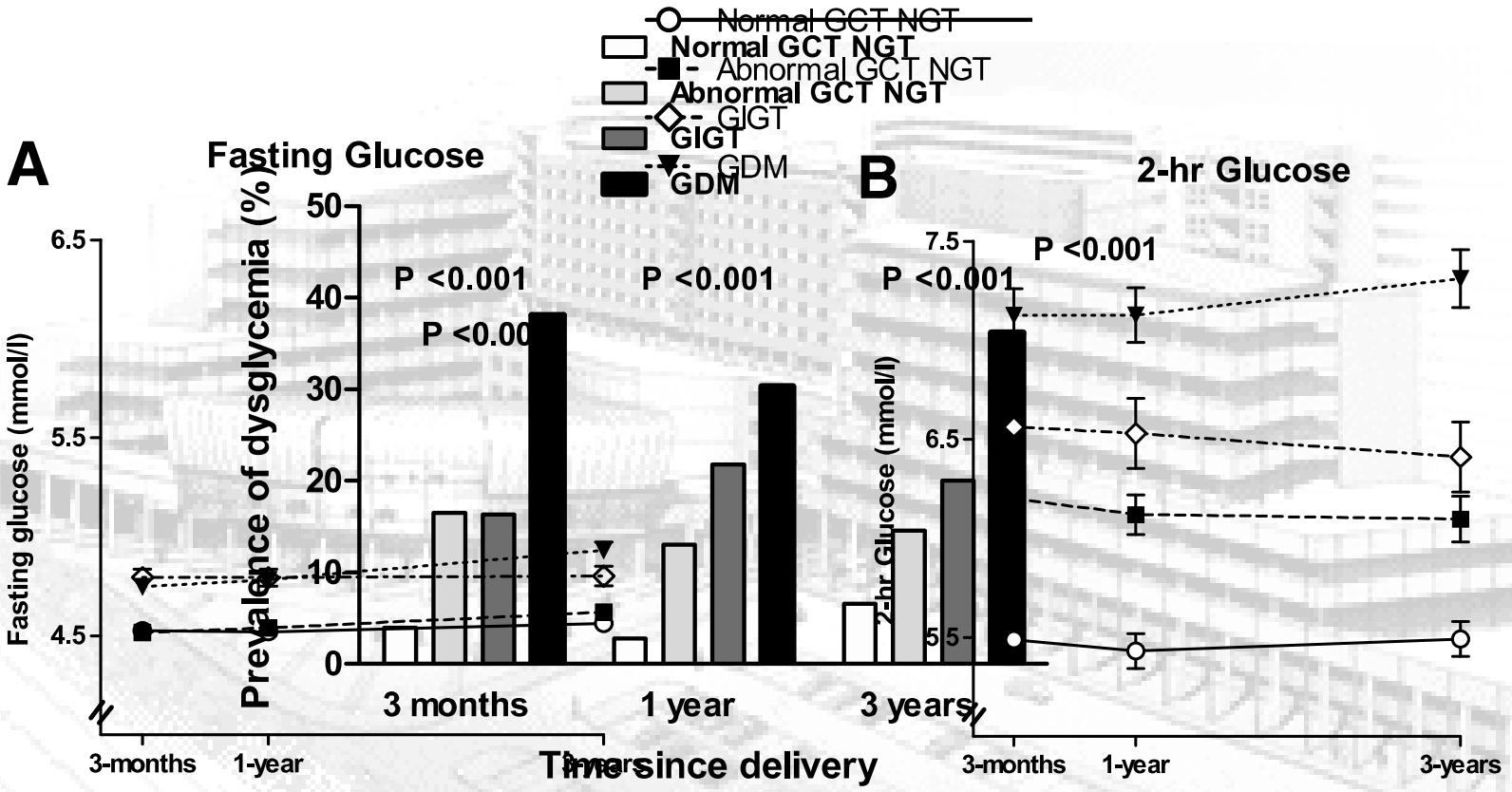
Nishikawa T *et* al J Diabetes Investig, 2018 Apr 6

Glicemia 1 h durante OGTT e HbA1c predittori indipendenti di necessità di terapia insulinica in GDM

	B	standard error	p value	odds ratio (95% CI)
Gestational weeks at GDM diagnosis	-0.043	0.020	0.033	0.958 (0.921-0.997)
History of pregnancy	-0.334	0.196	0.088	0.716 (0.488-1.051)
Family history of DM (1: no, 2: yes)	0.583	0.341	0.087	1.792 (0.919-3.493)
Pregestational BMI	0.025	0.034	0.456	1.026 (0.960-1.096)
PG at 1-hour in 75g OGTT at GDM diagnosis	0.023	0.007	0.001	1.023 (1.009-1.037)
PG at 2-hour in 75g OGTT at GDM diagnosis	0.009	0.007	0.200	1.009 (0.995-1.024)
Number of abnormal points in 75g OGTT at GDM diagnosis	-0.151	0.314	0.632	0.860 (0.464-1.593)
HbA1c	1.161	0.509	0.023	3.192 (1.177-8.659)

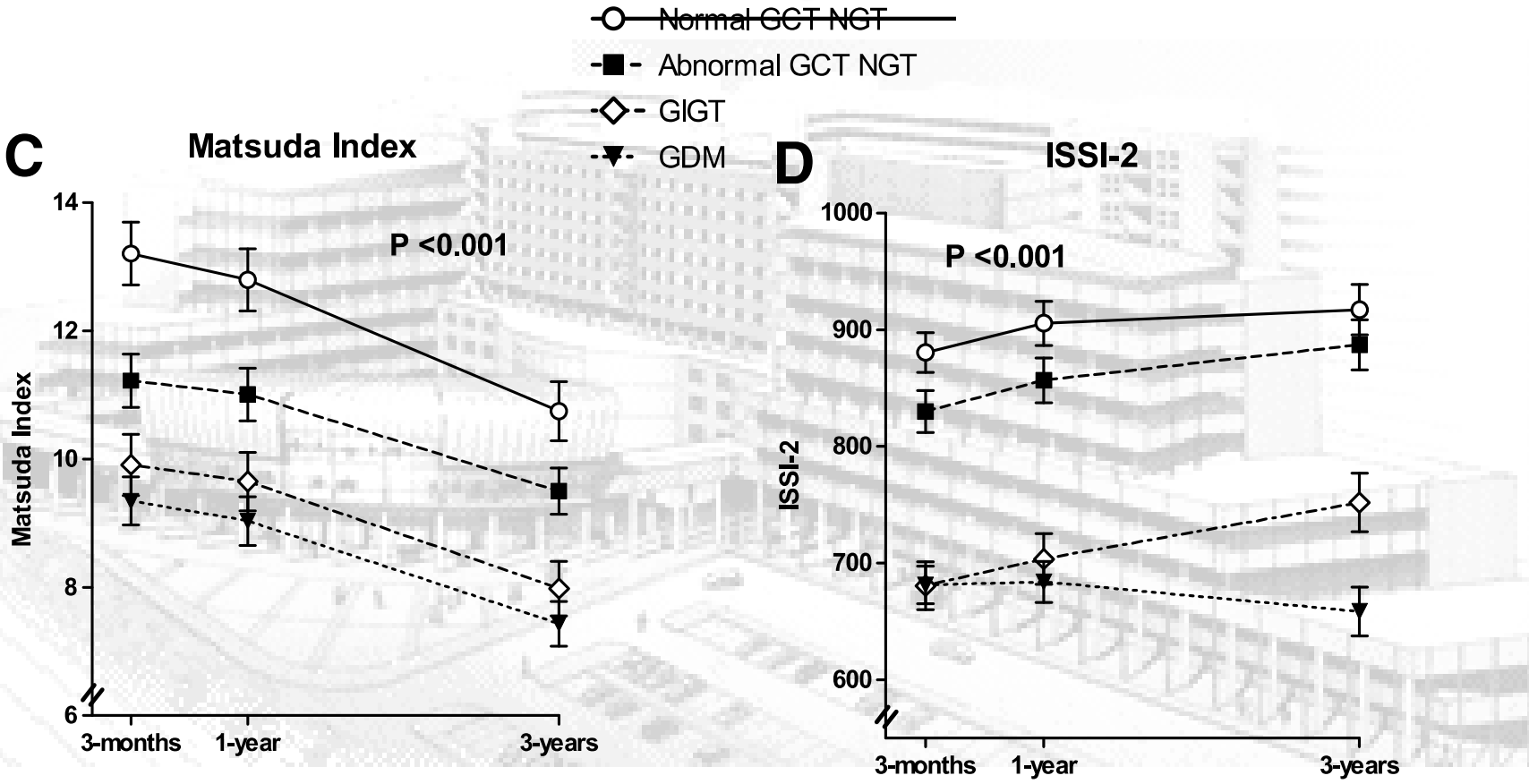
Nishikawa T *et* al J Diabetes Investig, 2018 Apr 6

GDM ma anche un aumento della glicemia a 1h e a 2 h si associano a disglicemia al follow-up



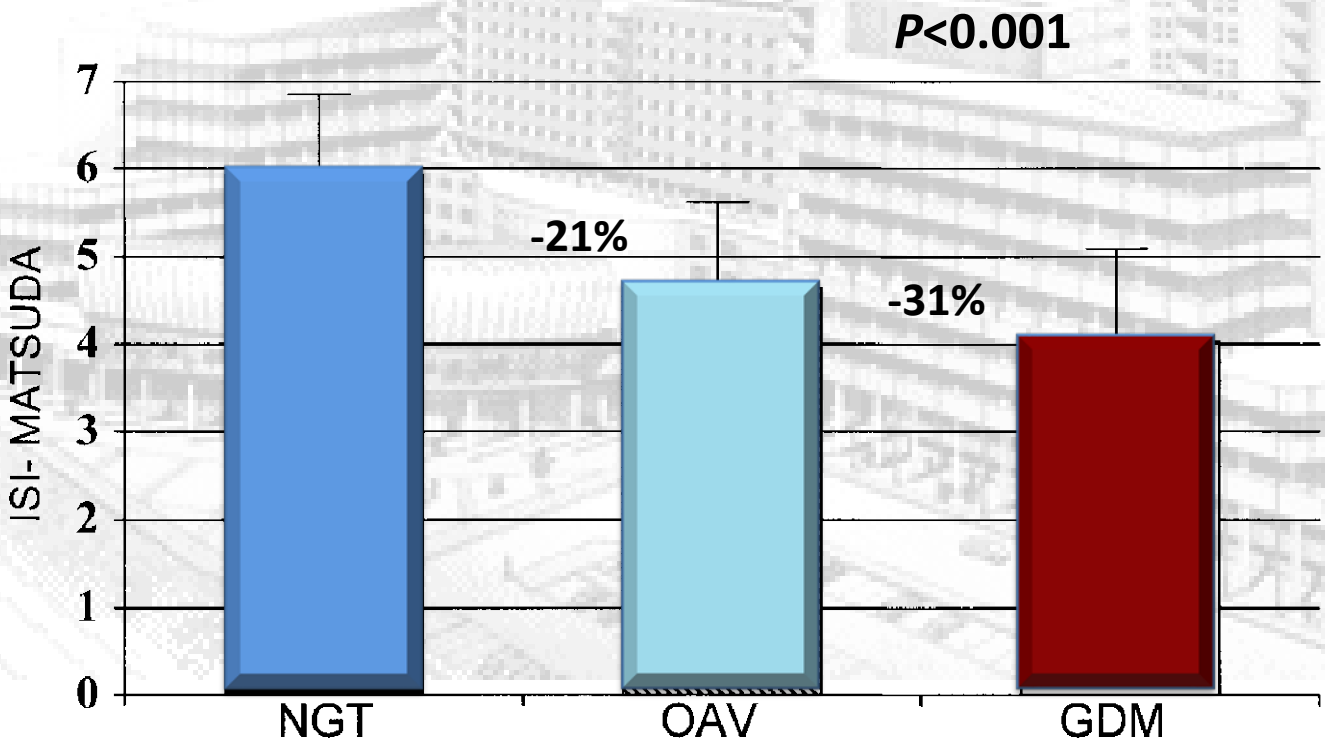
Kramer et al Diabetes Care 2014, 37:3262–3269

GDM si associa a riduzione della sensibilità insulinica e della funzione b-cellulare durante il follow-up



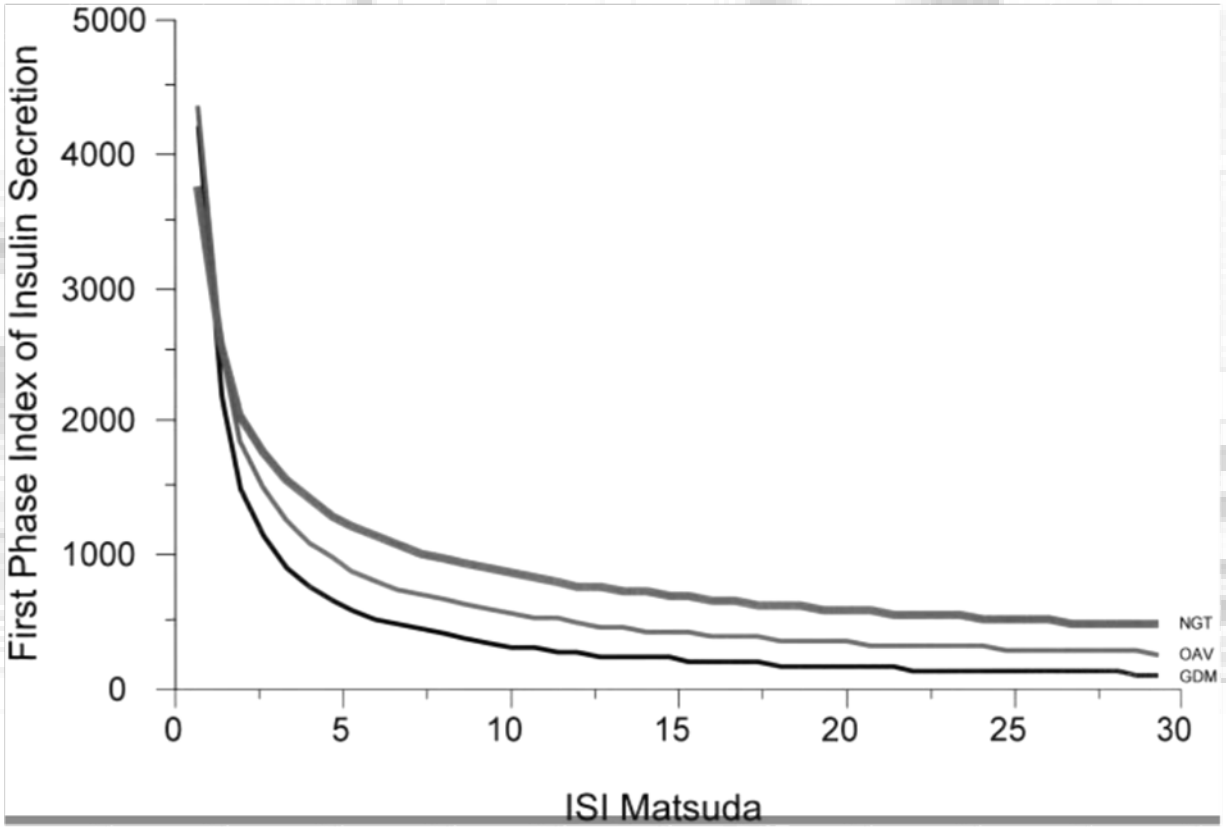
Kramer et al Diabetes Care 2014, 37:3262–3269

GDM e Glicemia 1 h o 2-3 OGTT durante la gravidanza si associano a ridotta sensibilità insulinica rispetto a NGT



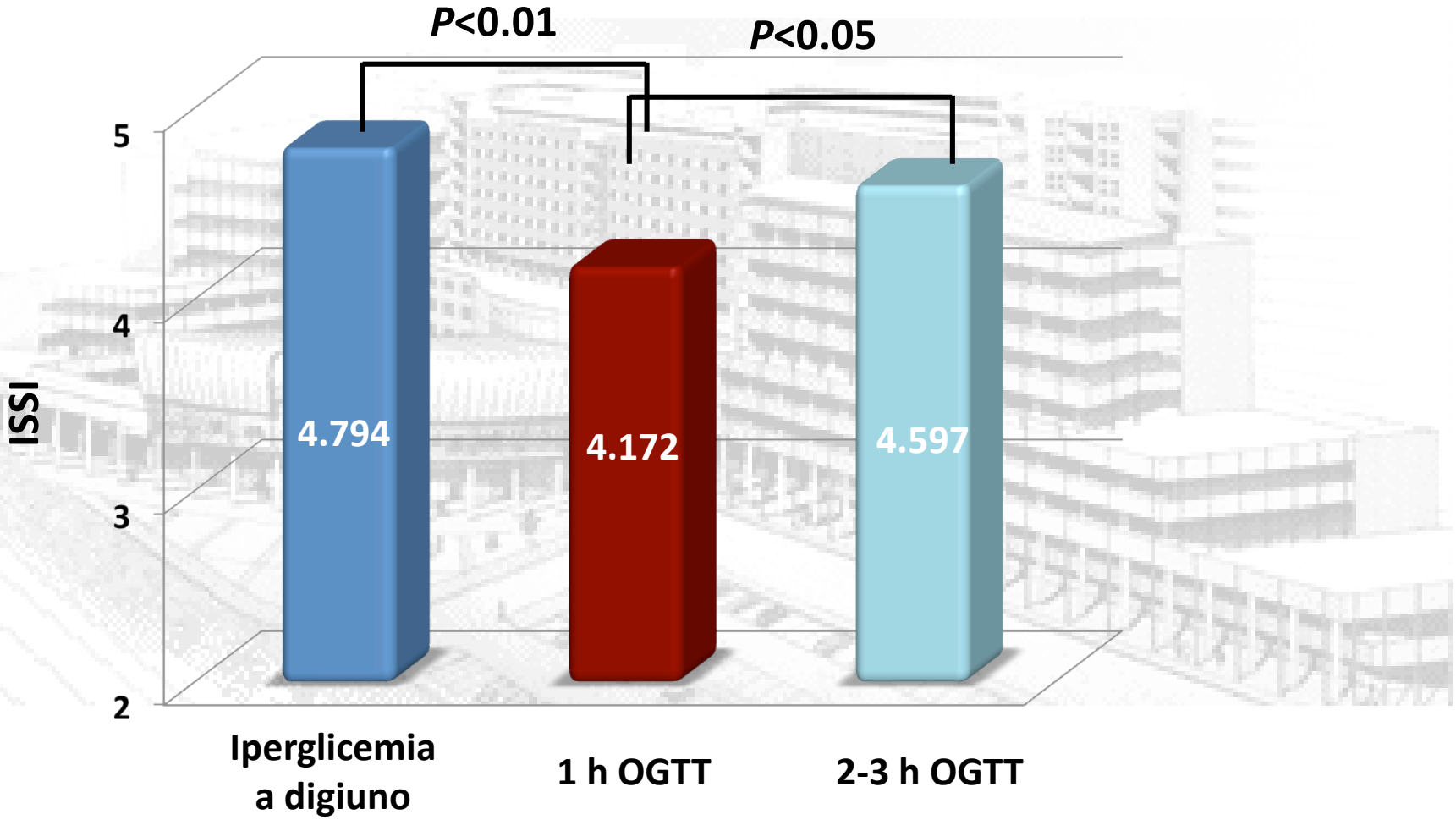
DI Cianni G et al Diabetes Care, 2007 30:1783–1788

GDM e Glicemia 1 h o 2-3 OGTT durante la gravidanza si associa ad una ridotta secrezione insulinica rispetto a NGT



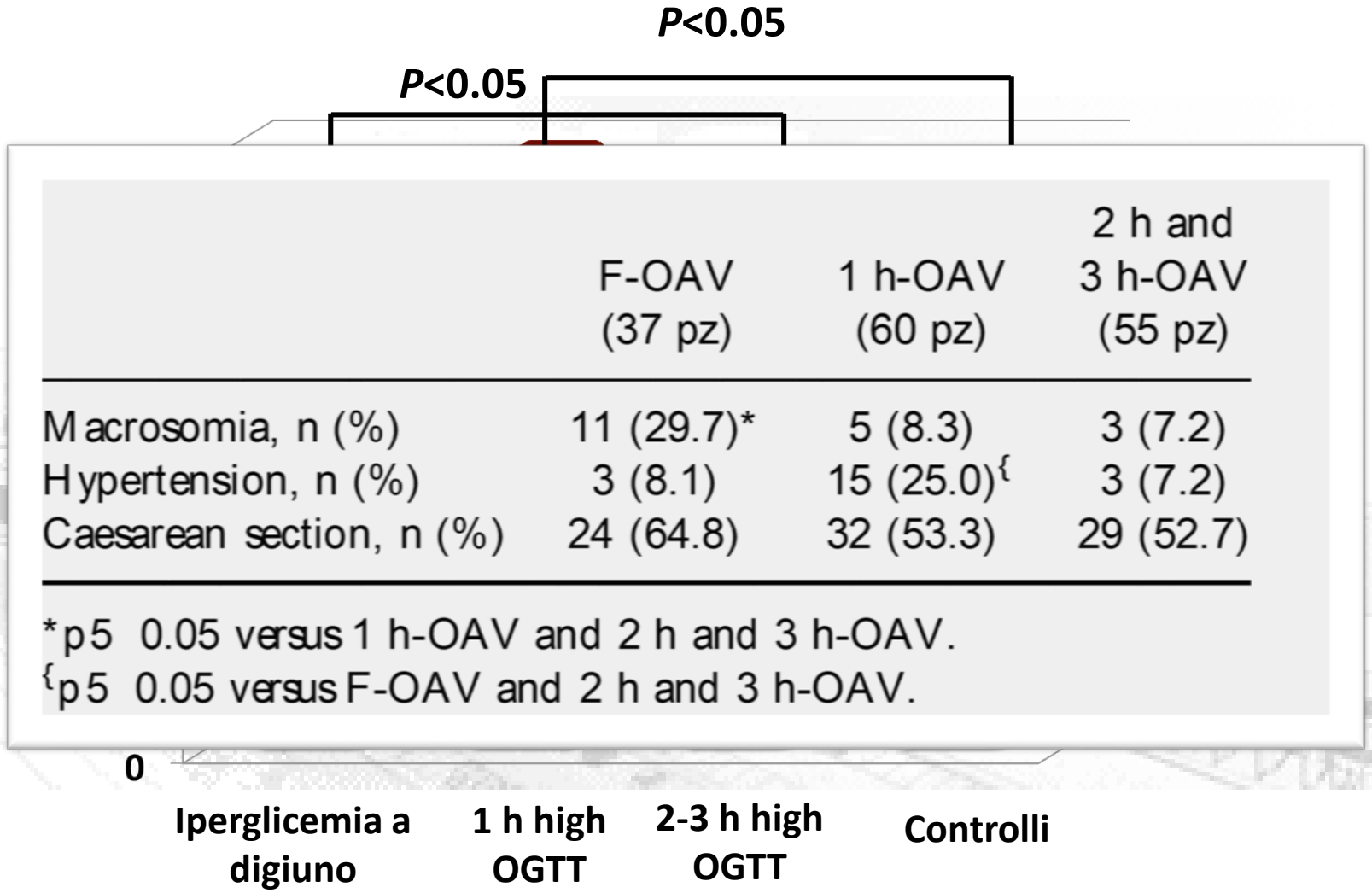
DI Cianni G et al Diabetes Care, 2007 30:1783–1788

Glicemia 1 h durante OGTT si associa ad una ridotta secrezione insulinica rispetto a FPG e 2 h OGTT



DI Cianni G et al Diabetes Care, 2007 30:1783–1788

Iperglicemia a digiuno e Glicemia 1 h OGTT alterati durante la gravidanza si associano a riduzione della sensibilità insulinica



	F-OAV (37 pz)	1 h-OAV (60 pz)	2 h and 3 h-OAV (55 pz)
Macrosomia, n (%)	11 (29.7)*	5 (8.3)	3 (7.2)
Hypertension, n (%)	3 (8.1)	15 (25.0){	3 (7.2)
Caesarean section, n (%)	24 (64.8)	32 (53.3)	29 (52.7)

*p5 0.05 versus 1 h-OAV and 2 h and 3 h-OAV.
{p5 0.05 versus F-OAV and 2 h and 3 h-OAV.

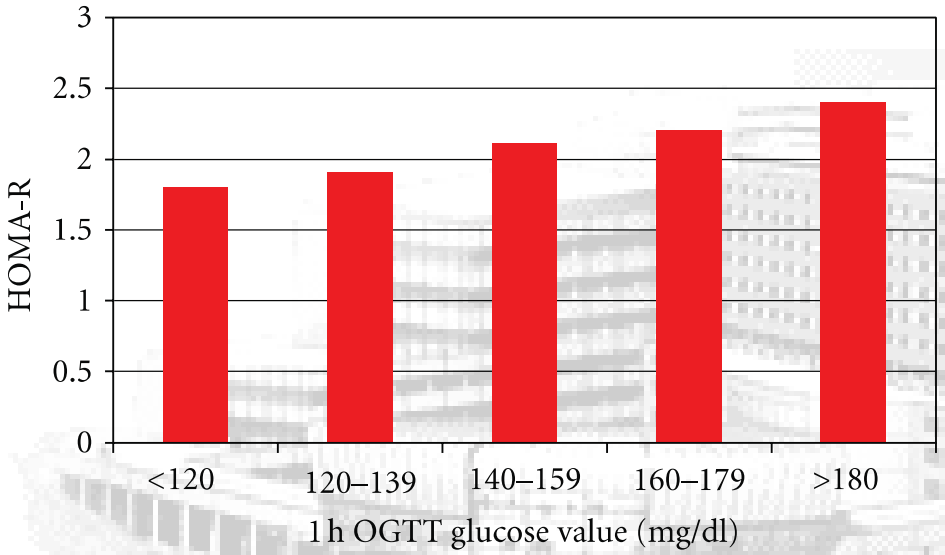
Corrado F et al Journal of Maternal- Fetal and Neonatal Medicine 2009

Ridotti livelli di adiponectina in GDM e in 1h OGTT rispetto a NGT e 2-3 h OGTT



Retnakaran R et al. *Diabetes Care* 29:57–62, 2006

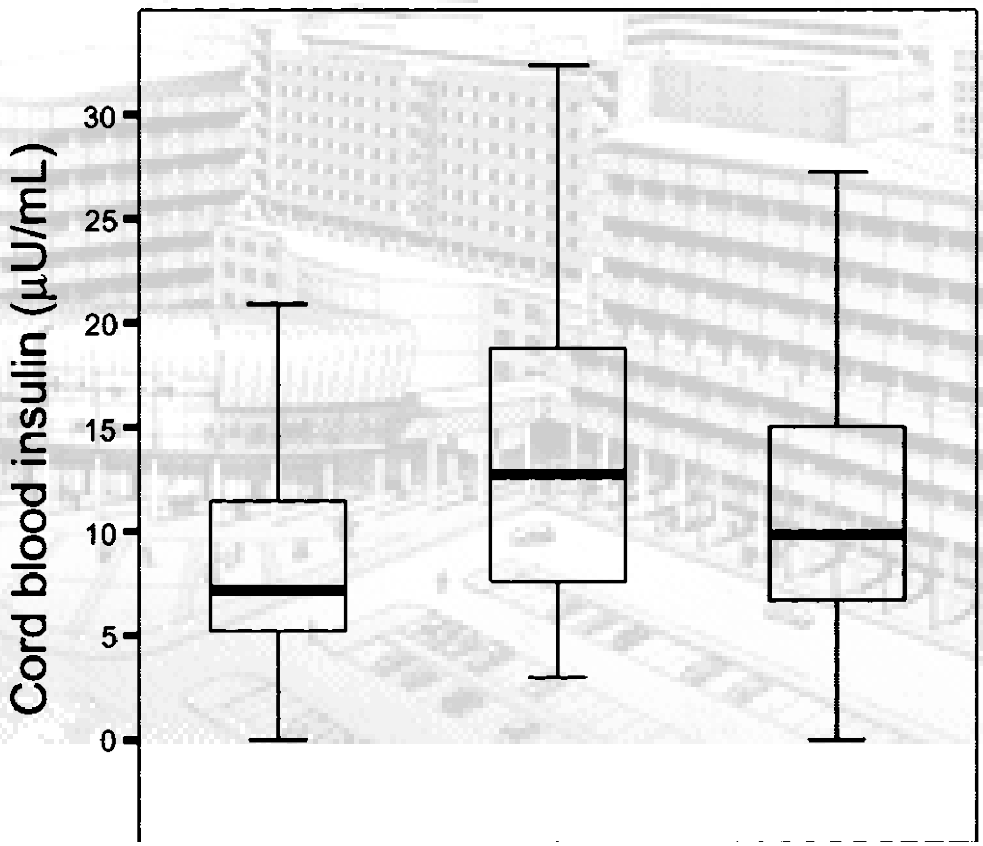
Glicemia 1 h OGTT durante la gravidanza si associa a ridotta sensibilità e secrezione insulinica



n=4053

Ghio et al International Journal of Endocrinology 2012

Glicemia 1 h OGTT durante la gravidanza si associa ad una maggiore iperinsulinismo fetale



Leopold H et al Obstet Gynecol 2004;104: 1301–6.

Glicemia 1 h OGTT durante la gravidanza si associa a macrosomia

Table 2. Cord Blood Insulin Values, Glucose Levels, and Birthweight (N = 930)

	Group I	Group II	Group III	*P**
Cord blood insulin (μU/mL)	7.25 (0–98)	12.8 (3–130)	9.9 (0–61)	< .001†
Cord blood glucose (mg/dL)	79 (32–153)	77 (32–153)	77 (34–146)	.52
Postpartum hyperinsulinism	46 (8.1)	18 (23.3)	43 (15.2)	.01‡
Birthweight (g)	3460 (1,340–4,550)	3480 (1,850–4,470)	3,330 (630–4,560)	.09
Birthweight > 95% percentile	58 (10.3)	17 (21.6)	47 (16.5)	.01§

Leopold H et al Obstet Gynecol 2004;104: 1301–6.

Glicemia 1 h OGTT durante la gravidanza si associa a caratteristiche antropometriche neonatali anomali

Variables	Neonatal CC/CT ratio ≤10th percentile for GA	Neonatal ponderal index ≥90th percentile for GA	Macrosomia
Logit model with fasting 75-g glucose load values			
Maternal age >35 years	1.57 (1.08–2.28)	1.48 (1.00–2.21)	2.09 (1.36–3.21)
Fasting 75-g glucose load value	1.07 (1.05–1.10)	1.04 (1.01–1.06)	1.03 (1.00–1.06)
Area under ROC curve	0.6683	0.6214	0.6540
Logit model with 1-h, 75-g glucose load values			
Maternal age >35 years	1.36 (0.88–2.11)	1.25 (0.81–1.91)	1.05 (1.04–1.05)
1-h, 75-g glucose load value	1.86 (1.19–2.91)	1.03 (1.02–1.03)	1.02 (1.01–1.03)
Area under ROC curve	0.8154	0.7499	0.7313
Logit model with 2-h, 75-g glucose load values			
Maternal age >35 years	1.05 (1.03–1.06)	1.37 (0.90–2.09)	1.99 (1.28–3.09)
2-h, 75-g glucose load value	1.04 (1.03–1.05)	1.03 (1.02–1.04)	1.02 (1.00–1.03)
Area under ROC curve	0.7244	0.7102	0.6996

Data are *n* or adjusted ORs (95% CI).

Mello G et al Diabetes Care 2003, 26:1206 –1210

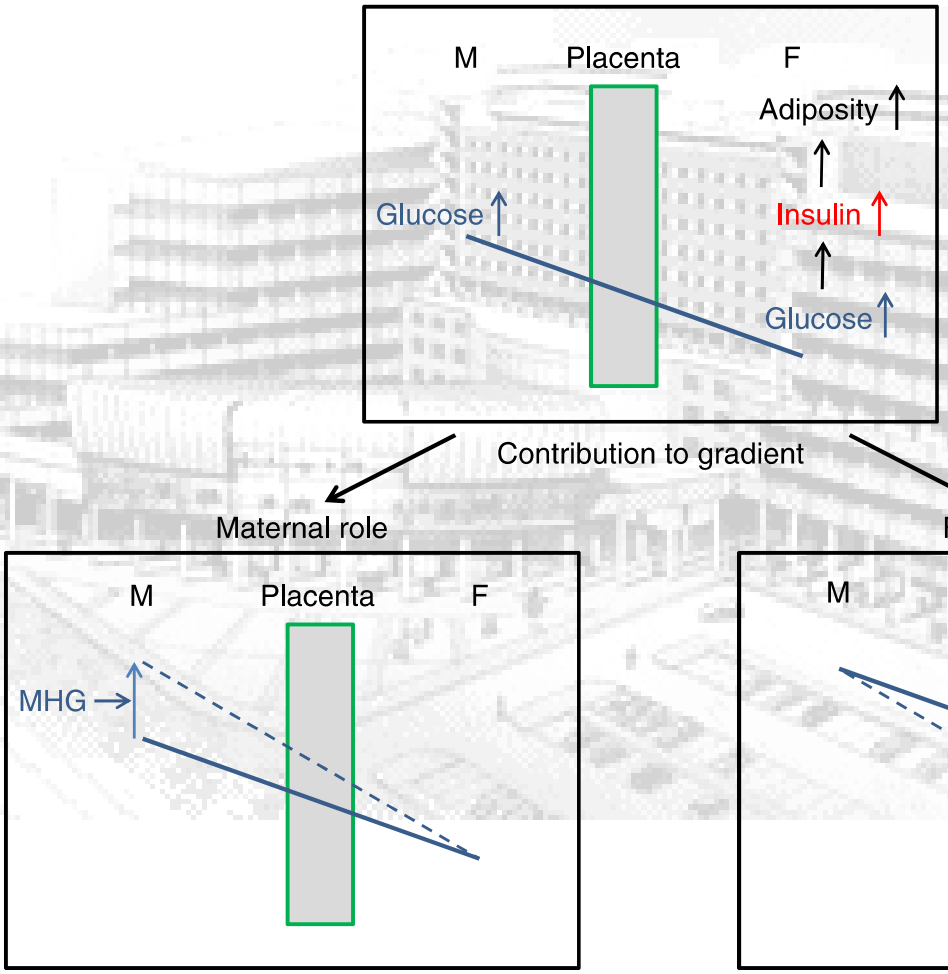
Glicemia 1 h OGTT durante la gravidanza si associa a caratteristiche antropometriche neonatali anomali

	Threshold of 150 mg/dl (early period)	Threshold of 160 mg/dl (late period)
OR (95% CI)	112.3 (8.3–422.7)	67.4 (32.2–141.2)
True positive	66	71
False negative	46	35
False positive	9	7
True negative	708	710
Sensitivity (%)	58.9	68.8
Specificity (%)	98.7	99.02
Positive predictive value (%)	88	91.7
Negative predictive value (%)	93.9	93.3
Likelihood ratio (abnormal)	45.3	70.2

Data are *n* or %.

Mello G et al Diabetes Care 2003, 26:1206 –1210

Fenomeno del furto del glucosio feto-placentare
Ruolo dell'iperinsulinemia fetale



Iperglicemia materna

Iperinsulinemia fetale

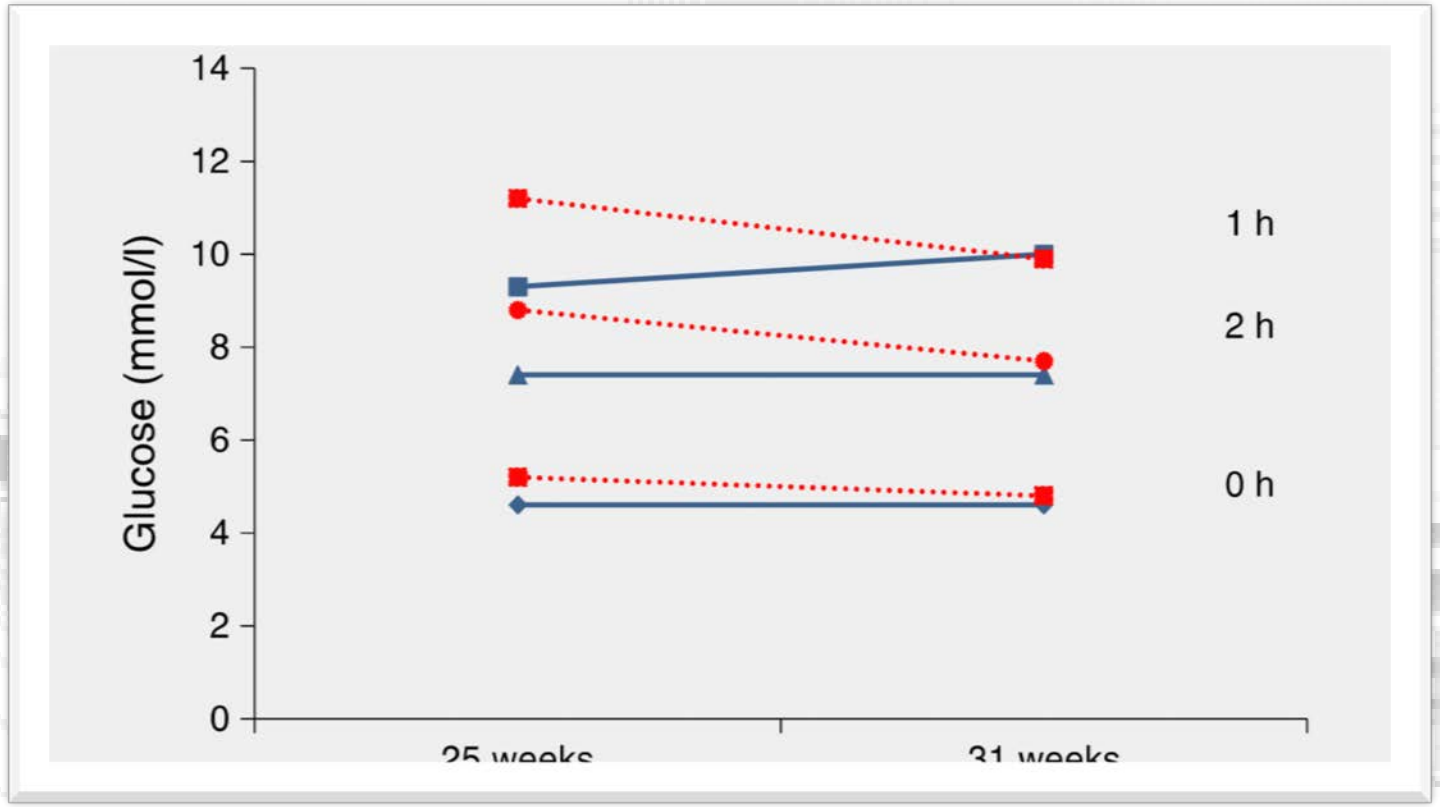
Fetopatia diabetica

Aumento adiposità

Ipoglicemia neonatale

Desoye G, Nolan CJ et al Diabetologia 2016

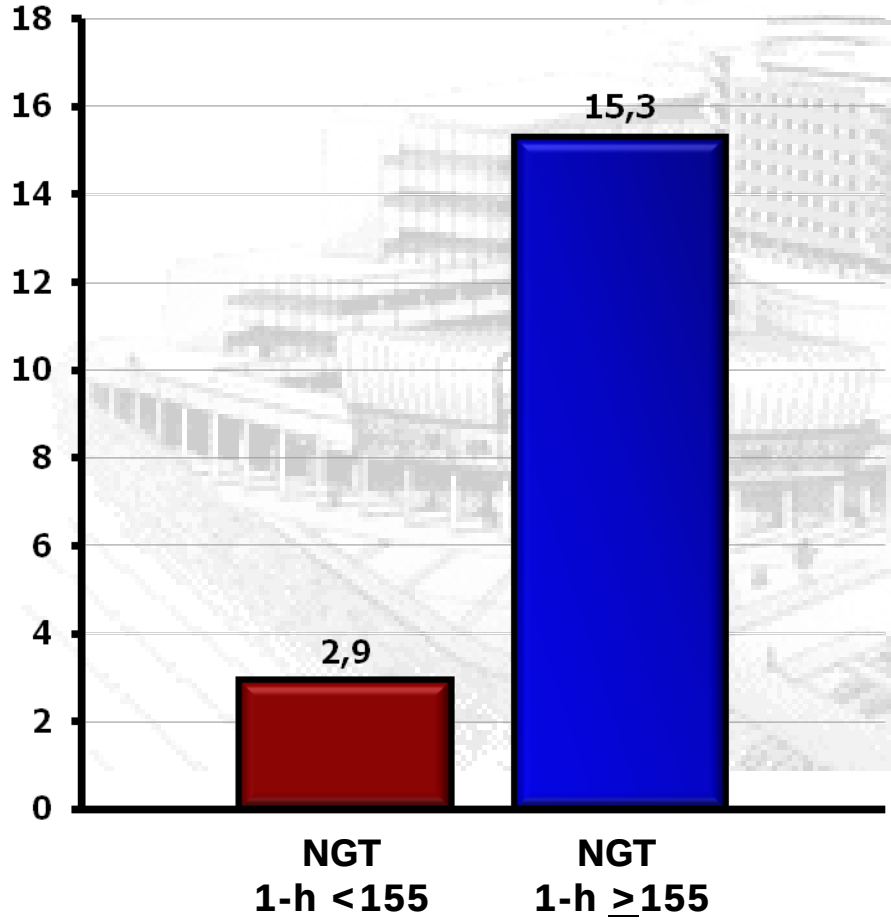
L'iperinsulinemia fetale, valutata attraverso misurazione dell'insulina nel liquido amniotico, può mascherare GDM



GDM con iperinsulinismo fetale
GDM senza iperinsulinismo fetale

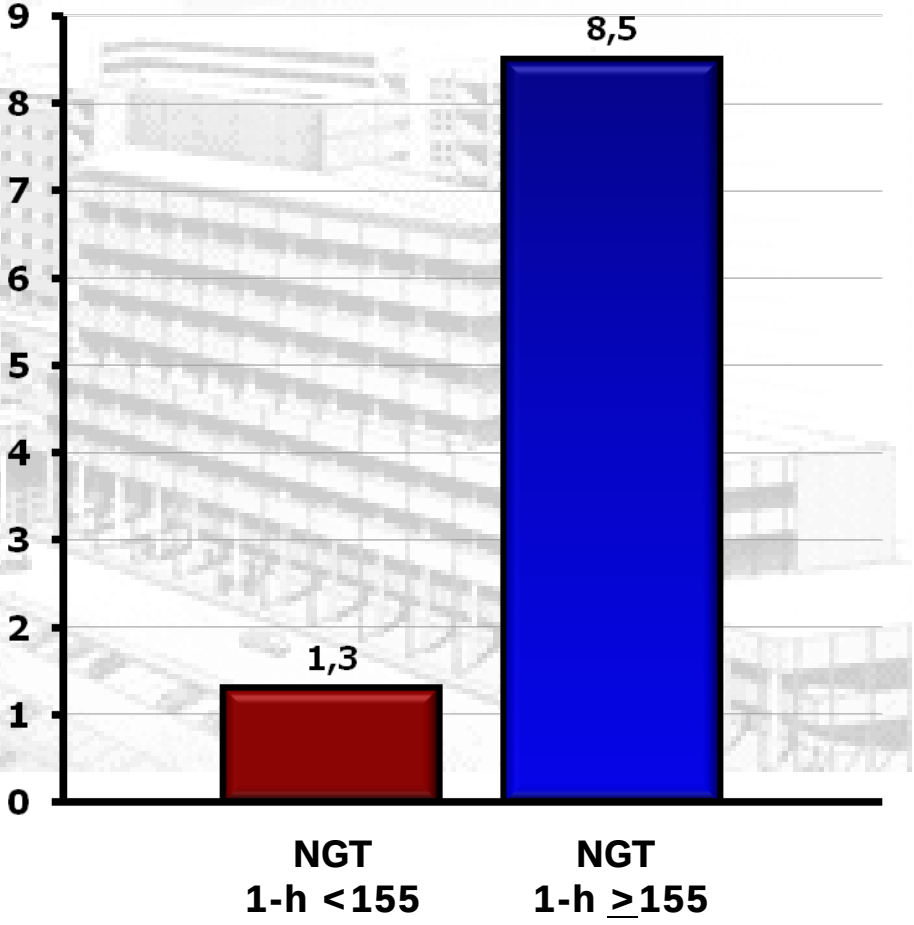
Desoye G, Nolan CJ et al Diabetologia 2016

Incidenza di diabete secondo la glicemia dopo 1 ora dal carico di glucosio ≥ 155 mg/dl



San Antonio Heart Study

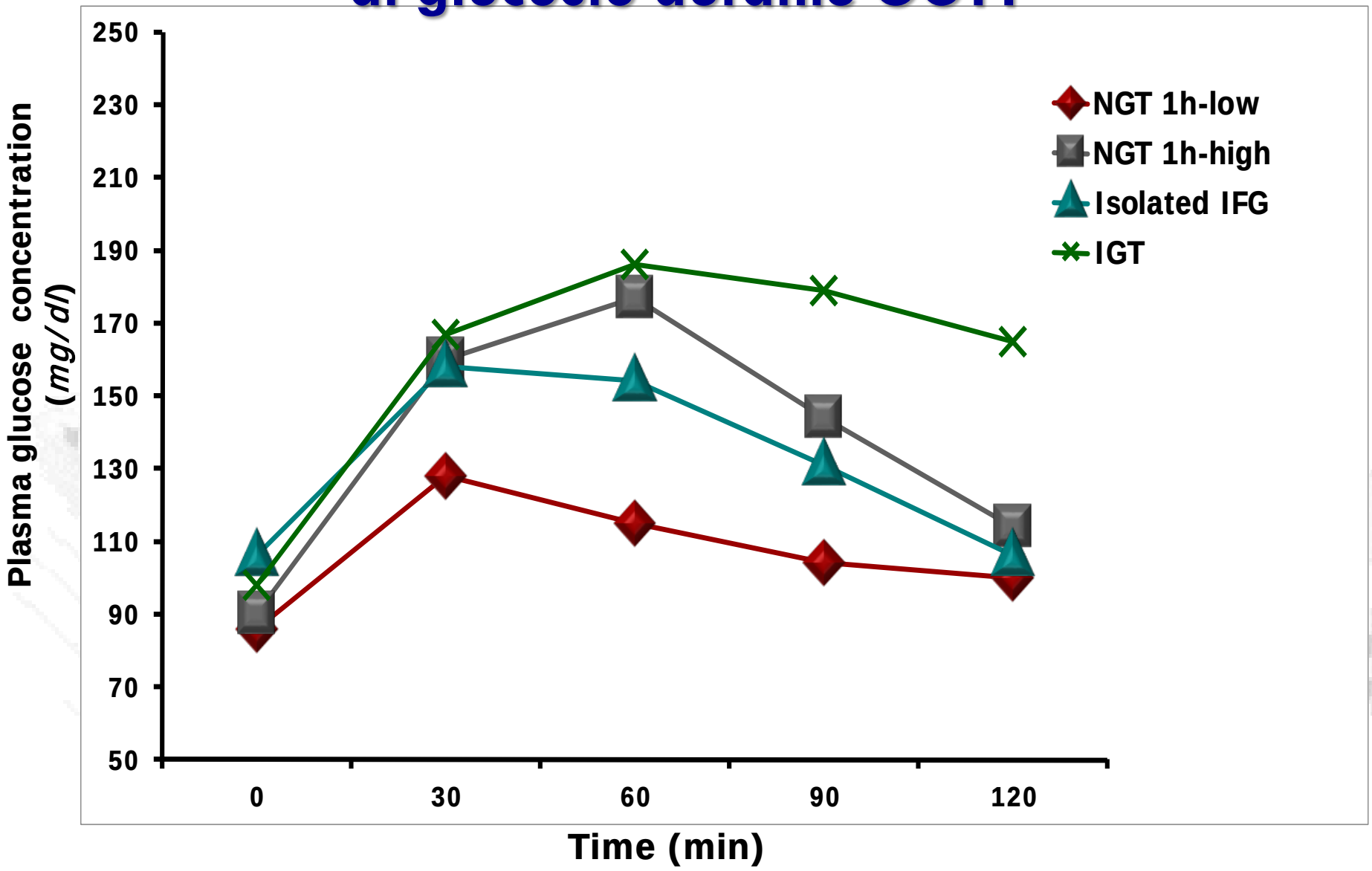
Abdul-Ghani MA et al. Diabetes Care 31:1650–1655, 2008



Botnia Study

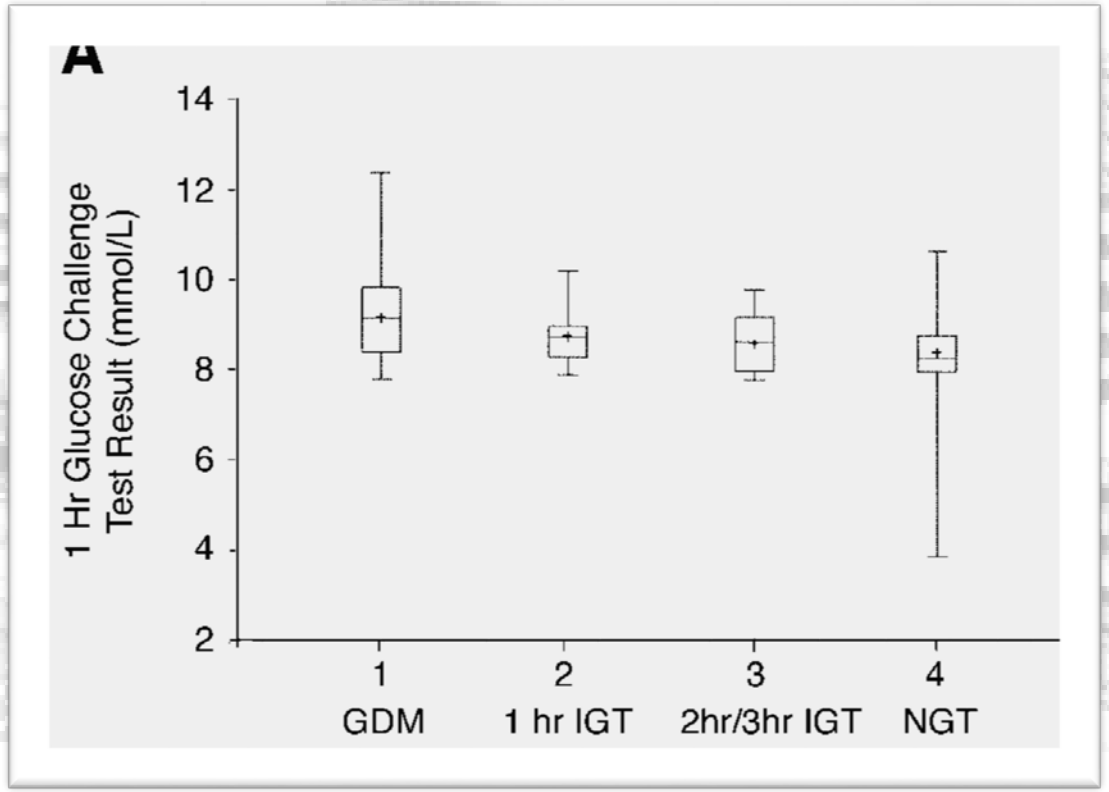
Abdul-Ghani MA et al. Diabetes Care 32:281–286, 2009

Media delle concentrazioni plasmatiche di glucosio durante OGTT



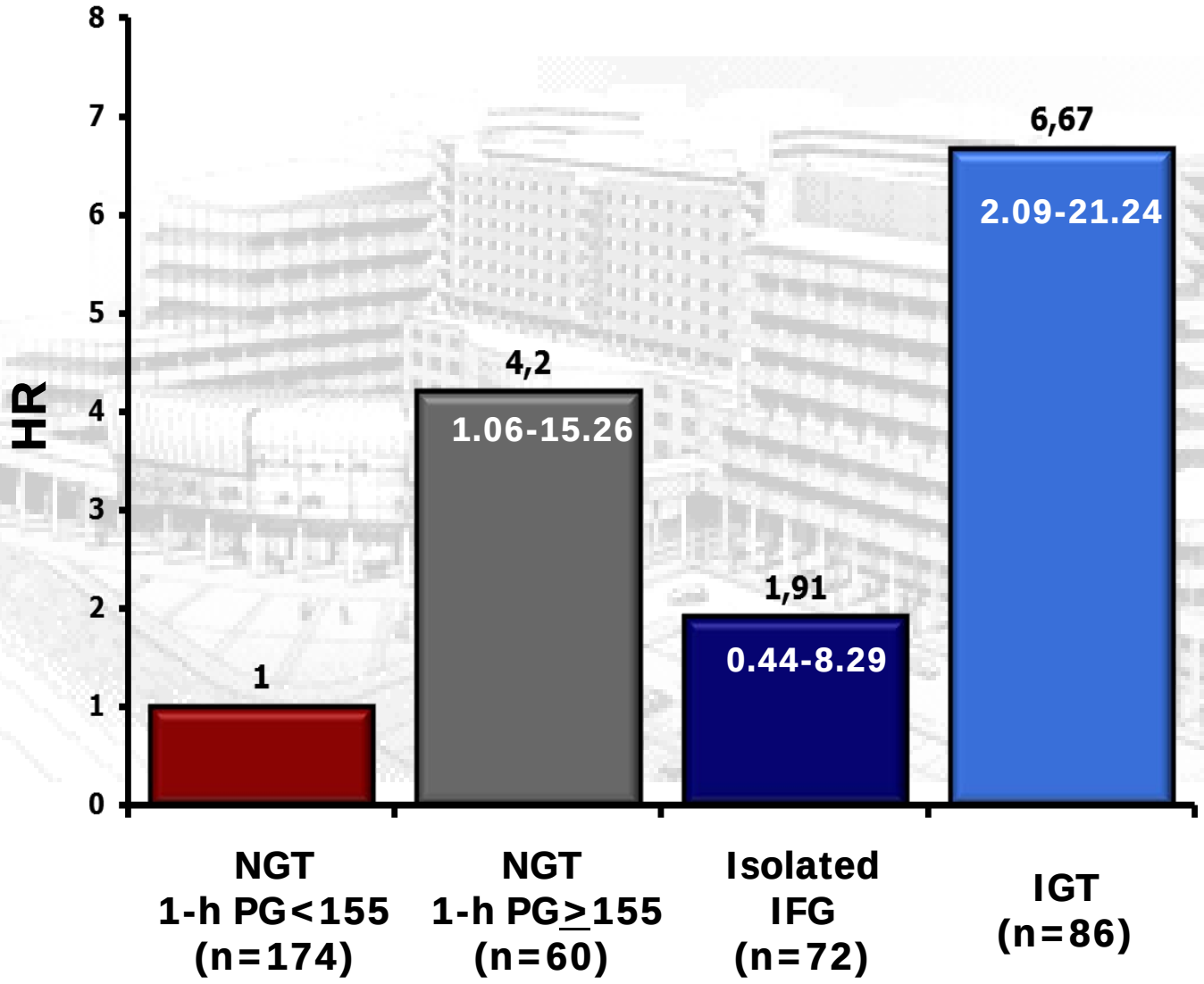
Fiorentino TV et al. J Clin Endocrinol Metab 2015

Media delle concentrazioni plasmatiche di glucosio durante OGTT in gravidanza



Retnakaran R et al. *Diabetes Care* 29:57–62, 2006

Incidenza di diabete in NGT 1h-high



Fiorentino TV et al. J Clin Endocrinol Metab 2015

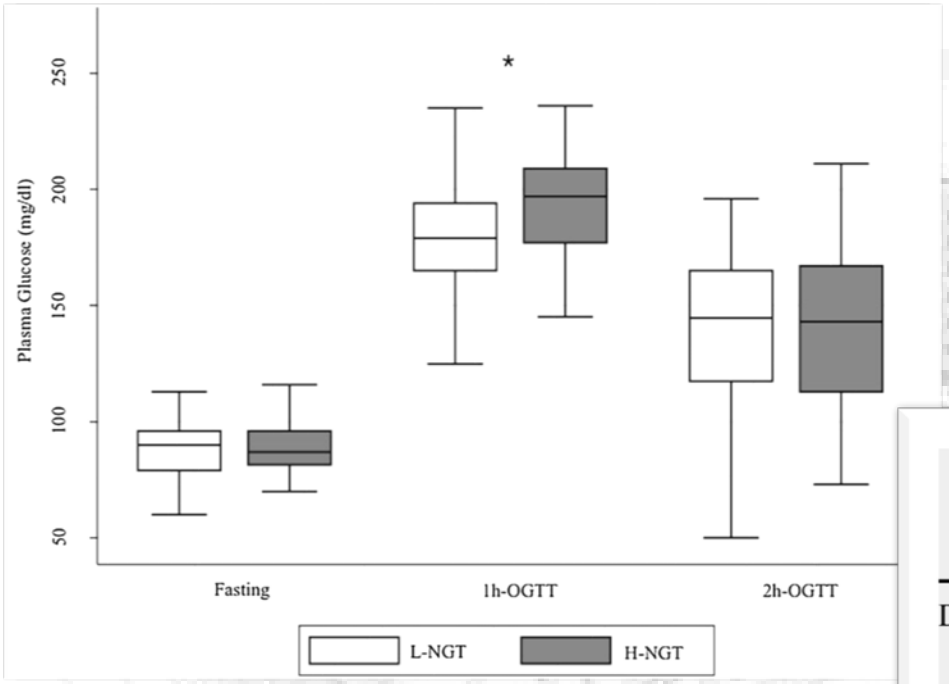
Glicemia 1 h durante OGTT in gravidanza predittore di NGT 1h-high al follow-up in donne con GDM

Abnormal glycemia	L-NGT ($n = 188$) (1-h OGTT < 155 mg/dl) n (%)	H-NGT ($n = 56$) (1-h OGTT ≥ 155 mg/dl) n (%)	Odds ratio[a]	p
Fasting (≥ 92 mg/dl)	58 (30.8)	8 (14.3)	**0.4** [95% CI 0.1–0.7]	**0.028**
1-h (≥ 180 mg/dl)	46 (24.6)	22 (39.3)	**3.7** [95% CI 1.4–9.6]	**0.016**
2-h (≥ 153 mg/dl)	27 (14.4)	6 (10.7)	0.8 [95% CI 0.4–4.6]	0.32
Fasting and 1-h	32 (17.0)	7 (12.5)	0.7 [95% CI 0.3–4.2]	0.28
Fasting and 2-h	4 (2.1)	1 (1.8)	0.9 [95% CI 0.6–3.9]	0.68
1-h and 2-h	17 (9.0)	6 (10.7)	1.3 [95% CI 0.8–5.7]	0.67
Fasting, 1-h and 2-h	4 (2.1)	6 (10.7)	**4.5** [95% CI 1.5–20.3]	**0.038**

Odds ratio corretti per età, BMI e HOMA-IR pre- e post-partum incremento di peso durante la gravidanza

Tumminia A et al. J Endocrinol Invest 2017

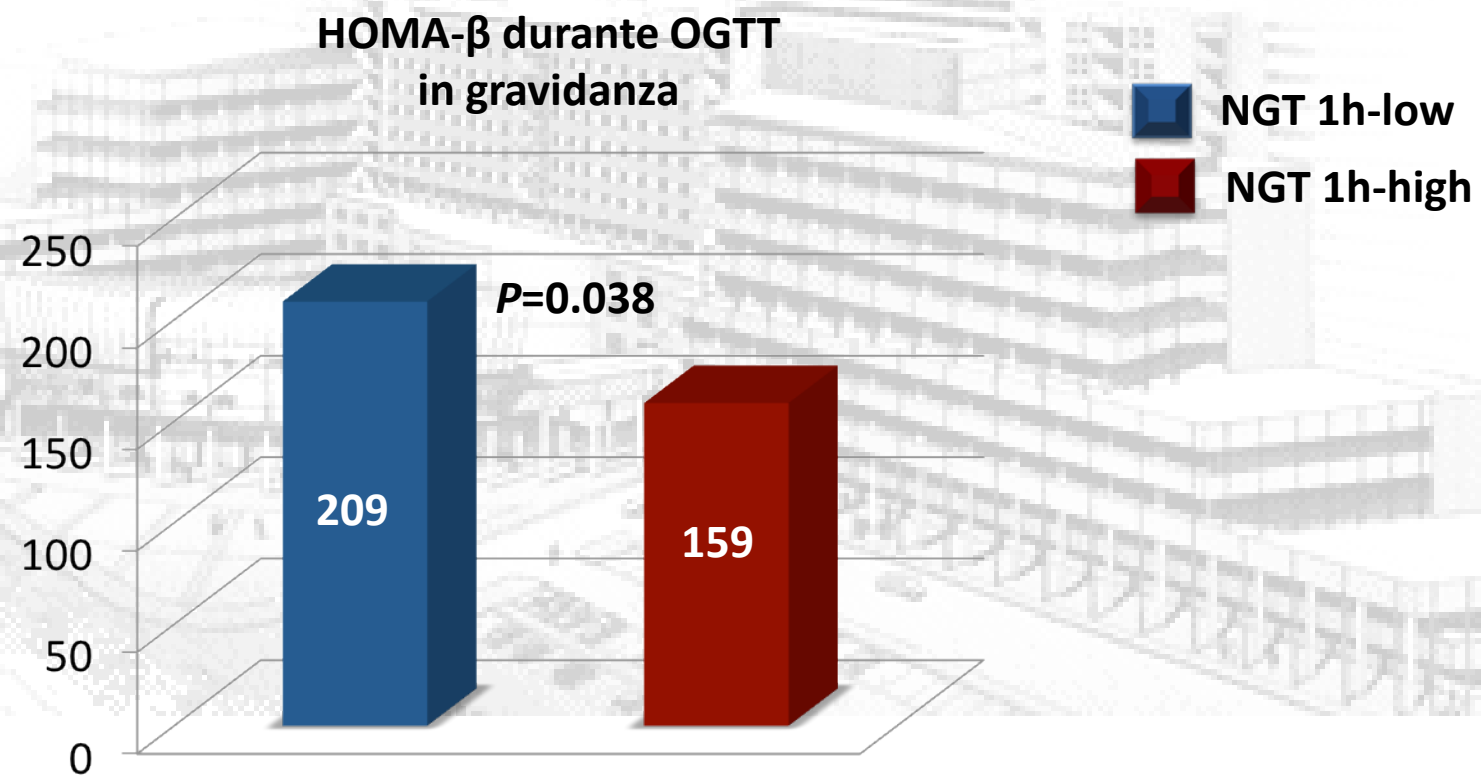
Livelli di glicemia e insulinemia in gravidanza in donne con GDM e NGT 1h-low e NGT 1h-high al follow-up



	L-NGT ($n = 188$) (1-h OGTT < 155 mg/l) Insulin (μIU/ml)	H-NGT ($n = 56$) (1-h OGTT ≥ 155 mg/dl) Insulin (μIU/ml)	p
During pregnancy			
(HOMA-IR = 2.5 ± 1.7)			
Fasting	12.1 ± 7.4	9.8 ± 5.9	0.54
1-h	143.5 ± 59.5	93.6 ± 29.7	**0.021**
2-h	113.9 ± 63.7	73.9 ± 48.0	0.10
Post-partum			
(HOMA-IR = 1.9 ± 1.5)			
Fasting	9.6 ± 9.9	7.8 ± 6.6	0.44
1-h	64.8 ± 54.2	76.3 ± 46.2	0.31
2-h	37.3 ± 30.3	48.7 ± 42.1	0.38

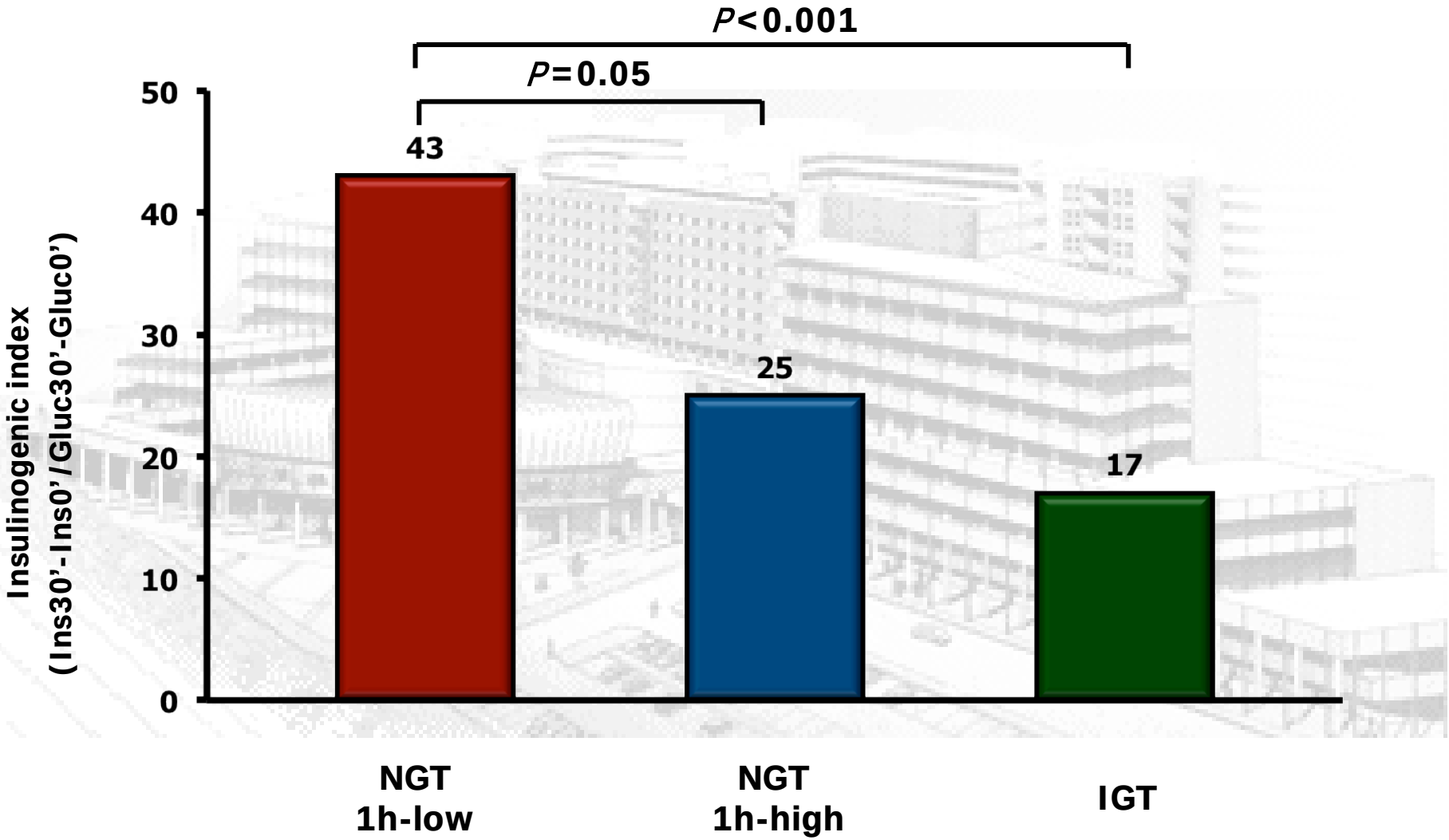
Tumminia A et al. J Endocrinol Invest 2017

Ridotti indici di secrezione insulinica durante gravidanza in donne con GDM NGT 1h-high al follow-up



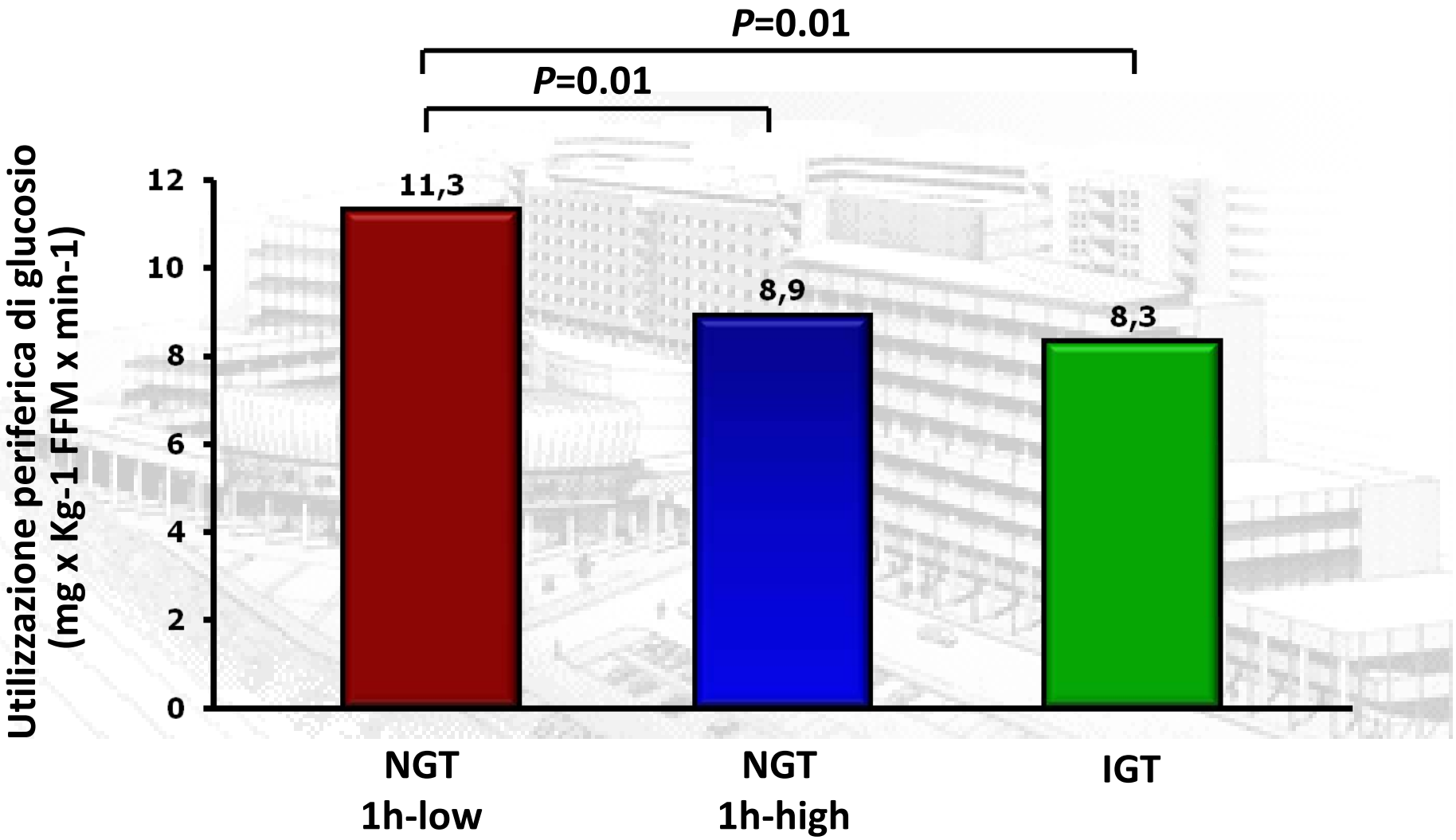
Tumminia A et al. J Endocrinol Invest 2017

Ridotta secrezione insulinica in NGT 1h-high



Marini MA et al. Diabetes Care 2012; 35:1–5

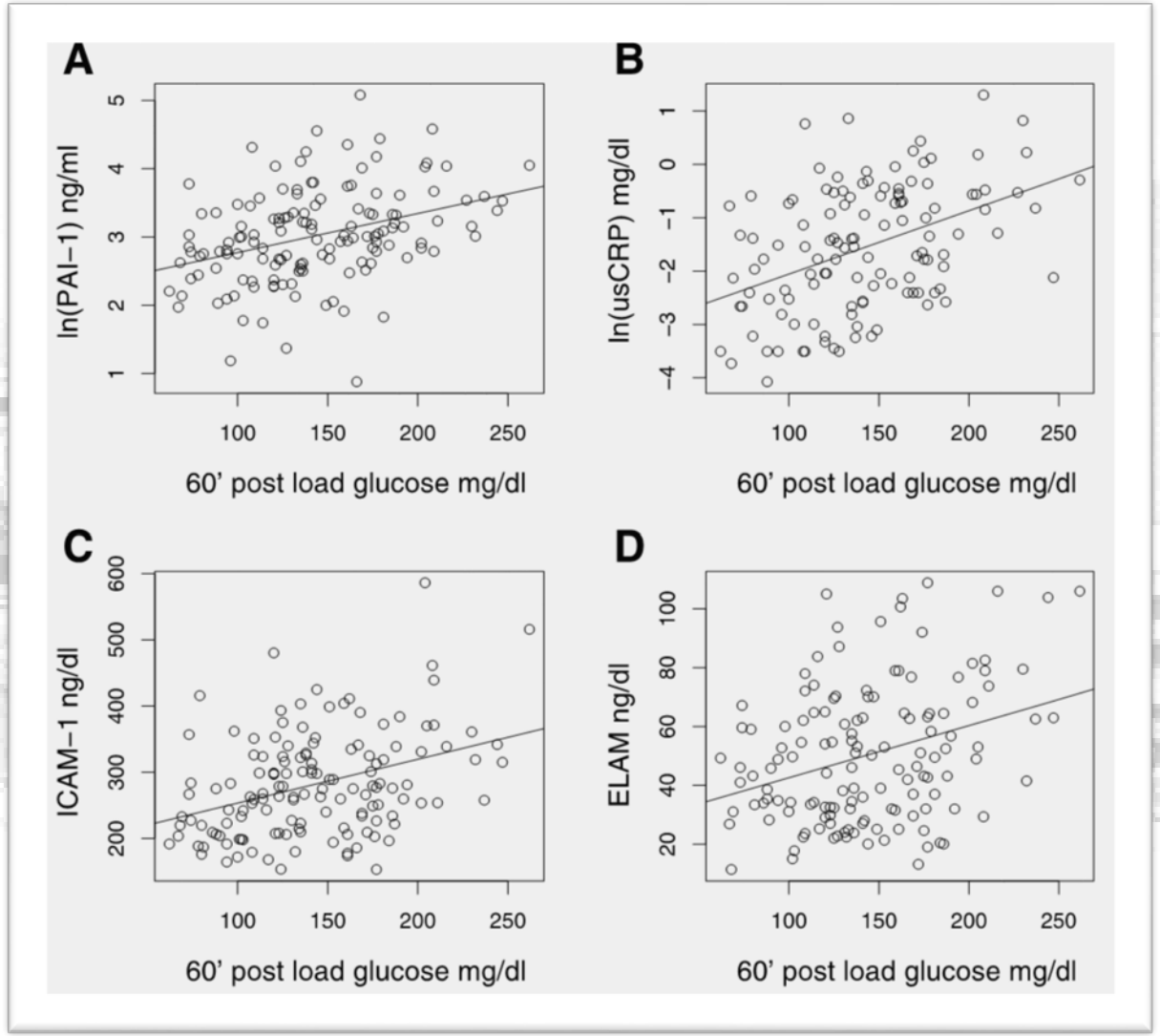
Ridotta sensibilità insulinica in NGT 1h-high



Analisi corretta per età, sesso e BMI

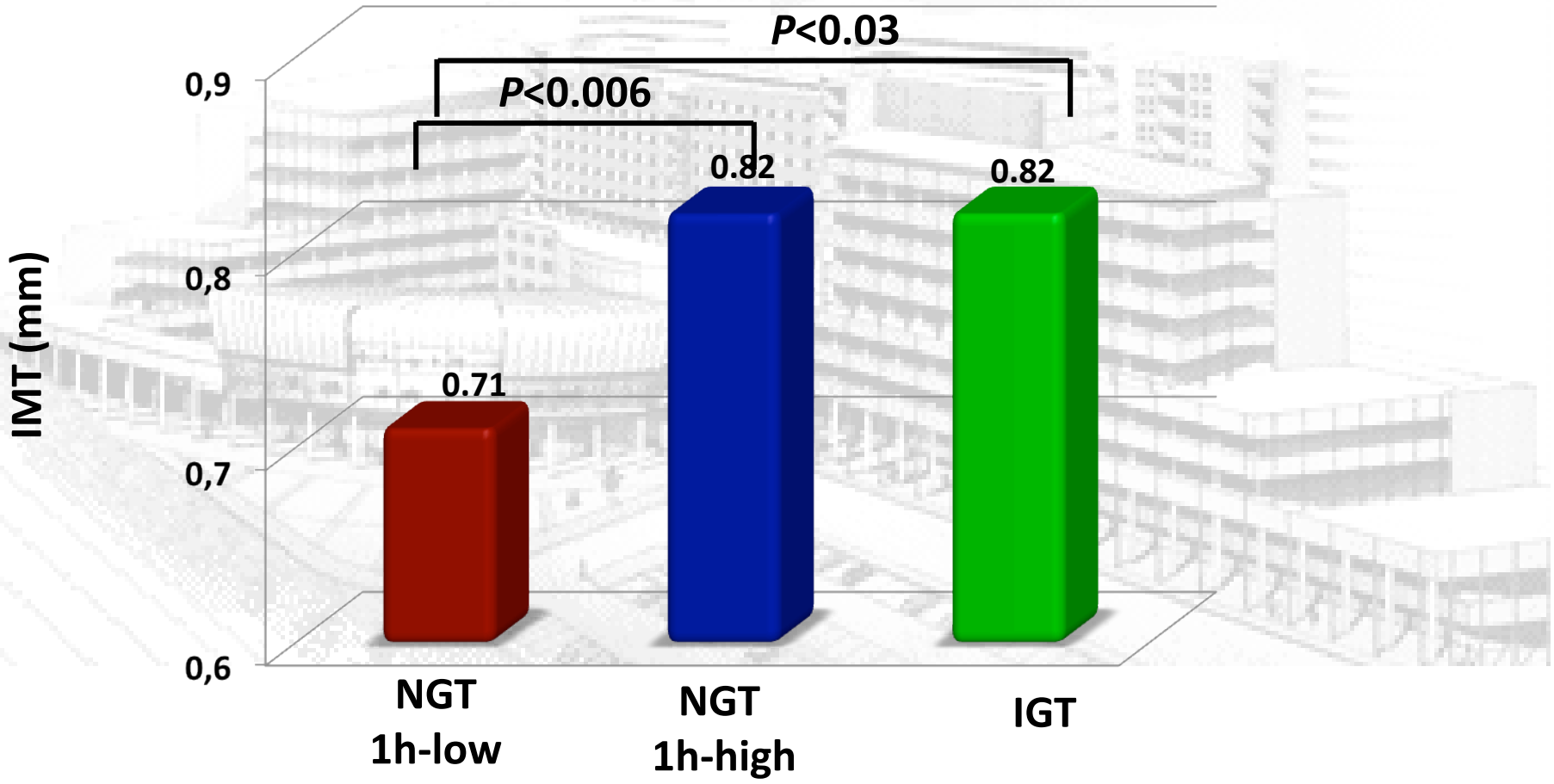
Marini MA et al. Diabetes Care 2012; 35:1–5

Aumentati indici infiammatori e molecole di adesione pro-aterogene in NGT 1h-high con pregresso GDM



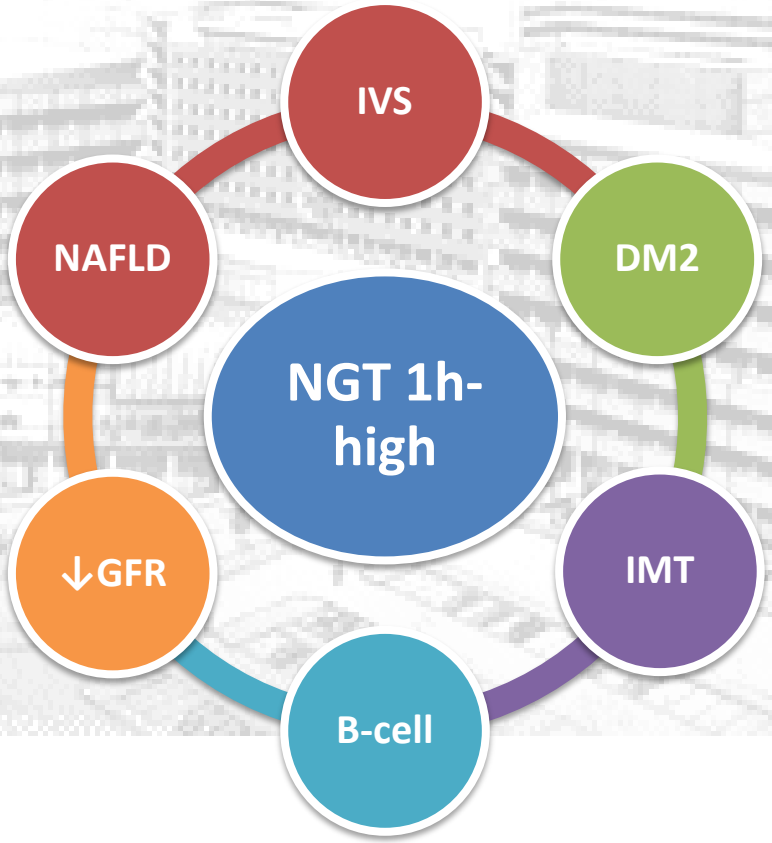
Gobl CS et al. *Am J Physiol Endocrinol Metab 2013,* 304: E524–E530

Ridotta sensibilità insulinica in NGT 1h-high

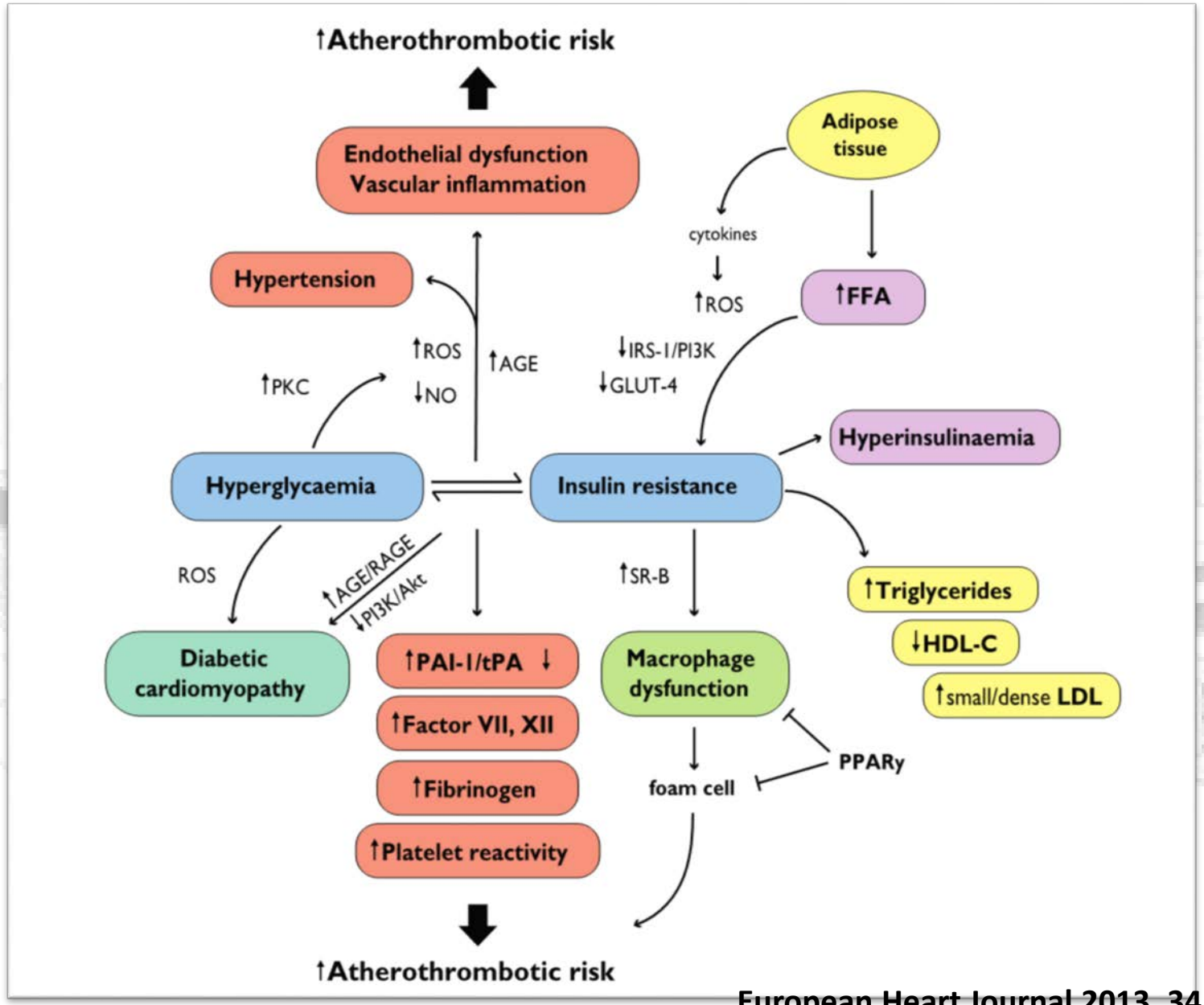


Succurro et al. Atherosclerosis 2009, 207: 245–249

Rischio cardiometabolico in NGT 1h-high



Iperglicemia acuta e rischio cardiometabolico



European Heart Journal 2013, 34, 3035–3087

Take home messages

- La glicemia alla prima ora in gravidanza è predittore indipendente di outcome avversi materno-neonatali ma anche di aumentato rischio di diabete tipo 2 e malattie cardiovascolari.

- La glicemia alla prima ora può, pertanto, essere utile per stratificare le donne ad alto rischio.

- Numerose evidenze dimostrano come un valore di glicemia alla prima ora $\geq$ 155 mg/dl identifica donne ad elevato rischio di diabete e cardiovascolare.



… e in futuro

Pre-diabete	ADA, EASD, IDF, Standard italiani di cura
Alterata glicemia digiuno (IFG)	Glicemia 100-125 mg/dl
Ridotta tolleranza agli idrati di carbonio (IGT)	Glicemia 2 h dopo OGTT 140-199 mg/dl
Pre-diabete	HbA1c 5.7-6.49 % (39-48 mmol/mol) Dosaggio standardizzato IFCC
Pre-diabete	Glicemia 1 h dopo OGTT $\geq$155 mg/dl

Riflettere sul valore soglia della glicemia 1 h durante gravidanza

Weiss PA, BJOG. 2000; 107(12):1480-5.

Grazie per l'attenzione!

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