Diabete, ipertensione e insulino-resistenza in gravidanza



Gemelli sergio.ferrazzani@unicatt.it

Gravidanza e Sindrome Metabolica…

…*quali similitudini*?



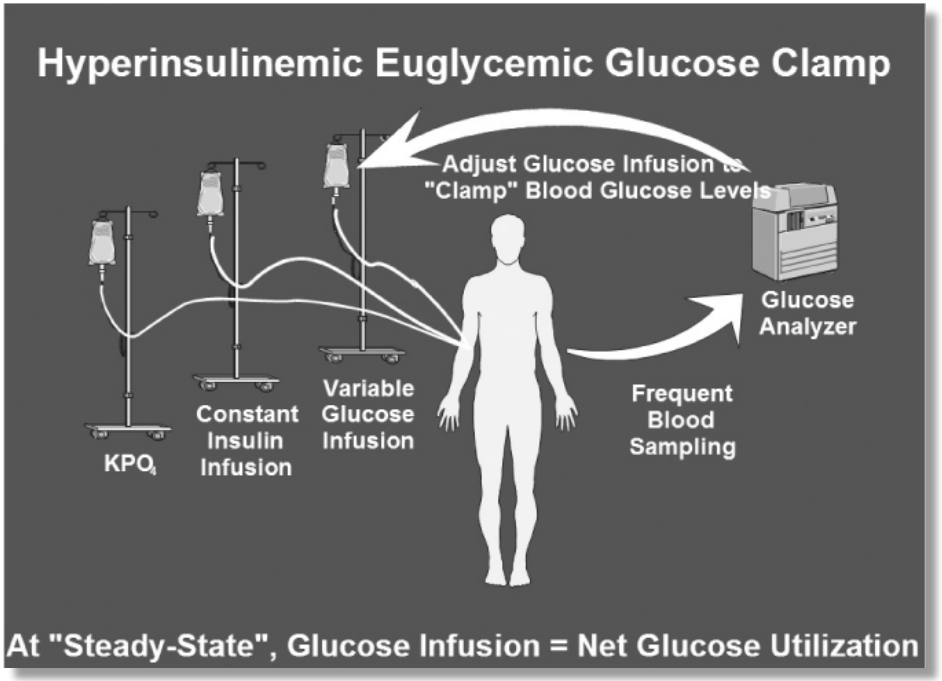
- Aumento della glicemia postprandiale
- Livelli più elevati di trigliceridi
- Livelli più elevati di insulina
- Aumento dell'insulino-resistenza
- Up-regulation della cascata infiammatoria

Come si misura l'insulino-resistenza?

Insulin sensitivity *in vivo* during pregnancy can be estimated using a variety of techniques. The gold standard, however, is the hyperinsulinemic–euglycemic clamp techniques as described by DeFronzo *et al.*

Patrick M Catalano

Reproduction (2010) **140** 365–371



In conseguenza della complessità, del costo, e del tempo speso nel Clamp, tale metodica **si usa primariamente nella ricerca**

Altri Metodi

- Minimal model (Bergman et al. 1987)

  Stima sensibilità all'insulina mediante test da carico di glucosio per endovena

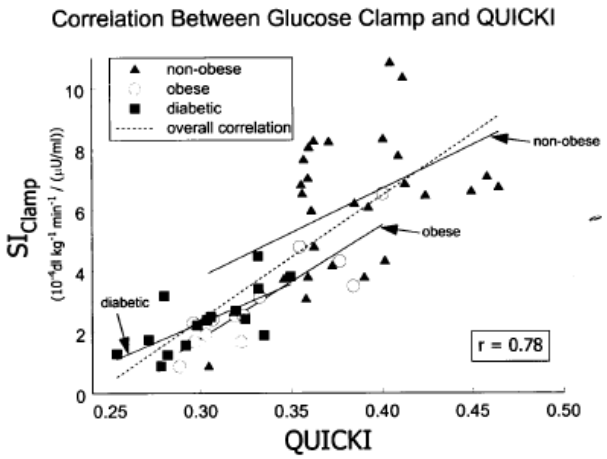
  LIMITI: ⬆ variabilità nella stima dell'insulino-sensibilità a termine di gravidanza se paragonato al clamp

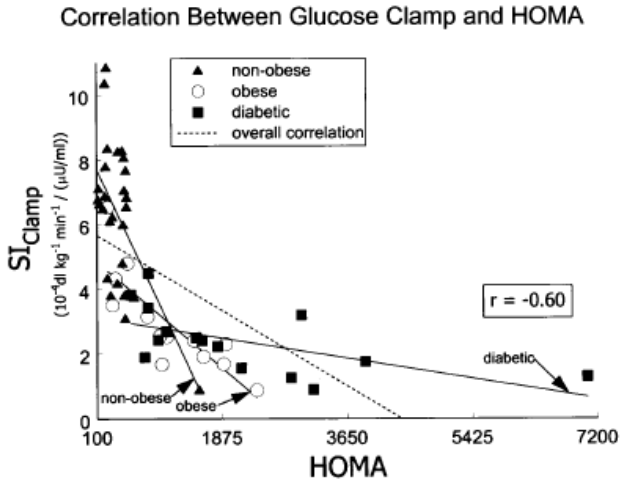
- Indici di insulino-sensibilità derivati dalla glicemia e dall'insulinemia a digiuno:
  - Homeostasis Model Assessment (Mattews et. al 1985)
  - Quantitative Insulin Sensitivity Check Index (Katz et. al 2000)

0021-972X/00/$03.00/0
The Journal of Clinical Endocrinology & Metabolism
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Vol. 85, No. 7
Printed in U.S.A.

Quantitative Insulin Sensitivity Check Index: A Simple, Accurate Method for Assessing Insulin Sensitivity In Humans

ARIE KATZ, SRIDHAR S. NAMBI, KIEREN MATHER, ALAIN D. BARON, DEAN A. FOLLMANN, GAIL SULLIVAN, AND MICHAEL J. QUON





LIMITI: passaggio, attraverso la placenta non insulina-mediato, del glucosio dalla madre al feto per diffusione facilitata

Sovrastima dell'insulino-sensibilità materna particolarmente a termine di gravidanza

Patrick M Catalano

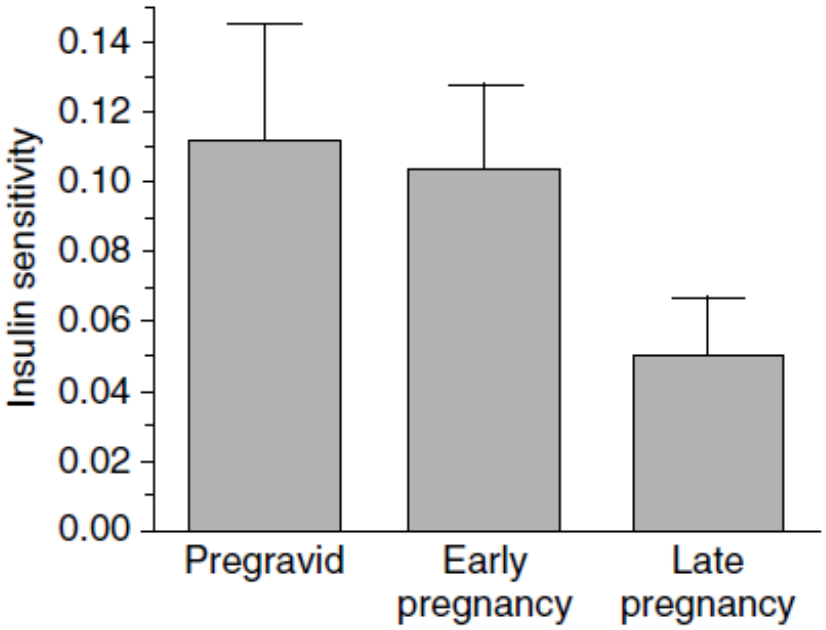
Reproduction (2010) **140** 365–371

Modificazioni longitudinali dell'insulino-sensibilità nella gravidanza normale

Focus on Obesity

Obesity, insulin resistance, and pregnancy outcome

Patrick M Catalano



GRAVIDANZA

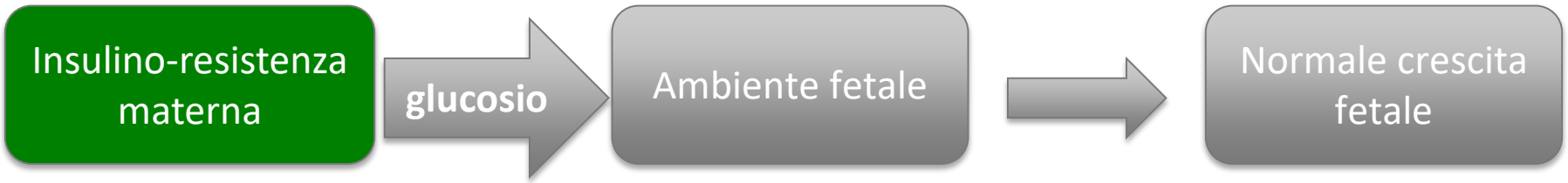
⬇ insulino-sensibilità da difetto post-recettoriale per

⬇ capacità dell'insulina di mobilizzare GLUT4* dall'interno della cellula alla superficie

** Glucose transporter type 4*

- *Ormoni (hPL, cortisolo, PRL, estrogeni, progesterone)*
- *Infiammazione (citochine, TNFα)*
- *Elevata concentrazione di lipidi*

Insulino-resistenza e crescita fetale



Effect of Maternal Carbohydrate Metabolism on Fetal Growth

ALESSANDRO CARUSO, MD, GIANCARLO PARADISI, MD,
SERGIO FERRAZZANI, MD, ANGELA LUCCHESE, MD, SIMONETTA MORETTI, MD,
AND ANNA MARIA FULGHESU, MD

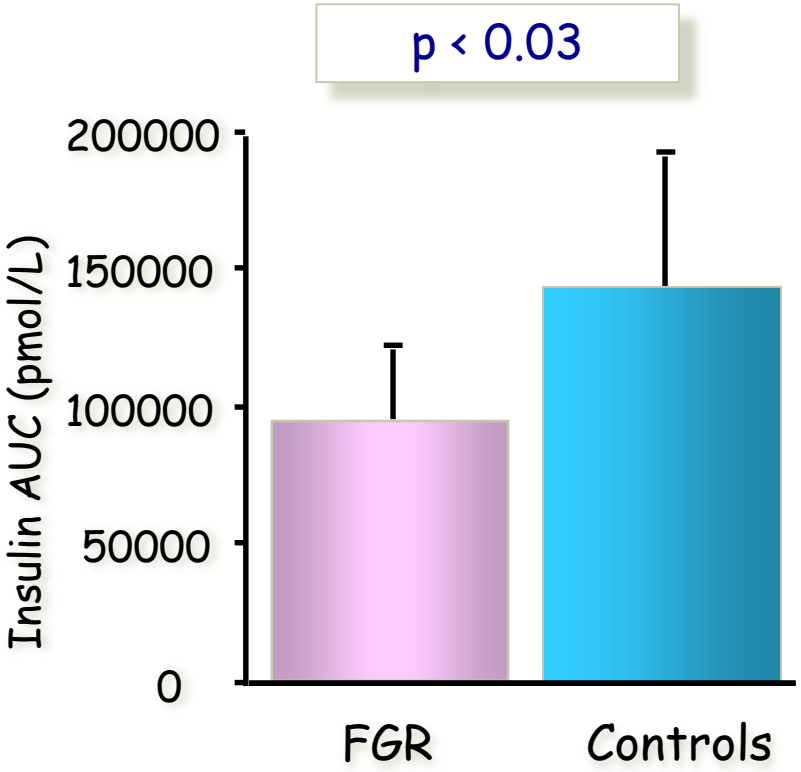
Obstet Gynecol 1998

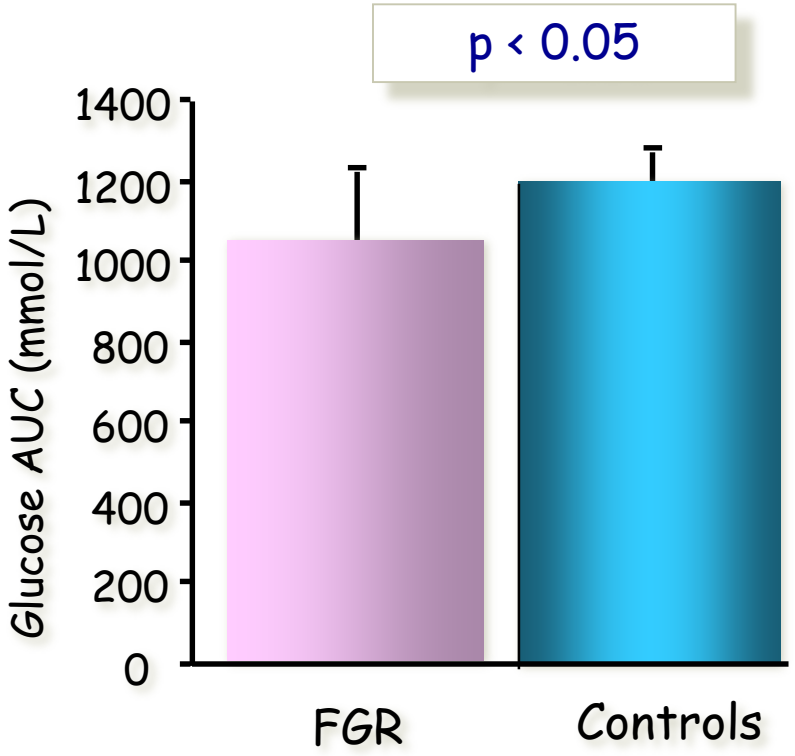
	FGR group (n = 8)	Controls (n = 11)	P
Wk of study	34.8 ± 3.4	33.7 ± 3.6	NS
Fasting insulin (pmol/ L)	61.6 ± 48.9	90.7 ± 74.1	NS
Fasting glucose (mmol/ L)	3.9 ± 0.2	4.0 ± 0.2	NS
AUC insulin/ AUC glucose ratio	92.2 ± 23.3	120.7 ± 42.1	NS
GIR (μmol/ kg × min)	21.6 ± 4.4	16.7 ± 4.8	<.05
hPL (μg/ mL)	3.9 ± 2.2	5.1 ± 1.3	NS

Effect of Maternal Carbohydrate Metabolism on Fetal Growth

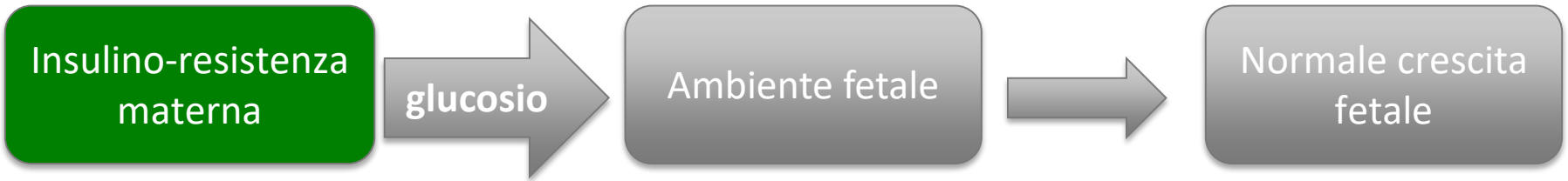
ALESSANDRO CARUSO, MD, GIANCARLO PARADISI, MD,
SERGIO FERRAZZANI, MD, ANGELA LUCCHESE, MD, SIMONETTA MORETTI, MD,
AND ANNA MARIA FULGHESU, MD

Obstet Gynecol 1998





Insulino-resistenza e crescita fetale



Clamp

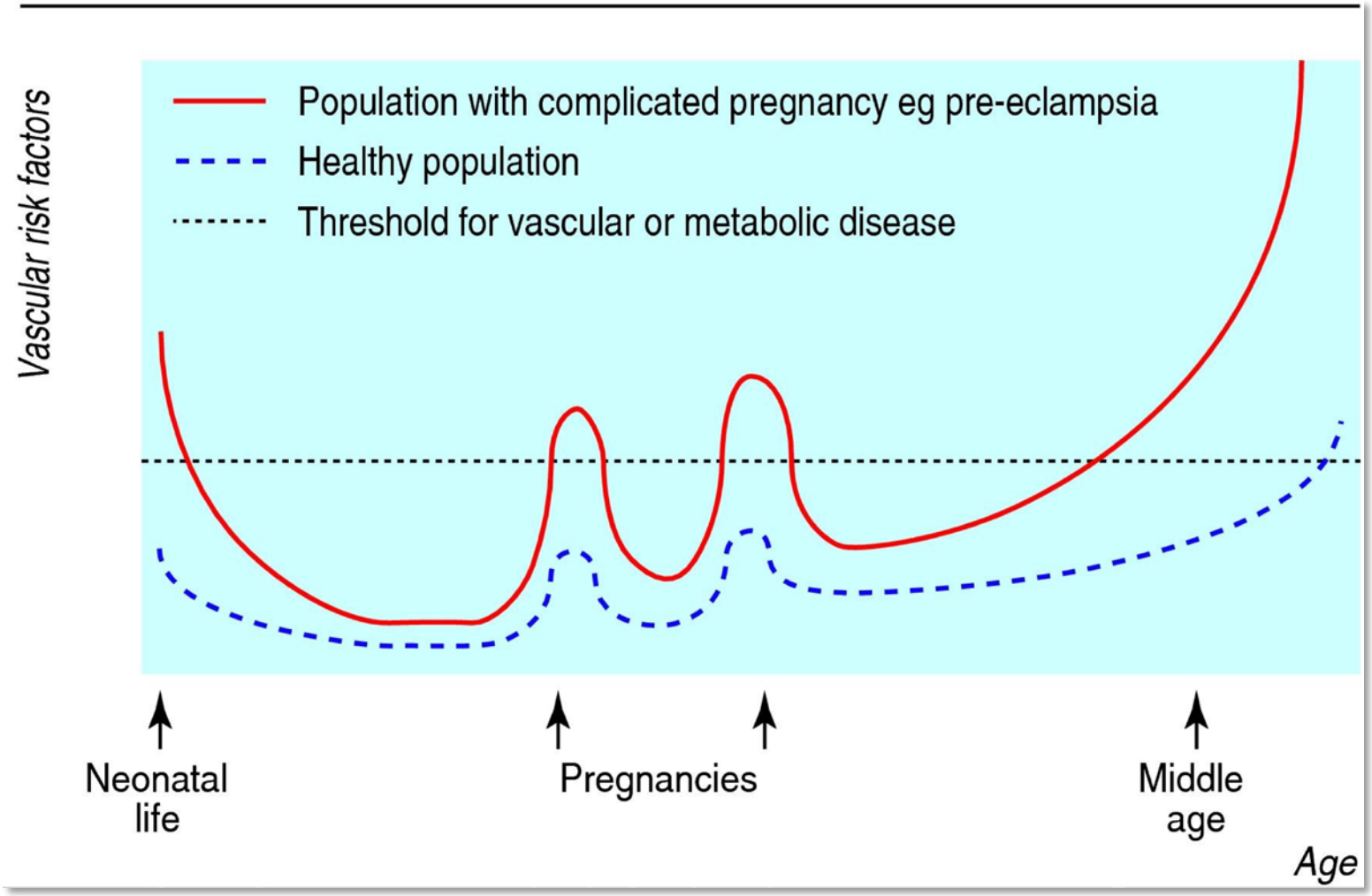


Preeclampsia (PE) e insulino-resistenza

In aggiunta all'ipertensione si associano alla PE diverse caratteristiche della sindrome da insulino-resistenza:

- Obesità
- Dislipidemia
- Malattia cardiovascolare
- Infiammazione sistemica
- Difetto di fibrinolisi

Il modello



I fattori di rischio per la malattia cardiovascolare sono identificabili durante le escursioni all'interno della sindrome metabolica della gravidanza

Sattar & Greer 2002

Ma la PE si associa sempre a un ambiente di aumentata insulino-resistenza?

Pregnancy is itself an insulin-resistant state. The diabetogenic influence of pregnancy has been recognised for over 100 years[10]. As gestation advances, there is a progressive increase in the secretory response of the maternal pancreas to glucose, and the maintenance of euglycaemia is associated with progressively increasing levels of circulating insulin. Indirect evidence of insulin resistance in normal pregnancy is provided by the blunted response to an intravenous injection of exogenous insulin[11]. Direct

The aim of this study was to investigate whether pre-eclampsia is associated with an increase in insulin resistance over and above that seen in normotensive pregnancy. Insulin sensitivity was determined using the minimal model technique originally described by Bergman *et al.*[18]. We considered that the minimal model approach was better suited than the euglycaemic glucose clamp to investigating pregnant and potentially ill women. The experimental protocol is simpler and does not involve the infusion

(P = 0·006). There was no significant difference in the first or second phase insulin response, or in $AIR_{glucose}$ (Table 2).

Total glucose disposal correlated with the intravenous glucose clearance K_G in the combined group of women (r = 0·72, P = 0·001). The relative contributions of insulin and glucose-mediated glucose disposal to total glucose disposal are shown in Table 3. In the group with pre-eclampsia the relative contribution of glucose-mediated glucose disposal to total glucose disposal was significantly lower (29·1% [3·0] *vs* 47·2% [5·0]; P = 0·005) compared with the women in the control group. The mean arterial blood pressure (MAP) in the normotensive women was signifi-

ence between the glucose decay curves (Fig. 1), and there was no significant difference between the glucose clearance rate K_G in the two groups (pre-eclamptic *vs* normotensive: 1·86 [0·21] *vs* 2·02 [0·16]; P = 0·56). In contrast, there was a small but prolonged decrease in the insulin response of the women

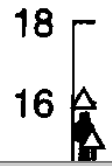


Table 1. Comparison of demographic features and biochemical factors which might influence insulin sensitivity between women with

Age		
BMI		
Perc		
Gest		
Corti		
Progesterone (nmol/L)	670 [230]	605 [104]

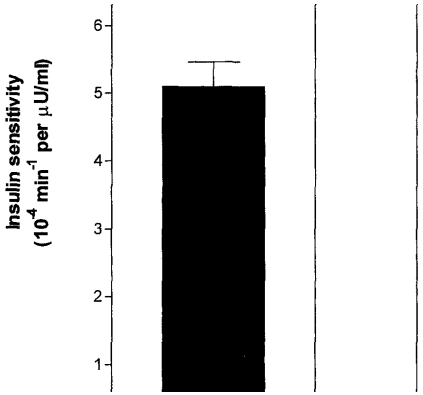
Lo studio, con la tecnica del minimal model, depone per **non** insulino-resistenza nella PE

reprint requests to Risto Kaaja, MD, PhD, Department of and Gynaecology, Helsinki University Central Hospital, PO IN-00029 HYKS, Finland.

ht © 1999 by W.B. Saunders Company

95/99/4807-0015$10.00/0

using the minimal model developed by Bergman.[12] A bolus (0.3 g/kg body weight) was injected intravenously at 9 A overnight fast, followed by a bolus of human regular insulin Human; Novo Nordisk Pharmaceuticals, Bagsvaerd, Den IU/kg) 20 minutes later. Blood samples were collected as fo



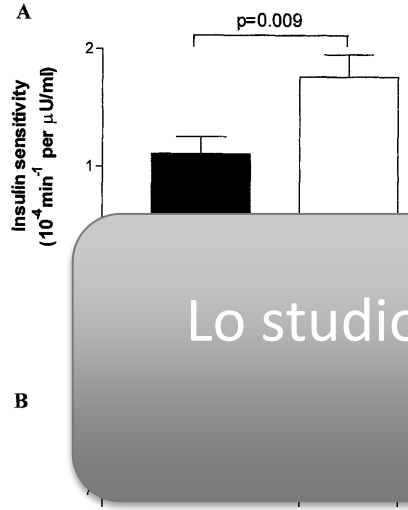
tance in Preeclampsia

Body mass index at reexamination (kg/m^2)	23.9 ± 0.8	23.5 ± 1.0
Systolic BP at reexamination (mm Hg)	115 ± 2§	107 ± 2
Diastolic BP at reexamination (mm Hg)	75 ± 2‡	66 ± 2

NOTE. Data are the mean ± SE.

*P = .0001, †P = .0003, ‡P = .002, §P = .02: v normotensive pregnant women.

at baseline and 4, 6, 8, 10, 19, 22, 29, 37, 67, 90, and 180 minutes after administration of the glucose bolus. Insulin sensitivity was evaluated from the disappearance curves for glucose and insulin by the minimal model computer program. This model accurately reflects true insulin sensitivity, as confirmed and validated by use of the hyperinsulinemic-euglycemic clamp technique.[12] Moreover, during pregnancy, values for insulin sensitivity evaluated by the hyperinsulinemic-euglycemic clamp or the minimal model are in good correlation (r = .58).[13] The first-phase



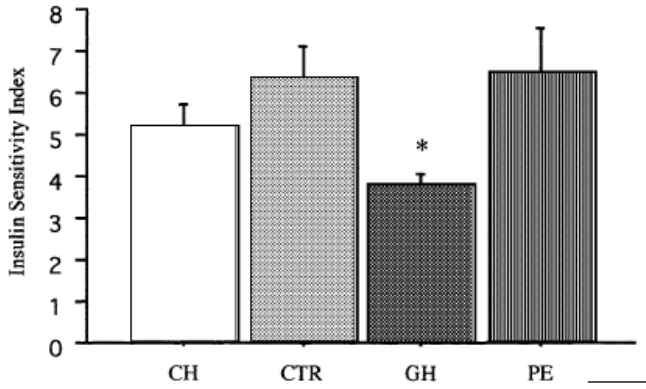
Lo studio, con la tecnica del minimal model, depone per ⬆ insulino-resistenza nella PE

Human Reproduction vol.14 no.1 pp.219–223, 1999

Gestational hypertension but not pre-eclampsia is associated with insulin resistance syndrome characteristics

A.Caruso[1,3], S.Ferrazzani[1], S.De Carolis[1], A.Lucchese[1], A.Lanzone[2], L.De Santis[1] and G.Paradisi[1]

Human Reproduction vol.14 no.1 pp.219–223, 1999



*$P < 0.03$ versus controls.

Table I. Demographic characteristics of control and hypertension groups

	Controls ($n = 10$)	Chronic hypertension ($n = 6$)	Gestational hypertension ($n = 10$)	Pre-eclampsia ($n = 10$)
Age (years)	30.9 ± 1.5	34.7 ± 2.5	32.1 ± 1.1	33.3 ± 1.9
Parity (nulliparous/parous)	4/6	1/5	8/2	8/2
Week of pregnancy	33.5 ± 1.1	31.0 ± 1.5	36.1 ± 0.8	32.1 ± 1.4
BMI (weight/height^2)	21.3 ± 0.8	25.7 ± 1.9	24.6 ± 1.2	25.2 ± 0.9

Il nostro studio, con il clamp iperinsulinemico-euglicemico, dimostra **non** insulino-resistenza nella PE, ⬆ solo nella GH

Insulin, insulin-like growth factor-1, and insulin resistance in women with pregnancy-induced hypertension

September 2002
Am J Obstet Gynecol

Jose L. Bartha, MD, Raquel Romero-Carmona, MD, Rafael Torrejon-Cardoso, MD, and Rafael Comino-Delgado, MD

Table I. Demographics and general outcomes in the studies groups

	Group						
	Control (n = 20) Insulin resistance was measured with the short insulin-tolerance test		*Preeclampsia (n = 20)*		*Gestational hypertension (n = 18)*		
Demographic/outcome	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*P value*
Age (y)	26.5	5.0	26.2	6.5	27.0	4.0	NS
Gestational age (wk)	35.7	3.9	34.9	3.7	36.2	3.3	NS
Pregestational body mass index (kg/m^2)	24.7	7.8	26.1	6.1	27.2	6.7	NS
Gestational body mass index (kg/m^2)	29.6	5.4	31.5	5.1	32.5	6.0	NS
Birth weight (g)*	3646.2	296.1	2617.1	895.2	3736.3	721.1	.0001
Gestational age at birth (wk)†	40.3	1.0	36.0	3.1	39.4	2.1	.0004

Questo studio, con il test breve di tolleranza all'insulina, dimostra **non** insulino-resistenza nella PE, ⬆ solo nella GH

Insulino-resistenza & preeclampsia: evidenze conflittuali

↑ Insulino-resistenza

- Joffe AJOG 1998
- Kaaja Obstet Gynecol 1995
- Lorentzen Acta Obstet Gynecol Scand 1998
- Kaaja Metabolism 1999

non Insulino-resistenza

- Roberts Br J Obstet Gynaecol 1998
- Caruso Hum Reprod 1999
- Bartha AJOG 2002

Insulin Resistance and Its Potential Role in Pregnancy-Induced Hypertension

ELLEN W. SEELY AND CAREN G. SOLOMON

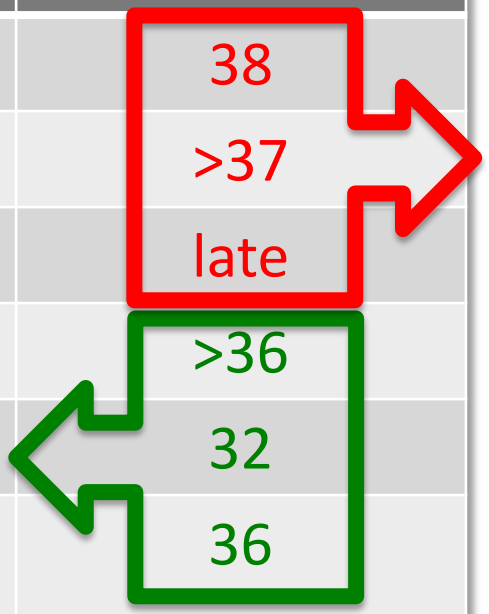
Queste apparenti osservazioni discrepanti si possono spiegare con

- campioni di dimensioni ridotte
- diagnosi incoerenti
- e/o con la probabile natura multifattoriale della condizione.

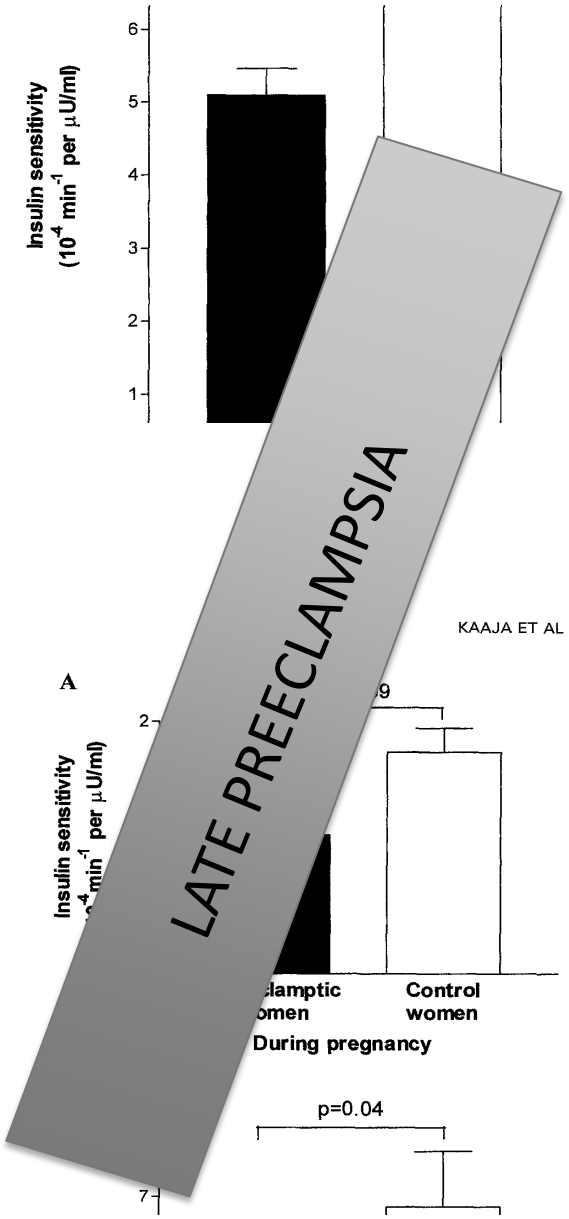
The Journal of Clinical Endocrinology & Metabolism 88(6):2393–2398
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Insulino-resistenza & PE: evidenze conflittuali

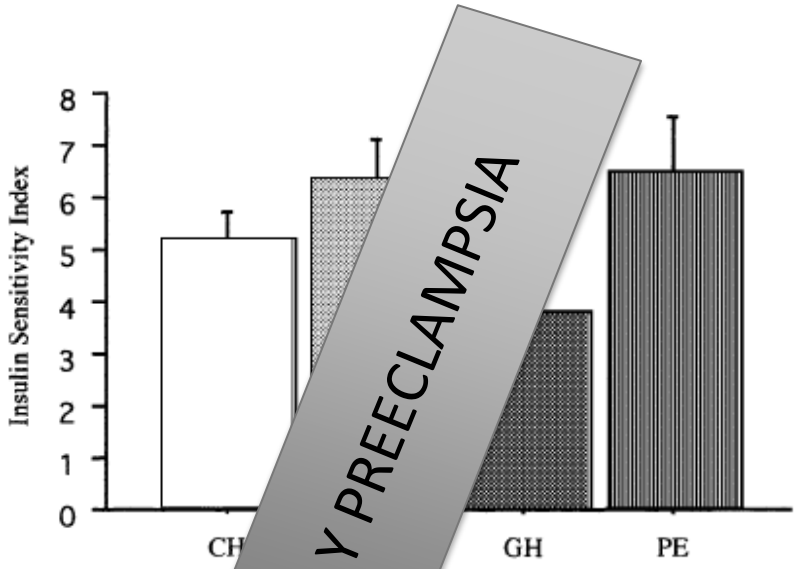
Insulino-resistenza	Autore	Metodo	Settimana del parto
SI	Kaaja 1999	Minimal model	38
SI	Lorentzen 1998	OGTT 75 g	>37
SI	Joffe 1998	Minitest 50 g	late
NO	Roberts 1998	Minimal model	>36
NO	Caruso 1999	Glucose clamp	32
NO	Bartha 2002	Short insulin tolerance test	36



Le modificazioni fisiologiche della gravidanza conducono a ⬆ dell'insulino-resistenza in condizioni patologiche come la PE tardiva e la GH



LATE PREECLAMPSIA

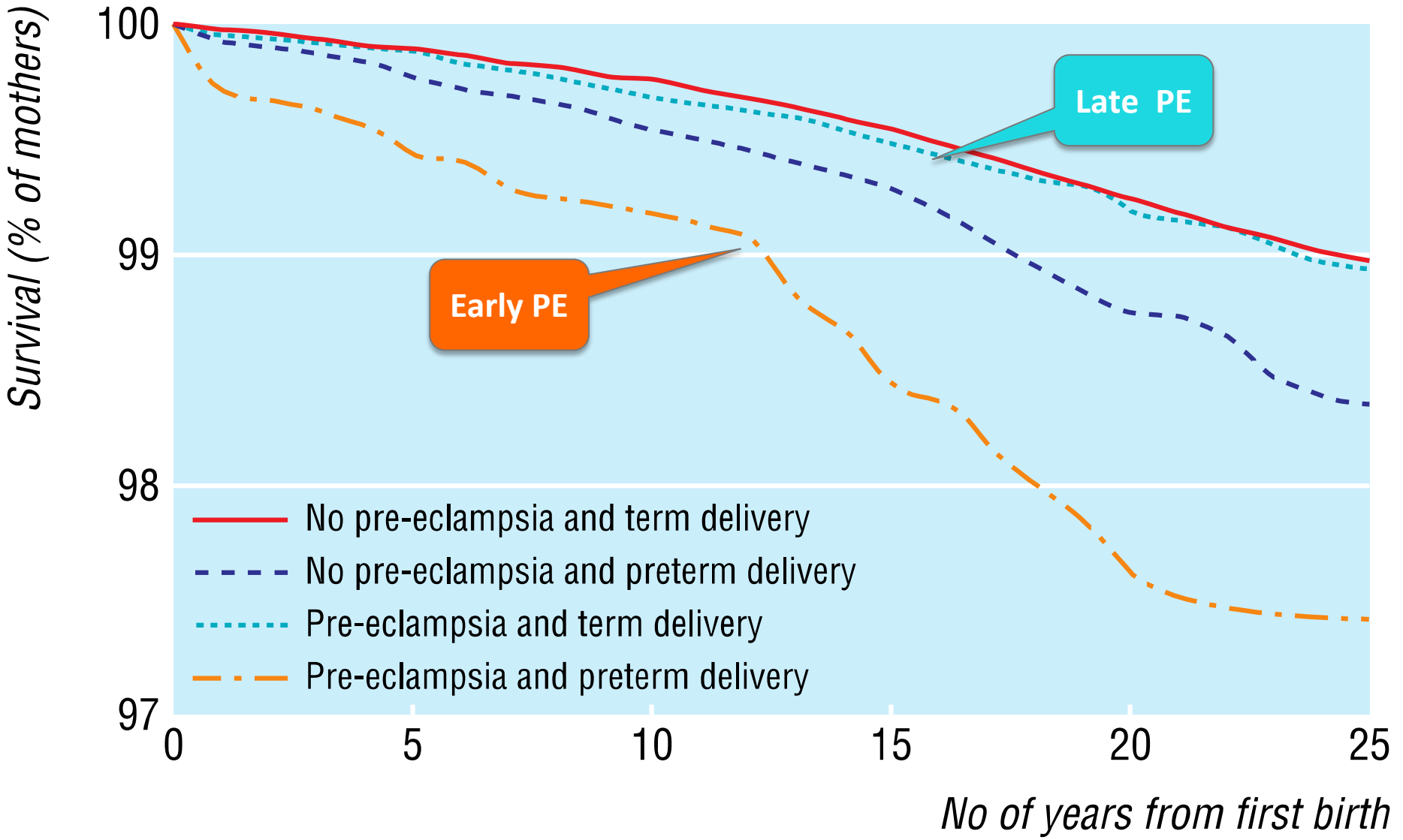


EARLY PREECLAMPSIA

Kaaja et al. 1999

Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study

Henrik U Irgens, Lars Reisæter, Lorentz M Irgens, Rolv T Lie **BMJ** VOLUME 323 24 NOVEMBER 2001



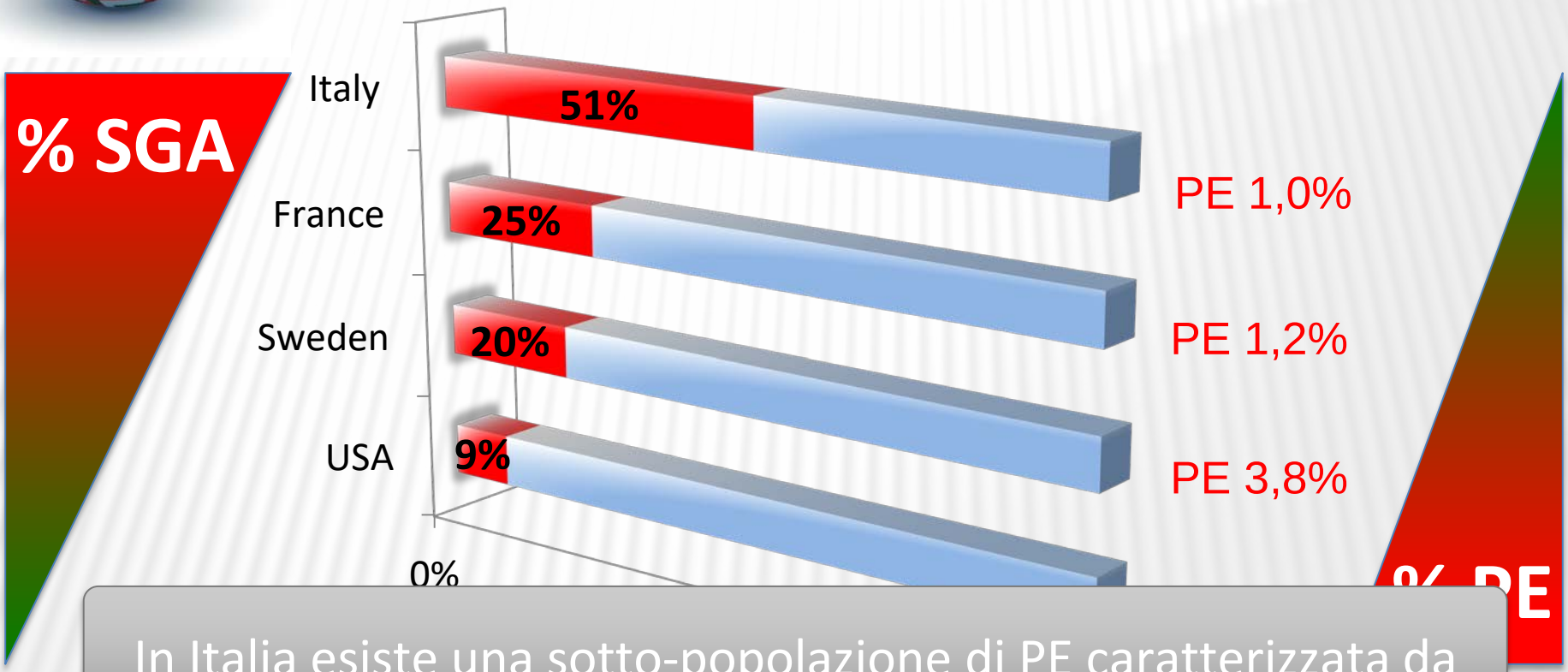
Il paradosso è….

- …che la mortalità materna da malattia cardiovascolare è più elevata nella early PE rispetto alla late PE?
- Questo fenomeno non si correla affatto con l'insulino-resistenza (sindrome metabolica)

…La early e la late PE sono ugualmente distribuite nel mondo (occidentale)?

Preeclampsia and SGA





In Italia esiste una sotto-popolazione di PE caratterizzata da minor frequenza e maggior severità

Ferrazzani Early Hum Dev 2011

…e c'è una early e una late PE nella gravidanza gemellare?

Preeclampsia in twin pregnancy



Hypertensive disorders in twin versus singleton gestations

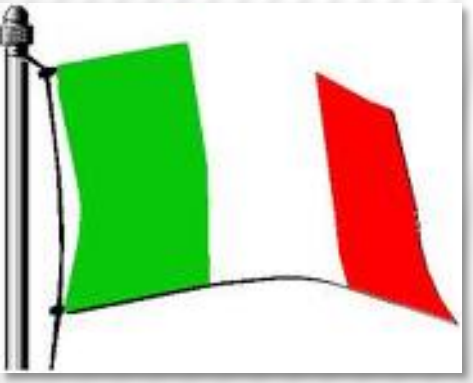
Baha M. Sibai, MD, John Hauth, MD, Steve Caritis, MD, Marshall D. Lindheimer, MD, PhD, Cora MacPherson, PhD, Mark Klebanoff, MD, J. Peter VanDorsten, MD, Mark Landon, MD, Menachem Miodovnik, MD, Richard Paul, MD, Paul Meis, MD, Gary Thurnau, MD, Mitchell Dombrowski, MD, James Roberts, MD, and Donald McNellis, MD, for the National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units

Bethesda, Maryland

2000

Volume 182, Number 4
Am J Obstet Gynecol

VS



Birth weight in pre-eclamptic and normotensive twin pregnancies: an analysis of discordance and growth restriction

Sergio Ferrazzani, Annamaria Merola, Sara De Carolis, Brigida Carducci, Giancarlo Paradisi and Alessandro Caruso

Human Reproduction
2000

Frequenza di SGA nelle donne con preeclampsia

	US		*Italy*	
	Twins (n=87)	Singleton (n=143)	Twins (n=77)	Singleton (n=423)
SGA (%)	12	10	40	51

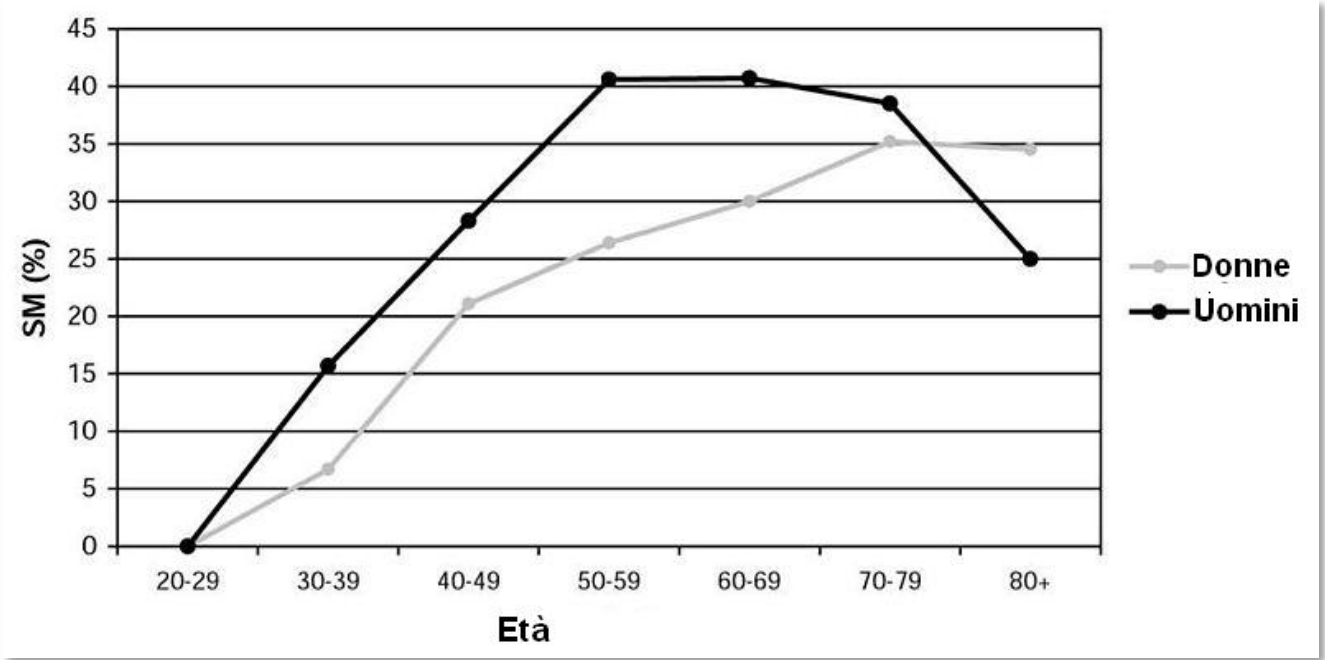
Sibai AJOG 2000, Ferrazzani Hum Reprod 2000

Differenti tipi di PE in alcuni paesi industrializzati

- Possono spiegare differenze nell'epidemiologia della mortalità cardiovascolare materna
- La curva di mortalità materna a lungo termine delineata in Danimarca potrebbe non essere adattabile a quella in Italia?

Malattia cardiovascolare (CVD)

- Tra 20 aa e 49 aa la frequenza di insulino-resistenza nella donna raggiunge il 20%
- Molte meno donne sviluppano la PE
- È solo l'insulino-resistenza causa di CVD?



DOI: 10.1111/1471-0528.12191
www.bjog.org

Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study

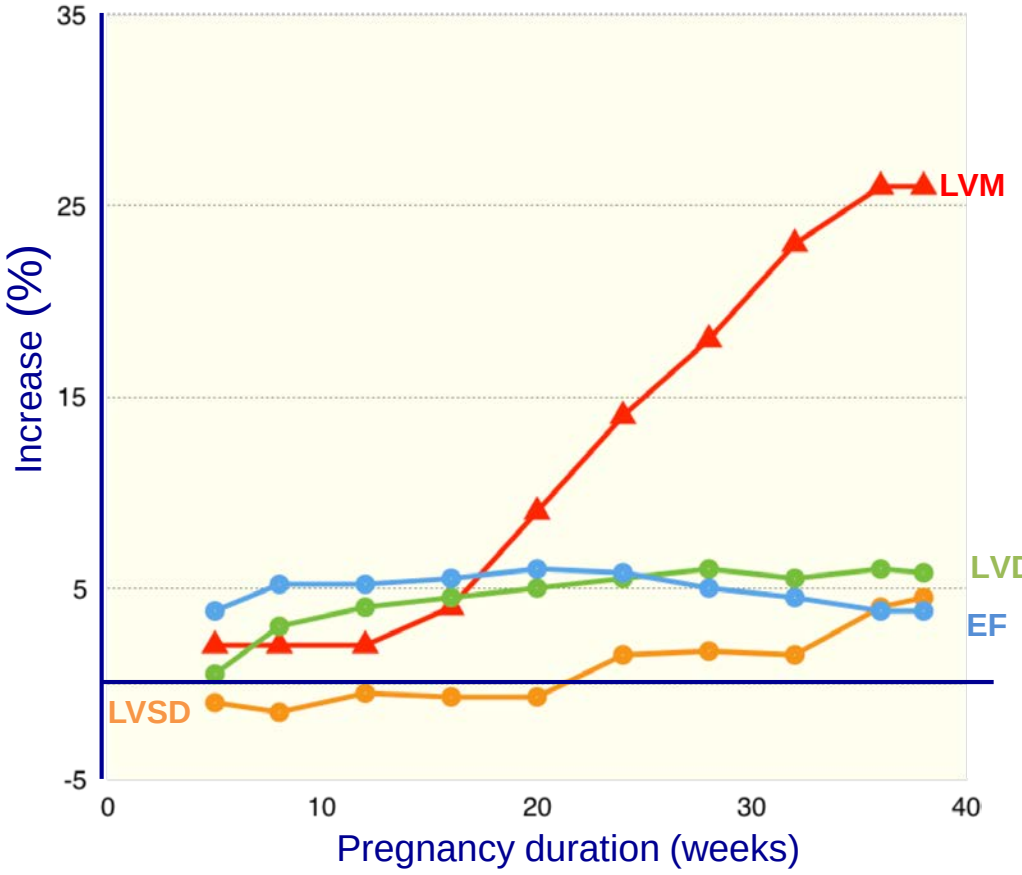
D Berks,[a] M Hoedjes,[b] H Raat,[b] JJ Duvekot,[a] EAP Steegers,[a] JDF Habbema[b]

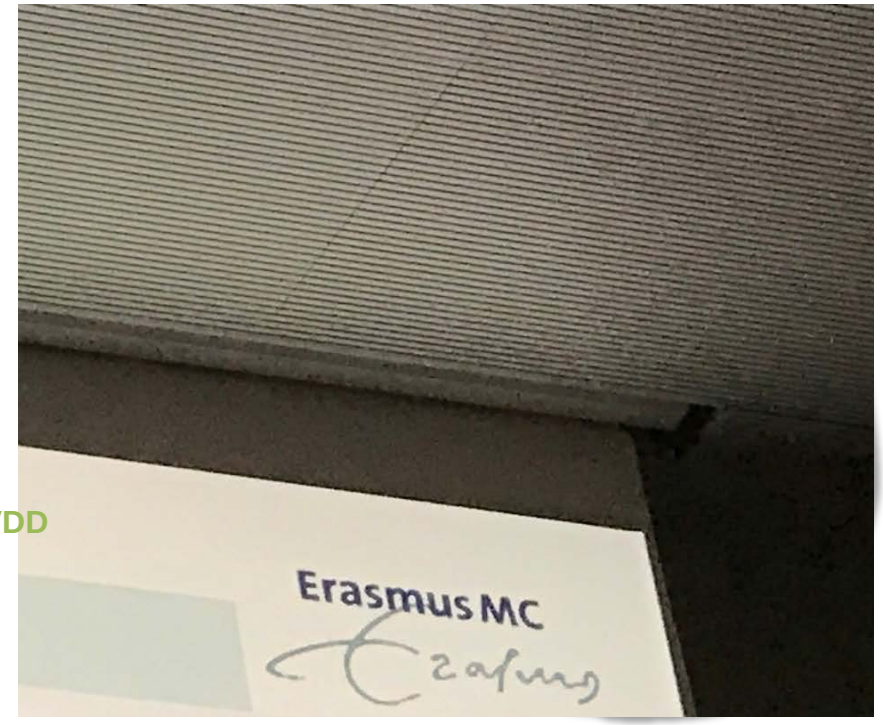
Conclusions Cardiovascular risk factors do not fully explain the risk of cardiovascu[illegible] after pre-eclampsia. The gap between

- I fattori di rischio CVS non spiegano completamente l'esito in malattia CVS tardiva
- Il gap tra OR stimati e osservati spiegabile da un rischio aggiuntivo della PE
- La PE stessa sarebbe un fattore di rischio piuttosto che un marker di malattia CVS

….. forse c’è altro?

Remodelling cardiaco





ORIGINAL ARTICLE

Maternal Cardiovascular Function in Normal Pregnancy

Evidence of Maladaptation to Chronic Volume Overload

Karen Melchiorre, Rajan Sharma, Asma Khalil and Baskaran Thilaganathan

2016



Rimodellamento cardiaco

- Massa del LV
  - Atleta in allenamento (dopo 2 aa) +25%
  - Gravidanza (38 settimane) +40%



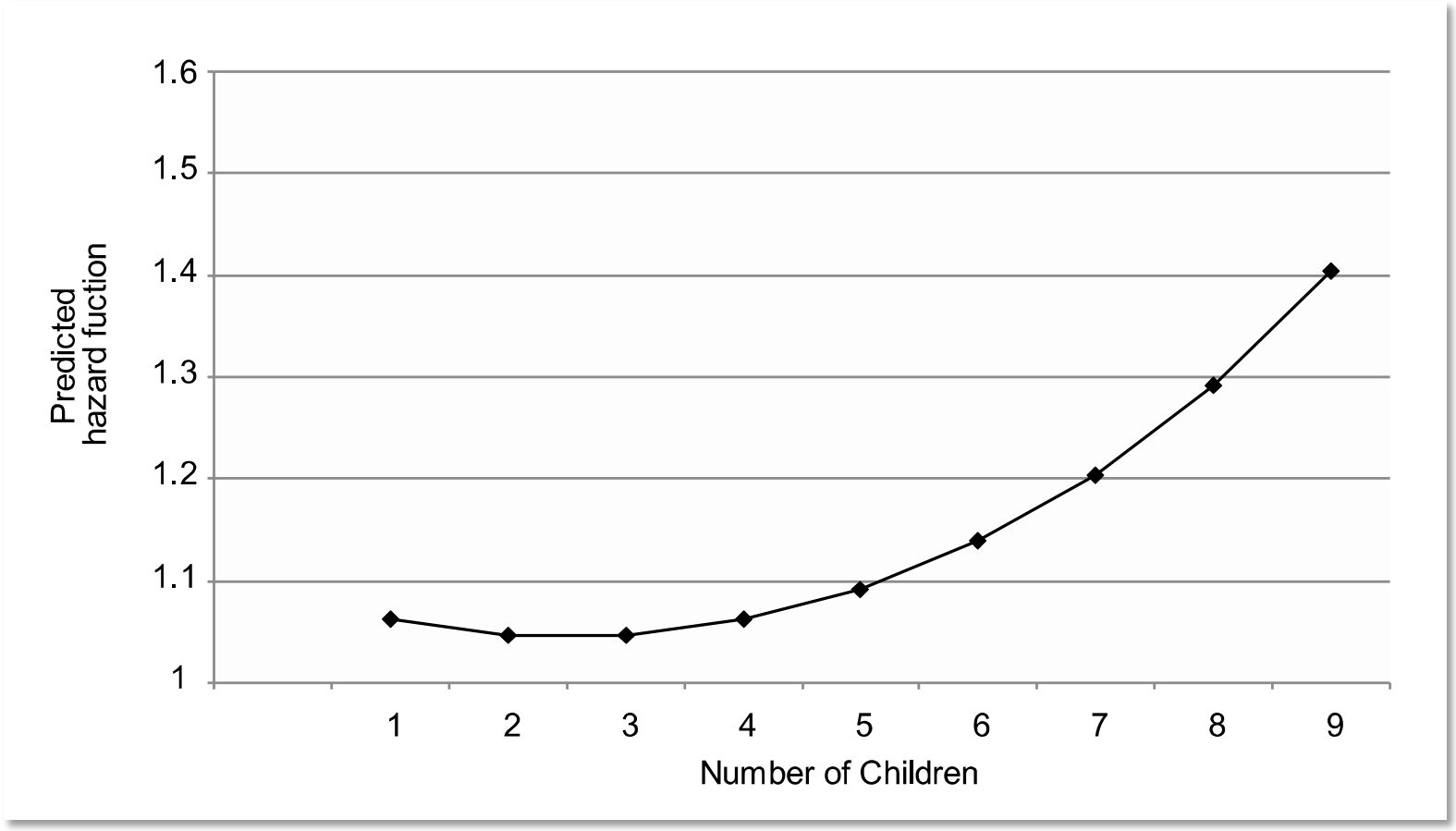
Le origini delle complicanze della gravidanza

- Tutti i sistemi organici devono lavorare al massimo
- Le complicanze compaiono quando richieste superano offerta
- L'invecchiamento dei sistemi organici riduce le riserve conducendo a una ricorrenza dei sintomi anni più tardi

2013

Association between number of children and mortality of mothers: results of a 37-year follow-up study

Uri P. Dior MD, MPH [a,b,*,1], Hagit Hochner PhD [a,1], Yechiel Friedlander PhD [a], Ronit Calderon-Margalit MD, MPH [a], Dena Jaffe PhD [a], Ayala Burger MSc [a], Meytal Avgil PhD [a], Orly Manor PhD [a], Uriel Elchalal MD [b]



Due importanti teorie

The disposable soma

- A causa delle richieste competitive della riproduzione si investe di meno nel mantenimento dei tessuti somatici di quanto non sia necessario per una lunga sopravvivenza

The antagonistic pleiotropy

- Certi alleli che sono favoriti in conseguenza di un effetto benefico precoce (fertilità e crescita della prole) presentano anche effetti deleteri tardivi

Risk factors for cardiovascular disease

Risk factor	Risk Ratio (95% C.I.) CVD
PCOS	1.38 (1.34-1.83)
POF	1.61 (1.22-2.12)
IUGR	1.66 (1.26-2.18)
Premature delivery	2.06 (1.58-2.18)
Preeclampsia	2.15 (1,76-2.61)
Abdominal obesity	2.26 (1.90-2.68)
Smoking	2.86 (2.36-3.48)
Hypertension	2.96 (2.57-3.39)
Diabetes	4.26 (3.51-5.18)
Early preeclampsia	7.71 (4.40-13.52)
Familiar Hypercholesterolemia	8.54 (5.29-13.80)

Yusuf 2004, Umans-Eckenausen 2002, Atsma 2006

Risk factors for cardiovascular disease

Risk factor	Risk Ratio (95% C.I.) CVD
PCOS	1.38 (1.34-1.83)
POF	1.61 (1.22-2.12)
IUGR	1.66 (1.26-2.18)
Premature delivery	2.06 (1.58-2.18)
Preeclampsia	2.15 (1,76-2.61)
Abdominal obesity	2.26 (1.90-2.68)
Smoking	2.86 (2.36-3.48)
Hypertension	2.96 (2.57-3.39)
Diabetes	4.26 (3.51-5.18)
Early preeclampsia	7.71 (4.40-13.52)
Familiar Hypercholesterolemia	8.54 (5.29-13.80)

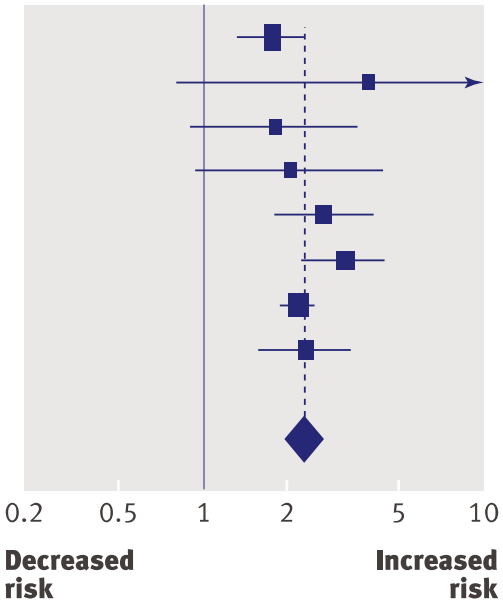
Yusuf 2004, Umans-Eckenausen 2002, Atsma 2006

Cardiopatia ischemica dopo la preeclampsia

Study	Ischaemic heart disease: Total No of cases/ women who had pre-eclampsia	Ischaemic heart disease: Total No of cases/ women who did not have pre-eclampsia	Relative risk (random) (95% CI)
Hannaford 1997[w8]	69/2371	216/14 831	1.65 (1.26 to 2.16)
Irgens 2001[w15]	27/24 155	325/602 117	3.61 (0.76 to 17.18)*
Smith 2001[w16]	12/22 781	31/106 509	1.70 (0.86 to 3.35)
Wilson 2003[w13]	26/1043	10/796	1.95 (0.90 to 4.22)
Kestenbaum 2003[w14]	35/20 552	64/92 902	2.55 (1.70 to 3.83)†
Funai 2005[w17]	41/1070	269/35 991	3.01 (2.18 to 4.33)
Ray 2005[w18]	228/36 982‡	1262/950 885	2.10 (1.82 to 2.42)
Wirkstrom 2005[w19]	176/12 533	2306/383 081	2.21 (1.56 to 3.31)†
Total (95% CI)	614/121 487	4483/2 187 112	2.16 (1.86 to 2.52)

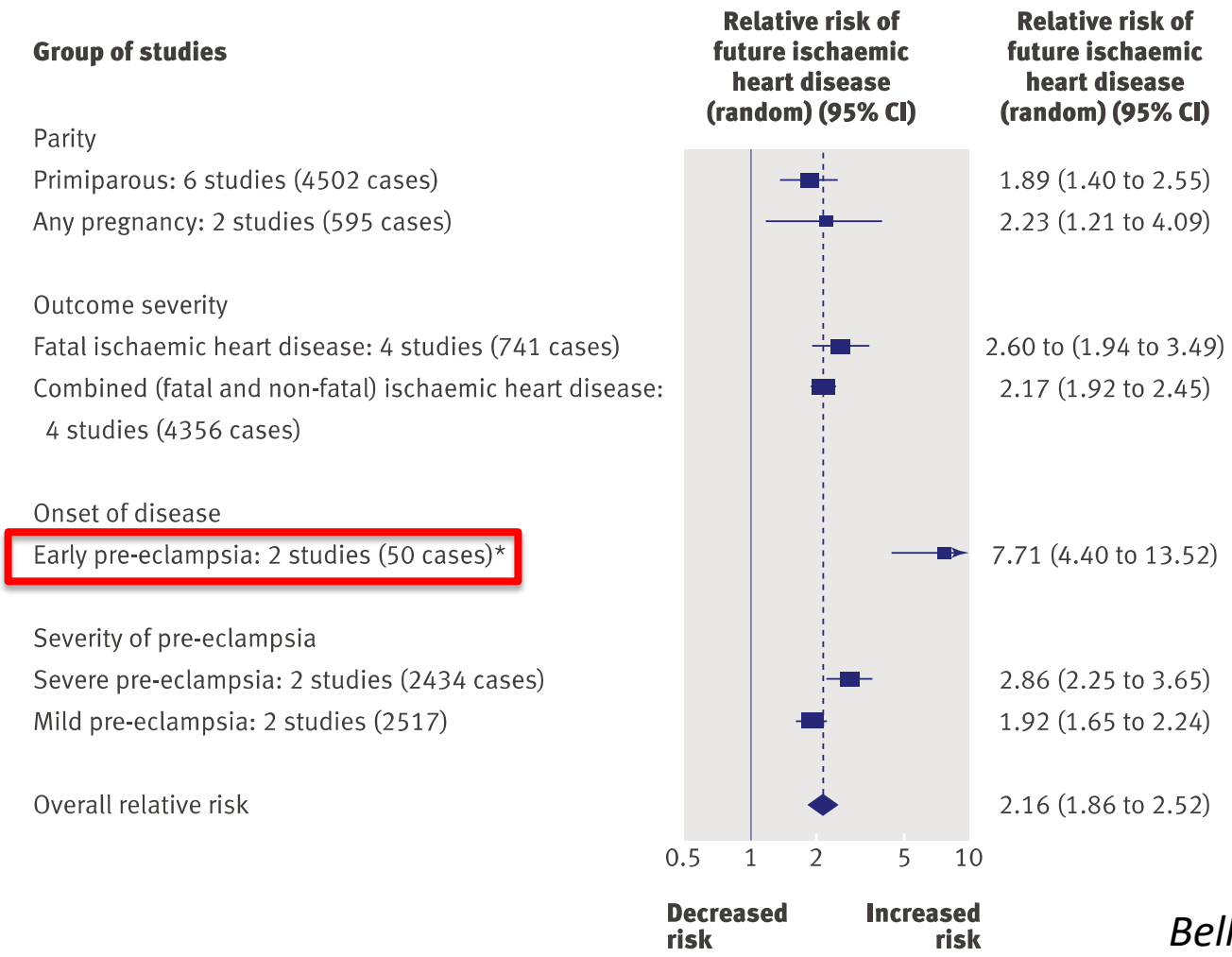
Test for heterogeneity: χ^2=9.60, df=7, P=0.21, I^2=27.1%

Test for overall effect: z=10.00, P=0.001



Bellamy 2007

Relazione con la severità della patologia?



Bellamy 2007

Early PE

e-PE preclinica	e-PE manifesta	anni dopo la e-PE
Rimodellamento concentrico e ipertrofia concentrica LV	Danno sub-endocardico precoce?! Deficit di contrattilità Lavoro cardiaco al limite della propria riserva	Rischio più elevato di ipertensione cronica, scompenso cardiaco e cardiopatia ischemica rispetto a gravide normali o PE a termine

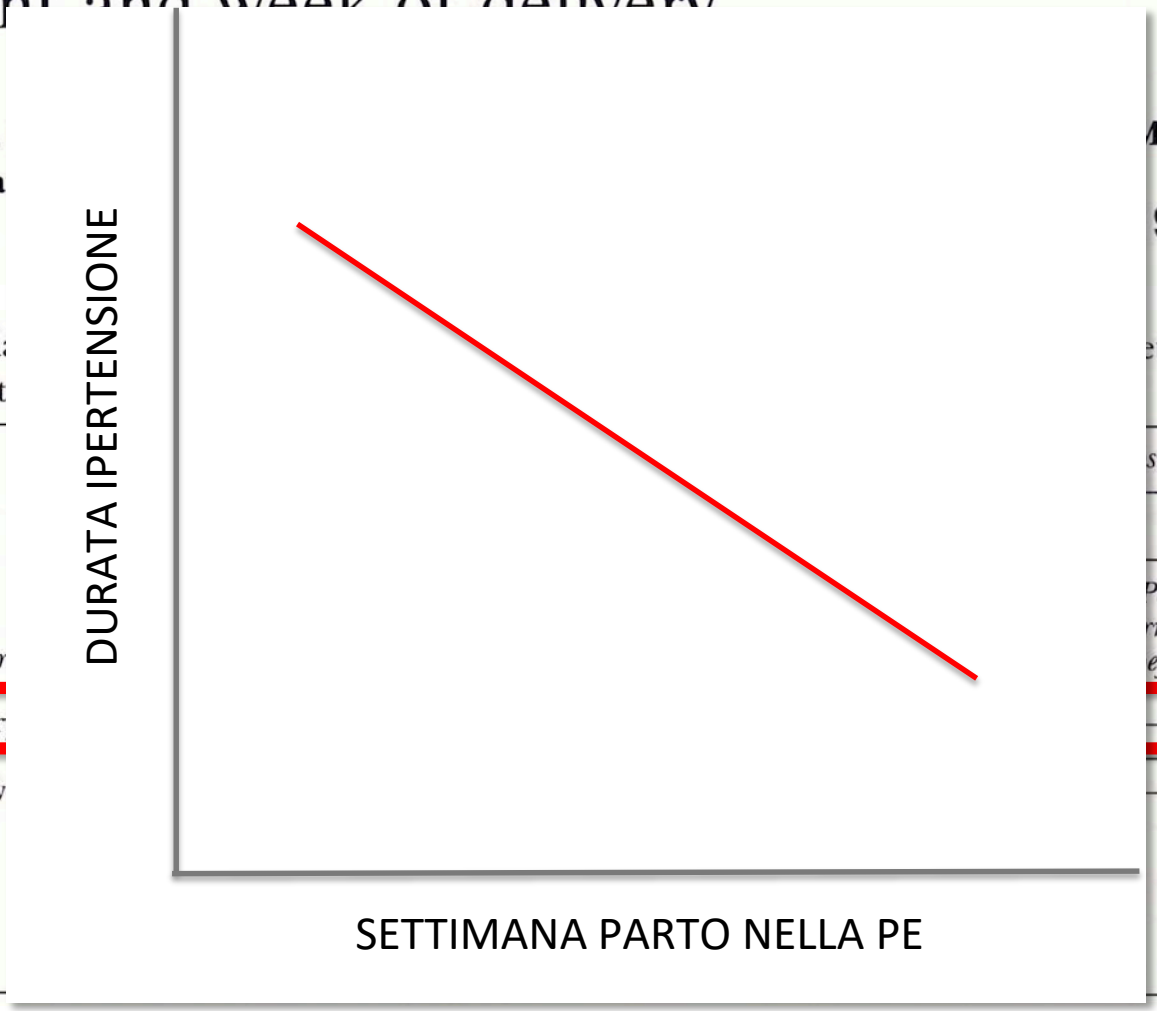
Valensise 2001, Valensise 2008, Bijnens 2009, Novelli 2012, Melchiorre 2013, Lykke 2009, Mongraw-Chaffin 2010

The duration of hypertension in the puerperium of preeclamptic women: Relationship with renal impairment and week of delivery

Sergio Ferrazzani,
Carmen Mastroma
Rome, Italy

MD,

994;171:506-12.)



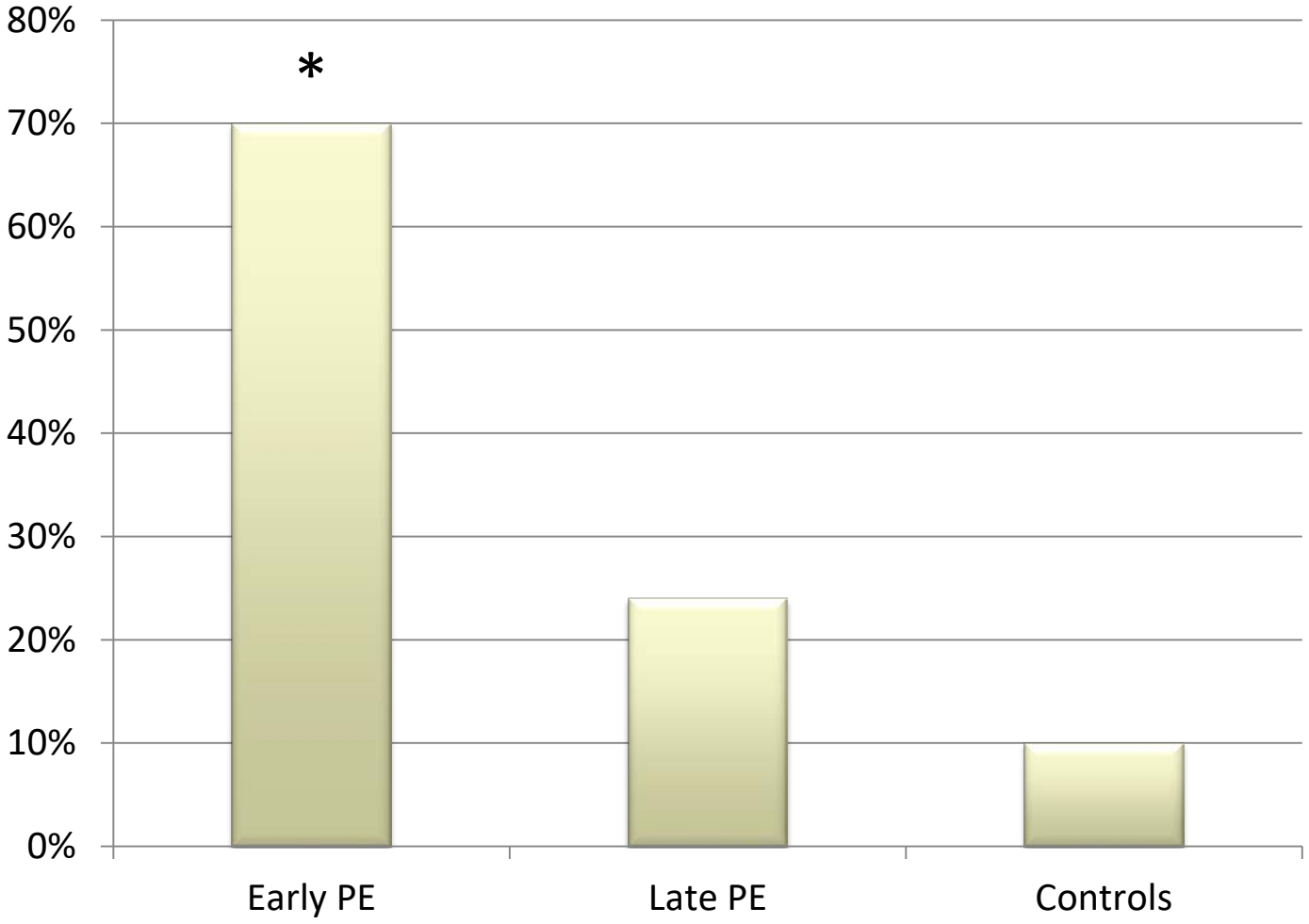
Correl
gestational hypert

tween

sia

Clinical featur			*Multiparas*	
			Partial rrelation efficient	*Significance*
Week of deliver			−0.54	$p < 0.025$
Birth weight			−0.39	NS
Relative birth w			−0.06	NS
Uric acid			0.52	$p < 0.05$
Urea nitrogen			0.40	NS
Creatinine			0.56	$p < 0.025$
Platelet count			0.11	NS
Proteinuria			0.06	NS

Scompenso cardiaco Stadio B nella PE 1 anno post-partum



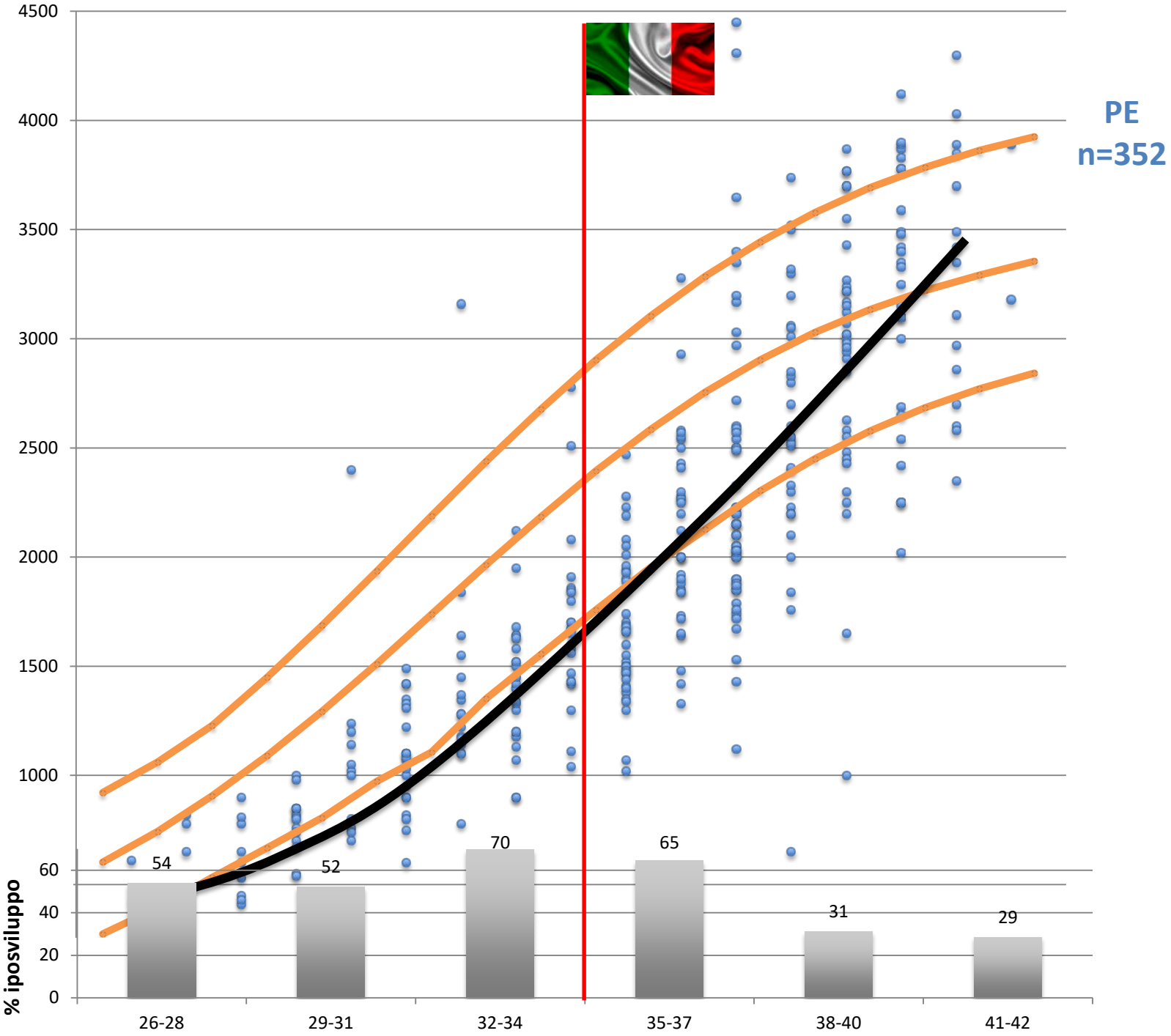
*p<0.05
vs Late PE
e Controls

Melchiorre 2011

Donne soggette a remodelling/ipertrofia del LV

- Sono maggiormente predisposte alla PE e al danno cardio-vascolare a lungo termine…
- … a prescindere che siano o no insulino-resistenti

…ovunque esiste un cut-off netto tra PE precoce e tardiva?


PE
n=352
4500
4000
3500
3000
2500
2000
1500
1000
60
40
20
0
% iposviluppo
54
52
70
65
31
29
26-28
29-31
32-34
35-37
38-40
41-42

Early e late PE in Italia

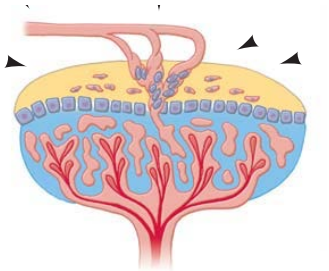
- PE precoce e tardiva
- PE placentare e materna

prescindono dalla
settimana di gestazione

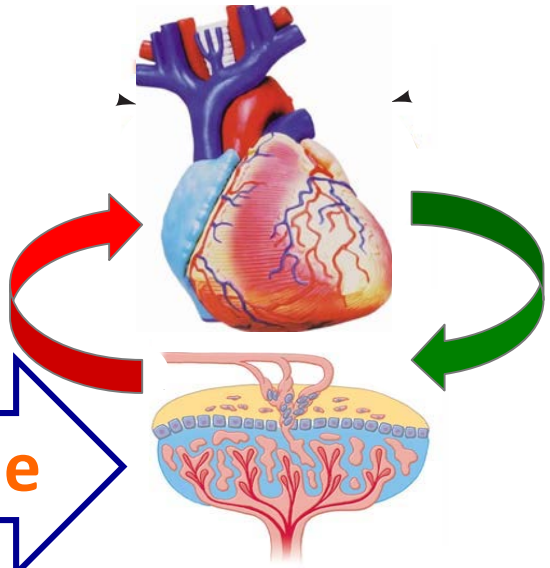
Conclusioni

- In Italia una sottopopolazione di PE meno frequente…
- … ma più grave perché associata a maggior frequenza di insufficienza placentare e quindi di FGR
- Il rischio vascolare a distanza negli anni rilevato in alcuni paesi industrializzati potrebbe non essere rappresentativo della nostra popolazione
- L'insulino-resistenza non si associa alla PE placentare e potrebbe quindi non essere la causa della prognosi cardiovascolare avversa nel follow-up della donna

Emodinamica materna e preeclampsia: è il momento di rinnovarci?



Nuova visione



Emodinamica materna e preeclampsia: è il momento di rinnovarci?

Pla-centrica

Nuova visione

Cardio/Pla-centrica


grazie

Insulin-resistance and Metabolic Syndrome

Insulin resistance

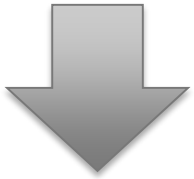
Decreased insulin sensitivity or increased insulin resistance is defined as the decreased biological response of a nutrient to a given concentration of insulin at the target tissue, e.g. liver, muscle, or adipose tissue.

Patrick M Catalano

Reproduction (2010) **140** 365–371

L'insulino-resistenza si associa a un insieme di rischi cardiovascolari:

- obesità addominale
- ipertensione
- dislipidemia
- intolleranza al glucosio
- iperinsulinemia



Sindrome da Insulino-Resistenza, Sindrome X, Sindrome Metabolica

National Library of Medicine PMC National Institutes of Health

The BMJ 2012

BMJ. 345: e7677

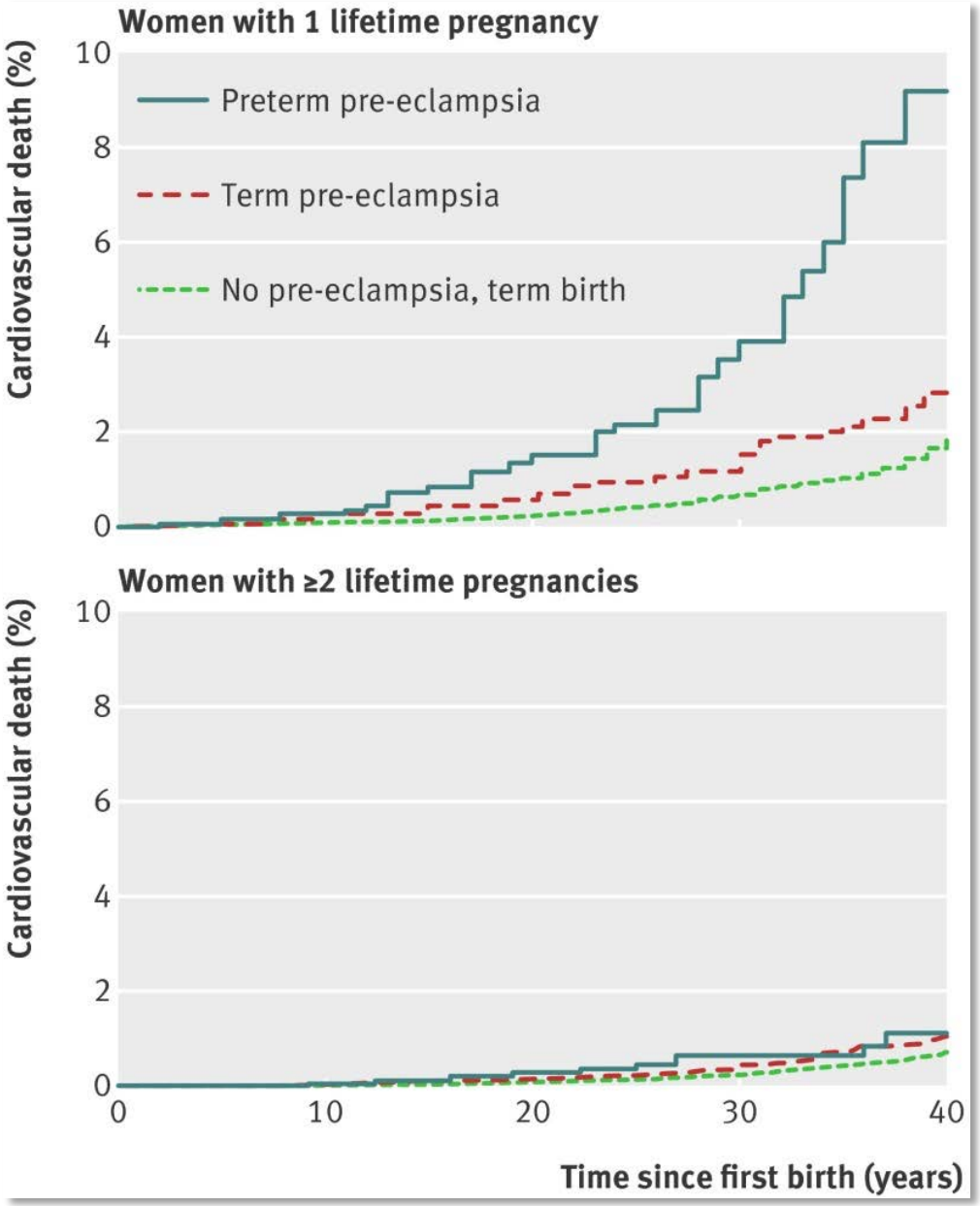
Cardiovascular mortality after pre-eclampsia in one child mothers: prospective, population based cohort study

Rolv Skjaerven, professor[12], Allen J Wilcox, senior investigator[3], Kari Klungsøyr, associate professor[12], Lorentz M Irgens, professor[12], Bjørn Egil Vikse, associate professor[45], Lars J Vatten, professor[6], Rolv Terje Lie, professor[12]

N=836.147

Rischio cardiovascolare in più di una gravidanza con PE

OR



Grazie