Ruolo della L-Arginina nella prevenzione e nel trattamento della preeclampsia

Dott.ssa Isabella Neri

Ricercatore Universitario Integrato

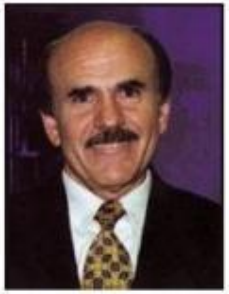
Dipartimento Materno-infantile

Azienda Ospedaliero-Universitaria Policlinico di Modena

The Nobel Prize in Physiology or Medicine 1998

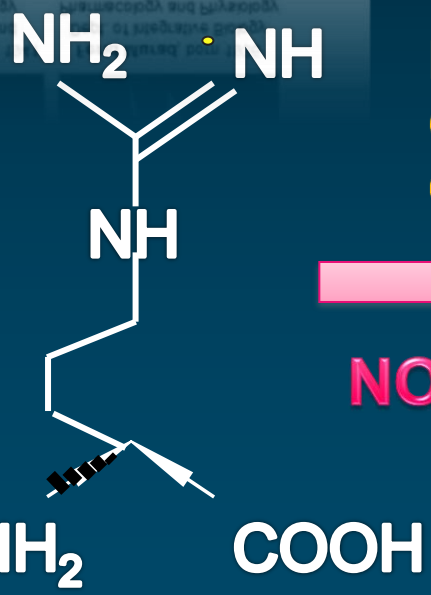
The Nobel Assembly at the Karolinska Institute in Stockholm, Sweden, has awarded the Nobel Prize in Physiology or Medicine for 1998 to **Robert F Furchgott, Louis J Ignarro** and **Ferid Murad** for their discoveries concerning "the nitric oxide as a signalling molecule in the cardiovascular system".

Robert F Furchgott, born 1916
Dept. of Pharmacology,
SUNY Health Science Center
New York



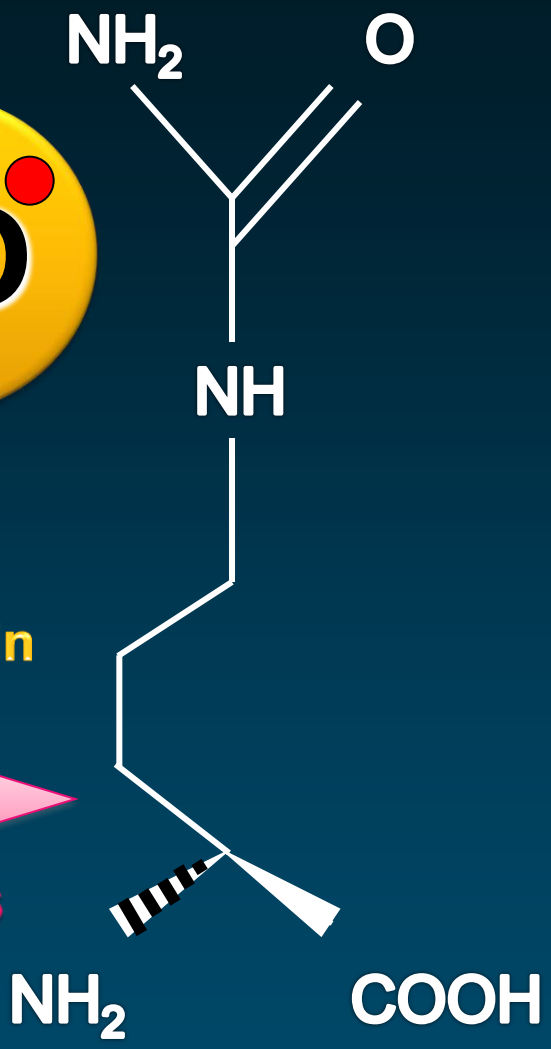
Louis J Ignarro, born 1941
Dept. of Molecular and
Medical Pharmacology
UCLA School of Medicine
Los Angeles

Ferid Murad, born 1936
Dept. of Integrative Biology
Pharmacology and Physiology
University of Texas Medical
School, Houston



NADPH
Ca-Calmodulin
O_2

NO synthases



L-ARGININE

L-CITRULLINE

In gravide con Preeclampsia e' stato dimostrato:

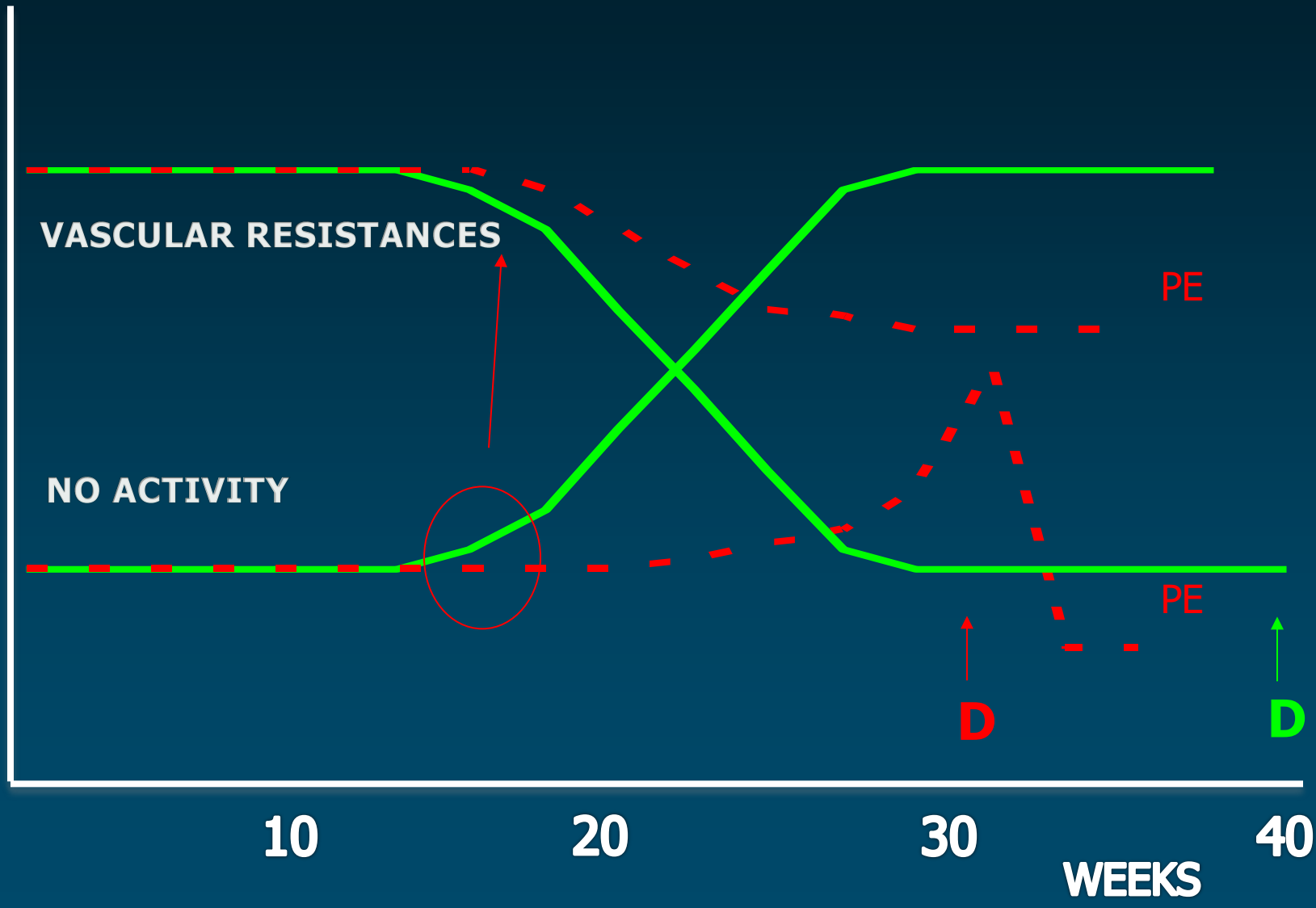
- **un alterato rilascio di NO da cellule del cordone ombelicale** (*Pinto 91*)

- **un alterata reattività vascolare con maggiore tendenza alla Vasocostrizione** (*Mc Carty 93*)

- **Livelli aumentati di ADMA (dimetil-arginina simmetrica), inibitore endogeno del NO** (*Fickling 93*)

- **Minor attività della NO sintasi a livello placentare** (*Morris 95*)

ATTIVITA' VASCOLARE E SVILUPPO DI PREECLAMPSIA



Donatori di ossido d'azoto

Effetto sulla flussimetria utero-placentare

Effetto sulla reattività piastrinica

Effetto sulla pressione arteriosa

Effetto acuto dei donatori di ossido d' azoto

- **Infusione di TRINITRINA e.v.**

  Riduce l' indice di pulsatilità della arterie uterine in gravide normotese (9-12 wk.) e a rischio di preeclampsia (24-26 wk.)

  Ramsay 1994

  Riduce la pulsatilità dell' arteria ombelicale in gravide affette da preeclampsia.

  Grunewald 1995

- **Infusione di ISOSORBIDE DINITRATO e.v.**

  Riduce la pressione arteriosa e l' indice di pulsatilità della arteria ombelicale in gravide affette da preeclampsia severa.

  Thaner 1996

- **Infusione di S-NITROSOGLUTATIONE e.v.**

  Riduce la pressione arteriosa, l' attivazione piastrinica e l' indice di pulsatilità delle arterie uterine in gravide affette da preeclampsia severa.

  Lees 1996

Effetto a lungo termine dei donatori di ossido d' azoto

- **TRINITRINA transdermica (5mg/16h da 10 wk.)**

  Donne a rischio di preeclampsia per alterazione della flussimetria uterina ed ombelicale: non riduce l'incidenza di PE e IUGR e non modifica gli indici di pulsatilità.

  Lees 1996

  Picciolo 2000

- **TRINITRINA transdermica (10mg/24h per 3 giorni)**

  Gravide affette da preeclampsia o IUGR: riduce la PA e gli indici di pulsatilità delle arterie uterine.

  Cacciatore 1998

- **TRINITRINA transdermica (10mg/16h per 2 settimane)**

  Riduce la pressione arteriosa (Holter-24h) in gravide affette da ipertensione gestazionale moderata

  Neri 2000

L'utilizzo dei donatori di NO…

…ha dei limiti…

Insorgenza di CEFALEA

È stata di mostrata una comorbidità tra emicrania e preeclampsia *(pattern comune?)*

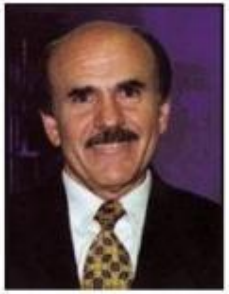
Possibile produzione di PEROSSINITRITI

È stato dimostrato che l'NO in eccesso produce perossinitriti in grado di determinare effetti opposti a quelli dell'NO stesso e quindi di peggiorare la funzionalità endoteliale.

The Nobel Prize in Physiology or Medicine 1998

The Nobel Assembly at the Karolinska Institute in Stockholm, Sweden, has awarded the Nobel Prize in Physiology or Medicine for 1998 to **Robert F Furchgott, Louis J Ignarro** and **Ferid Murad** for their discoveries concerning "the nitric oxide as a signalling molecule in the cardiovascular system".

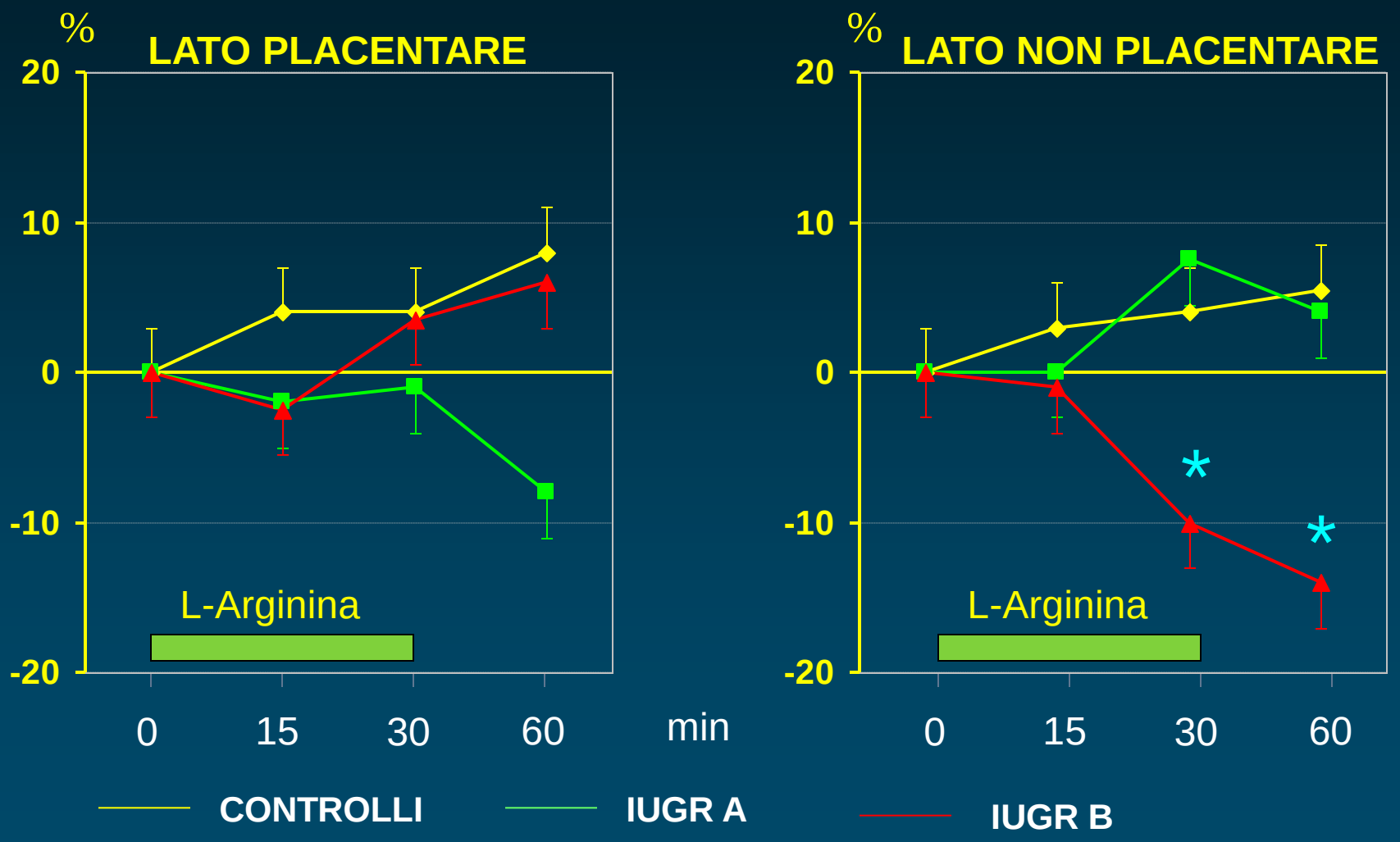
Robert F Furchgott, born 1916
Dept. of Pharmacology,
SUNY Health Science Center
New York



Louis J Ignarro, born 1941
Dept. of Molecular and
Medical Pharmacology
UCLA School of Medicine
Los Angeles

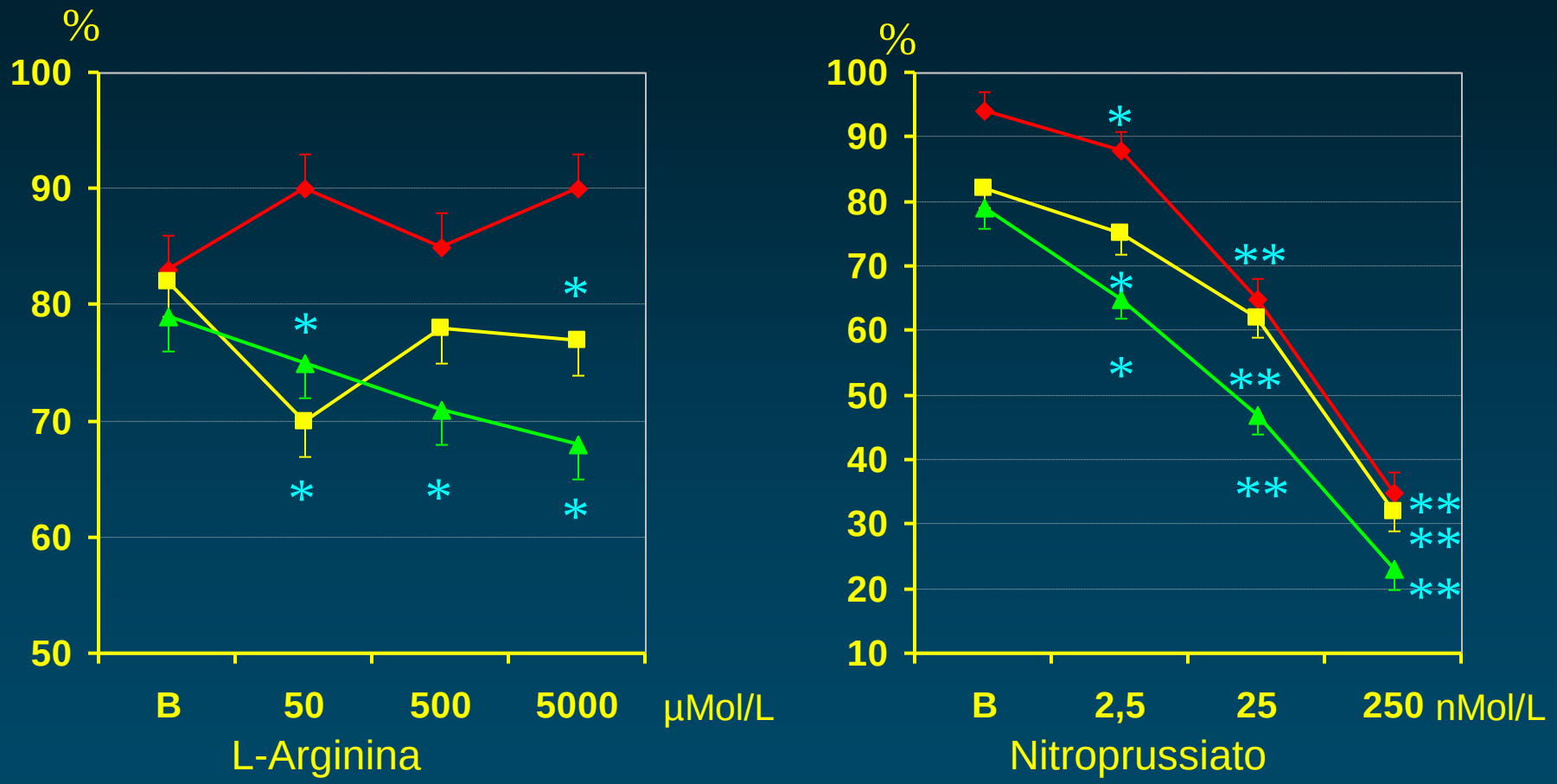
Ferid Murad, born 1936
Dept. of Integrative Biology
Pharmacology and Physiology
University of Texas Medical
School, Houston

EFFETTO *ACUTO* DI L-ARGININA
FLUSSIMETRIA UTERO-PLACENTARE



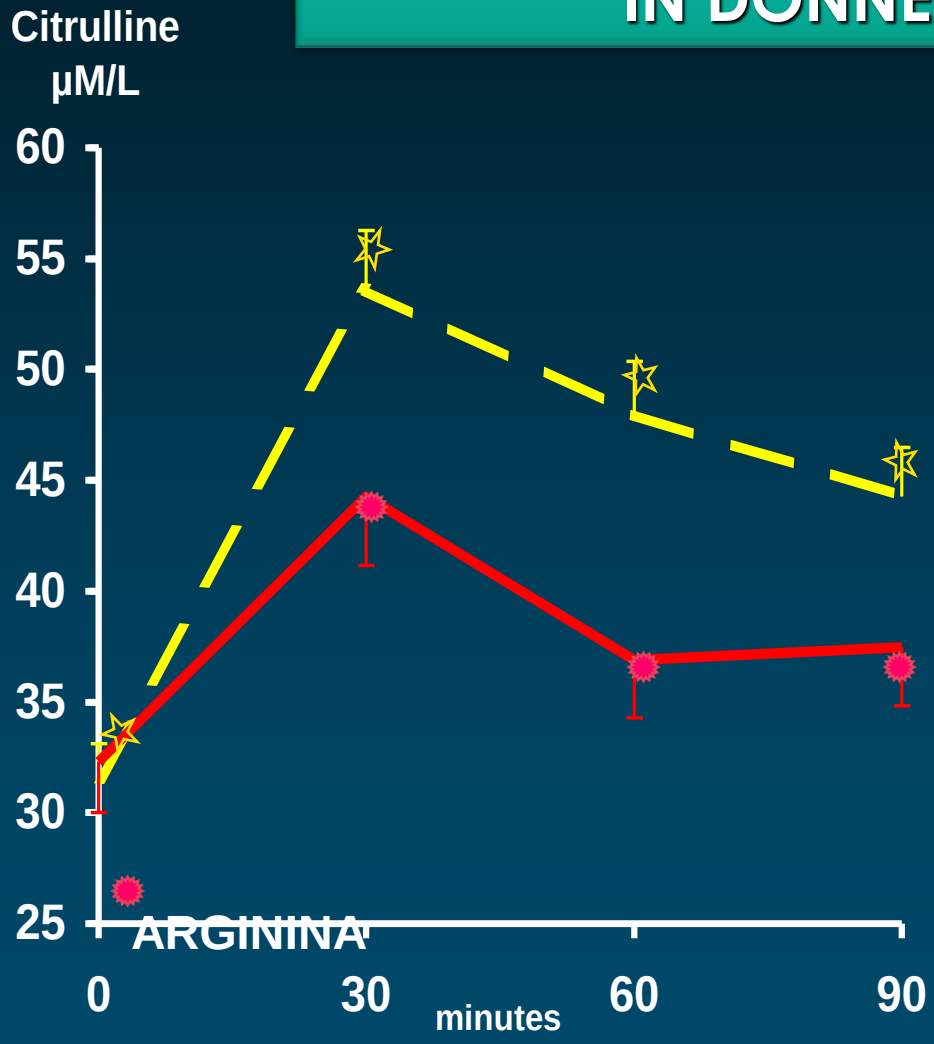
Neri et al Acta Obstet Gynecol Scand 1996; 75:208-12

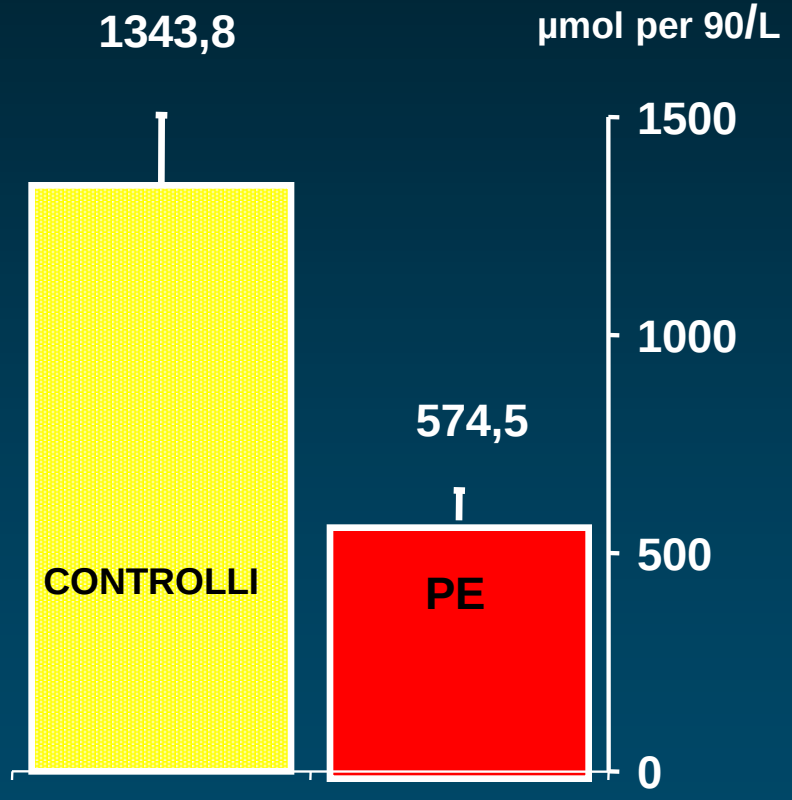
EFFETTO ACUTO DI L-ARGININA AGGREGAZIONE ADP-INDOTTA



Neri et al Hypert Pregn 2000; 19(3):323-30

EFFETTO *ACUTO* DI L-ARGININA SULLA PA MEDIATO DALLA PRODUZIONE DI NO IN DONNE PREECLAMPTICHE





Facchinetti et al. J Soc Gynecol Invest 1999; 6: 202-7

EFFETTO *A LUNGO TERMINE* DI L-ARGININA

17 gravide con aumento delle resistenze arterie uterine e notching bilaterale

→ L-arginina 0.1 g/kg/die da 10 settimane

	BASALE	DOPO 2 SETTIMANE
MAP (mmHg)	80 ± 2	75 ± 2 *
RI UTERINE	0.87 ± 0.01	0.76 ± 0.01 *

Germain, Hypertension 2004

30 gravide affette da preeclampsia

28-36 settimane

→ L-ARGININA 12 gr/os/die vs PLACEBO PER 5 GIORNI

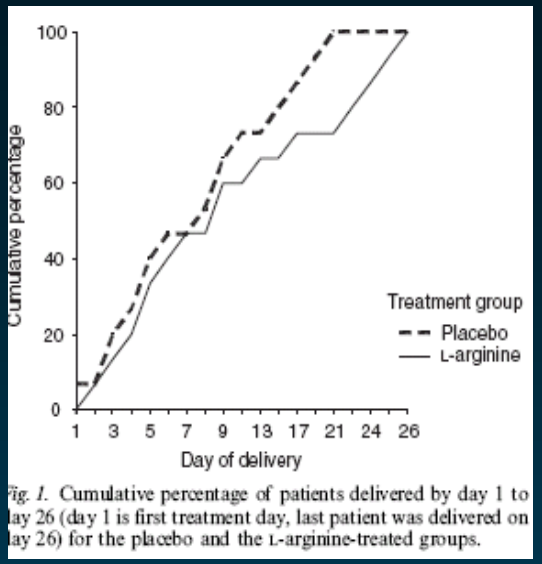


Fig. 1. Cumulative percentage of patients delivered by day 1 to day 26 (day 1 is first treatment day, last patient was delivered on day 26) for the placebo and the L-arginine-treated groups.

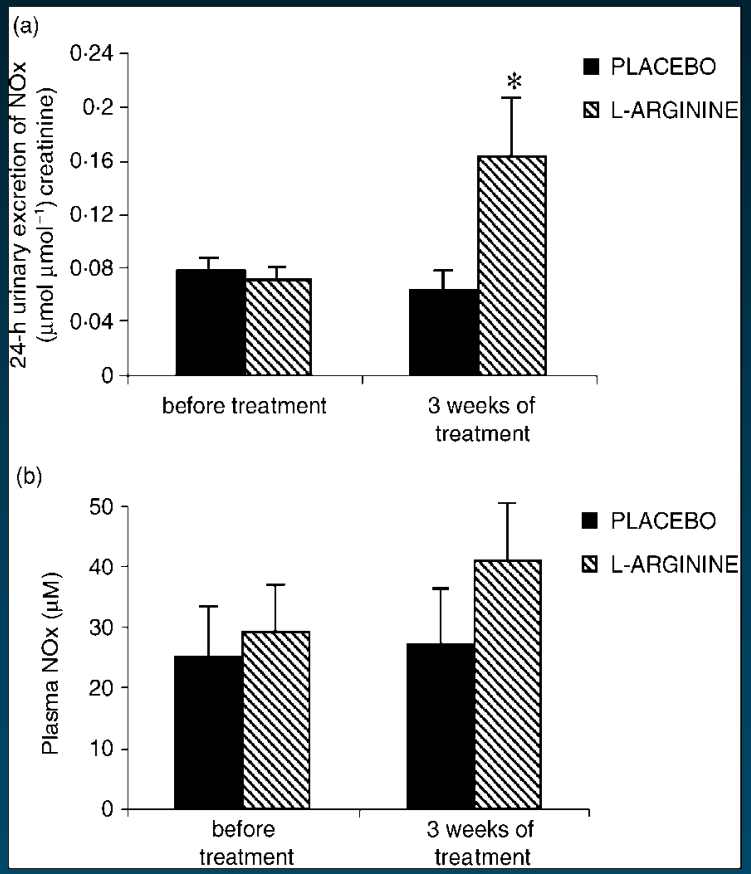
DOPO 15 GIORNI	L-ARG (N° 15)	PLACEBO (N° 15)
SBP (mmHg)	142 (95%CI 138-146)	153 (95%CI 149-158)
DBP (mmHg)	95 (95%CI 92-98)	102 (95%CI 98-106)

Staff et al Acta Obstet Gynecol Scand 2004

61 gravide affette da PREECLAMPSIA

L-ARGININA 3gr/os vs. PLACEBO PER 3 SETTIMANE

	L-ARG (n° 30)	PLACEBO (n° 30)
Epoca gestazionale all'inclusione	29.3±3.4	29.3±6.7
SBP (mmHg)	134.2±2.9*	143.1±2.8
DBP (mmHg)	81.6±1.7*	86.5±0.9
ADMA + SDMA (µmol/L)	0.51±0.3	0.82±0.5



Rytlewski et al Eur J Clin Invest 2005

83 gravide affette da PRECLAMPSIA

L-ARGININA 3gr/os vs. PLACEBO PER 4 settimane

	L-ARG (n° 42)	PLACEBO (n° 41)
Epoca all'inclusione	29.3±3.4	29.1±3.4
IUGR (%)	23.3%*	45.2%
LATENCY (days)	36.4±18.5*	25.2±15.6
PI MIDDLE CEREBRAL ARTERY (after 2weeks)	1.50±0.48 1.96±0.29*	1.41±0.54 1.33±0.18*
PI UMBILICAL ARTERY (after 3weeks)	1.16±0.32 1.05±0.44*	1.29±0.3 2.21±0.36*

Rytlewski et al Basic Clin Pharmacol 2006

80 gravide affette da IPERTENSIONE GESTAZIONALE

→ L-ARG e.v. per 5 giorni a seguire L-ARG per os vs. PLACEBO per 15 giorni

80

PLACEBO
40

SALINA
.500 ml/ev
(5 GIORNI)

36

.20 ml/os
(15 GIORNI)

20

-4

L-ARG E.V.

L-ARG OS

-10

ARGININA
40

30

L-ARGININA
• 20 gr in 500 ml/ev
(5 GIORNI)

• 2 gr in 20 ml/os
(15 GIORNI)

11

Facchinetti et al, Hypert Preg 2007

	PLACEBO (35 casi)	L-ARG (39 casi)	
EPOCA GESTAZIONALE AL PARTO	35.9±3.3 (25-40)	37±3.1 (27.6-41)	0.05 n. s.
PESO ALLA NASCITA	2523±803 (595-3640)	2753 ±857 (600-4260)	n. s.
PARTO<37 SETT	18 (51.4%)	13 (33.3%)	n. s.
PESO ALLA NASCITA <2500 g	15 (42.8%)	11 (28.2%)	n. s.
% DI TAGLIO CESAREO	17 (48.6%)	23 (50%)	n. s.
LATENZA (GIORNI)	18.3±15.4 (2-64)	31.2±24.2 (2-85)	.008
PAS PRE E POST INFUSIONE L-ARG	147.4 ±12.6 138.6 ± 9.1	144.4 ±13.1 133.2±10.1	.020
PAD PRE E POST INFUSIONE L-ARG	92.8 ±10.6 86.7±8.8	90.8 ±6.7 81.8±8.1	.020

Nitric oxide for preventing pre-eclampsia and its complications (Review)

Meher S, Duley L

2010
Six trials

Four trials (170 women) → NO or L-Arg vs. placebo or no intervention

One trials (36 women) → **NO vs. nifedipine**

One trials (76 women) → **NO vs. Antiplatelet agents**

There is insufficient evidence to draw reliable conclusion about whether nitric oxide donors and precursors prevent preeclampsia and its complications.

INCLUDED STUDIES

- Facchinetti F. et al, *Effect of arginine supplementation in patients with gestational hypertension.* American Journal of Obstetrics and Gynecology 2002
- Neri I. et al, *24-hour ambulatory blood pressure monitoring: a comparison between transdermal glyceryl-trinitrate and oral nifedipine*. Hypertension in Pregnancy 1999

Journal of Human Hypertension

2014

The role of L-arginine in the prevention and treatment of preeclampsia: a systematic review of randomized trials.

Pre-eclampsia is a significant health issue in pregnancy, complicating between 2-8% of pregnancies. L-arginine is an important mediator of vasodilation with a potential preventative role in pregnancy related hypertensive diseases. We aimed to systematically review randomised trials in the literature assessing the role of L-arginine in prevention and treatment of pre-eclampsia. We searched the Cochrane Controlled Trials Register, PUBMED, and the Australian and International Clinical Trials Registry, to identify randomised trials involving pregnant women where L-arginine was administered for pre-eclampsia to improve maternal and infant health outcomes.

We identified eight randomised trials, seven of which were included. The methodological quality was fair, with a combined sample size of 884 women. For women at risk of pre-eclampsia, L-arginine was associated with a reduction in pre-eclampsia (RR: 0.34, 95% CI: 0.21-0.55), when compared with placebo and a reduction in risk of preterm birth (RR: 0.48 and 95% CI: 0.28 to 0.81).

For women with established hypertensive disease, L-arginine was associated with a reduction in pre-eclampsia (RR: 0.21; 95% CI: 0.05-0.98). L-arginine may have a role in the prevention and/or treatment of pre-eclampsia.

Dorniak-Wall T. et al, J Hum Hypertens, 2014

Arginine supplementation for improving maternal and neonatal outcomes in hypertensive disorder of pregnancy: a systematic review.

Journal of the Renin-Angiotensin-Aldosterone System
(including other peptidergic systems)
jraas

OBJECTIVE: This meta-analysis was performed to assess whether arginine supplementation could reduce preeclampsia or eclampsia incidence and improve the outcomes of hypertensive disorders in pregnancy, and to evaluate the safety of L-arginine supplementation.
METHODS: The Cochrane Central Register of Controlled Trials (2011), MEDLINE (1980-2011) and Embase (1980-2011) were searched through July 2012, and randomized controlled trials (RCTs) comparing intravenous and/or oral L-arginine supplementation with placebo, or RCTs comparing any treatment with arginine were included. Qualities of RCTs were assessed with the Jadad method. Meta-analyses were performed with fixed- or random-effects models according to heterogeneity of studies.
RESULTS: Data from seven RCTs involving 916 patients were enrolled. The meta-analysis showed L-arginine was more effective in reducing preeclampsia or eclampsia incidence (odds ratio 0.384; 95% confidence limits 0.25, 0.58) than the placebo; meanwhile, L-arginine could prolong pregnancy weeks (MD 11.54; 95% CL 5.23, 17.85) than placebo; and its effect on blood pressure was unbalanced (diastolic pressure (MD 4.86; 95% CL 4.19, 5.52) and systolic pressure (MD 3.20; 95% CL -1.54, 7.94)) while the difference in increased neonatal weight (MD 256.24; 95% CL -28.66, 541.13) was not clear. Three of these studies reported some adverse effects, and no teratogenic or lethal effects were noted.
CONCLUSION This study demonstrates L-arginine supplementation is superior to placebo in lowering diastolic pressure and prolonging pregnancy in patients with gestational hypertension with or without proteinuria, but the effect on lowering systolic pressure and increasing neonatal weight was not statistically significant.

Gui et al, J Renin Angiotensin Aldosterone Syst, 2014

L-arginine supplementation in women with chronic hypertension: impact on blood pressure and maternal and neonatal complications.

OBJECTIVE: To evaluate L-arginine (L-Arg) supplementation in pregnant women with chronic hypertension and its effects on blood pressure (BP) and maternal and neonatal complications.

METHODS: We enrolled 80 women affected by mild chronic hypertension referred to the High Risk Clinic of the Mother-Infant Department of the University of Modena and Reggio Emilia. Each women after obtaining oral consent was randomized to receive oral L-Arg versus placebo and thereafter submitted to 24-h ambulatory BP monitoring. The primary outcome was BP change after 10-12 weeks of treatment. Secondary outcomes were as follows: percentage of women on antihypertensive treatment at delivery, maternal, and fetal outcome.

RESULTS:

-----A lower percentage of women received antihypertensive drugs in the L-Arg group than the placebo group.

-----The incidence of superimposed preeclampsia indicated delivery before the 34th weeks and certain neonatal complications tended to be higher in the placebo group.

CONCLUSIONS: L-Arg supplementation in pregnant women with mild chronic hypertension does not significantly affect overall BP but is associated with less need for antihypertensive medications and a trend toward fewer maternal and neonatal complications.

Neri I. et al, J Matern Fetal Neonatal Med 2010

Efficacy of L-arginine for preventing preeclampsia in high-risk pregnancies: A double-blind, randomized, clinical trial

E. E. Camarena Pulido[a], L. García Benavides[b], J. G. Panduro Barón[a], S. Pascoe Gonzalez[b], A. J. Madrigal Saray[a], F. E. García Padilla[a], and S. E. Totsuka Sutto[b]

Fattori di rischio per PE

Criteri di inclusione:
- **Nullipare**
- **Precedente storia di PE**
- **Ipertensione cronica**
- **BMI≥30 kg/m²**

Criteri di esclusione:
- **Patologie croniche**
- **Consumo di alcool**
- **Farmaci antiossidanti/ antinfia**
- **Infezioni**
- **Terapie concomitanti**

Follow-up ogni 3 settimane e 2 settimane nel post-partum

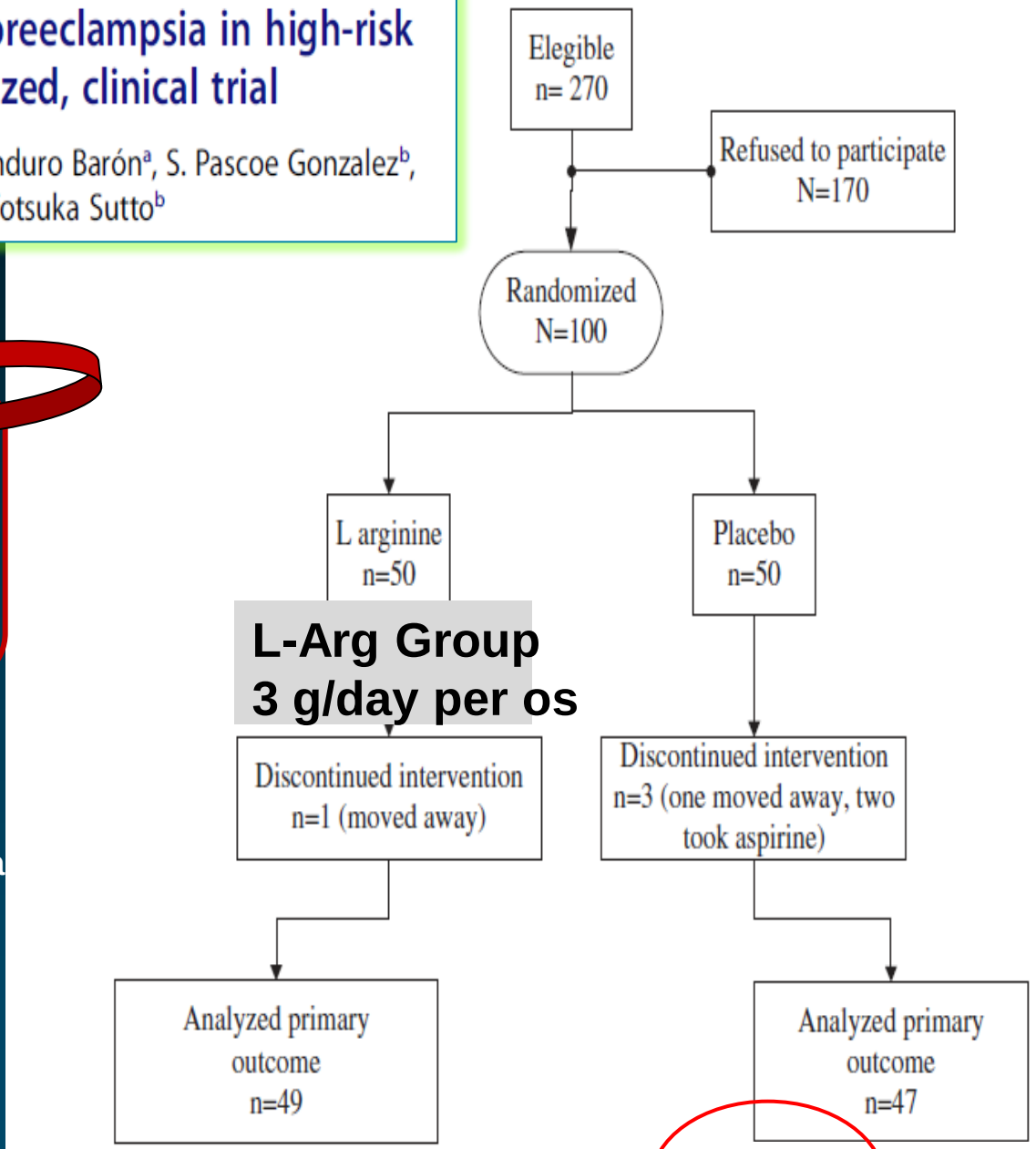


Figure 1. CONSORT flow diagram.

HYPERTENSION IN PREGNANCY 2016, VOL. 35, NO. 2, 217–225

Table 1. Characteristics of the women at baseline.

	Placebo $n = 47$	L-arginine $n = 49$	*P
Age (years)	20 ± 4.7	20 ± 5.4	0.881
Nulliparous	32 (68)	33 (67.3)	0.93
BMI (kg/m^2)	26.7 ± 2.9	28 ± 4.8	0.116
GA	19.5 ± 0.3	19.7 ± 0.6	0.18
Chronic hypertension	3/47 (6.3)	6/49 (12.2)	0.326
History of preeclampsia	15/47 (31.9)	15/49 (32)	0.894
SBP (mm/Hg)	111 ± 8.1	113 ± 10.5	0.173
DBP (mm/Hg)	68 ± 6.7	71 ± 7.1	0.052
MAP (mm/Hg)	82 ± 6.3	85 ± 7.6	0.059

Table 2. Primary outcome.

Preeclampsia	Placebo $n = 47$ (%)	L-arginine $n = 49$ (%)	*P
No	36 (75)	46 (93.8)	0.01
Mild	4 (8.4)	2 (4.2)	0.37
Severe	7 (14.6)	1 (2)	0.02

*χ^2 test.

PE **11 (23.4%)** **3 (6.1%)** **p=0.016**

Camarena Pulido EE et al, Hypertens Pregnancy, 2016

Table 5. Adverse effects.

	Placebo $n = 47$ (%)	L-arginine $n = 49$ (%)	*P
Dyspepsia	5 (10.6)	14 (28.5)	0.008
Vomiting	1 (2.1)	1 (2)	0.98
Diarrhea	1 (2.1)	1 (2)	0.98
Abdominal pain	2 (4.2)	1 (2)	0.97

*χ^2 test.

L-Arg riduce l'incidenza di PE

Numerosi studi dimostrano il coinvolgimento del sistema L-Arginina-Ossido d'Azoto nella patogenesi dell'ipertensione gestazionale e nella preeclampsia

I donatori di Ossido d'Azoto si sono dimostrati di difficile utilizzo per l'insorgenza di cefalea e altri effetti collaterali

Il miglior approccio terapeutico è costituito dalla L-Arginina substrato alla formazione di Ossido d'Azoto

prevenzione della preeclampsia

trattamento dell'ipertensione cronica e prevenzione della trasformazione in preeclampsia sovrapposta

Magnesio 350 mg

AZIONE IPOTENSIVA E MIORILASSANTE

L-Arginina 3 g

AZIONE DI VASODILATAZIONE, IPOTENSIVA E ANTIOSSIDANTE

Estratto di Salice 100 g

AZIONE ANTIAGGREGANTE, FLUIDIFICANTE ED ANTINFIAMMATORIA

- Insulino-resistenza
- Iperinsulinemia

Disfunzione endoteliale

Il metabolismo glucidico e la funzionalità endoteliale sono entrambe modulate dal sistema L-Arginine/NO

La sensibilità all'insulina è positivamente correlata alla produzione endoteliale di NO

Petrie JAR et al, Circulation 1996

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Original Article

The L-arginine/nitric oxide pathway is impaired in overweight/obese pregnant women

Elisabetta Petrella, Lucrezia Pignatti, Isabella Neri, Fabio Facchinetti *

Mother-Infant Department, University of Modena and Reggio Emilia, Modena, Italy

10 donne normopeso (BMI 18.8-24.9 Kg/m^2)
12 donne sovrappeso-obese (BMI 26.3-45.2 Kg/m^2)

→ infusione di L-Arginina (20 g in 3 ore) in due diverse epoche gestazionali 9-12 e 24-27 settimane

- glucosio
- insulina
- nitriti/nitrati

Table 1
Clinical features of women stratified for BMI categories.

	Normal-weight	Overweight/obese	*p* Value
Serum glucose levels	78.4 ± 5.3[a] (70–84)	82.8 ± 9.3 (71–101)	NS
Serum insulin levels	8.0 ± 5.1 (2.8–19.1)	17.6 ± 16.5 (6.5–74.0)	$p = 0.008$
HOMA index	1.7 ± 1.0 (0.5–4.0)	3.8 ± 4.2 (1.3–18.4)	NS
HOMA > 2.5	1 (10.0%)[b]	7 (58.3%)	NS
Systolic blood pressure (mmHg)	104.1 ± 10.4 (85.0–115.0)	121.6 ± 15.1 (95.0–137.0)	0.004
Diastolic blood pressure (mmHg)	61.8 ± 6.0 (53.0–68.0)	73.3 ± 9.6 (55.0–85.0)	0.002

[a] Mean ± SD with range in brackets.
[b] N with % in brackets.

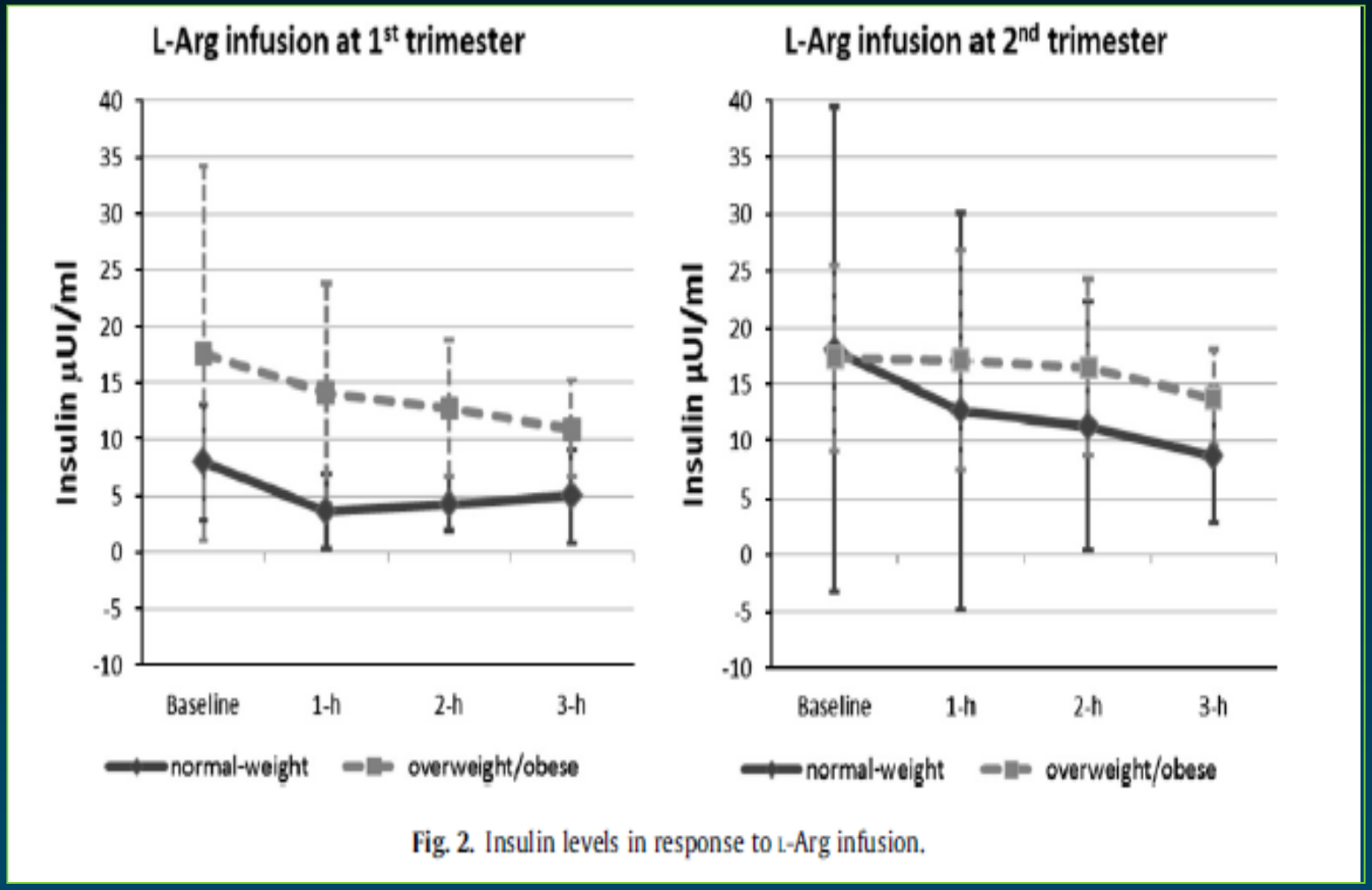


Fig. 2. Insulin levels in response to L-Arg infusion.