Il follow-up del diabete gestazionale

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Diabete Gestazionale: obiettivi della diagnosi

Identificare gestanti con la malattia per prevenire le complicanze materno-fetali

Identificare gestanti ad elevato rischio per l'insorgenza del diabete tipo 2

Problematiche legate al follow-up delle donne con pregresso diabete gestazionale

Frequenza del follow-up: < 50%

- sottostima del rischio
- donne impegnate che si occupano di bambini piccoli
- cambi frequenti di residenza e occupazione
- difficoltà a portare avanti programmi di attività fisica e di dieta

- *Clark Hd, Diabetes Care 2003*
- *Gabbe S, Obstet Gynecol 2004*
- *Rumbold J, Aus Nzel Obstet Gynecol 2001*
- *Lewis RB, Endocrine Metab 2008*

Tolleranza glucidica dopo il parto nelle donne con GDM

GDM → **Dopo il parto: >95% NGT** → **a distanza?**

- ✓ Analisi di 24 studi tra 1965 - 2001:

L'incidenza di DM tipo 2 aumenta nei primi cinque anni dopo il parto fino ad arrivare ad un plateau.

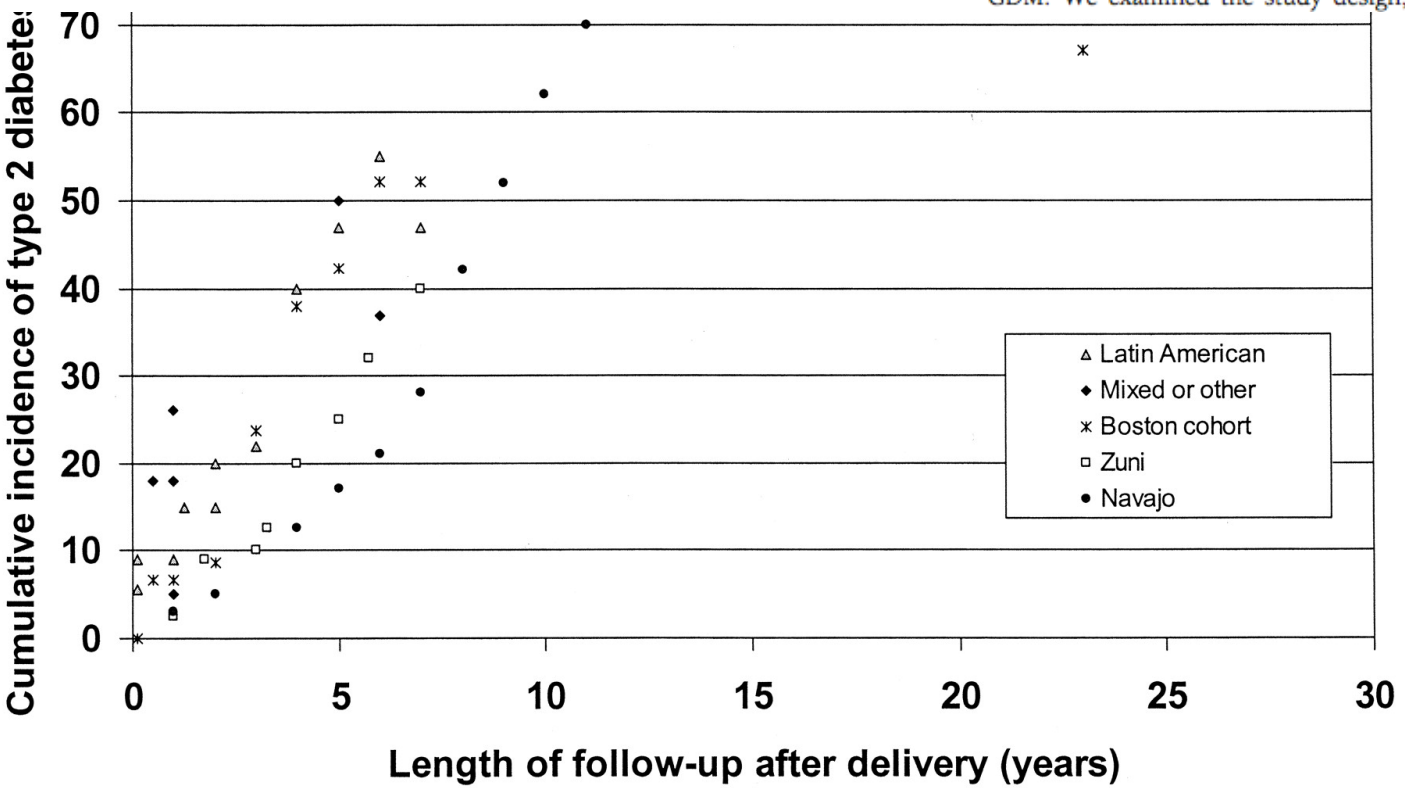
Reviews/Commentaries/Position Statements
REVIEW ARTICLE

Gestational Diabetes and the Incidence of Type 2 Diabetes

A systematic review

CATHERINE KIM, MD, MPH[1]
KATHERINE M. NEWTON, PHD[2]
ROBERT H. KNOPP, MD[3]

type 2 diabetes in women with GDM, we performed a systematic review of the literature, examining the cumulative incidence of type 2 diabetes in women with GDM. We examined the study design,



Kim C et al. Dia Care 2002;25:1862-1868

Risk of development of type 2 diabetes

Cumulative Probability (95% CI)

Follow-up Years	pGDM (5470)	Controls (783)
1	1.7 (1.3-2.1)	0
2	2.6 (2.1-3.2)	0
5	8.1 (7.1-9.2)	0
10	17.3 (15.5-19.3)	2 (1.0-3.8)
15	25.8 (23-28.9)	3.9 (2.0-7.3

Hazard risk 9.6 times greater for pGDM than Controls

Lee A,Diabetes Care 2007

DIAGEST 2 STUDY
(6.75 years follow-up)

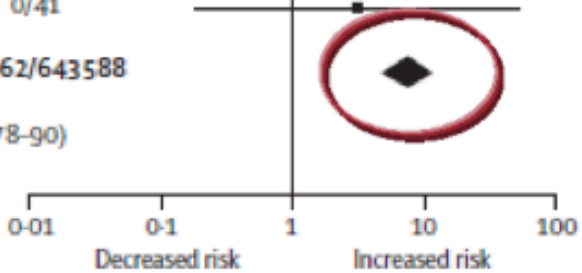
	DM (%)	IGT (%)	IFG (%)	ALL (%)
control (221)	0.9	2.1	3.6	8.3
previous GDM (466)	18	13.4	8.5	43.5
p vs control	<0.001	<0.001	NS	<0.001
previous AGT (322)	6.3	11.3	6.3	28.7
p vs control	<0.05	<0.05	Ns	=0.005
total	11.2	11.3	6.9	34.4

Vambergue A – Diabet Med 25:58-64, 2008

Risk of development of type 2 diabetes

	Country	T2DM/GDM	T2DM/no GDM	Relative risk (95% CI)
Feig et al.[18] 1995–2002	Canada	2874/21823	6628/637341	12·66 (12·15–13·19)
Lee H et al.[15] 1995–97	Korea	71/620	22/868	4·52 (2·83–7·21)
Madarasz et al.[21] 1995	Hungary	21/68	0/39	24·93 (1·55–400·64)
Gunderson et al.[22] 1985–206	USA	43/166	150/2242	3·87 (2·87–5·22)
Vambergue et al.[23] 1992	France	53/295	1/111	19·94 (2·79–142·47)
Lee A et al.[24] 1971–2003	Australia	405/5470	16/783	3·62 (2·21–5·93)
Ferraz et al.[17]*	Brazil	6/70	7/108	1·32 (0·46–3·78)
Krishnaveni et al.[25] 1997–98	India	13/35	8/489	22·70 (10·09–51·08)
Morimitsu et al.[26] 1999–2001	Brazil	7/23	0/11	7·50 (0·47–120·11)
Järvelä et al.[5] 1984–94	Finland	23/435	0/435	47·00 (2·86–771·65)
Albareda et al.[27] 1966–93	Spain	44/696	0/70	9·07 (0·56–146·25)
Åberg et al.[28] 1991–99	Sweden	21/229	1/61	5·59 (0·77–40·66)
Linné et al.[16] 1964–65	Sweden	10/28	0/52	38·38 (2·33–631·74)
Bian et al.[29] 1964–65	China	15/45	1/39	13·00 (1·80–93·93)
Ko et al.[30] 1988–95	China	105/801	7/431	8·07 (3·79–17·19)
Osei et al.[31] 1990–91	USA	10/15	0/35	47·25 (2·95–757·28)
Damm et al.[32] 1978–85	Denmark	33/241	0/57	16·06 (1·00–258·06)
Benjamin et al.[33] 1961–88	New Mexico	14/47	3/47	4·67 (1·43–15·21)
O'Sullivan,[34] 1954–60 and 1962–70	USA	224/615	18/328	6·64 (4·19–10·52)
Persson et al.[35] 1961–84	Sweden	5/145	0/41	3·16 (0·18–55·76)
Total		**3997/31867**	**6862/643588**	**7·43 (4·79–11·51)**

Test for heterogeneity: τ^2=0·50, χ^2=126·67, df=19 (p<0·0001), I^2=85·0% (95%CI 78–90)
Test for overall effect: Z=9·39 (p<0·0001)



Bellamy L. The Lancet, 2009

Fattori predittivi per la comparsa del DM2 nelle donne con pregresso GDM

- BMI al momento della diagnosi del GDM
- Diagnosi del GDM < 20 settimane
- Etnie ad alto rischio
- Familiarità per il DM2
- Grado di alterazione dell'OGTT
- Terapia insulinica in gravidanza
- Eccessivo incremento ponderale in gravidanza

OBSTETRICS

Positive association between a single abnormal glucose tolerance test value in pregnancy and subsequent abnormal glucose tolerance

Francesco Corrado, MD; Rosario D'Anna, MD; Maria L. Cannata, MD; Desirée Cannizzaro, MD; Francesco Caputo, MD; Emanuela Raffone, MD; Antonino Di Benedetto, MD

Am J Obstet Gynecol 2007;196:339.e1-339.e5.

TABLE 2

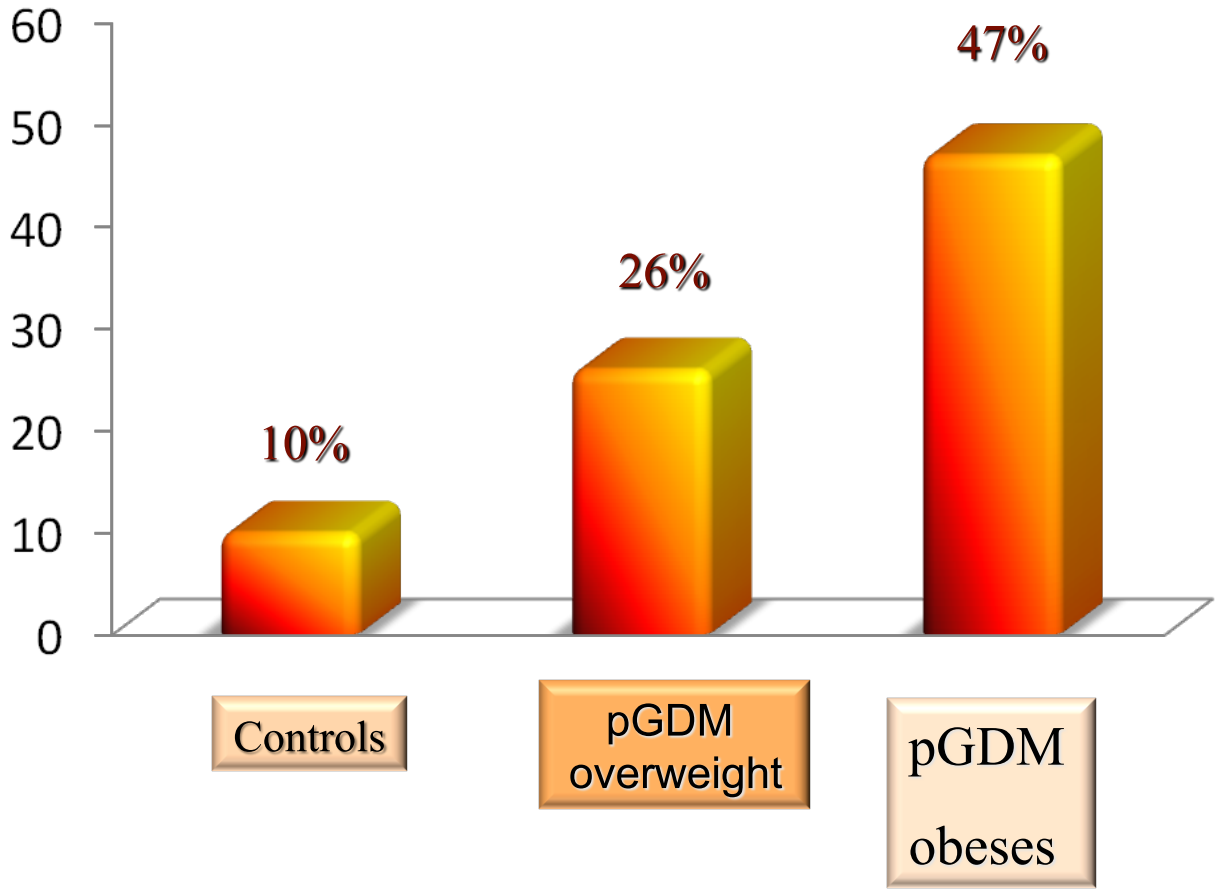
Risk factors for subsequent glucose intolerance in OAV and GDM subjects, stratified by presence or absence of AGT at a mean of 7.15 years after the index pregnancy

	OAV affected by AGT			GDM affected by AGT		
	Yes	No	*P*	Yes	No	*P*
Sample size	n = 19	n = 47		n = 20	n = 38	
Prepregnancy BMI, kg/m^2, mean ± SD	28.2 ± 2.6	25.2 ± 4.4	.009	30.2 ± 4.1	27.6 ± 4.2	.02
Maternal age, years, mean ± SD	33.4 ± 5.5	33.4 ± 4.8	.9	36.7 ± 2.6	33.5 ± 3.9	.002
OGTT,* mg/dL, mean ± SD	85.6 ± 8.9	78.6 ± 11.9	.002	87.2 ± 9.3	78.4 ± 10.5	.003
parity > 1, no. (%)	13 (68.4)	16 (34.0)	.01	13 (65.0)	12 (31.5)	.02
Family history of DM, no. (%)	12 (63.1)	15 (31.9)	.02	13 (65.0)	10 (26.3)	.006

AGT, abnormal glucose tolerance; *BMI*, body mass index; *DM*, diabetes mellitus; *GDM*, gestational diabetes mellitus; *OAV*, 1 abnormal value for OGTT; *OGTT*, oral glucose tolerance test; *SD*, standard deviation.

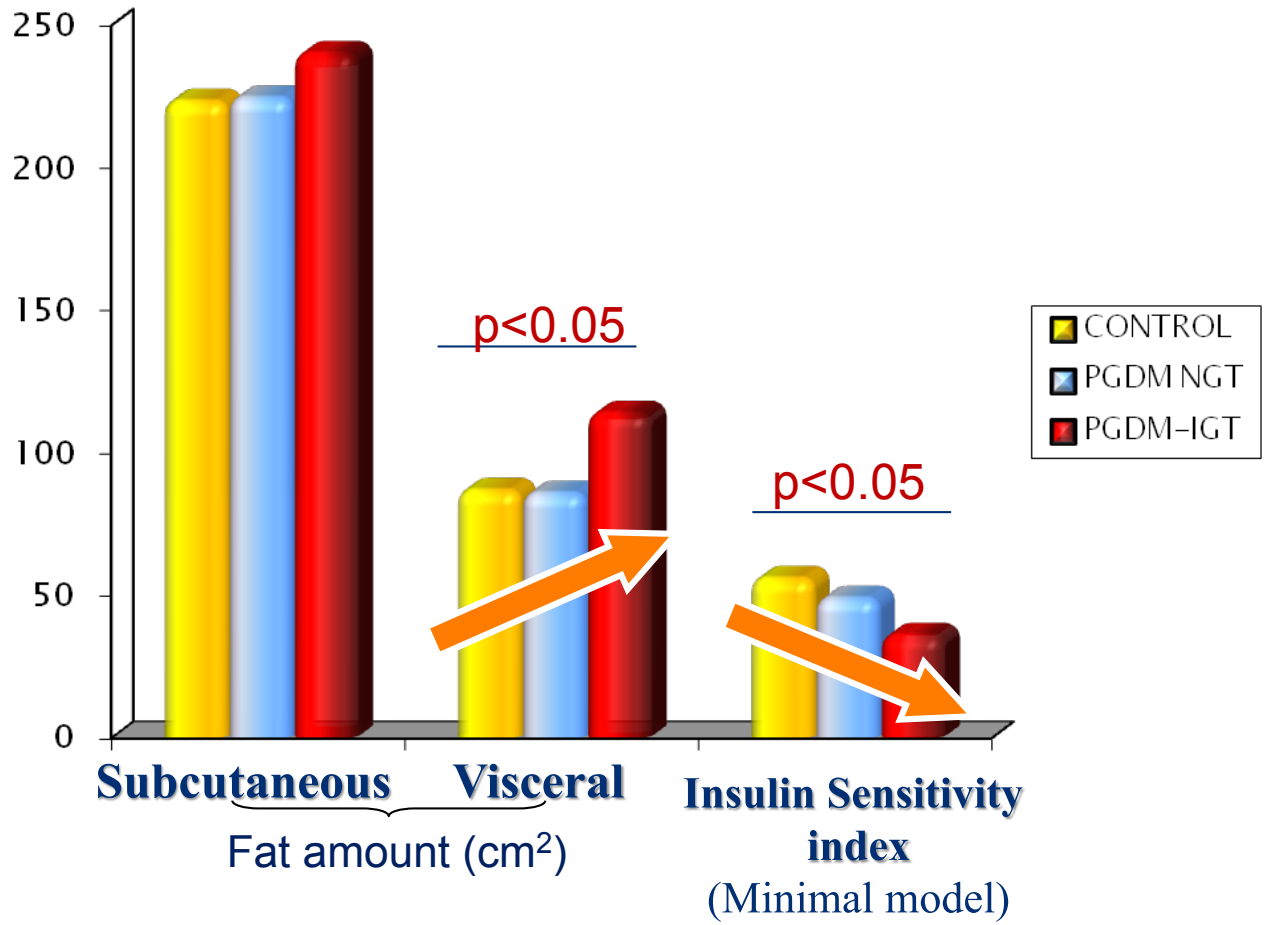
* Fasting value.

GDM and Type 2 Diabetes
"Boston Gestational Diabetes Study"



O' Sullivan 1982

Visceral fatness and insulin sensitivity in pGDM women

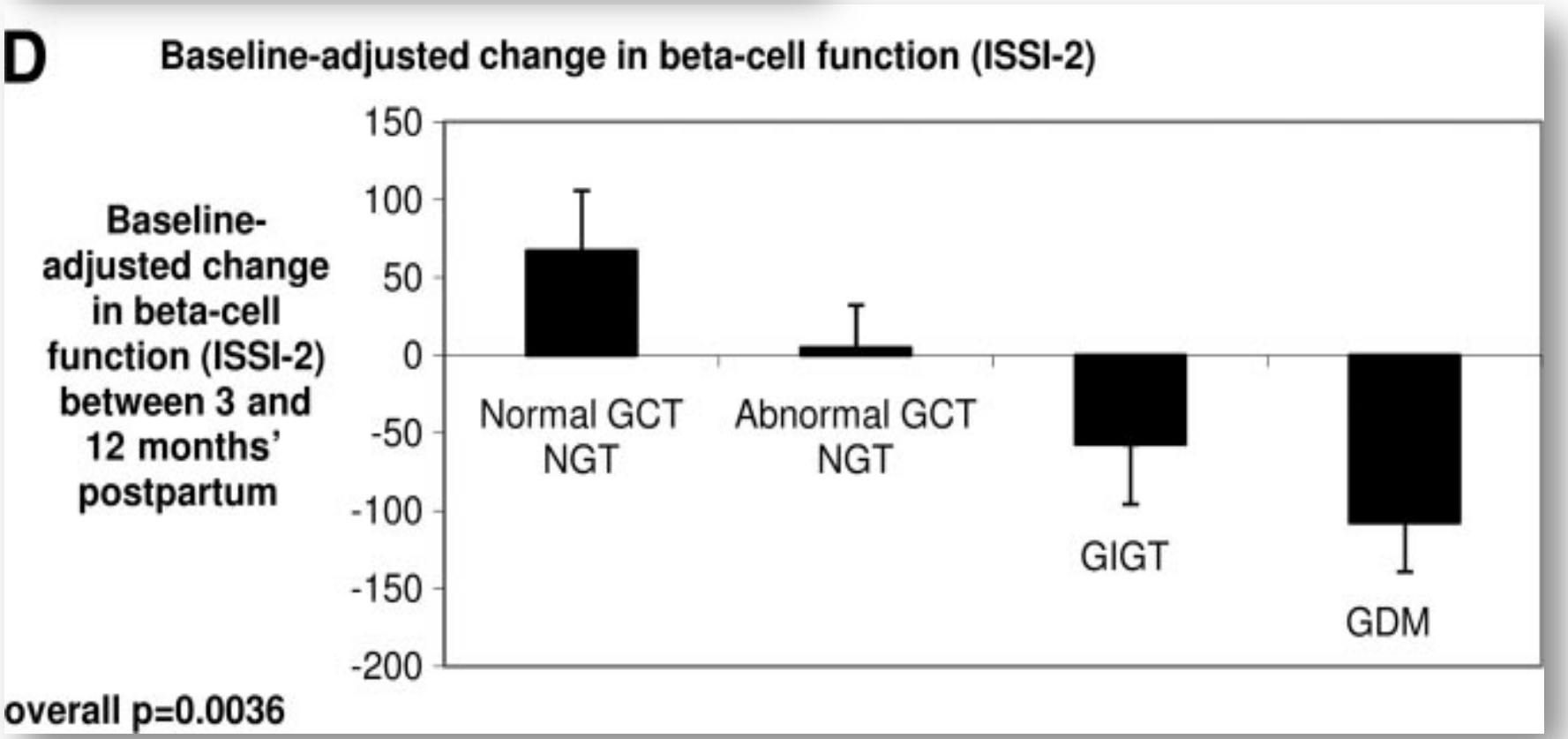


Lim S. et al, Diabetes Care,2007

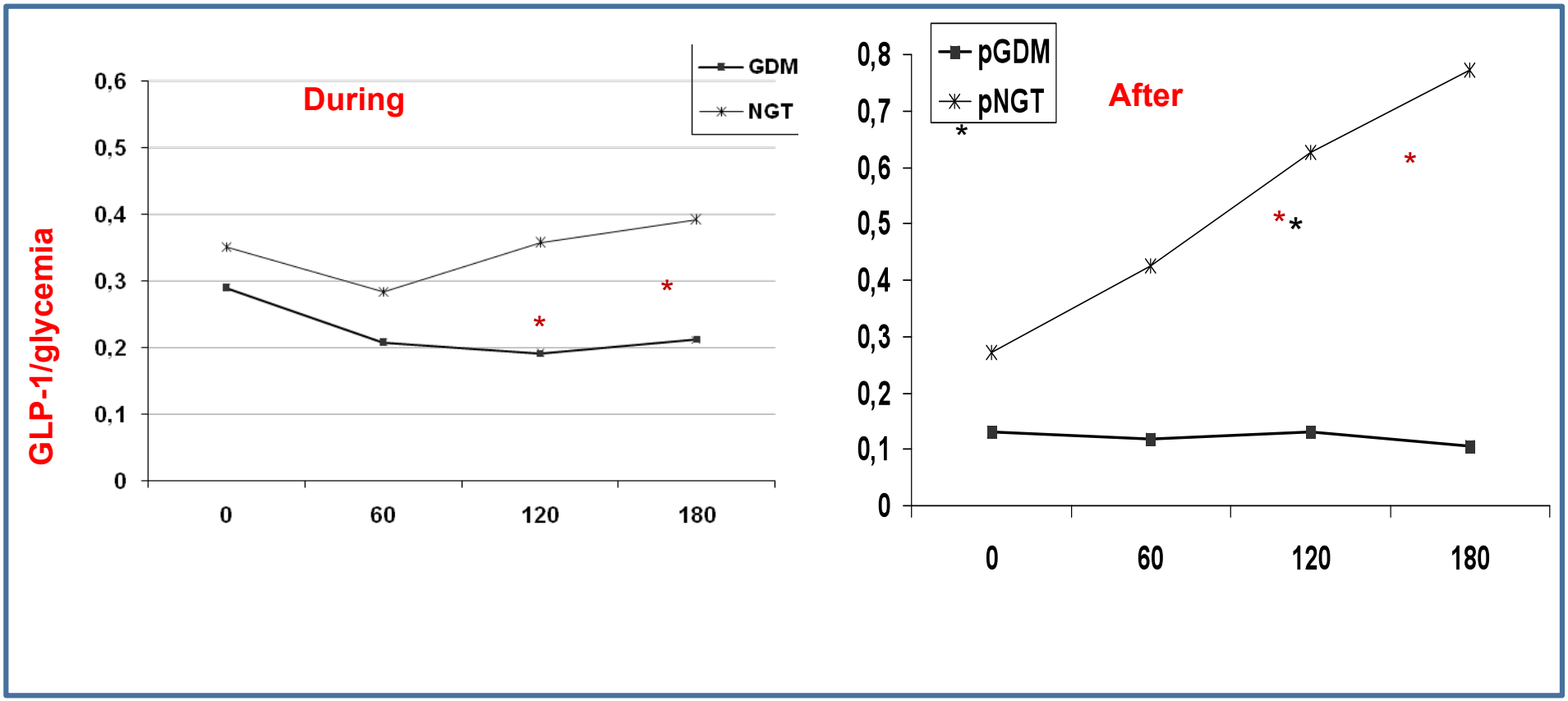
β-Cell Function Declines Within the First Year Postpartum in Women With Recent Glucose Intolerance in Pregnancy

Ravi Retnakaran, MD[1,2]
Ying Qi, MSc[1]
Mathew Sermer, MD[3]
Philip W. Connelly, PhD[2,4]
Anthony J.G. Hanley, PhD[1,2,5]
Bernard Zinman, MD[1,2]

Diabetes Care 33:1798–1804, 2010



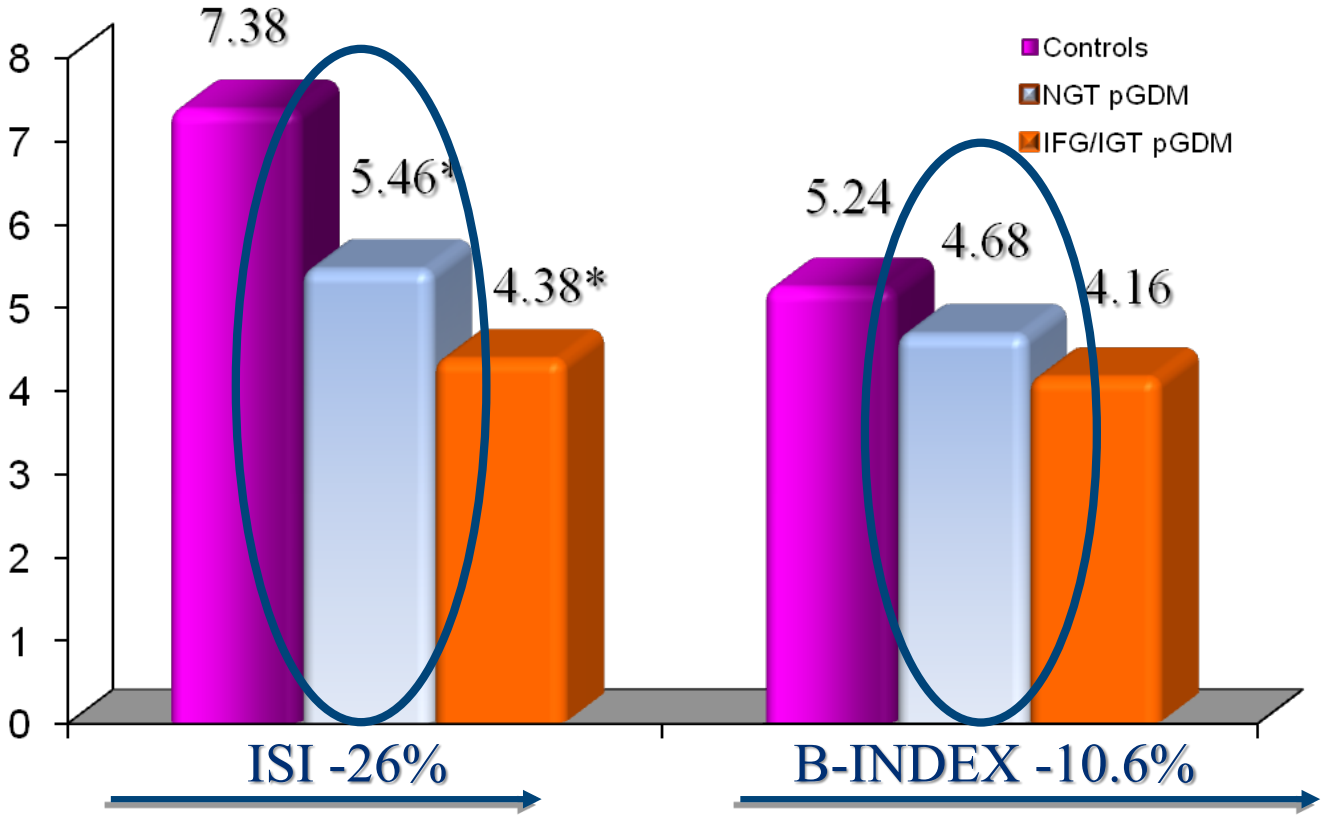
Glucagons-like peptide-1 (GLP-1) secretion in women with gestational diabetes mellitus during and after pregnancy



GLP-1 concentrations are lower during and after pregnancy in GDM, * p<0.05 pGDM vs pNGT

C. Lencioni, G Di Cianni JEI, 2011

Impairment of β-cell function and insulin sensitivity in normotolerant women with pGDM
(2 years after delivery)



* p<0.05

C. Lencioni, Nutr Met Cardiovasc Dis 2006

CVD risk factors in women with a history of GDM

	NO GDM (N.633)	*PRIOR GDM (N.313)*	*P**
Waist (cm)	104 ± 0.7	106.4 ± 1	0.2
Systolic Blood Pressure (mmHg)	127.9 ± 0.8	127.9 ± 1.1	0.07
Diastolic Blood Pressure (mmHg)	76.4 ± 0.4	77.1 ± 0.7	0.3
HDL-C (mmol/l)	**1.09 ± 0.01**	**1.09 ± 0.02**	**1**
Non HDL-C (mmol/l)	**3.83 ± 0.05**	**3.95 ± 0.07**	**0.02**
LDL-C (mmol/l)	**3.08 ± 0.04**	**3.21 ± 0.05**	**0.01**
Total-C (mmol/l)	**4.93 ± 0.05 3**	**5.05 ± 0.06**	**0.009**
Triglycerides (mmol/l)	**1.669 ± 0.068**	**1.732 ± 0.09**	**0.007**
Fasting Plasma Glucose (mmol/l)	8.04 ± 0.15	9.36 ± 0.24	<0.001
Fasting Insulin (pmol/l)	83.5	102	<0.001

* Adjusted for age, menopausal status and clustering on the proband

Carr D.B., Diabetes Care 2006

Epidemiology/Health Services Research
BRIEF REPORT

Increased Risk of Hypertension After Gestational Diabetes Mellitus

Findings from a large prospective cohort study

RESULTS—During 16 years of follow-up, GDM developed in 1,414 women (5.6%) and hypertension developed in 3,138. A multivariable Cox proportional hazards model showed women with a history of GDM had a 26% increased risk of developing hypertension compared with those without a history of GDM (hazard ratio 1.26 [95% CI 1.11–1.43]; $P = 0.0004$). These results were independent of pregnancy hypertension or subsequent type 2 diabetes.

CONCLUSIONS—These results indicate that women with GDM are at a significant increased risk of developing hypertension after the index pregnancy.

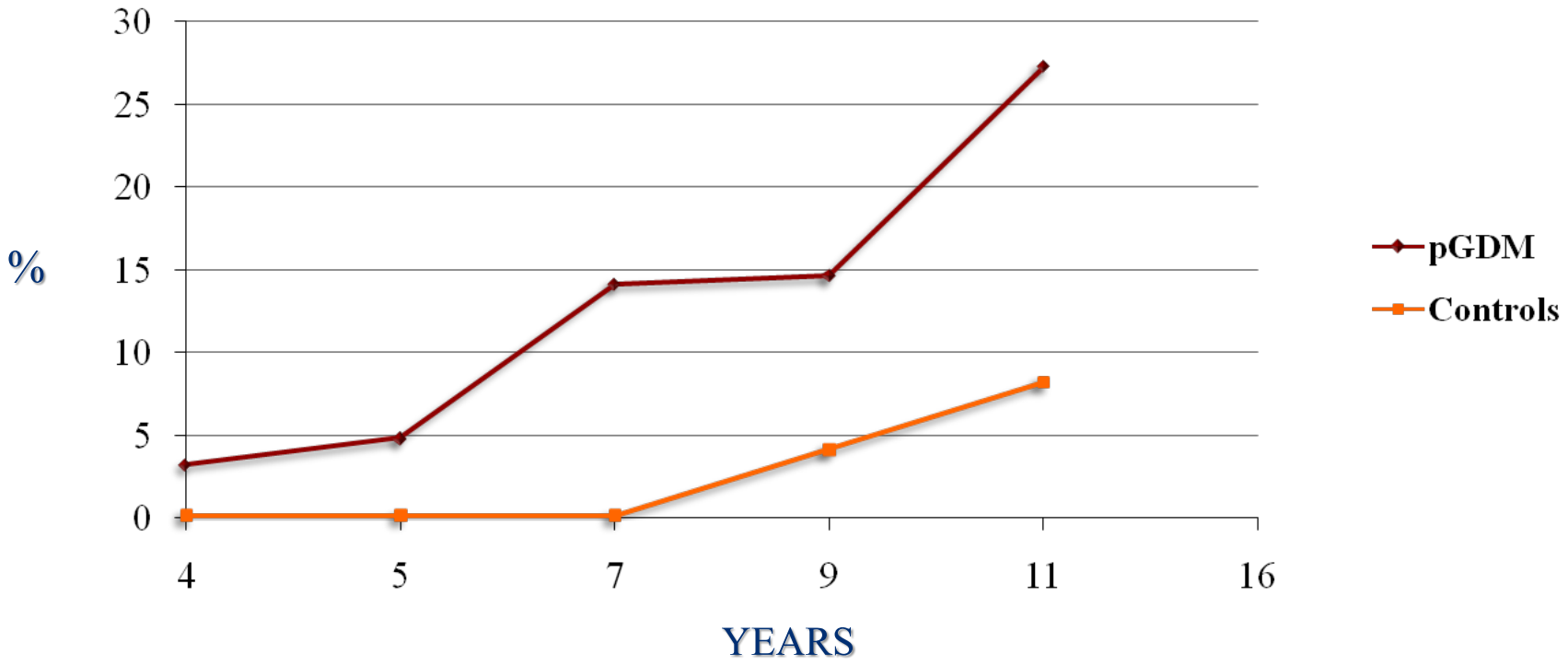
Table 1—*Association of GDM with future risk of hypertension*

Model	HR (95% CI)	*P*
Model 1: age	1.83 (1.65–2.12)	<0.0001
Model 2: + BMI	1.42 (1.25–1.61)	<0.0001
Model 3: + history of pregnancy, HTN	1.29 (1.14–1.46)	<0.0001
Model 4: + family history of HTN/T2D, parity, DASH score, alcohol, total physical activity, smoking status, race/ethnicity, analgesic use, OC use, birth weight, BMI at age 18 years	1.26 (1.11–1.43)	0.0004

DASH, Dietary Approaches to Stop Hypertension; HTN, hypertension; OC, oral contraceptive; T2D, type 2 diabetes.

Diabetes Care 34:1582–1584, 2011

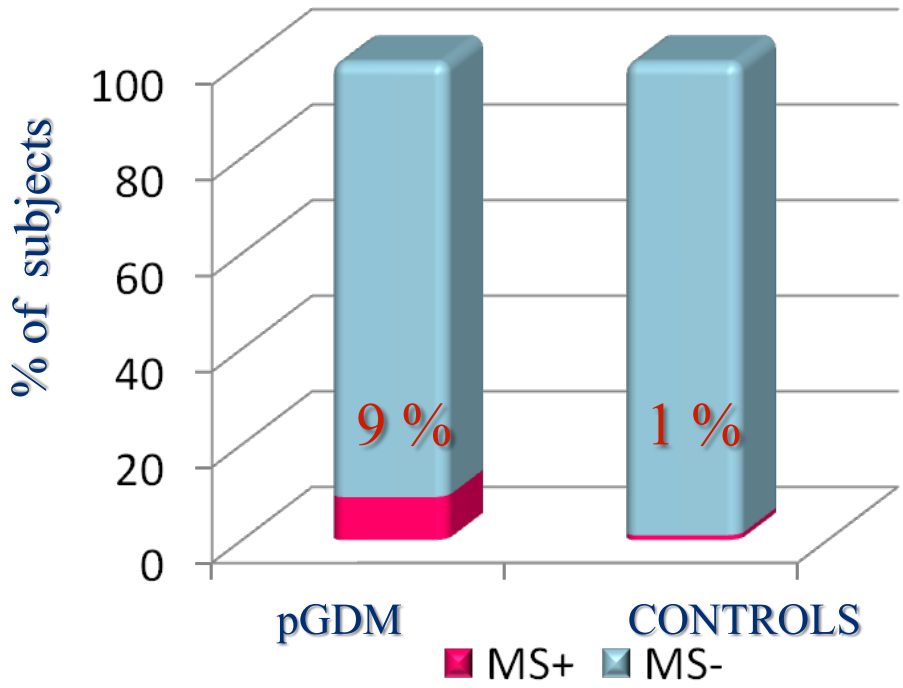
Insulin Resistance Syndrome in women with prior history of Gestational Diabetes Mellitus



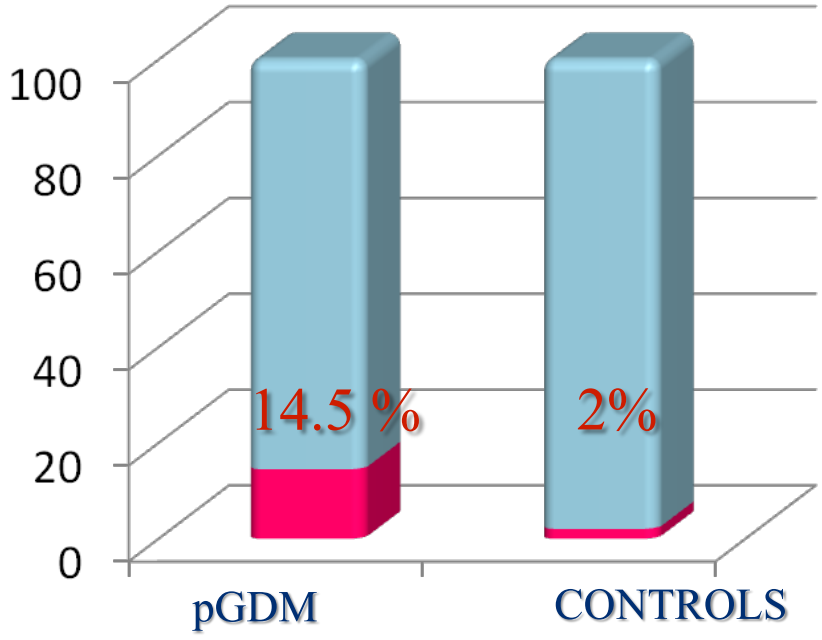
Verma A, J Clin End Met ,87,2002

Prevalence of Metabolic Syndrome (16 Months After Delivery)

NCEP ATPIII CRITERIA, 2001



IDF CONSENSUS, 2005



European Ethnic Group :
Central Obesity (waist circumference ≥80cm)
Plus 1 of the following 4 factors:
Low HDL cholesterol < 42 mg/dl
Hypertrygliceridemia > 150 mg/dl
Fasting plasma glucose > 100 mg/dl
Hypertension: Blood Pressure ≥130/85 mmHg

G. Di Cianni et al. Diabetes Metab Res Rev 2007

Glucose Intolerance in Pregnancy and Postpartum risk of Metabolic Syndrome in Young Women

R.Retankaran, JCEM 2010

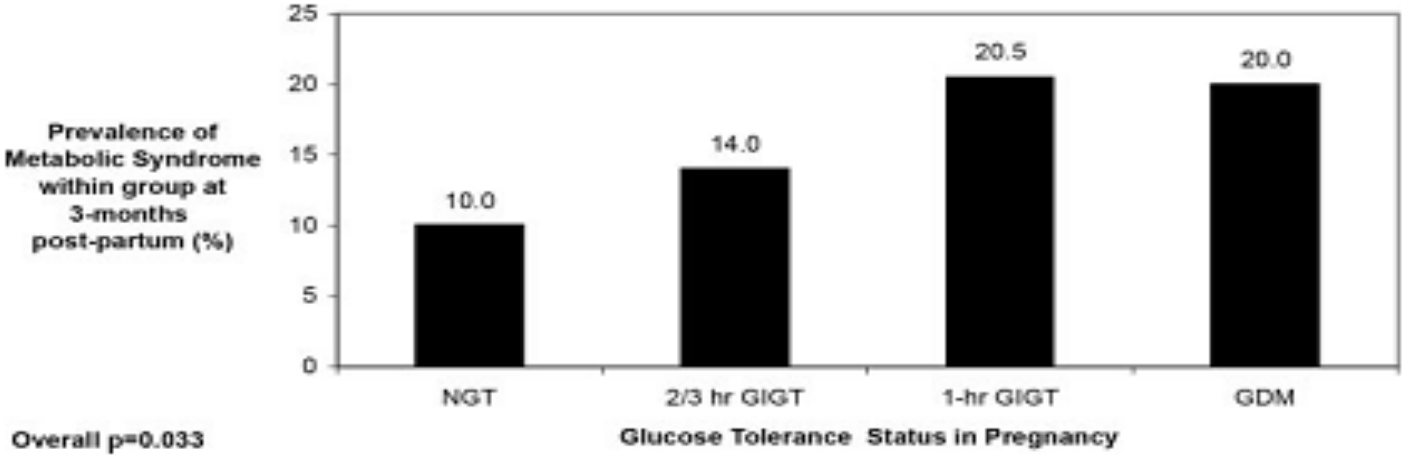


FIG. 3. Prevalence of metabolic syndrome (IDF criteria) at 3 months postpartum by glucose tolerance status in pregnancy, stratified as NGT, 2- to 3-h GIGT, 1-h GIGT, and GDM.

Conclusions: Both GDM and mild glucose intolerance in pregnancy predict an increased likelihood of metabolic syndrome at 3 months postpartum, supporting the concept that women with gestational dysglycemia may have an underlying latent metabolic syndrome. (***J Clin Endocrinol Metab* 95: 670–677, 2010**)

Markers di infiammazione nelle donne con GDM e pGDM

- Proteina C reattiva (PCR)
- Adiponectina
- Leucocitosi
- Interleuchina (IL 6)
- Tumor necrosis factor (TNF)-α
- Inibitore dell'attivatore del plasminogeno (PAI)-1
- Fibrinogeno

Inflammatory Markers in women with a recent history of GDM

A case-control study GDM vs NGT (2 years after delivery)

pGDM women showed higher

- ✓**CRP (p=0.007)**
- ✓**Fibrinogen (p=0.002)**

CRP levels significantly correlated with :

- **BMI (r=0.40, p=0.03)**
- **WHR(r=0.44 p =.001)**
- **FASTING INSULIN (r=0.27 p=0.04)**
- **HOMA (r=0,28, p=0.04)**

A.Di Benedetto et al, JEI 2005

Vascular function after GDM

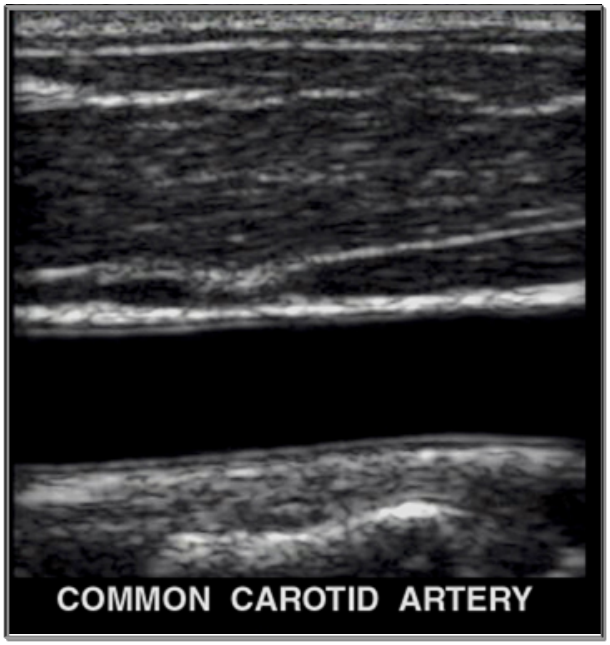
STUDY	*PGDM (N.)*	*METHOD OF ASSESSMENT*	*RESULTS*
Hu (1988)	17	Echo tracking of aorta	Impaired
Anastasiou (1998)	33	Flow-mediated dilatation	Impaired
Honnemann (2002)	17	Flow-mediated dilation	Normal
Paradisi (2002)	25	Flow-mediated dilation	Impaired
Heitritter (2005)	23	Echo tracking of aorta	Reduction of stroke volume Increased Total peripheral resistance
Bo (2006)	82	**Intimal medial thickness**	Higher
Volpe (2008)	28	**Intimal media thickness**	Higher

Carotid Artery Intimal Media Thickness in pGDM women

Methods:

41 pGDM women and 25 controls.

4 points measured at common and internal carotid arteries at the thickest point for both arteries



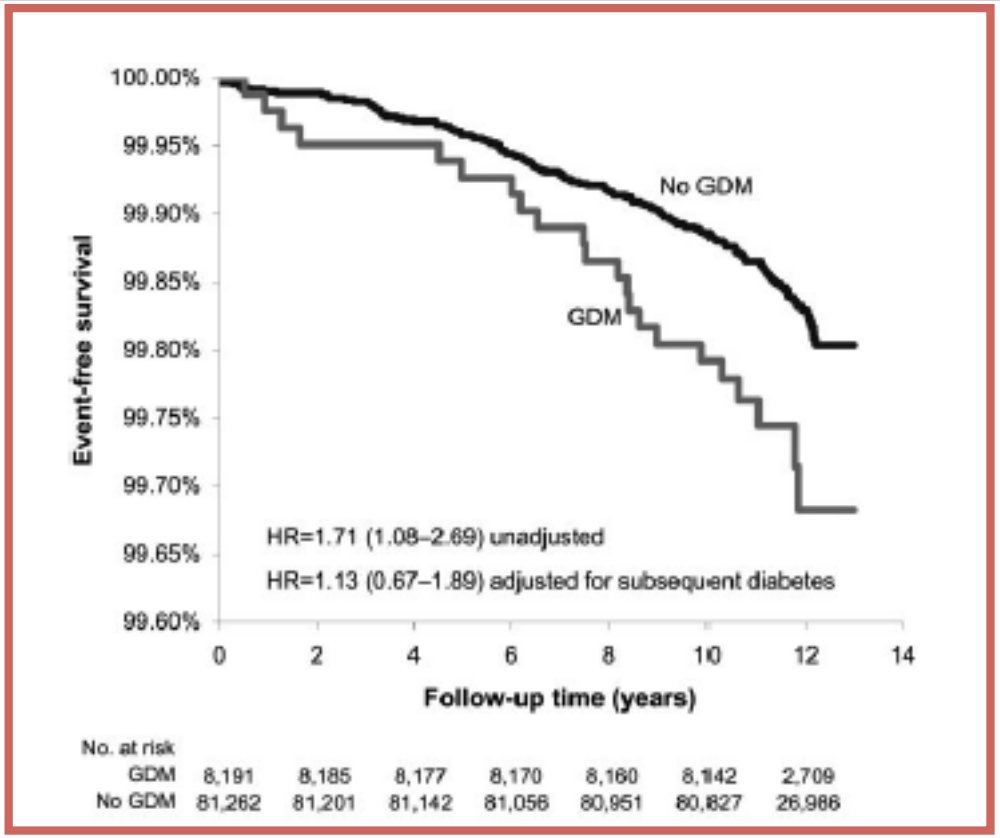
	PGDM (N=41)	*CONTROLS (N=25)*
IMT CCA Right	0.58 ± 0.079	0.51 ± 0.059*
IMT CCA Left	0.55 ± 0.051	0.51 ± 0.066 *
IMT CCA R/L	0.57 ± 0.058	0.51 ± 0.051*

* $p < 0.01$ Controls vs pGDM

L.Volpe, Diabetes Care 2008,5:31-32

Increased Risk of Cardiovascular Disease in Young pGDM women

Young women with GDM had a substantially increased risk for CVD compared with women without GDM. Much of this increased risk was attributable to subsequent development of type 2 diabetes



B.R. Shah, Diabetes Care 2008

Diabetologia
DOI 10.1007/s00125-010-2009-0

ARTICLE

Increased prevalence of non-alcoholic fatty liver disease in European women with a history of gestational diabetes

S. Forbes · S. D. Taylor-Robinson · N. Patel · P. Allan · B. R. Walker · D. G. Johnston

Table 3 US scan grades of steatosis

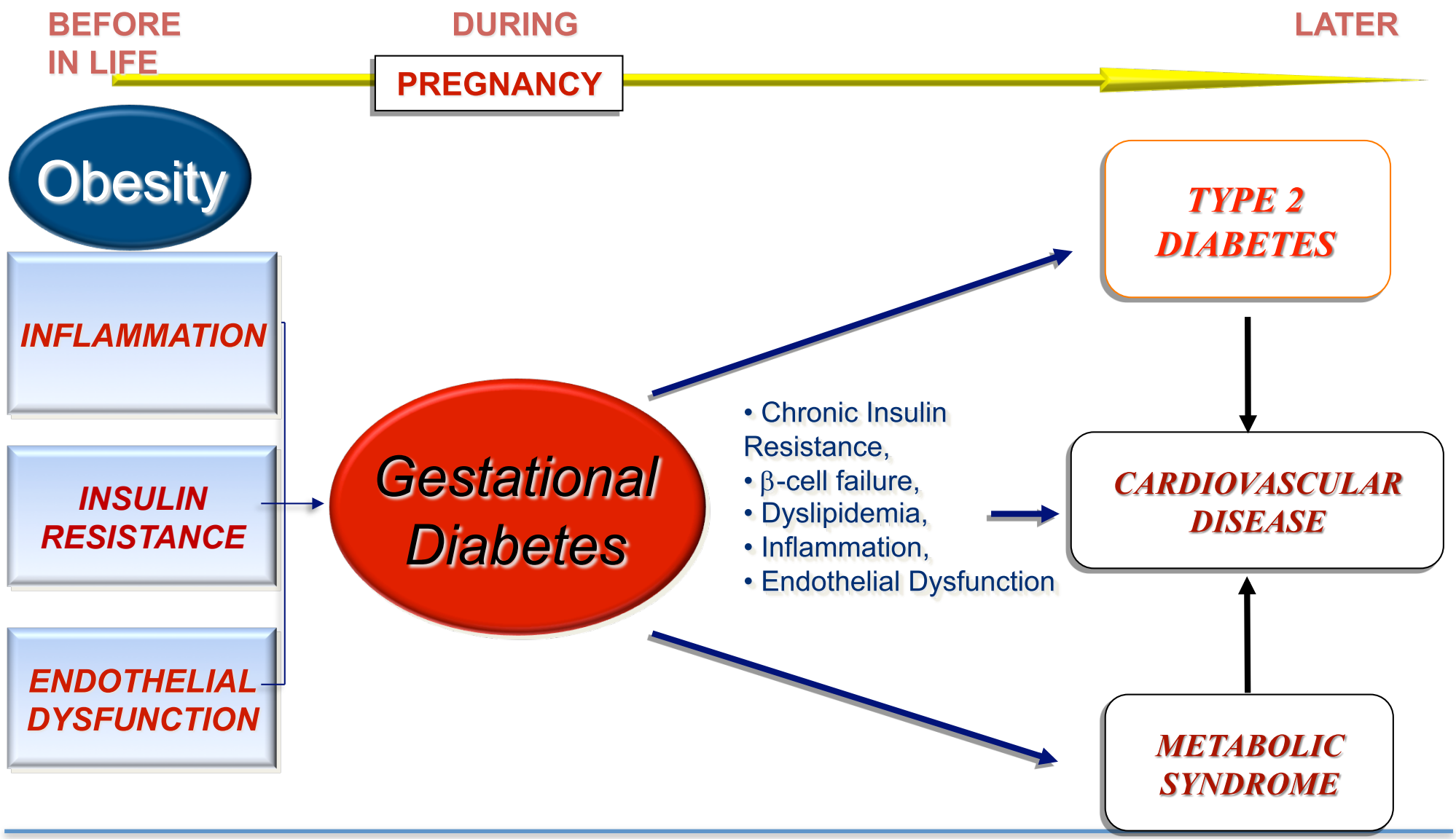
Group	No steatosis	Mild steatosis	Severe steatosis
Previous GDM, % (*n*)	62 (68)	37 (40)	2 (2)
No previous GDM, % (*n*)	83 (94)	17 (19)	0 (0)

Participants with previous GDM and no previous GDM and the different grades of steatosis: normal/no steatosis, mild steatosis and severe steatosis, as determined by US scan

The difference in the distribution of the women with and without previous GDM in these groups was compared using Pearson's χ^2 test, $p=0.001$

GDM, inflammation and late vascular disease

Volpe L et al. JEI, 2007



Diabetes prevention with pharmacological intervention in pGDM women

STUDY	*N CASES*	*INTERVENTION*	*DIABETES RISK REDUCTION VS PLACEBO (%)*
TRIPOD	266	Troglitazone	-55
PIPOD	89	Pioglitazone	-61.9
DPP	350	Metformin Lifestyle	-50.4 -53.4

DPP: *diabetes prevention program Ratner RE, 2007.*

PIPOD: *pioglitazone in prevention of diabetes, Xiang AH, Buchanan TA, 2006.*

TRIPOD: *troglitazone in the prevention of diabetes Buchanan, 2002.*

A systematic review of the literature associating breastfeeding with T2DM and GDM

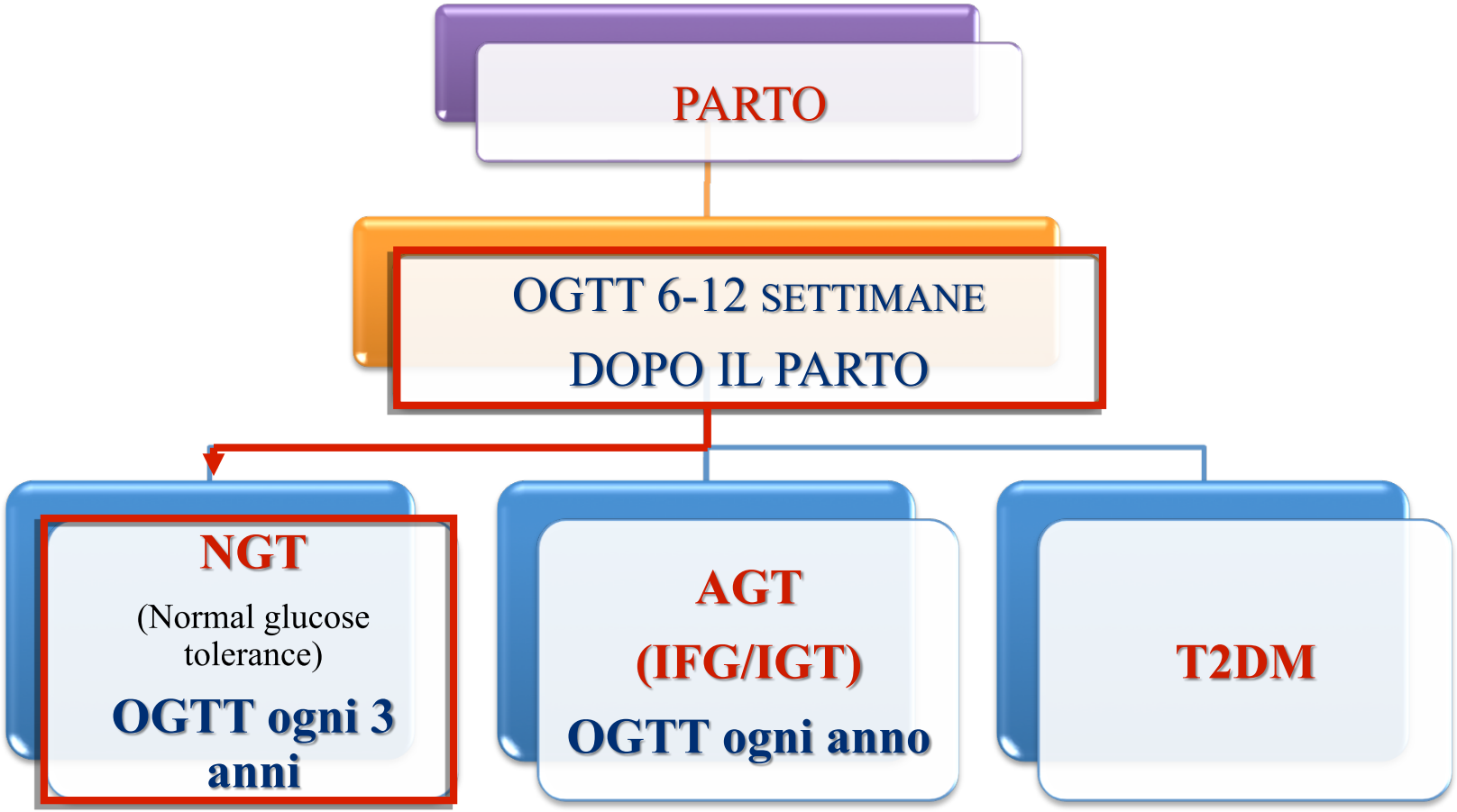
..Low estrogen levels in breastfeeding women may have a protective effect on glucose metabolism and subsequent risk of diabetes..

Breastfeeding may lower both maternal and pediatric rates of diabetes.

THE PROMOTION OF A COMBINATION OF *BREAST-FEEDING*, *DIET* AND *PHYSICAL ACTIVITY* COULD REDUCE MATERNAL T2DM RISK

Taylor JS, Kacmar JE, J. Am. Coll. Nutr. 2005

Follow-up del GDM per prevenire il DM tipo 2 e le malattie cardiovascolari



monitoraggio periodico dei fattori di rischio cardiovascolare (peso, circonferenza addominale, ipertensione, dislipidemia)

Conclusioni

- **Il follow-up del diabete gestazionale offre una opportunità di prevenzione su una popolazione di donne giovani, con un elevato rischio metabolico e cardiovascolare**

- **Possibili interventi utili a favorire il follow-up:**
  - ✓ **campagne informative**
  - ✓ **PDTA multidisciplinari di follow-up a lungo termine**