Il dr. Ferrazzani Sergio dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

IL DIABETE IN GRAVIDANZA

Chieti, 19-20 aprile 2018

DALLA RICERCA ALLA PRATICA CLINICA



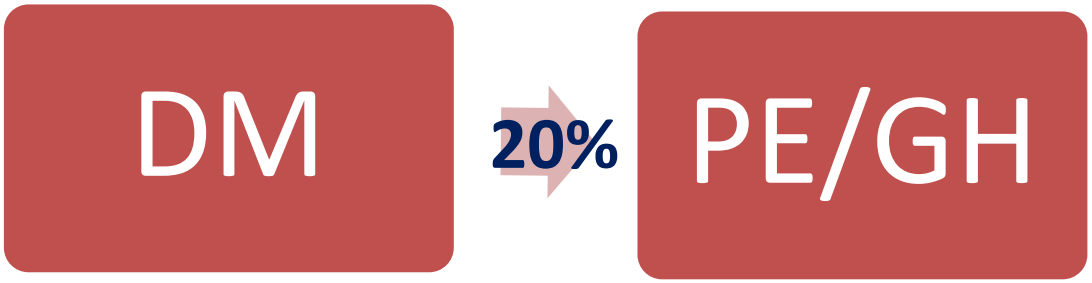
L'ipertensione e la preeclampsia nella gravida obesa e/o con diabete

Gemelli

sergio.ferrazzani@unicatt.it

Hypertension Complicating Diabetic Pregnancies: Pathophysiology, Management, and Controversies

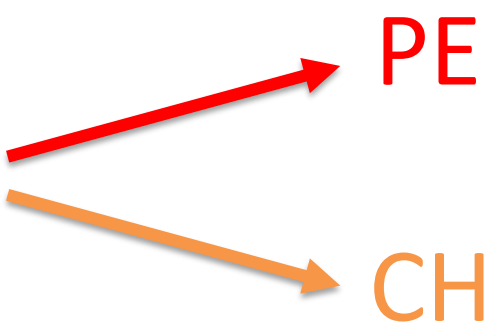
Shannon D. Sullivan, MD, PhD;[1] Jason G. Umans, MD, PhD;[2,3]
Robert Ratner, MD[2,3]



THE JOURNAL OF CLINICAL HYPERTENSION 2011

Preeclampsia & ipertensione gestazionale

- PE
- GH



Hypertension Complicating Diabetic Pregnancies: Pathophysiology, Management, and Controversies

Shannon D. Sullivan, MD, PhD;[1] Jason G. Umans, MD, PhD;[2,3]
Robert Ratner, MD[2,3]

- Danno micro-vascolare sottostante
- Ipertensione preesistente
- Scarso controllo glicemico
- Insulino-resistenza

THE JOURNAL OF CLINICAL HYPERTENSION 2011

Hypertension Complicating Diabetic Pregnancies: Pathophysiology, Management, and Controversies

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THE JOURNAL OF CLINICAL HYPERTENSION 2011

Prevalence of preeclampsia in 11,518 women with type 1 diabetes compared with the background population.

Author	Study design	Number of pregnancies in women with type 1 diabetes	Prevalence of preeclampsia in women with type 1 diabetes (%)	Prevalence of preeclampsia in the background population (%)	Odds ratio (95% CI)
Castiglioni [18][a]	Prospective	291	9.3	–	–
Hanson [22]	Register-based	491	11.5	–	–
Ekbom [20]	Prospective	240	12.5	–	–
Evers [4]	Prospective	323	12.7	–	–
Temple [16]	Prospective	290	12.8	–	–
Howarth [15]	Retrospective	138	14.0	–	–
Eidem [3]	Register-based	1307	19.1	3.6	6.0
Lauszus [21]	Prospective	151	21.0	–	–
Klemetti [23]	Retrospective	1094	23.8	–	–
Hsu [17]	Retrospective	131	33.6	–	–
Persson [19]	Register-based	7062	[illegible]	[illegible]	[illegible]
		Total 11,518	Mean 16.9	Mean 3.2	Mean 5.8

[a]Study excluding women with diabetic nephropathy.

The Journal of Maternal-Fetal & Neonatal Medicine 2017

Associations between possible clinical predictors in early pregnancy and the development of preeclampsia in women with type 1 diabetes.

	Studies *with* association	Studies *without* association	If consistency among studies, odds ratios in studies with associations
Diabetic nephropathy	[15,20–23] $n = 1020$		23.5 [15], 15.7 [20] 4.7 [21], 6.3 [22], 3.7 [23]
Microalbuminuria	[18,20,21] $n = 682$		3.8 (95% CI 1.2–11.6) [18], 11.7 [20]
Pre-existing hypertension	[15,18,23] $n = 1523$		17.1 (95% CI 3.2–91.0) [18], 3.8 [15]
Blood pressure high within normal range	[18,20,21] $n = 682$		
Retinopathy	[15,22] $n = 629$		2.9 [15], 1.9 [22]
HbA1c	[16,18,22,23] $n = 2,166$	[17,20] $n = 371$	
Nulliparity	[16,20,21] $n = 681$	[15,18,22] $n = 920$	
Duration of diabetes		[15,16,18,22] $n = 1210$	
BMI	[19] $n = 7062$	[15,16,20] $n = 668$	
Smoking		[15,16,20] $n = 668$	

The association of circulating angiogenic factors and HbA1c with the risk of preeclampsia in women with preexisting diabetes

Allison L. Cohen, Julia B. Wenger, Tamarra James-Todd, Brooke M. Lamparello, Elizabeth Halprin, Shanti Serdy, Shuling Fan, Gary L. Horowitz, Kee-Hak Lim, Sarosh Rana, Tamara C. Takoudes, Jennifer A. Wyckoff, Ravi Thadhani, S. Ananth Karumanchi & Florence M. Brown

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Table 2. Multiple of the median (MOM)* for various angiogenic markers in diabetic pregnancies.

Markers	Gestational age (years)	Non-diabetic controls† (median) N = 139	Diabetes non-PE (MOM) N = 103	p Value‡	Diabetes PE (MOM) N = 19	p Value‡	p Value§	Diabetes GHTN (MOM) N = 37	p Value‡	p Value§
sFlt-1/PlGF	11–18	39.3	1.34 (0.66, 2.26)	0.04¶	1.49 (0.99, 3.05)	0.08	0.40	1.45 (0.57, 2.24)	0.10	0.82
	19–26	5.0	1.66 (0.83, 3.34)	0.05	1.10 (0.58, 2.00)	0.77	0.33	2.20 (0.75, 4.40)	0.08	0.58
	27–34	2.8	1.45 (0.78, 11.95)	0.12	15.18 (2.37, 26.86)	0.001¶	0.03¶	5.56 (0.94, 25.29)	0.01¶	0.14
	35–40	39.6	3.21 (1.19, 7.24)	0.0001¶	8.61 (1.20, 18.27)	0.01¶	0.32	6.17 (2.28, 10.87)	<0.0001¶	0.16
sFlt-1	11–18	2218	1.16 (0.58, 1.81)	0.32	0.94 (0.37, 1.17)	0.49	0.13	0.87 (0.57, 1.78)	0.96	0.45
	19–26	2080	1.28 (0.68, 2.18)	0.25	0.83 (0.31, 1.42)	0.22	0.05	1.27 (0.56, 2.17)	0.40	0.90
	27–34	1746	1.86 (0.89, 4.48)	0.03¶	2.78 (1.09, 5.93)	0.05	0.50	2.01 (0.80, 4.51)	0.11	0.98
	35–40	8266	2.21 (0.87, 3.76)	0.001¶	2.74 (0.75, 6.56)	0.12	0.86	2.89 (1.09, 4.69)	0.002¶	0.29
PlGF	11–18	78.7	0.80 (0.46, 1.30)	0.39	0.52 (0.38, 0.95)	0.09	0.17	0.60 (0.32, 1.26)	0.11	0.21
	19–26	412.3	0.84 (0.52, 1.31)	0.18	0.62 (0.33, 1.34)	0.15	0.32	0.68 (0.46, 1.19)	0.09	0.46
	27–34	581.6	1.01 (0.43, 1.68)	0.75	0.24 (0.20, 0.37)	<0.0001¶	0.001¶	0.75 (0.31, 1.41)	0.15	0.23
	35–40	181.3	0.66 (0.48, 1.39)	0.004¶	0.50 (0.32, 0.69)	0.001¶	0.04¶	0.59 (0.41, 0.83)	<0.0001¶	0.10

DM vs controls

DM+PE vs controls

Hypertension in Pregnancy 2014

The association of circulating angiogenic factors and HbA1c with the risk of preeclampsia in women with preexisting diabetes

Allison L. Cohen, Julia B. Wenger, Tamarra James-Todd, Brooke M. Lamparello, Elizabeth Halprin, Shanti Serdy, Shuling Fan, Gary L. Horowitz, Kee-Hak Lim, Sarosh Rana, Tamara C. Takoudes, Jennifer A. Wyckoff, Ravi Thadhani, S. Ananth Karumanchi & Florence M. Brown

- Alterato stato anti-angiogenico (sFlt1/PlGF) ulteriormente esacerbato nelle donne che sviluppavano PE
- L'alterazione dei fattori angiogenetici potrebbe essere un meccanismo dell'aumentato rischio di PE

Hypertension in Pregnancy 2014

Hypertension Complicating Diabetic Pregnancies: Pathophysiology, Management, and Controversies

Shannon D. Sullivan, MD, PhD;[1] Jason G. Umans, MD, PhD;[2,3]
Robert Ratner, MD[2,3]

- Danno micro-vascolare sottostante
- Ipertensione preesistente
- Scarso controllo glicemico
- Insulino-resistenza

THE JOURNAL OF CLINICAL HYPERTENSION 2011

A multicenter Italian study on pregnancy outcome in women with diabetes

Annunziata Lapolla*,[1], Maria Grazia Dalfrà, Graziano Di Cianni [1], Matteo Bonomo, Elena Parretti, Giorgio Mello, for the Scientific Committee of the GISOGD Group

Maternal morbidity in pregnant diabetic women, % (*n*)

	Type 1 (504)	Type 2 (164)
Ketoacidotic episodes	5.4 (27)	0 (0)
Severe hypoglycemic episodes	14.9 (75)	1.2 (2)
Progression of retinopathy	5.1 (26)	1.8 (3)
Progression of nephropathy	3.4 (17)	1.2 (2)
Gestational hypertension	12.8 (65)	9.1(15)
Pre-eclampsia	4.3 (22)	3.1(5)

Nutrition, Metabolism & Cardiovascular Diseases (2008) **18**, 291—297

Optimal Glycemic Control, Pre-eclampsia, and Gestational Hypertension in Women With Type 1 Diabetes in the Diabetes and Pre-eclampsia Intervention Trial

Belfast

Valerie A. Holmes, PhD[1]
Ian S. Young, MD[2]
Christopher C. Patterson, PhD[2]
Donald W.M. Pearson, MD[3]
James D. Walker, MD[4]
Michael J.A. Maresh, MD[5]
David R. McCance, MD[6]
for the Diabetes and Pre-eclampsia Intervention Trial Study Group

Time point	Pre-eclampsia *n* (%)	Pre-eclampsia Adjusted odds ratio (95% CI)†
Prepregnancy‡		
A1C		
Optimal (reference)	47 (9)	1.00
Good	89 (16)	1.68 (0.40–7.07)
Moderate	152 (28)	2.44 (0.66–9.05)
Poor	254 (47)	3.46 (0.95–12.6)
	542	
First antenatal visit‡		
A1C		
Optimal (reference)	49 (7)	1.00
Good	147 (20)	1.13 (0.33–3.92)
Moderate	221 (31)	2.55 (0.81–8.04)
Poor	304 (42)	3.68 (1.17–11.6)
	721	
26 weeks' gestation‡		
A1C		
Optimal (reference)	137 (23)	1.00
Good	275 (46)	2.09 (1.03–4.21)
Moderate	140 (24)	3.20 (1.47–7.00)
Poor	40 (7)	3.81 (1.30–11.1)
	592	
34 weeks' gestation‡		
A1C		
Optimal (reference)	131 (25)	1.00
Good	276 (53)	1.78 (0.83–3.81)
Moderate	92 (18)	3.27 (1.31–8.20)
Poor	20 (4)	8.01 (2.04–31.5)
	519	

Livelli di HbA1C

Optimal	(<6.1%)
Good	(6.1–6.9%)
Moderate	(7.0–7.9%)
Poor	(≥8.0%)

749 gravidanze dallo studio DAPIT
Diabetes and Pre-eclampsia Intervention Trial

Diabetes Care 2011

The association of circulating angiogenic factors and HbA1c with the risk of preeclampsia in women with preexisting diabetes

Allison L. Cohen, Julia B. Wenger, Tamarra James-Todd, Brooke M. Lamparello, Elizabeth Halprin, Shanti Serdy, Shuling Fan, Gary L. Horowitz, Kee-Hak Lim, Sarosh Rana, Tamara C. Takoudes, Jennifer A. Wyckoff, Ravi Thadhani, S. Ananth Karumanchi & Florence M. Brown

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Relative risk of preeclampsia with HBA1C cut-offs among diabetics.

			Univariate		Multivariable†	
HBA1C	% (*n*) <HBA1C	% (*n*) ≥HBA1C	RR (95% CI)	*p* Value	RR (95% CI)	*p* Value
≥6.5	48.1 (76)	51.9 (82)	4.63 (1.40–15.38)	0.01*	4.42 (1.35–14.47)	0.01*
≥7	67.1 (106)	32.9 (52)	5.30 (2.00–14.07)	0.001*	5.26 (2.06–13.41)	0.001*
≥7.5	78.5 (124)	21.5 (34)	5.73 (2.41–13.66)	<0.0001*	5.60 (2.50–12.56)	<0.0001*
≥8	85.4 (135)	14.6 (23)	4.70 (2.08–10.64)	0.0002*	4.60 (2.18–9.69)	<0.0001*

*Significant at <0.05 level.
†Controlling for parity and body mass index.

Hypertension in Pregnancy 2014

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THE JOURNAL OF CLINICAL HYPERTENSION 2011

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Hypertension Complicating Diabetic Pregnancies: Pathophysiology, Management, and Controversies

Shannon D. Sullivan, MD, PhD;[1] Jason G. Umans, MD, PhD;[2,3]
Robert Ratner, MD[2,3]

- **Donne non diabetiche**:
  - PE correlazione positiva con glicemia a digiuno, anormalità subcliniche al carico di glucosio
  - Rischio di PE x 2 nel più alto quartile di glicemia post-carico rispetto al quartile più basso
  - Con HDP rischio x 3 di sviluppare T2DM nel futuro
- **Donne con PE non diabetiche**:
  - Presentano insulino-resistenza residua dopo il parto persistente per anni
- Tutte queste osservazioni insieme suggeriscono che l'insulino-resistenza può giocare un ruolo causale nello sviluppo della HDP, PE particolarmente

Joffe 1998, HAPO 2008, Likke 2009, Fuh 1995, Laivori 1996

Gravidanza e Sindrome Metabolica…

…*quali similitudini*?





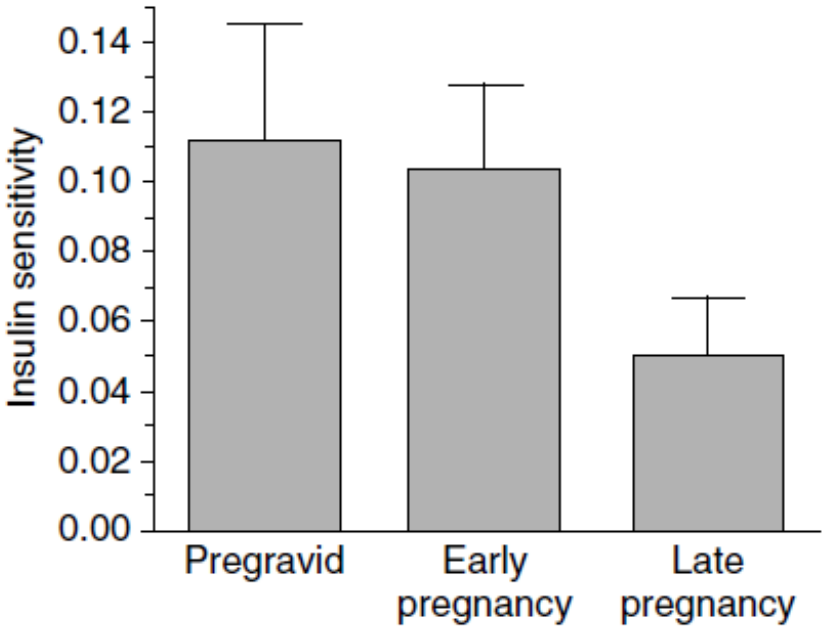
- Aumento della glicemia postprandiale
- Livelli più elevati di trigliceridi
- Livelli più elevati di insulina
- Aumento dell’insulino-resistenza
- Up-regulation della cascata infiammatoria

Modificazioni longitudinali dell'insulino-sensibilità nella gravidanza normale

Focus on Obesity

Obesity, insulin resistance, and pregnancy outcome

Patrick M Catalano



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

Reproduction 2010

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

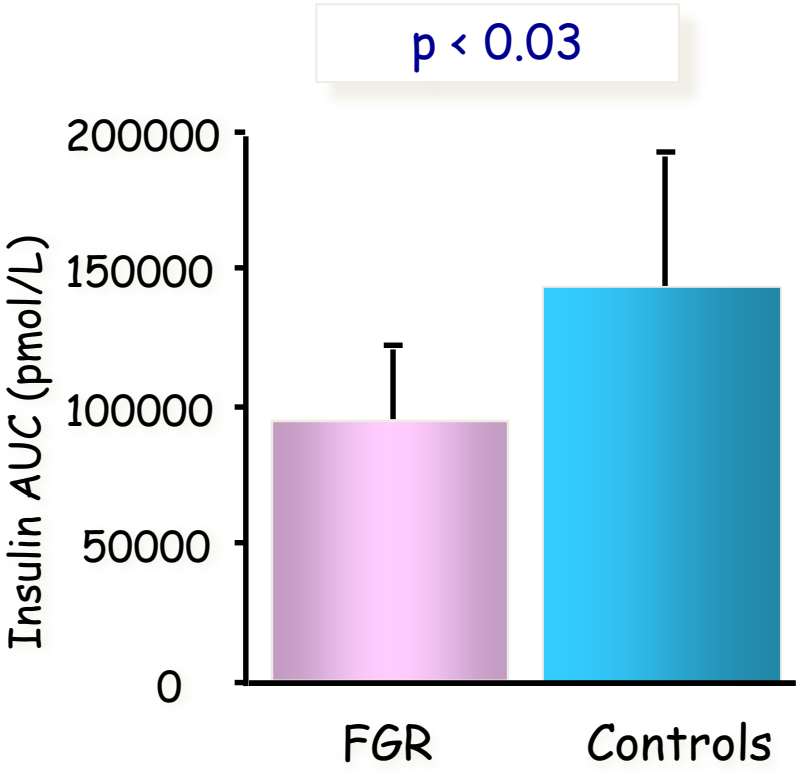
Obstet Gynecol 1998

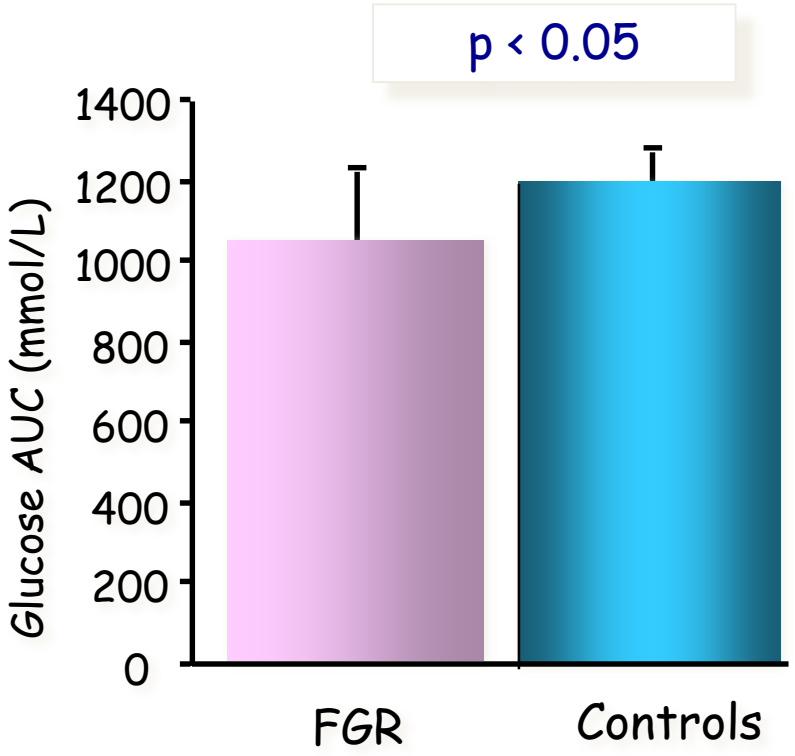
	FGR group ($n = 8$)	Controls ($n = 11$)	P
Wk of study	34.8 ± 3.4	33.7 ± 3.6	NS
Fasting insulin (pmol/ L)	61.6 ± 48.9	90.7 ± 74.1	NS
Fasting glucose (mmol/ L)	3.9 ± 0.2	4.0 ± 0.2	NS
AUC insulin/ AUC glucose ratio	92.2 ± 23.3	120.7 ± 42.1	NS
GIR (μmol/ kg × min)	21.6 ± 4.4	16.7 ± 4.8	<.05
hPL (μg/ mL)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

Effect of Maternal Carbohydrate Metabolism on Fetal Growth

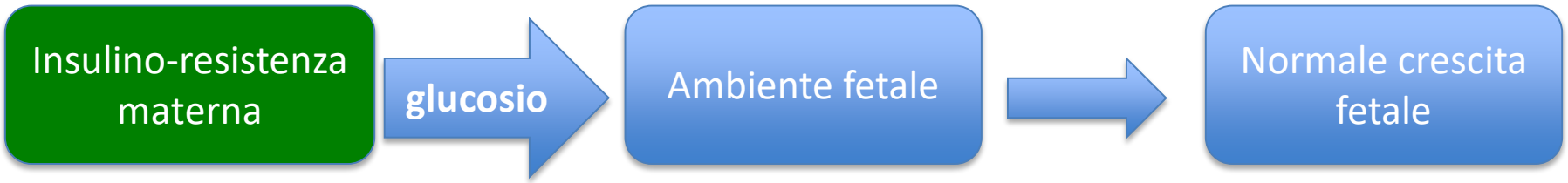
ALESSANDRO CARUSO, MD, GIANCARLO PARADISI, MD,
SERGIO FERRAZZANI, MD, ANGELA LUCCHESE, MD, SIMONETTA MORETTI, MD,
AND ANNA MARIA FULGHESU, MD

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

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

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
Copyright © 2003 by The Endocrine Society

Placental (early) preeclampsia

Maternal (late) preeclampsia

Ok`bdms`k'd`qkx( oqddbk`lmorsh`

Due stadi di presentazione:

Preclinica

- Placentazione anomala/insufficiente

Clinica

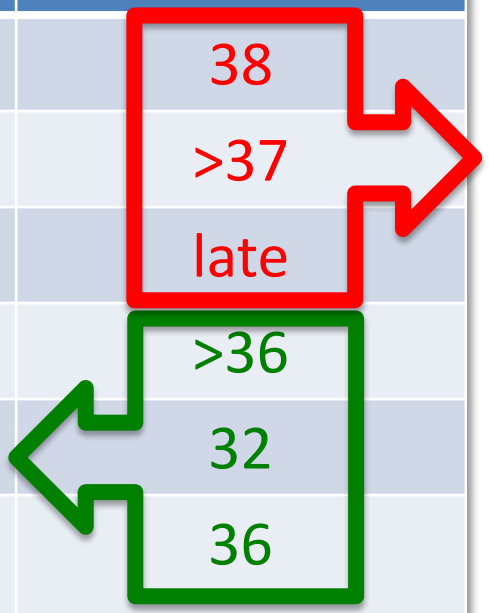
- Placenta progressivamente ipossica

L'asse madre-placenta

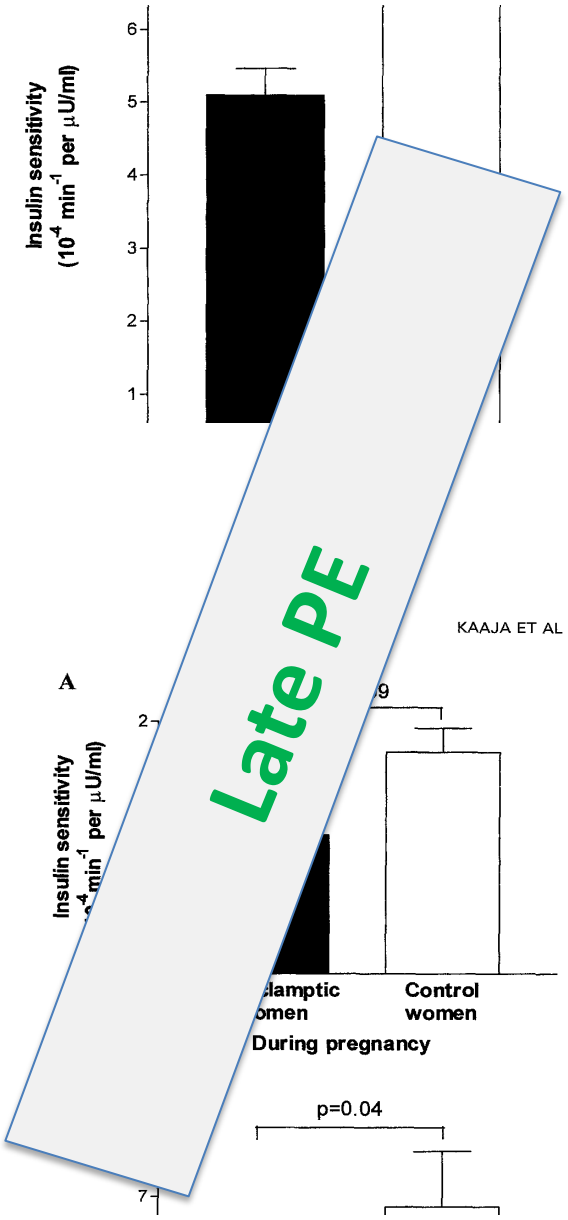
- Basso grado di risposta infiammatoria sistemica negli adulti con patologia arteriosa, ipertensione, obesità o diabete…
- Fattori costituzionali che conducono alla "PE materna"
- Qui la questione è più una risposta anomala materna che non una gravidanza anomala

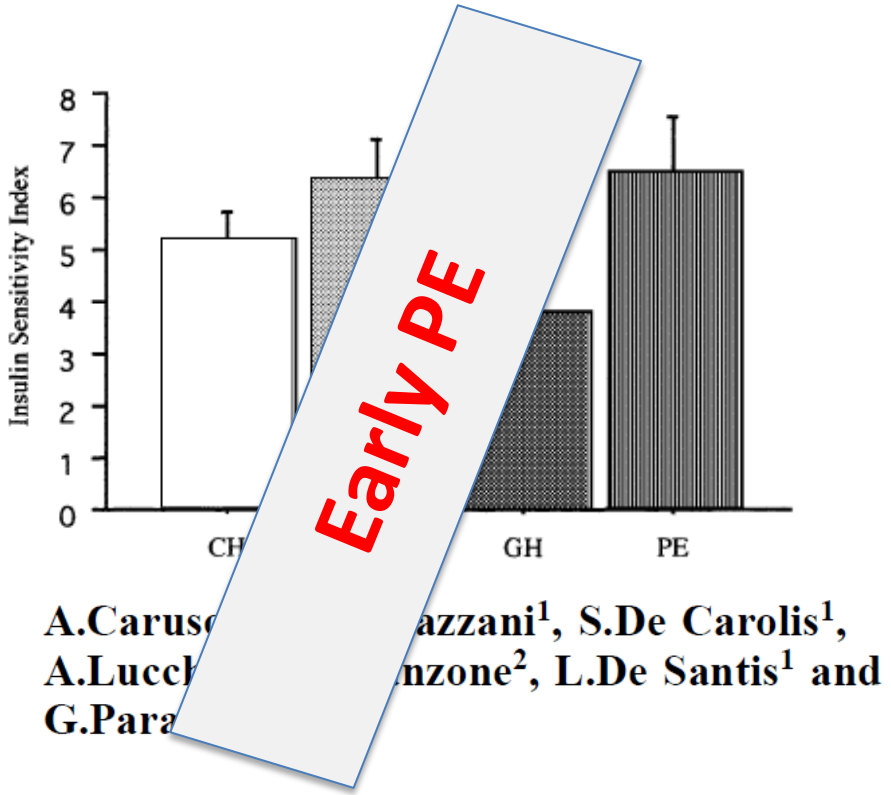
Insulino-resistenza & PE: evidenze conflittuali

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



⬆ dell'insulino-resistenza condizioni patologiche come la Late PE e la GH





A.Caruso azzani[1], S.De Carolis[1], A.Lucch nzone[2], L.De Santis[1] and G.Para

Kaaja et al. 1999

…dalla nostra esperienza

STUDIO DELL'INSULINO-RESISTENZA NELLE GRAVIDANZE COMPLICATE DA IPERTENSIONE

<34 settimane

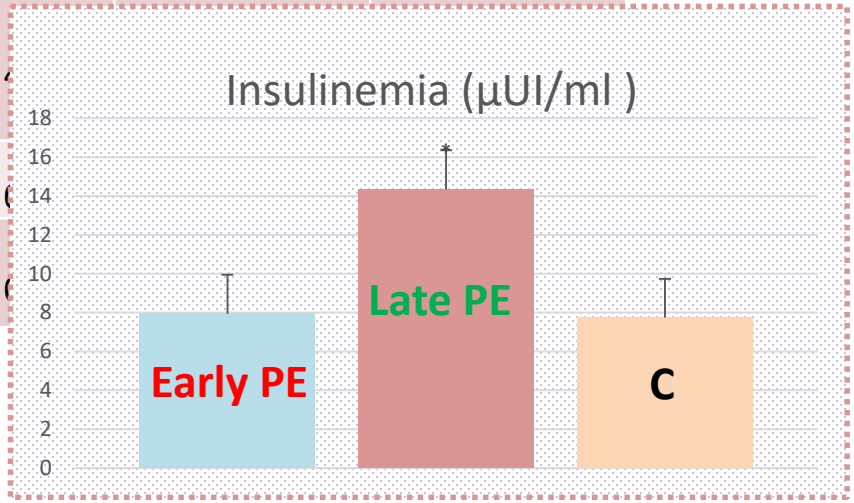
	GH N= 6	CH N= 9	PE N= 10	C N= 10	p
Insulinemia (µUI/ml) media ± DS	15,2 ± 9,4	11,3 ± 4,7	8,0 ±4,0	7,0 ± 3,8	0,026
HOMA-IR	2,9 ± 2,1	2,1 ± 1,0	1,4 ± 0,7	1,2±0,9	0,059
QUICKI index	0,34± 0,04	0,34±0,03	0,38 ±0,04	0,37±0,03	0,083

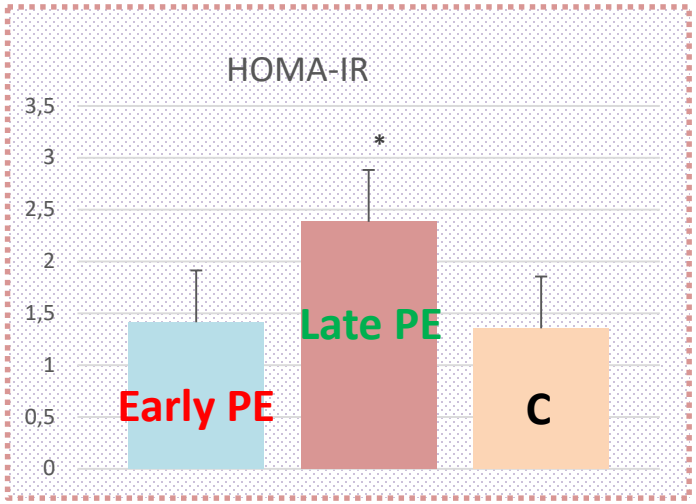
≥34 settimane

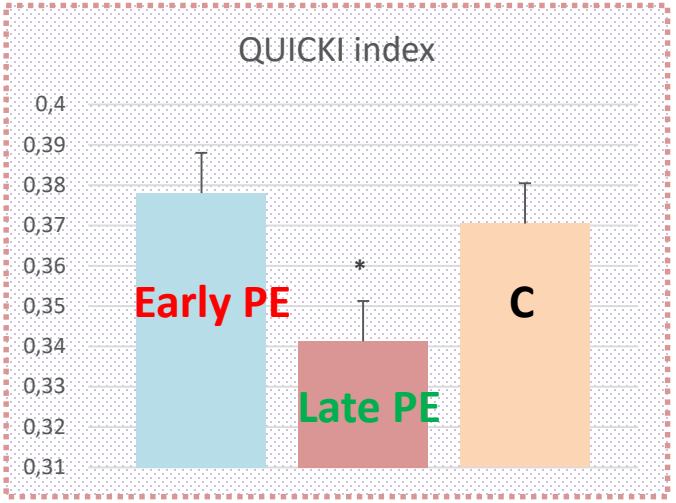
	GH N= 15	CH N= 7	PE N= 8	C N= 10	p
Insulinemia (µUI/ml) media ± DS	13,2 ±9,1	19,5 ±3,4	14,4 ±4,3	8,5 ±3,9	**0,013**
HOMA-IR	2,2 ± 1,5	3,5 ± 0,9	2,3 ± 1,0	1,5 ± 0,7	**0,018**
QUICKI index	0,4 ± 0,04	0,32 ±0,01	0,34 ± 0,02	0,37±0,04	**0,028**

Insulino resistenza nella Late PE

	Early PE (n=10)	Late PE (n=8)	Controls (n=20)
Insulinemia (µg/ml)	8,0 ± 4		
HOMA-IR	1,4 ± (		
QUICKI index	0,38 ± (		







PE & insulino-resistenza

- **Early PE** non presenta insulino-resistenza
- **Late PE** si associa a insulino-resistenza

GDM

Association between Gestational Diabetes and Pregnancy-induced Hypertension

Chris L. Bryson, George N. Ioannou, Stephen J. Rulyak, and Cathy Critchlow

Group	No.	Prevalence of gestational diabetes (%)	Crude OR†	95% CI†	Adjusted OR‡	95% CI
Eclampsia	154	3.9	1.47	0.65, 3.34	1.27	0.52, 3.15
Severe preeclampsia	1,180	4.5	1.71**	1.29, 2.26	1.53*	1.13, 2.06
Mild preeclampsia	5,468	4.4	1.69**	1.47, 1.95	1.50**	1.28, 1.76
Gestational hypertension	8,943	4.4	1.69**	1.51, 1.90	1.40**	1.23, 1.58
Controls	47,237	2.7	1		1	

@ I Dohcdl hmk1//2

RESEARCH ARTICLE

Fatty acid-binding protein 4 predicts gestational hypertension and preeclampsia in women with gestational diabetes mellitus

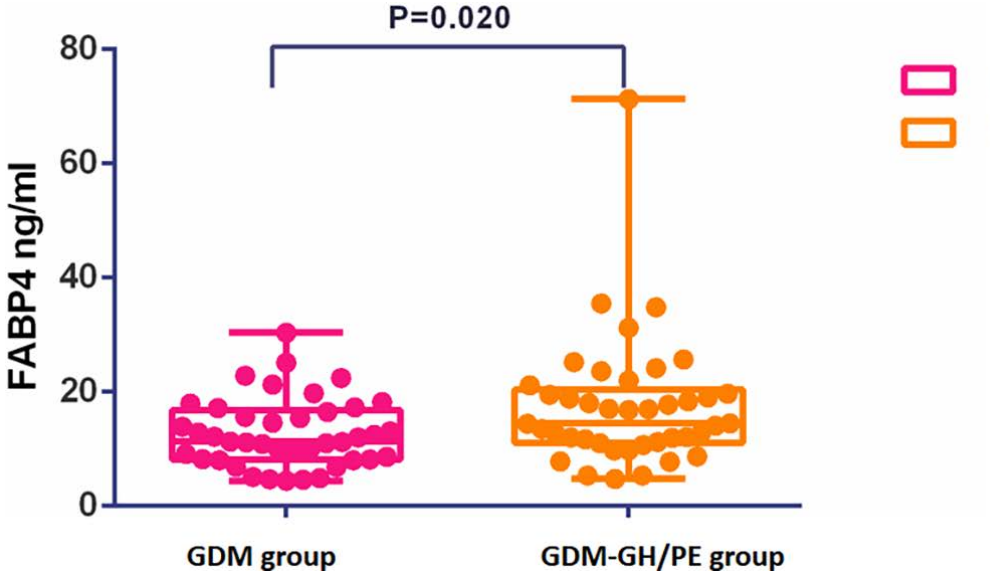
Boya Li[1], Huixia Yang[1]*, Wanyi Zhang[1], Yundi Shi[2], Shengtang Qin[1], Yumei Wei[1], Yingdong He[1], Wenshuang Yang[1], Shiju Jiang[1], Hongyan Jin[1]

1 Peking University First Hospital, Beijing, China, **2** Department of Pharmacology, School of Basic Medical, Peking University Health Science Center, Beijing, China

2018

- 1344 donne con GDM
- GH 6,2%
- PE 3,7%

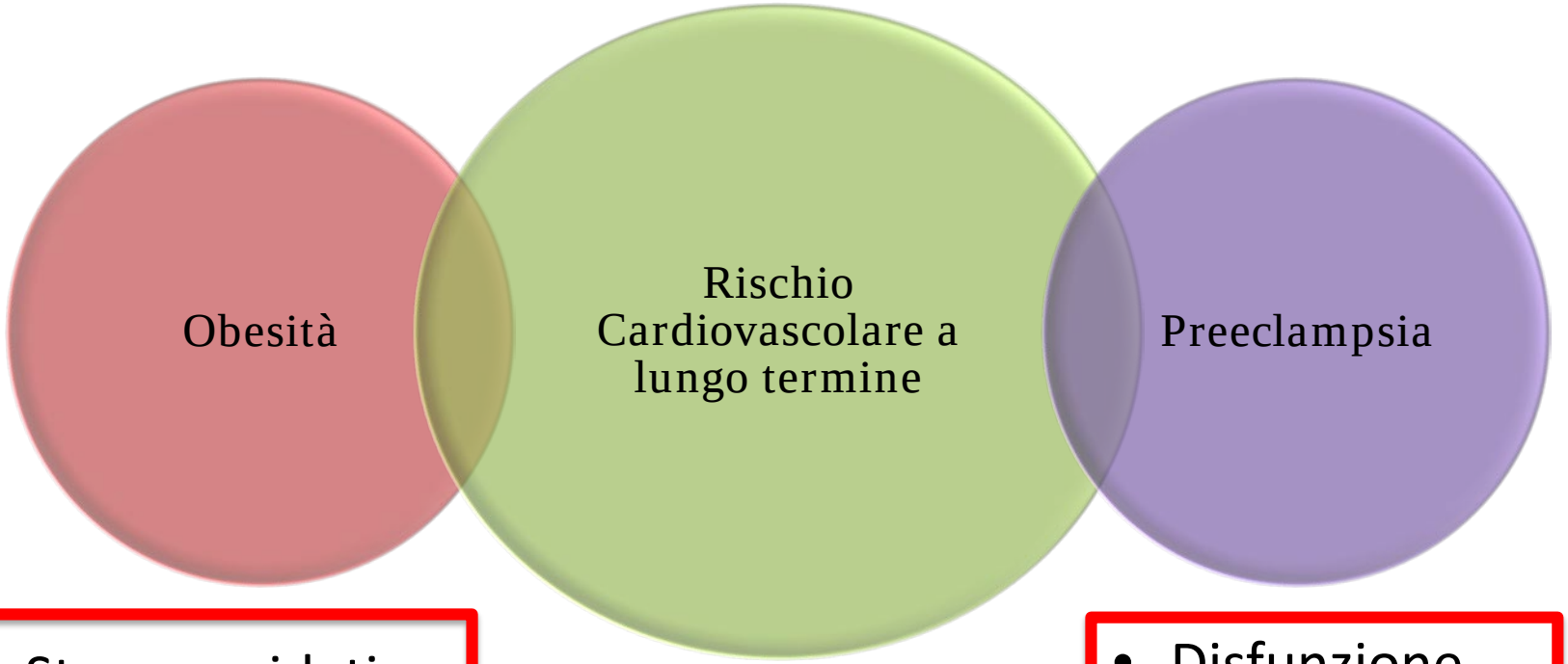
15 ospedali a Pechino popolazione generale
GH 3.8%
PE 2.4%



FABP4 suggerita come la 3ª adipochina in aggiunta a leptina e adiponectina

- ❑ FABP4 risultava positivamente correlato con BMI, HOMA-IR, HbA1c, MAP nell'analisi univariata

Obesità e Ipertensione in gravidanza…
…*quali similitudini*?



- Stress ossidativo
- Disfunzione endoteliale
- Up-regulation della cascata infiammatoria

American Journal of Obstetrics and Gynecology
Volume 178, Issue 3, March 1998, Pages 551-556

Plasma concentrations of asymmetric dimethylarginine, a natural inhibitor of nitric oxide synthase, in normal pregnancy and preeclampsia ☆ ☆☆ ★ ★★ London

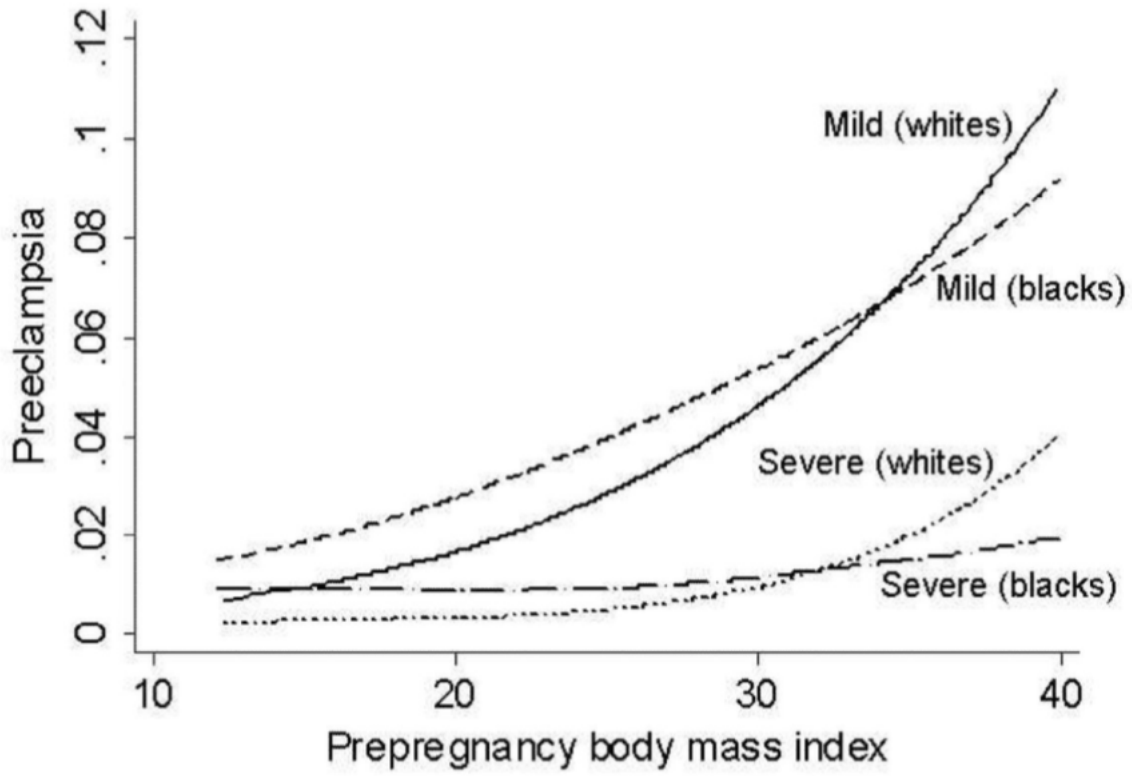
Desmond P. Holden MB, BS, Sara A. Fickling PhD, Guy St.J. Whitley PhD, Stephen S. Nussey DPhil

↑ [ADMA] nelle pazienti con PE ⟷ ↑ [ADMA] nelle pazienti obese

Genera stress ossidativo e scarsa produzione di NO
↑dislipidemia, infiammazione, insulino resistenza, iperomocisteinemia
↑PE e obese con o senza insulino-resistenza

The Role of Obesity in Preeclampsia

James M. Roberts, **Lisa M. Bodnar**, **Thelma E. Patrick**, and **Robert W Powers**

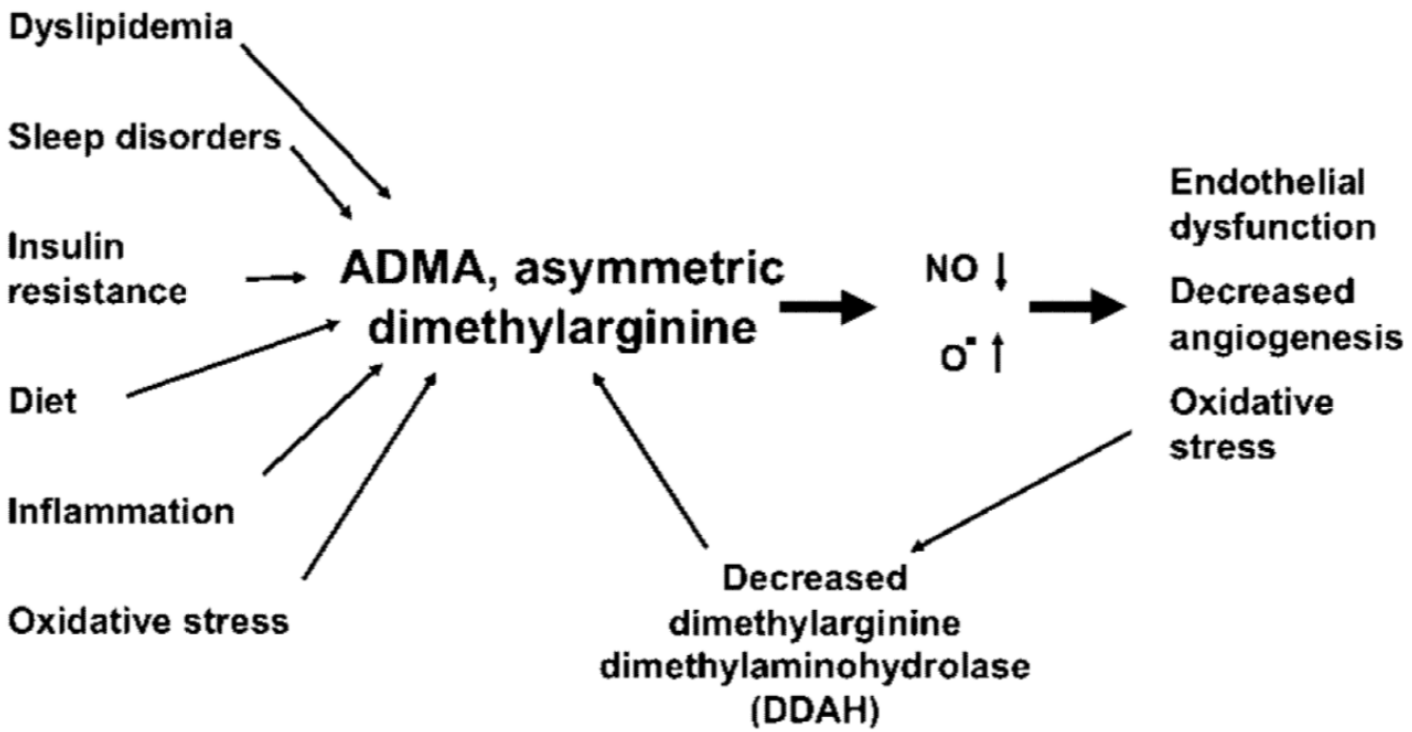


38.000 gravidanze

Pregnancy Hypertens. 2011

The Role of Obesity in Preeclampsia

James M. Roberts, **Lisa M. Bodnar**, **Thelma E. Patrick**, and **Robert W Powers**



Asymmetric Dimethylarginine (ADMA) has been proposed as the "Uber Risk Factor"[145] where many of the risk factors for cardiovascular disease and we propose for obesity and preeclampsia converge

Pregnancy Hypertens. 2011

Associations of maternal obesity with blood pressure and the risks of gestational hypertensive disorders. The Generation R Study

Romy Gaillard, Eric A.P. Steegers, Albert Hofman and Vincent W.V. Jaddoe

6902 gravidanze

Prepregnancy BMI, gestational weight gain and risk of pregnancy-induced hypertension and preeclampsia ($N = 6902$)[a]

Prepregnancy BMI	Pregnancy-induced hypertension[b,c] ($n = 264$)	Preeclampsia[b,c] ($n = 131$)
Lean (<20 kg/m^2)	0.66 (0.42–1.03) $n_{cases} = 23$	1.22 (0.74–2.00) $n_{cases} = 22$
Normal (20–24.9 kg/m^2)	Reference $n_{cases} = 117$	Reference $n_{cases} = 60$
Overweight (25–29.9 kg/m^2)	2.12 (1.54–2.91)† $n_{cases} = 64$	1.82 (1.16–2.83)* $n_{cases} = 31$
Obese (30–34.9 kg/m^2)	4.67 (3.07–7.09)† $n_{cases} = 35$	2.49 (1.29–4.78)* $n_{cases} = 12$
Morbidly obese (≥35 kg/m^2)	11.34 (6.80–18.86)† $n_{cases} = 25$	3.40 (1.39–8.28)* $n_{cases} = 6$
Trend[d]	*1.16 (1.13–1.19)*†	*1.08 (1.04–1.12)*†
Gestational weight gain	**Pregnancy-induced hypertension[b,e] ($n = 252$)**	**Preeclampsia[b,e] ($n = 121$)**
<7 kg	Reference $n_{cases} = 55$	Reference $n_{cases} = 36$
7–11.9 kg	1.50 (1.04–2.16)* $n_{cases} = 103$	0.78 (0.48–1.25) $n_{cases} = 42$
≥12 kg	1.86 (1.27–2.70)* $n_{cases} = 94$	1.08 (0.67–1.74) $n_{cases} = 43$
Trend[d]	*1.06 (1.13–1.19)*†	*1.02 (0.99–1.05)*

J Hypertens 2011

OBSTETRICS

Gestational weight gain as a risk factor for hypertensive disorders of pregnancy

Corrie Macdonald-Wallis, PhD; Kate Tilling, PhD; Abigail Fraser, PhD; Scott M. Nelson, PhD, MRCOG; Debbie A. Lawlor, PhD, FFPH

Bristol England

Predicted probabilities of HDP by prepregnancy weight and early-pregnancy GWG (n = 9536)[a]

Prepregnancy weight, kg	GWG up to 18 wks, g/wk	Probability of gestational hypertension, % (SE)	Probability of Preeclampsia, % (SE)
50	200	11.5 (0.9)	1.8 (0.4)
	400	14.1 (1.0)	2.3 (0.5)
	600	17.0 (1.4)	2.9 (0.7)
60	200	19.4 (1.2)	2.9 (0.5)
	400	23.2 (1.4)	3.6 (0.6)
	600	27.3 (2.0)	4.4 (1.0)
70	200	30.7 (1.7)	4.4 (0.8)
	400	35.4 (1.9)	5.3 (1.0)
	600	40.4 (2.6)	6.2 (1.5)
80	200	44.2 (2.3)	6.0 (1.2)
	400	49.3 (2.5)	7.0 (1.5)
	600	54.1 (3.2)	7.9 (2.1)
90	200	57.9 (2.8)	7.5 (1.8)
	400	62.3 (3.0)	8.4 (2.1)
	600	66.1 (3.6)	9.2 (2.8)

GWG, gestational weight gain; *HDP*, hypertensive disorders of pregnancy; *SE*, standard error.

[a] Predicted probabilities are for a woman of average height (164 cm), age (25-29 years), nulliparous, having never smoked during pregnancy, O level educational qualification, and having a male offspring.

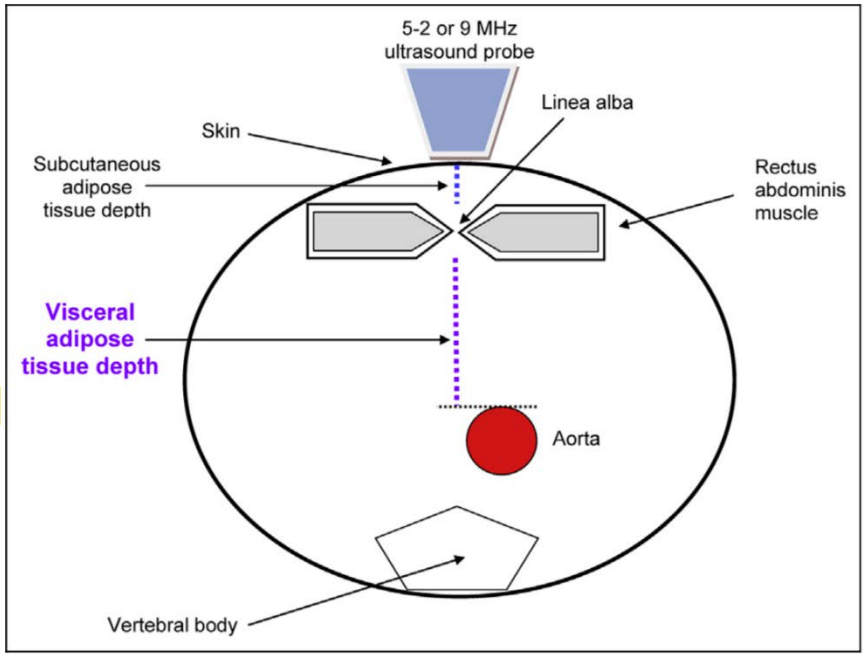
Macdonald-Wallis. Weight gain and blood pressure in pregnancy. Am J Obstet Gynecol 2013.

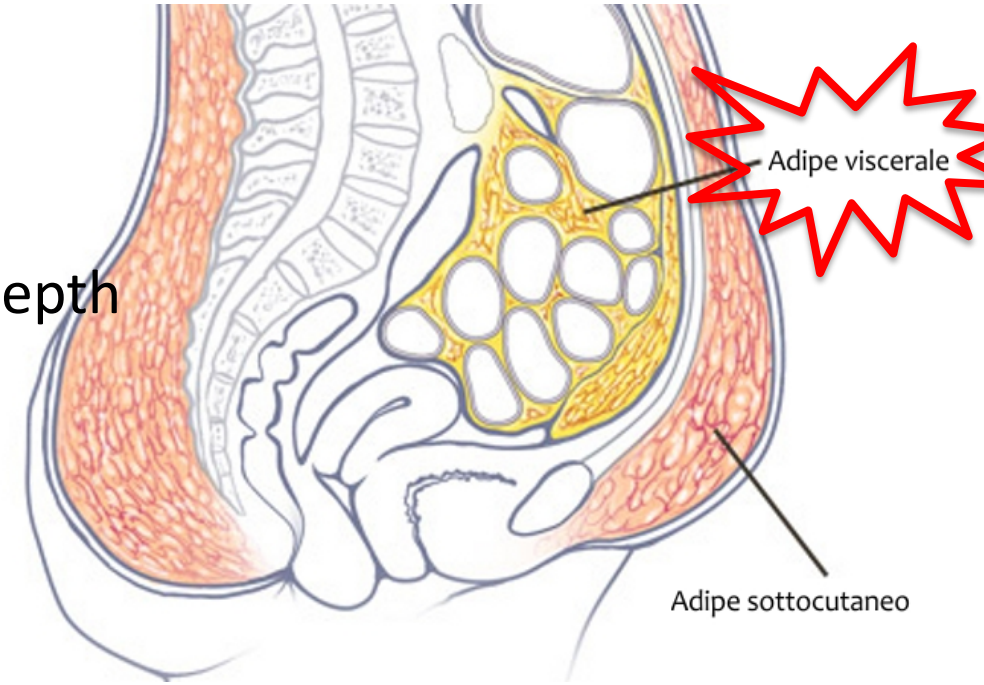
AJOG 2013

Preeclampsia and Preterm Birth Associated With Visceral Adiposity in Early Pregnancy

Joel G. Ray, Leanne R. De Souza, Alison L. Park, Philip W. Connelly, Emmanuel Bujold, Howard Berger

- ~~BMI~~
- Bioimpedenziometria
- VAT visceral adipose tissue depth





J Obstet Gynaecol Can 2016

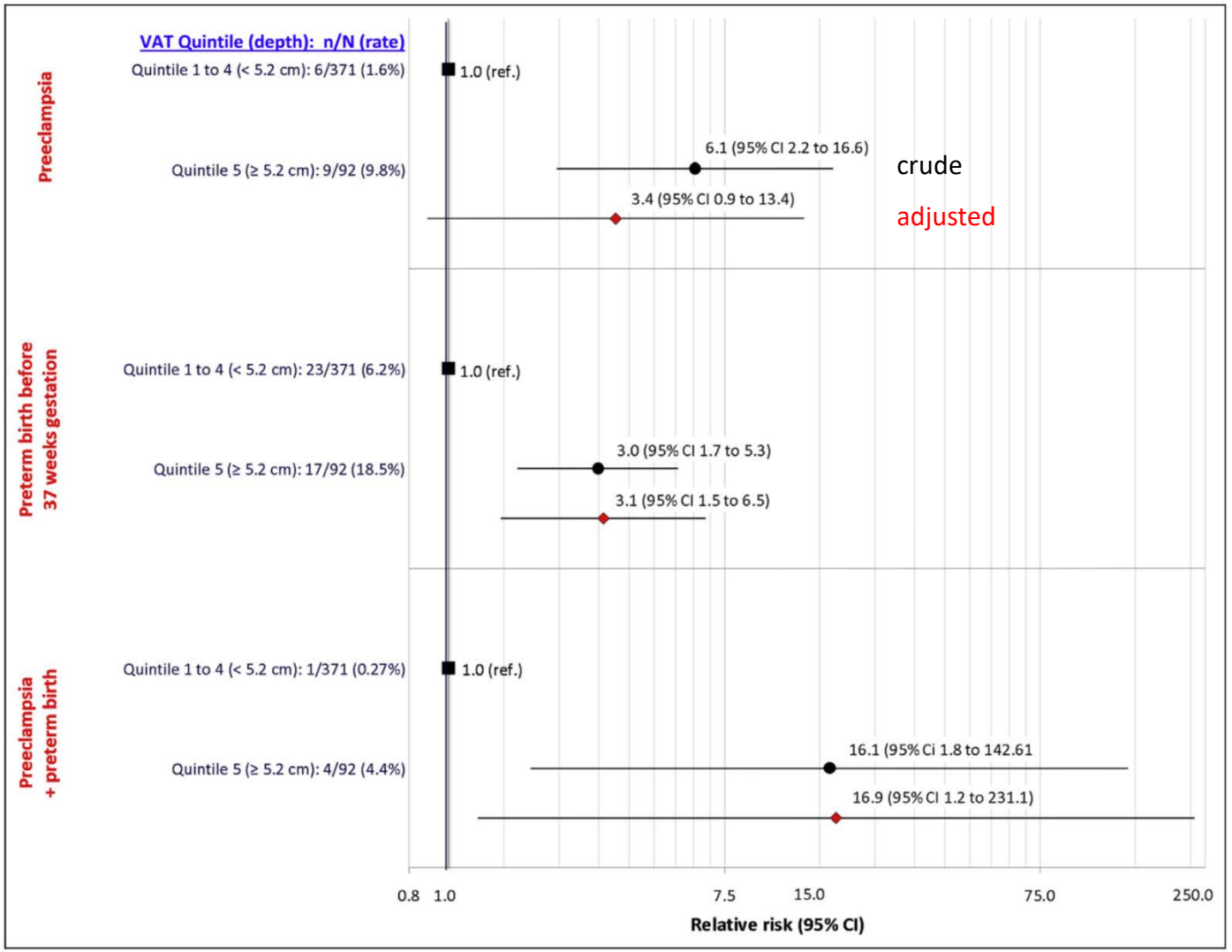
Preeclampsia and Preterm Birth Associated With Visceral Adiposity in Early Pregnancy

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J Obstet Gynaecol Can 2016

463 gravidanze

VAT= visceral adipose tissue depth



Association between insulin resistance and preeclampsia in obese non-diabetic women receiving metformin

Obstetric Medicine
2017

Jyoti Balani[1], Steve Hyer[1], Argyro Syngelaki[2], Ranjit Akolekar[3], Kypros H Nicolaides[2], Antoinette Johnson[4] and Hassan Shehata[4]

N=384

Trial doppio-cieco placebo-controllo sulla metformina da 12–18 settimane fino al parto in gravide non diabetiche con body mass index >35 kg/m^2 (MOP trial)

Comparison between outcome groups for biomarkers of insulin resistance at 15 and 28 weeks' gestation.

Marker	Metformin $n=196$	Placebo $n=188$	p Value	Preeclampsia $n=22$	No-preeclampsia $n=362$	p Value
At 15 weeks' gestation (enrolment)						
Fasting glucose mmol/L, Median (IQR)	4.4 (4.2–4.6)	4.5 (4.2–4.8)	0.052	4.5 (4.2–4.8)	4.4 (4.2–4.7)	0.331
Fasting insulin mIU/L Median (IQR)	18.4 (12.9–27.7)	18.1 (12.3–26.8)	0.584	21.0 (15.9–29.7)	18.1 (12.3–27.1)	0.170
HOMA-IR Median (IQR)	3.8 (2.4–5.4)	3.6 (2.4–5.5)	0.908	4.2 (3.2–6.0)	3.6 (2.3–5.4)	0.110
At 28 weeks' gestation						
Fasting glucose mmol/L Median (IQR)	4.4 (4.1–4.8)	4.4 (4.1–4.8)	0.804	4.5 (4.0–4.9)	4.4 (4.1–4.8)	0.990
Fasting insulin mIU/L Median (IQR)	19.7 (14.0–31.0)	22.9 (15.2–33.6)*	0.046	24.3 (15.3–39.7)	21.5 (14.6–32.0)	0.220
HOMA-IR Median (IQR)	3.9 (2.6–5.7)	4.6 (3.0–6.8)**	0.005	4.8 (3.4–8.5)	4.2 (2.7–6.0)	0.115

Association between insulin resistance and preeclampsia in obese non-diabetic women receiving metformin

Jyoti Balani[1], Steve Hyer[1], Argyro Syngelaki[2], Ranjit Akolekar[3], Kypros H Nicolaides[2], Antoinette Johnson[4] and Hassan Shehata[4]

Obstetric Medicine 2017

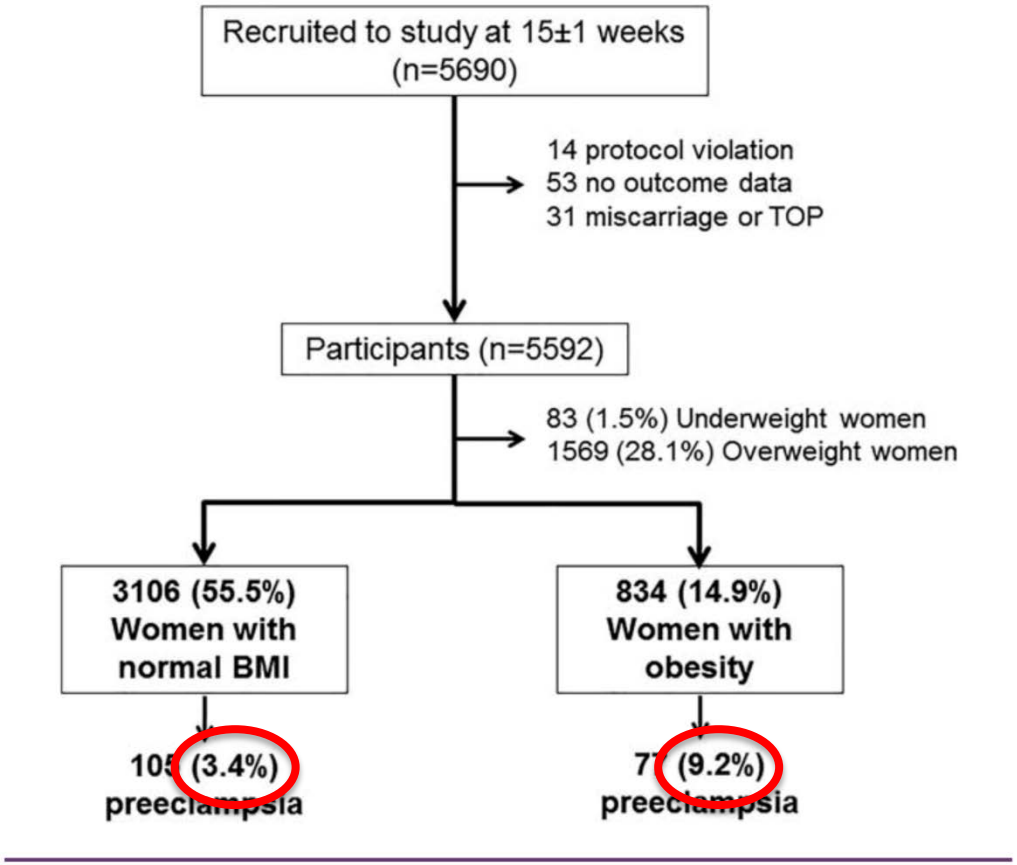
Preeclampsia vs No Preeclampsia

È improbabile che la ridotta incidenza di PE in donne non diabetiche obese trattate con metformina sia legata alle modificazioni dell'insulino-resistenza

Original Article
EPIDEMIOLOGY/GENETICS

Clinical and Biochemical Factors Associated with Preeclampsia in Women with Obesity

Matias C. Vieira[1], Lucilla Poston[1], Elaine Fyfe[2], Alexandra Gillett[1], Louise C. Kenny[3], Claire T. Roberts[4], Philip N. Baker[5], Jenny E. Myers[6], James J. Walker[7], Lesley M. McCowan[2], Robyn A. North[1], and Dharmintra Pasupathy[1] on behalf of the SCOPE Consortium



Obesity 2017

Original Article
EPIDEMIOLOGY/GENETICS

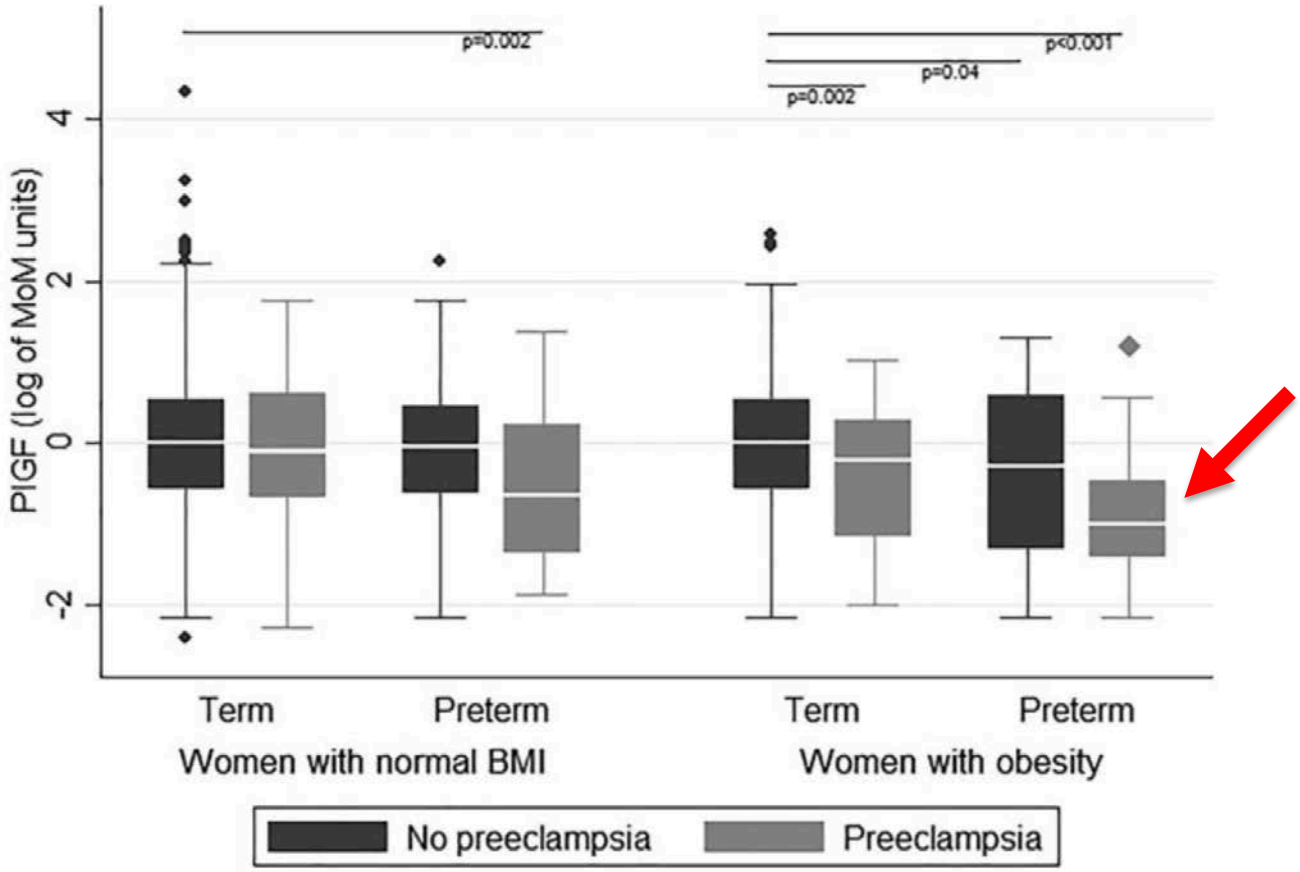
Fattori di rischio per PE in accordo con il BMI

Clinical and Biochemical Factors Associated with Preeclampsia in Women with Obesity

Matias C. Vieira[1], Lucilla Poston[1], Elaine Fyfe[2], Alexandra Gillett[1], Louise C. Kenny[3], Claire T. Roberts[4], Philip N. Baker[5], Jenny E. Myers[6], James J. Walker[7], Lesley M. McCowan[2], Robyn A. North[1], and Dharmintra Pasupathy[1] on behalf of the SCOPE Consortium

	Univariate OR (95% CI)	*P*	Multivariate[a] OR (95% CI)	*P*
Women with normal BMI				
FH of preeclampsia or GH	1.96 (1.22–3.16)	0.005	1.76 (1.08–2.86)	0.02
High fruit intake	0.56 (0.37–0.86)	0.008	0.61 (0.40–0.95)	0.03
Maternal arm circumference	1.12 (1.03–1.23)	0.01	1.09 (0.99–1.19)	0.08
MAP[b]	1.48 (1.31–1.69)	<0.001	1.45 (1.27–1.66)	<0.001
Cystatin[c]	1.76 (1.04–2.98)	0.04	2.01 (1.16–3.48)	0.01
Endoglin[c]	1.65 (1.07–2.55)	0.02	1.79 (1.14–2.79)	0.01
Uterine artery RI[b]	1.40 (1.16–1.68)	<0.001	1.40 (1.16–1.69)	0.001
Women with obesity				
FH of preeclampsia or GH	1.86 (1.09–3.18)	0.02	1.61 (0.90–2.86)	0.11
FH of thrombotic disease	2.77 (1.59–4.84)	<0.001	2.48 (1.38–4.45)	0.003
Maternal BMI	1.06 (1.02–1.11)	0.007	1.03 (0.94–1.14)	0.48
Maternal hip	1.03 (1.00–1.05)	0.02	1.01 (0.97–1.05)	0.71
Adiponectin[c]	1.72 (1.04–2.86)	0.03	1.48 (0.86–2.55)	0.16
HDL cholesterol[c]	3.21 (1.14–9.04)	0.03	1.84 (0.59–5.74)	0.29
ANP[c]	1.25 (1.00–1.57)	0.05	0.98 (0.77–1.26)	0.90
BNP[c]	1.54 (1.04–2.29)	0.03	1.41 (0.92–2.16)	0.11
PIGF[c]	1.82 (1.37–2.42)	<0.001	1.77 (1.29–2.42)	<0.001
Uterine artery RI[b]	1.39 (1.11–1.73)	0.004	1.28 (1.01–1.61)	0.04

The SCOPE study



Bassi livelli di PlGF sono un predittore per PE solo in donne **obese** con **Early PE**!

Vieira. Obesity 2017

Original Article
EPIDEMIOLOGY/GENETICS

Clinical and Biochemical Factors Associated with Preeclampsia in Women with Obesity

Matias C. Vieira[1], Lucilla Poston[1], Elaine Fyfe[2], Alexandra Gillett[1], Louise C. Kenny[3], Claire T. Roberts[4], Philip N. Baker[5], Jenny E. Myers[6], James J. Walker[7], Lesley M. McCowan[2], Robyn A. North[1], and Dharmintra Pasupathy[1] on behalf of the SCOPE Consortium

Conclusioni:

- Donne obese e con BMI normale presentano differenti bio-marker clinici, biologici e fattori di rischio precoci per PE
- L'obesità deve essere considerata in maniera indipendente quando si elaborano algoritmi di predizione per la PE

Obesity 2017

...dalla nostra esperienza

CHIRURGIA BARIATRICA IN GRAVIDANZA: VALUTAZIONE DELL'ESITO OSTETRICO IN RELAZIONE AI DIVERSI APPROCCI CHIRURGICI

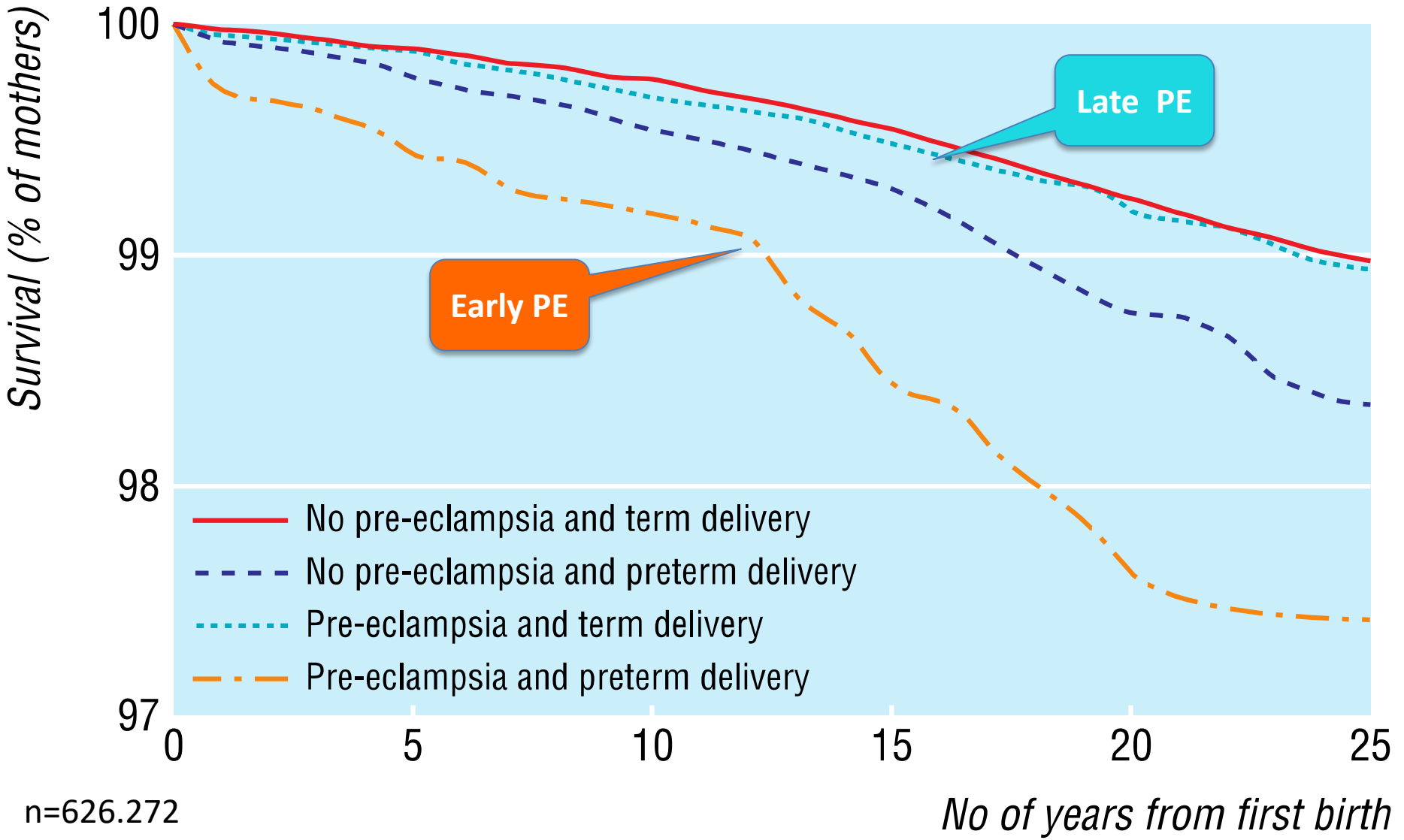
Confronto tra (n=27) gravidanze Pre-chirurgia e (n=97) gravidanze Post-chirurgia Bariatrica

COMPLICANZE MATERNE	Pre-chirurgia (n=27)	Post-chirurgia (n=97)
DIABETE GESTAZIONALE	7/22 31,8%	8/74 10,8%
DISTURBI IPERTENSIVI	4/22 18,2%	5/74 6,8%

…e il rischio cardiovascolare a lungo termine?

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)

Conclusioni

- Aumentato rischio di PE nel diabete tipo I e II, GDM e obesità
- Importanza
  - danno microvascolare (DM I e II)
  - ipertensione preesistente
  - scarso controllo glicemico
- Importanza selettiva
  - insulino-resistenza
    - No early PE
    - Si late PE

IL DIABETE IN GRAVIDANZA

Chieti, 19-20 aprile 2018

DALLA RICERCA ALLA PRATICA CLINICA



L'ipertensione e la preeclampsia nella gravida obesa e/o con diabete

Gemelli

sergio.ferrazzani@unicatt.it

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

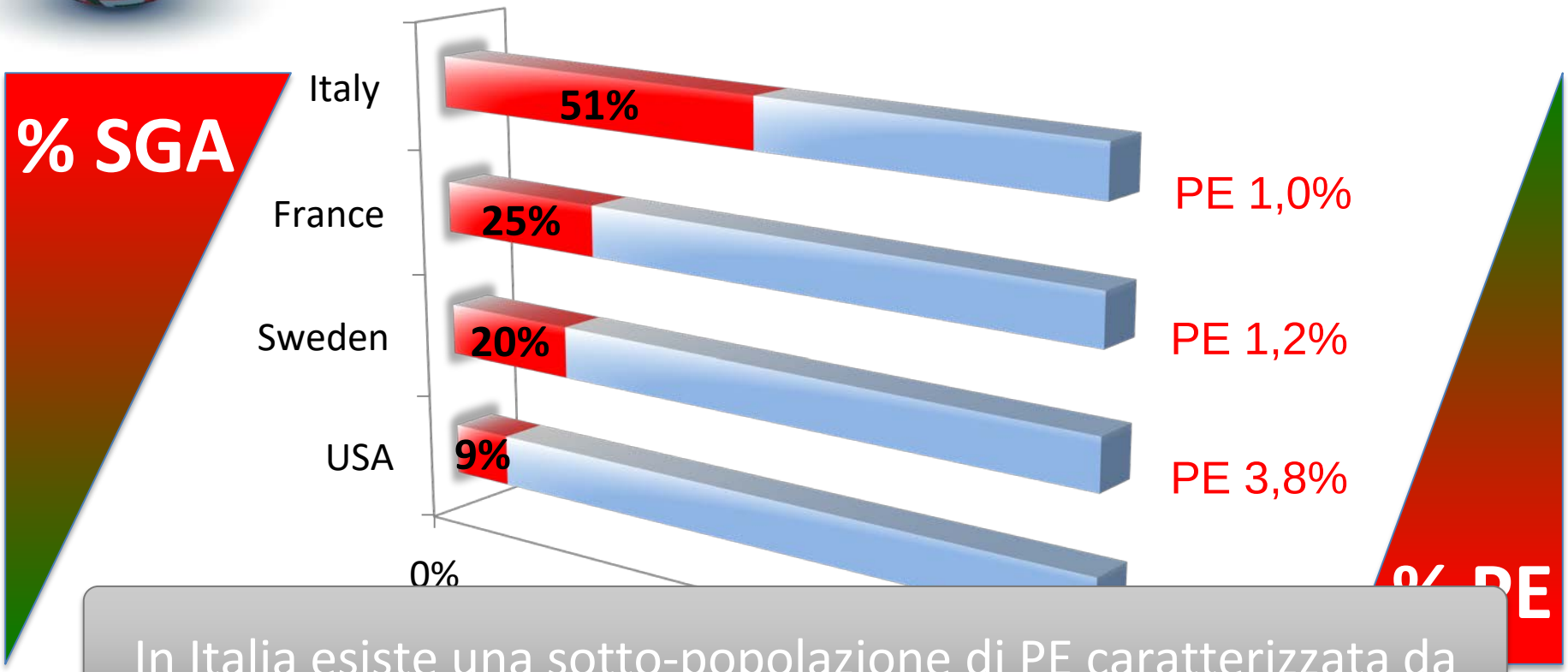
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Yusuf 2004, Umans-Eckenausen 2002, Atsma 2006

…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

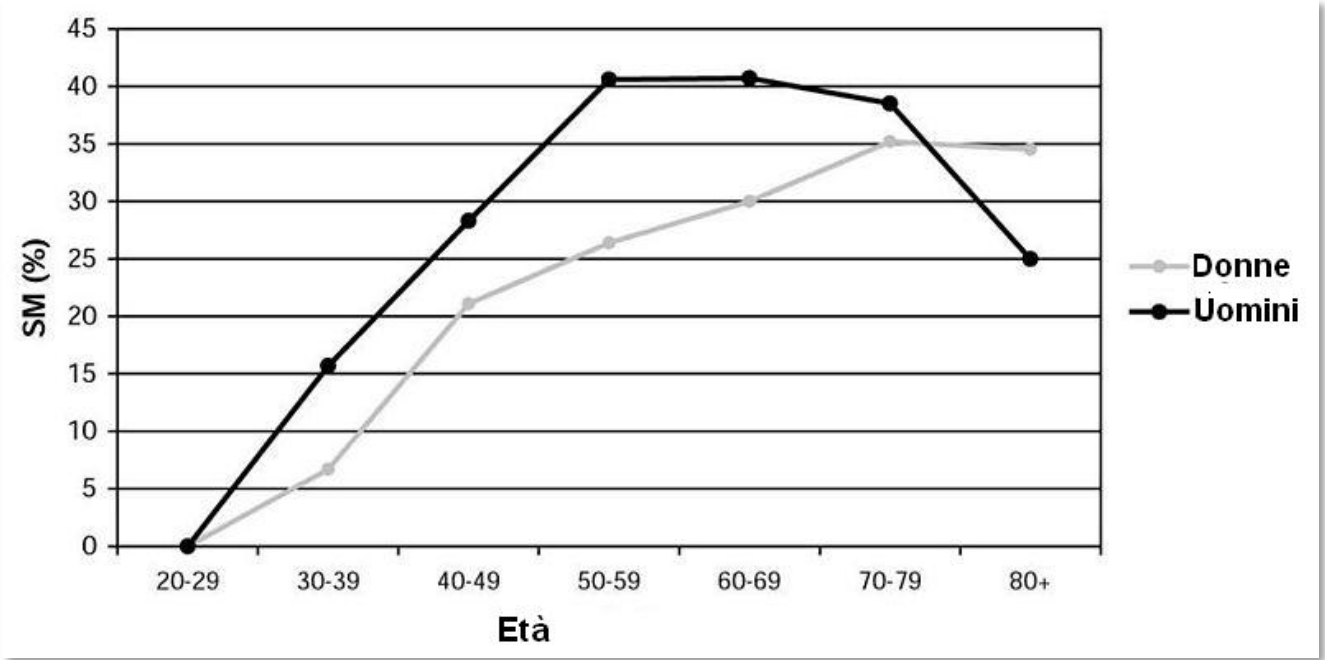
Ferrazzani Early Hum Dev 2011

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

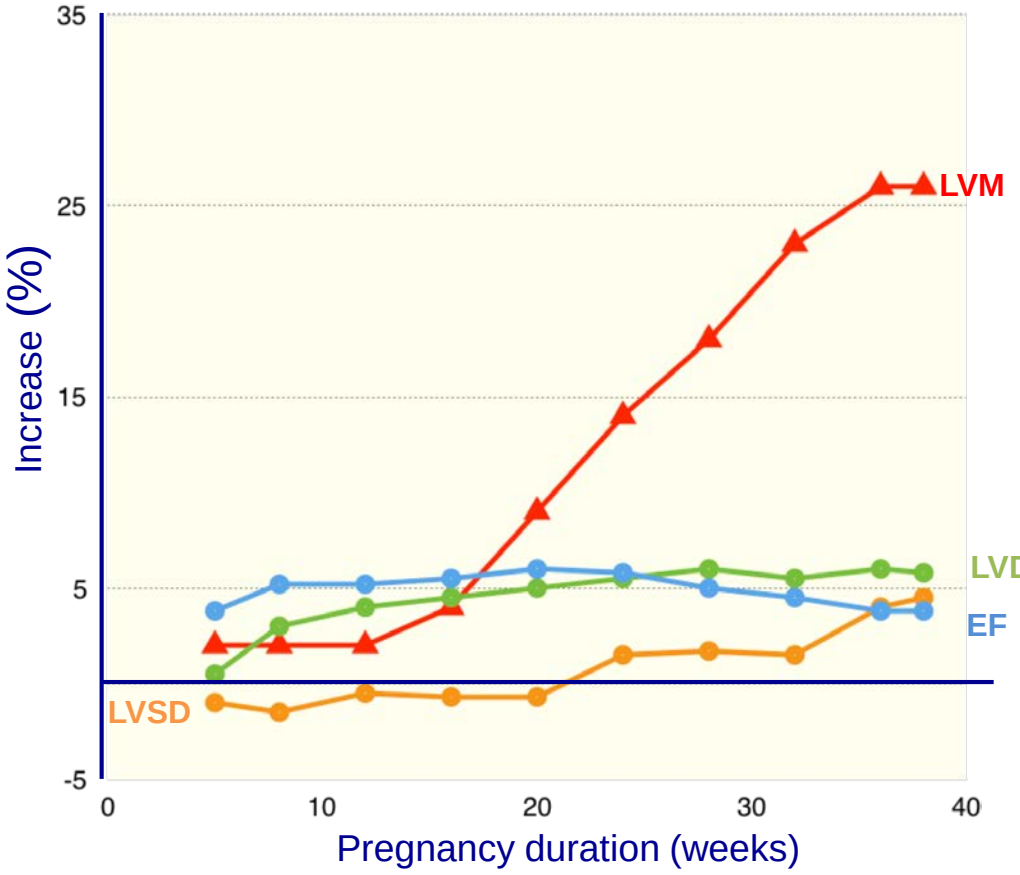
D Berks,[a] M Hoedjes,[b] H Raat,[b] JJ Duvekot,[a] EAP Steegers,[a] JDF Habbema[b]

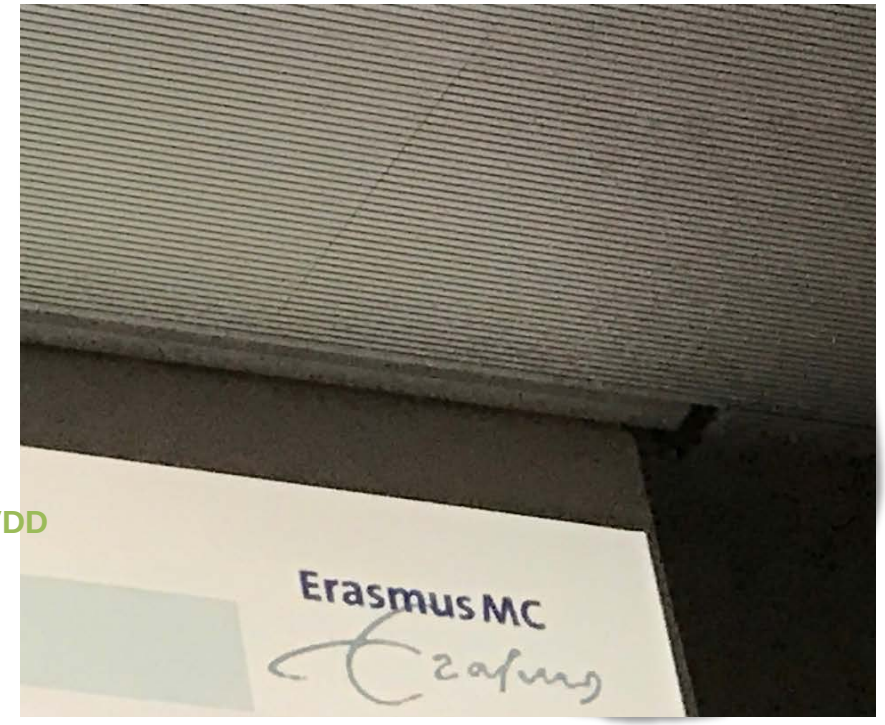
Conclusions Cardiovascular risk factors do not fully explain the risk of cardiovascu[illegible] after pre-eclampsia. The gap between

- 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%



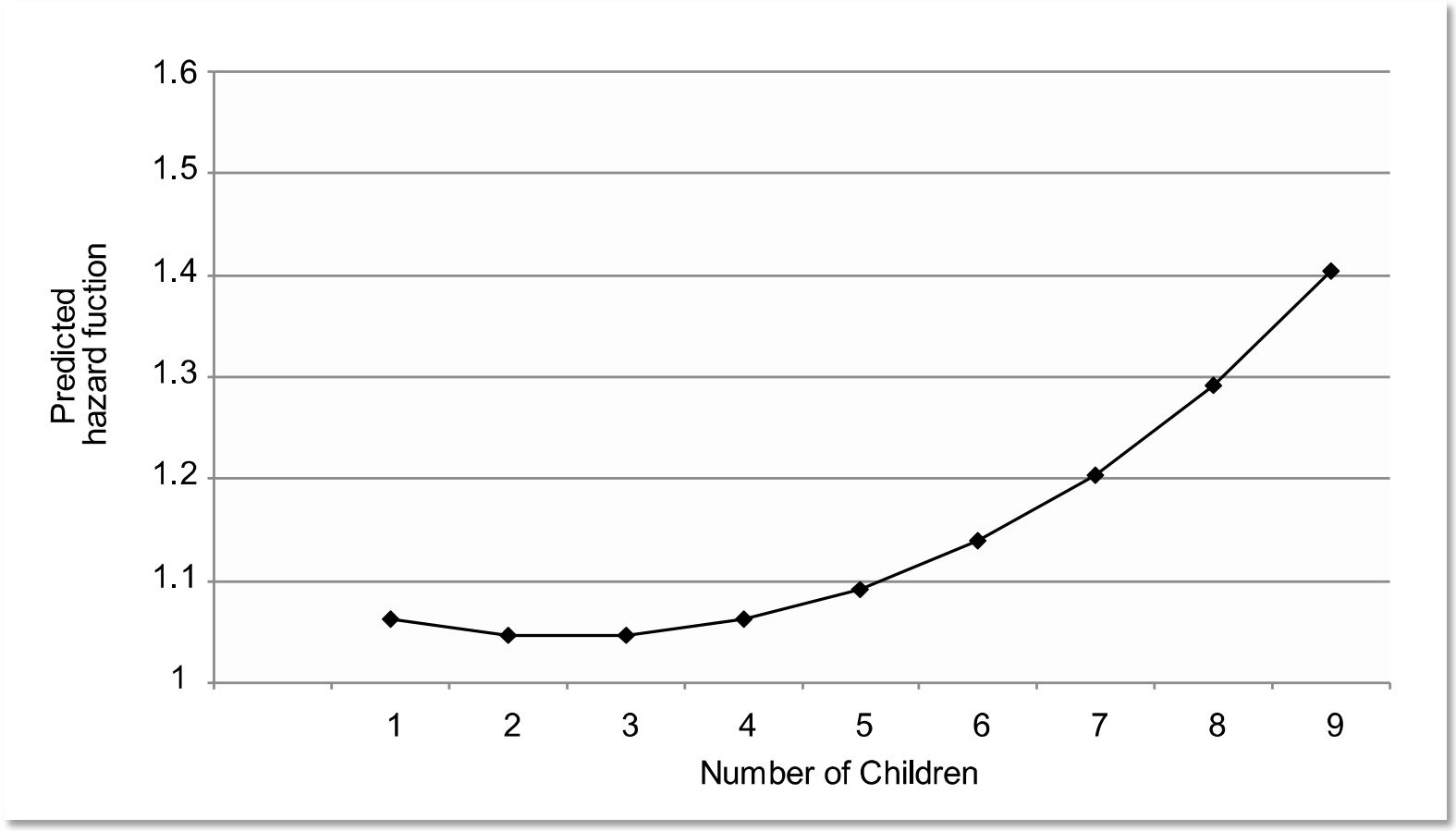
Le origini delle complicanze della gravidanza

- 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

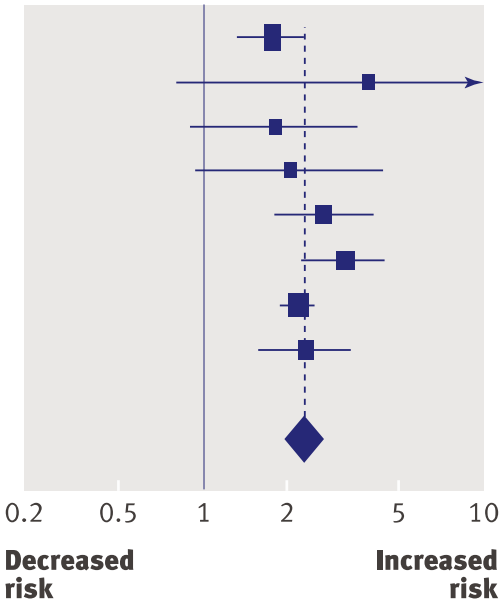
- Certi alleli che sono favoriti in conseguenza di un effetto benefico precoce (fertilità e crescita della prole) presentano anche effetti deleteri tardivi

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)

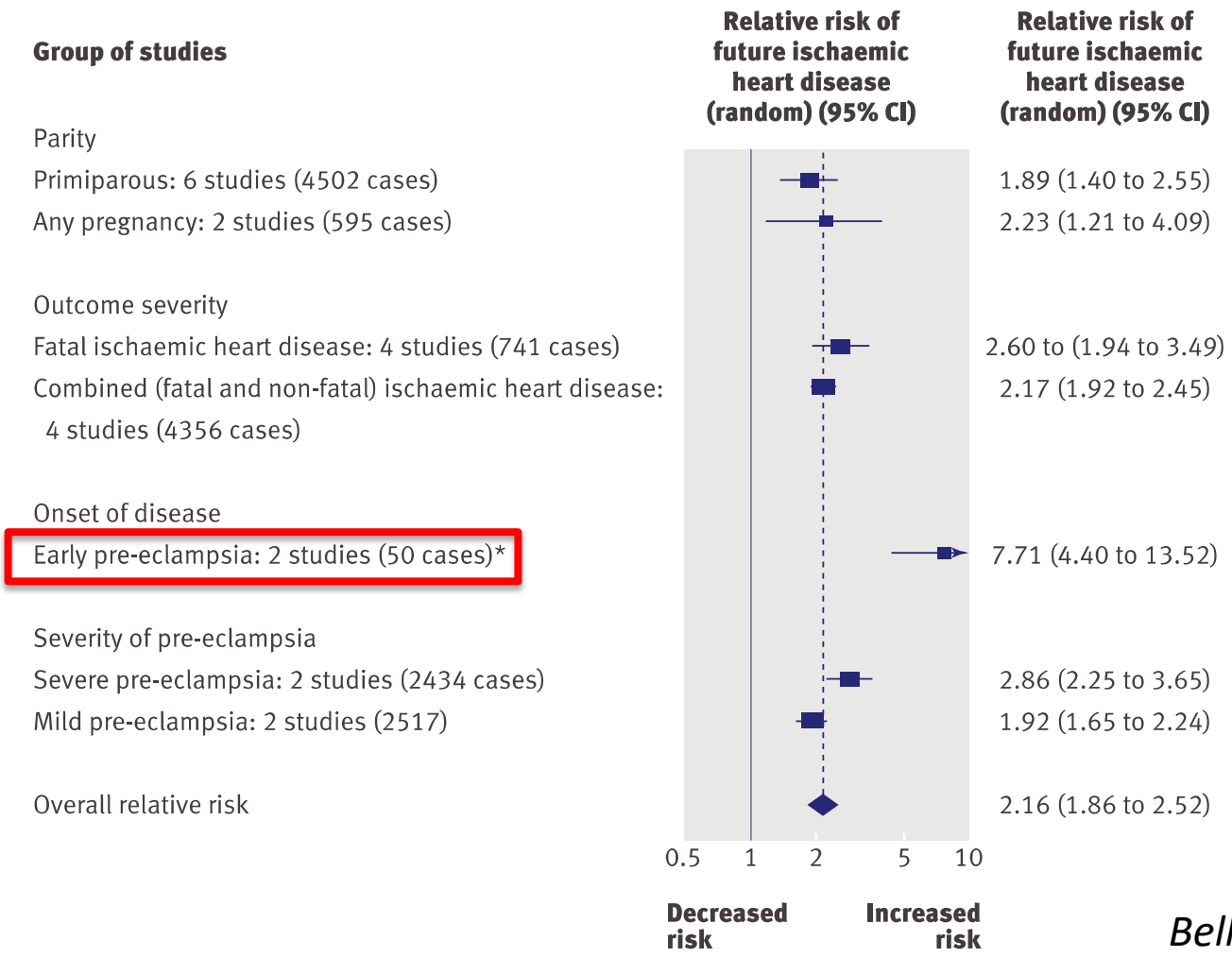
Test for heterogeneity: χ^2=9.60, df=7, P=0.21, I^2=27.1%

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



Bellamy 2007

Relazione con la severità della patologia?



Bellamy 2007

Early PE

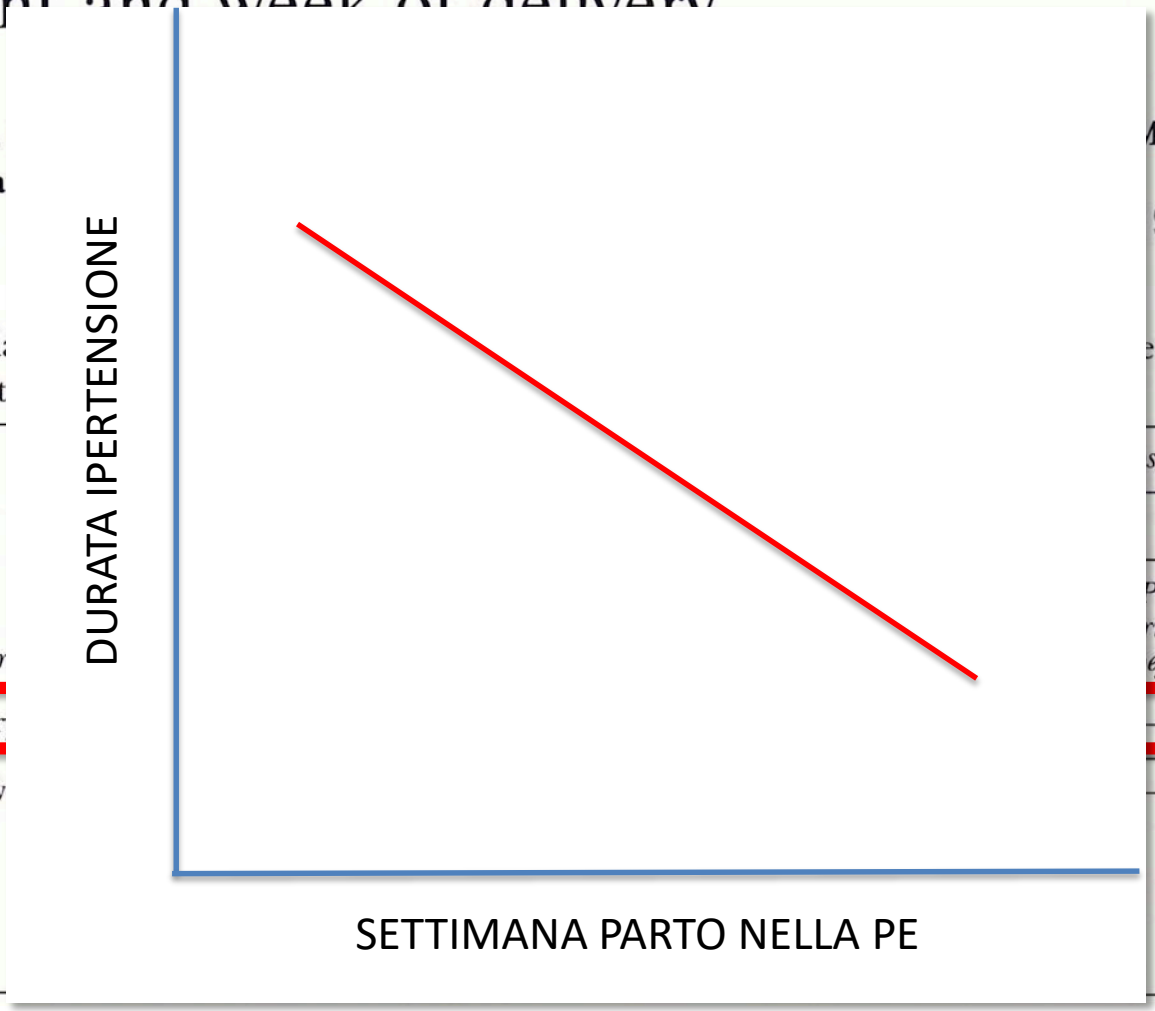
e-PE preclinica	e-PE manifesta	anni dopo la e-PE
Rimodellamento concentrico e ipertrofia concentrica LV	Danno sub-endocardico precoce?! Deficit di contrattilità Lavoro cardiaco al limite della propria riserva	Rischio più elevato di ipertensione cronica, scompenso cardiaco e cardiopatia ischemica rispetto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



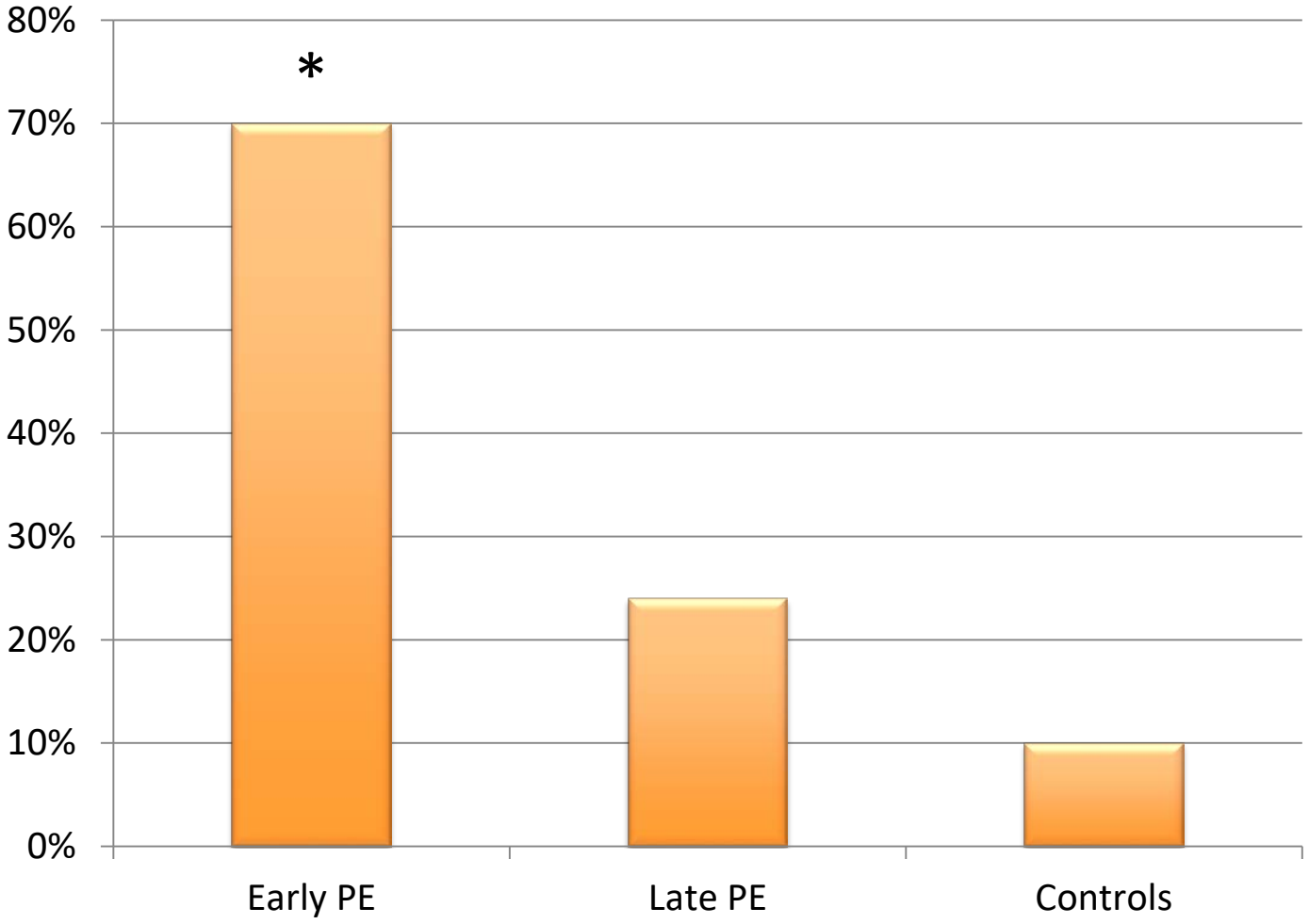
Correl
gestational hypert

tween

sia

Clinical featur		Multiparas	
		Partial correlation coefficient	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



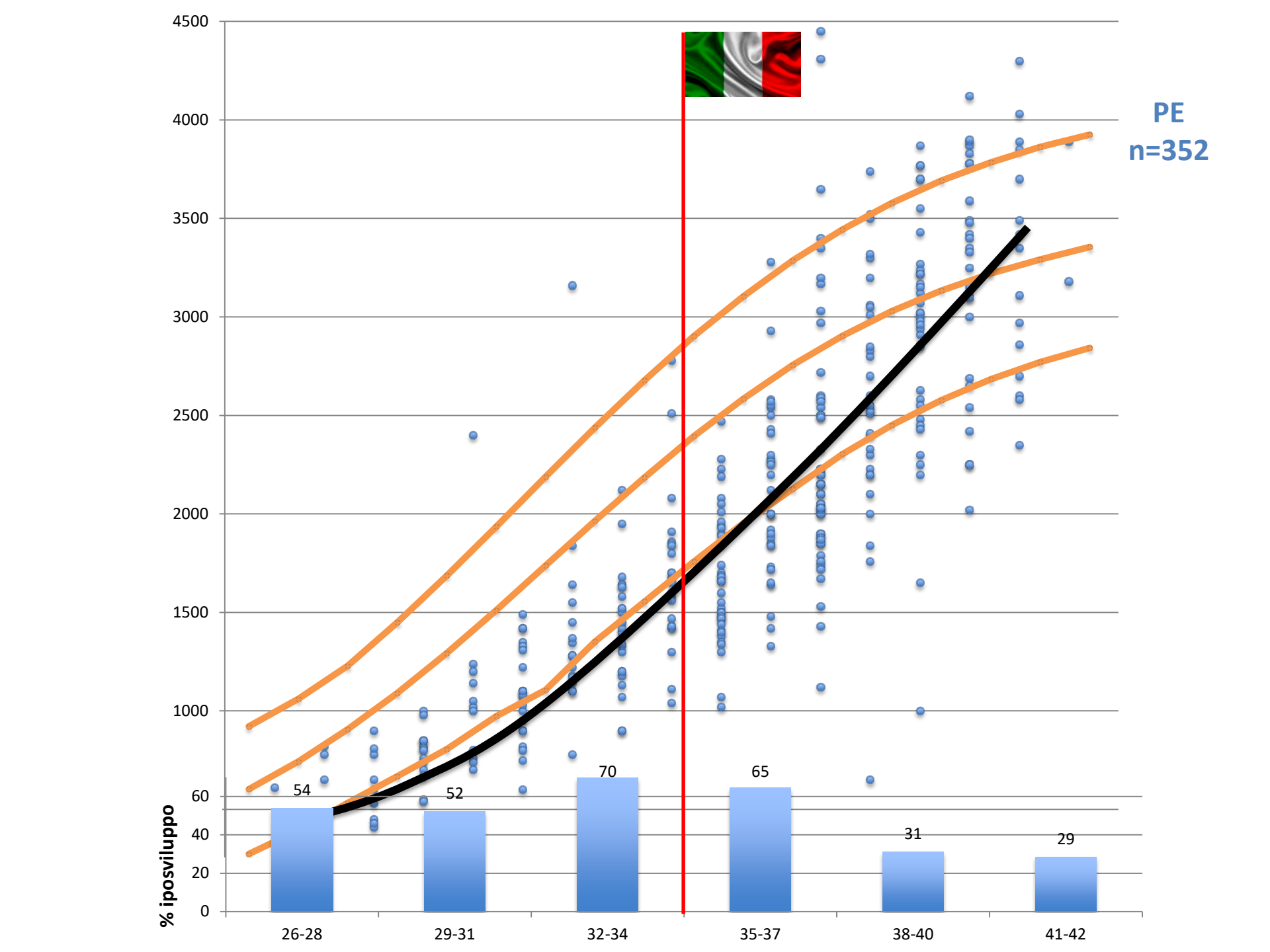
*p<0.05
vs Late PE
e Controls

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

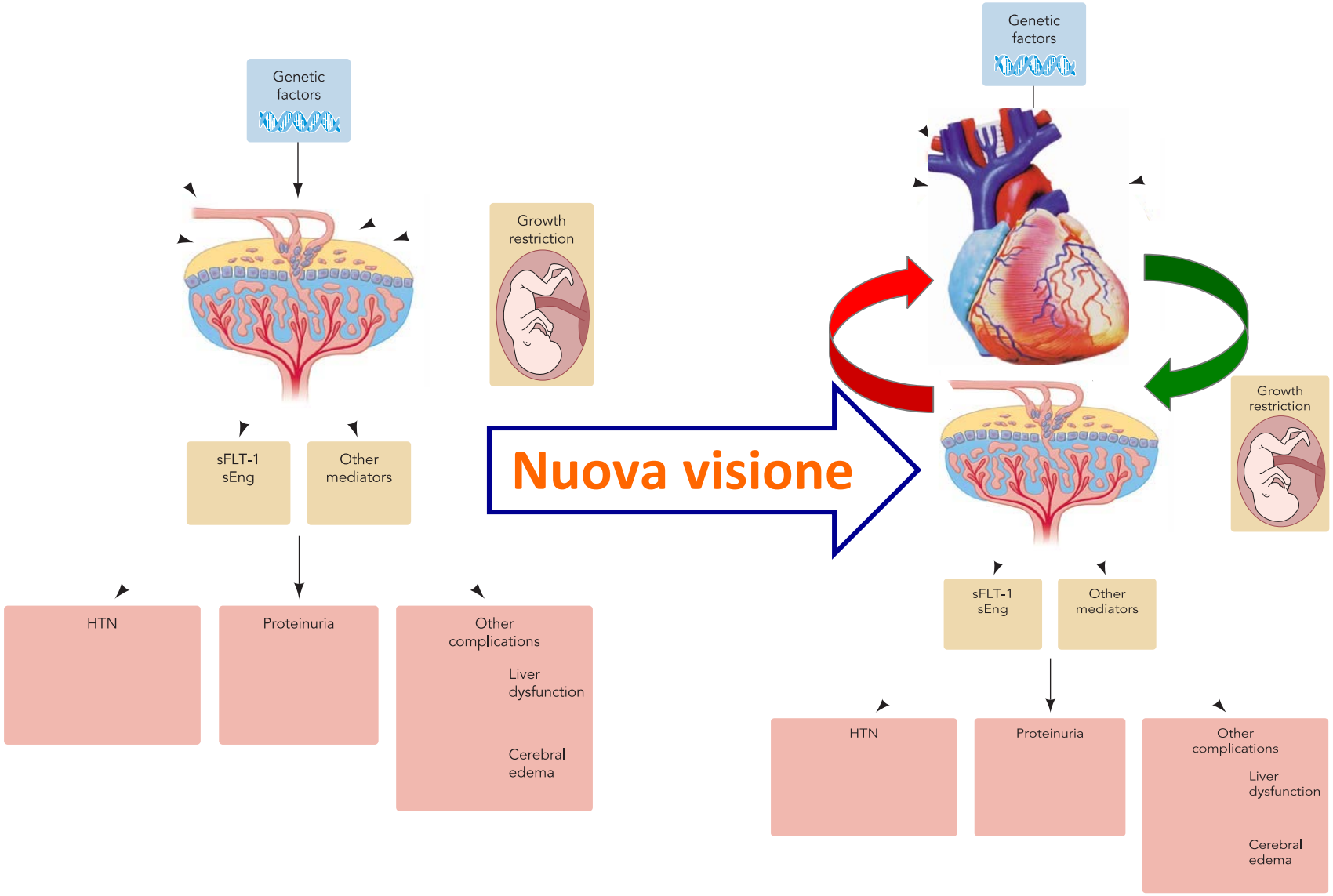
- PE precoce e tardiva
- PE placentare e materna

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?



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

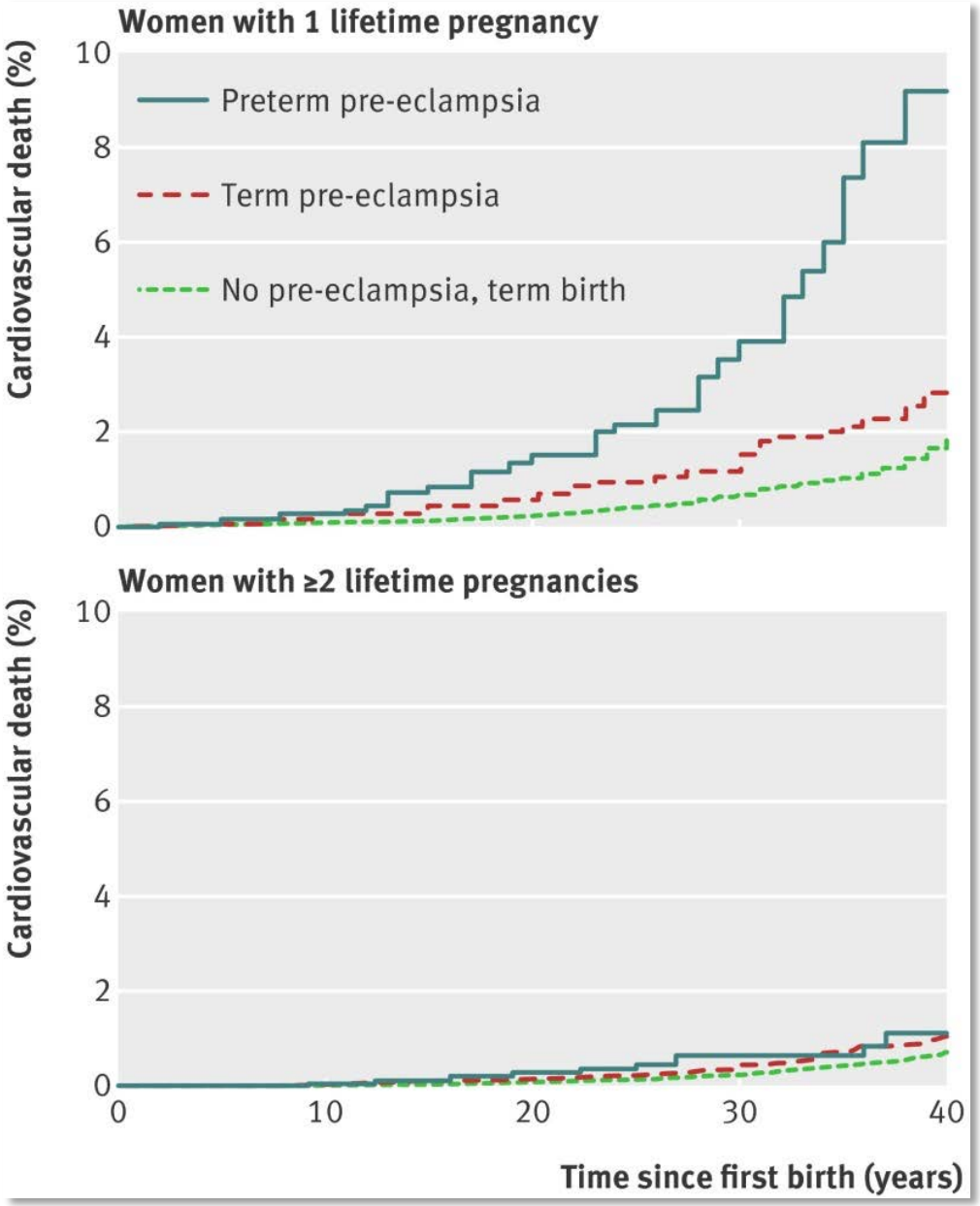
Cardiovascular mortality after pre-eclampsia in one child mothers: prospective, population based cohort study

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

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 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

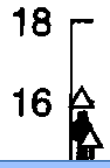


Table 1. Comparison of demographic features and biochemical factors which might influence insulin sensitivity between women with

grou

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

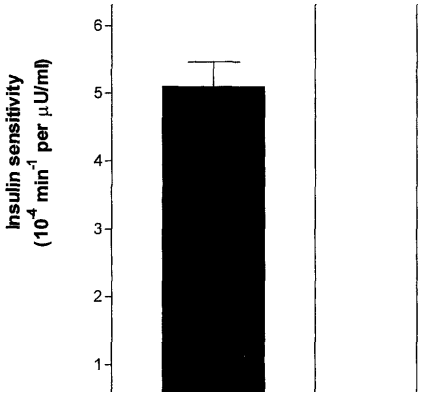
Lo studio, con la tecnica del minimal model, depone per **non** insulino-resistenza nella PE

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



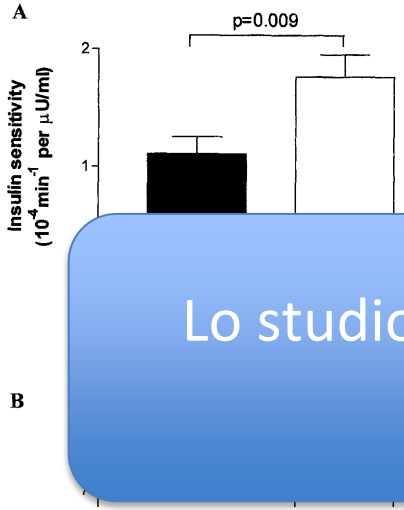
tance in Preeclampsia

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



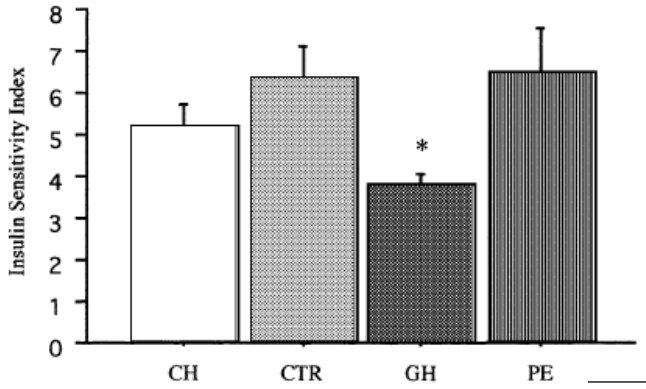
Lo studio, con la tecnica del minimal model, depone per ⬆ insulino-resistenza nella PE

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

Diabete e Ipertensione in gravidanza…

…*quali similitudini*?

Association between Gestational Diabetes and Pregnancy-induced Hypertension

Chris L. Bryson[1,2], George N. Ioannou[1,3], Stephen J. Rulyak[3], and Cathy Critchlow[4]

[1] VA Puget Sound Health Services Research and Development, Seattle, WA.
[2] Division of General Internal Medicine, Department of Medicine, University of Washington, Seattle, WA.
[3] Division of Gastroenterology, Department of Medicine, University of Washington, Seattle, WA.
[4] Department of Epidemiology, University of Washington School of Public Health, Seattle, WA.

TABLE 2. Risk of pregnancy-induced hypertension associated with gestational diabetes, Washington State, 1992–1998

Group	No.	Prevalence of gestational diabetes (%)	Crude OR†	95% CI†	Adjusted OR‡	95% CI
Eclampsia	154	3.9	1.47	0.65, 3.34	1.27	0.52, 3.15
Severe preeclampsia	1,180	4.5	1.71**	1.29, 2.26	1.53*	1.13, 2.06
Mild preeclampsia	5,468	4.4	1.69**	1.47, 1.95	1.50**	1.28, 1.76
Gestational hypertension	8,943	4.4	1.69**	1.51, 1.90	1.40**	1.23, 1.58
Controls	47,237	2.7	1		1	

* $p < 0.01$; ** $p < 0.001$.
† OR, odds ratio; CI, confidence interval
‡ Adjusted for age, ethnicity, body mass index, parity, and adequacy of prenatal care.

Hypertension Complicating Diabetic Pregnancies: Pathophysiology, Management, and Controversies

Shannon D. Sullivan, MD, PhD;[1] Jason G. Umans, MD, PhD;[2,3]
Robert Ratner, MD[2,3]

GDM **<20%** PE

- *insulino resistenza*
- *BMI*

The association of circulating angiogenic factors and HbA1c with the risk of preeclampsia in women with preexisting diabetes

Allison L. Cohen, Julia B. Wenger, Tamarra James-Todd, Brooke M. Lamparello, Elizabeth Halprin, Shanti Serdy, Shuling Fan, Gary L. Horowitz, Kee-Hak Lim, Sarosh Rana, Tamara C. Takoudes, Jennifer A. Wyckoff, Ravi Thadhani, S. Ananth Karumanchi & Florence M. Brown



↑ sFlt1, sFlt1/PlGF ratio between 27 and 34 weeks

↓ PlGF in the third trimester

↑ HbA1c at their first prenatal visit (≥6.5%)

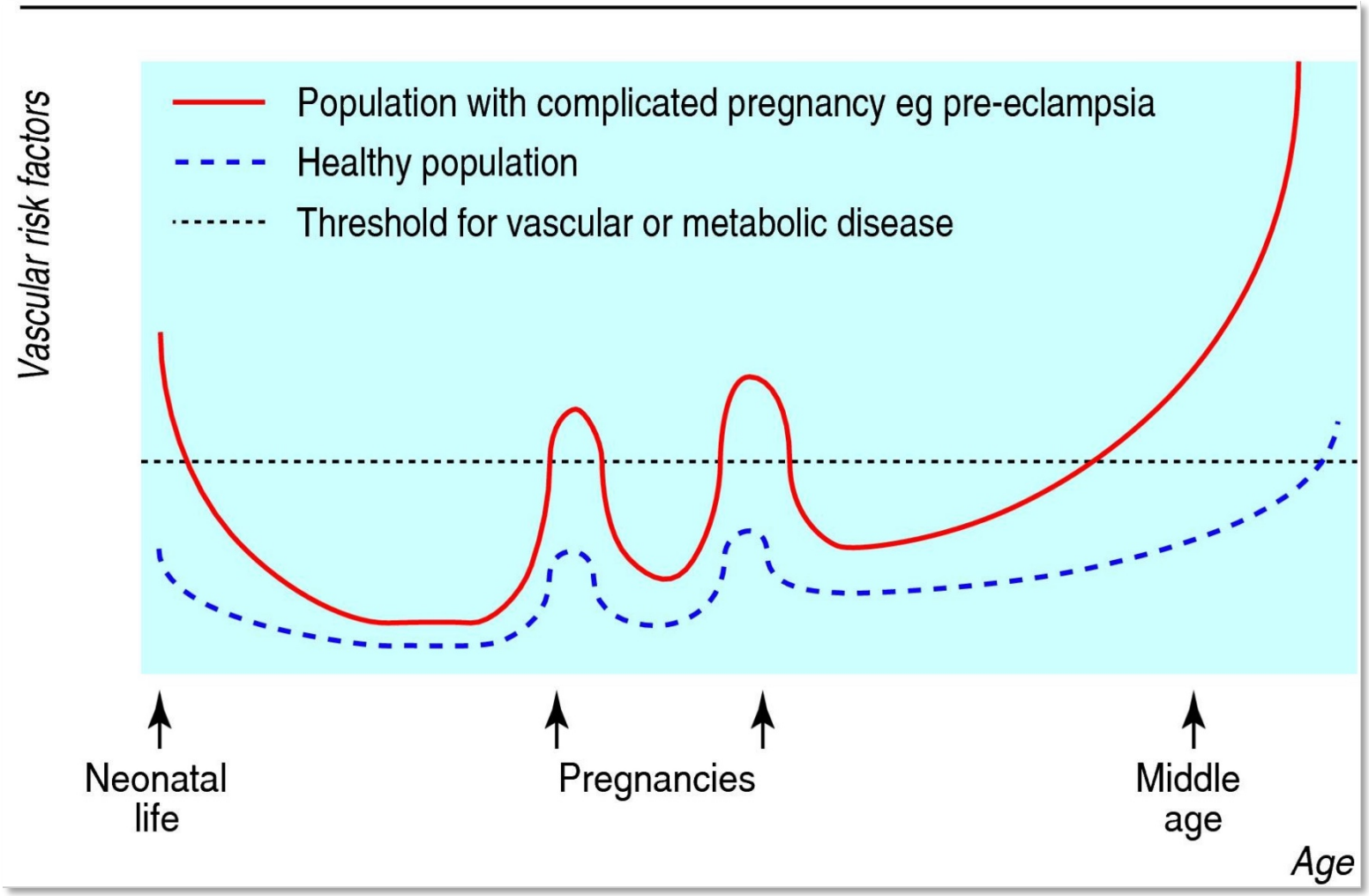
↑ Rates of Retinopathy

- 74% DM type 1
- 26% DM type 2

12% prevalence of PE

23% prevalence of GH

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

Early PE

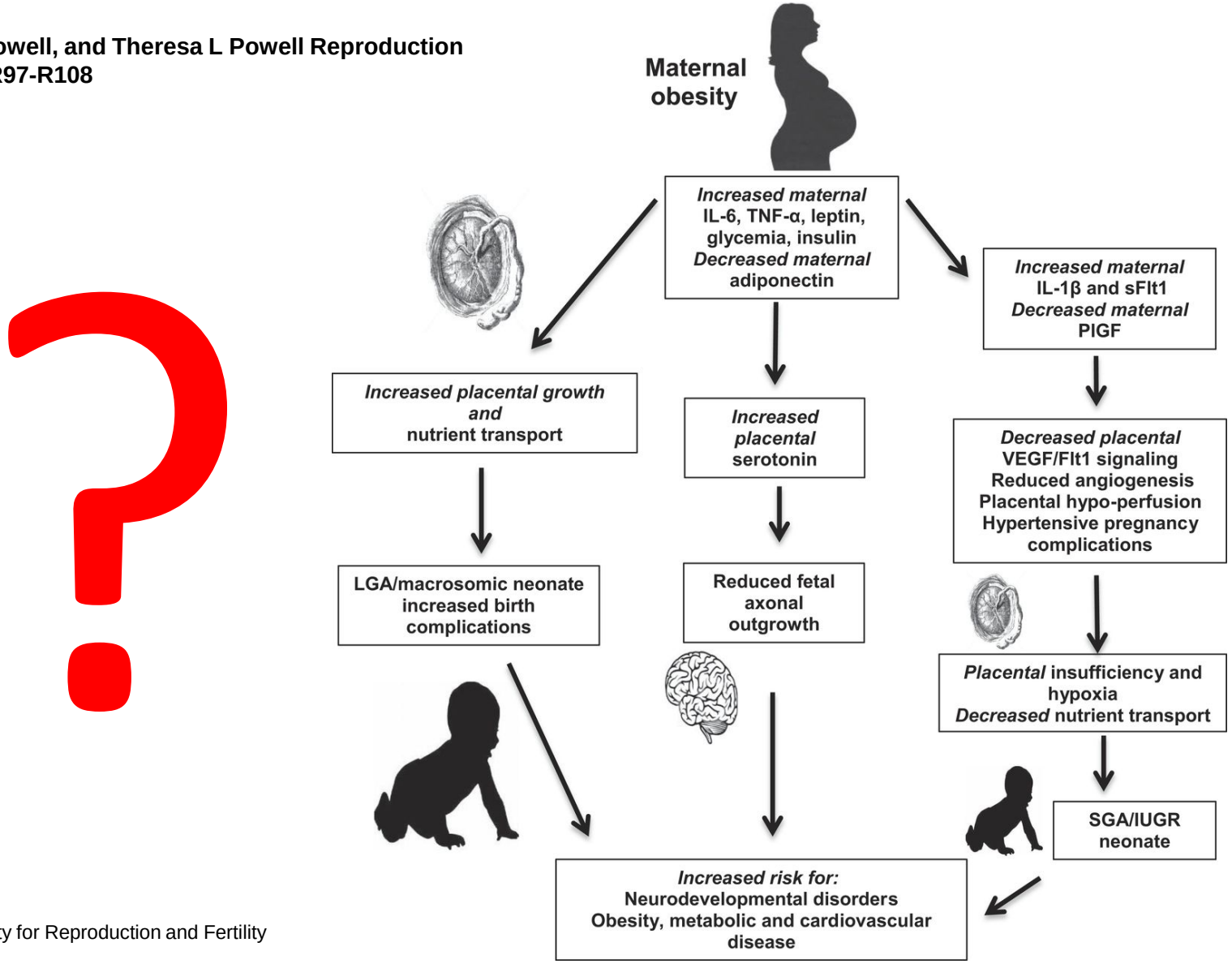
- Correlazione negativa tra i valori di insulinemia ed età materna.
- Assenza di correlazione con il BMI pre-gravidico

Late PE

- Nessuna correlazione tra i valori di insulinemia ed età materna o BMI.
- BMI > rispetto a **Early PE** e **controlli**

Effects of maternal obesity on placental function and fetal development

Kristy R Howell, and Theresa L Powell Reproduction 2017;153:R97-R108



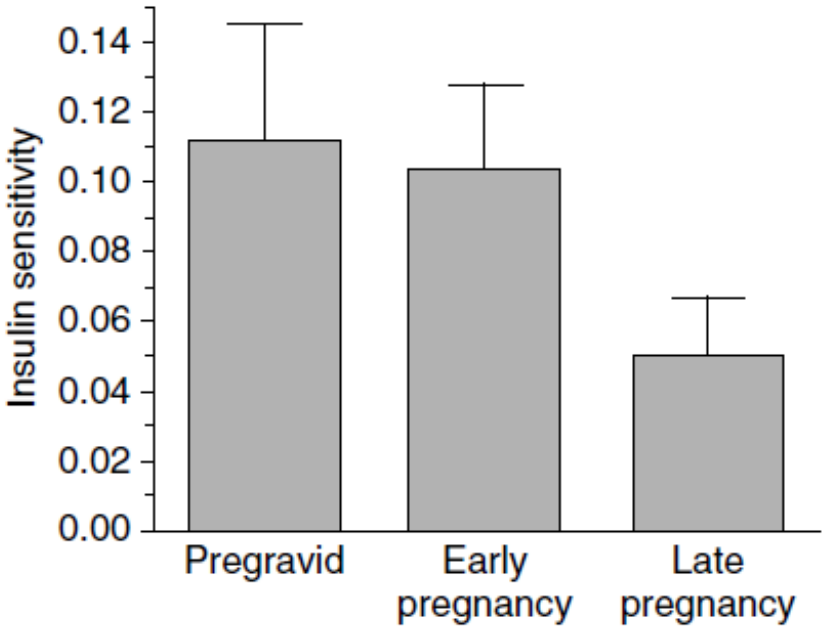
© 2017 Society for Reproduction and Fertility

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*