

**1° CONGRESSO REGIONALE LOMBARDIA**  
*in collaborazione con*  
Emilia Romagna e le altre Regioni della Macro Area NORD  
**della**  
**FEDERAZIONE ITALIANA di OSTETRICIA e GINECOLOGIA**



**IPERTENSIONE IN GRAVIDANZA**  
Aspetti fisiopatologici e prospettive nello screening

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# Due forme di Pre-eclampsia (PE)

## EARLY ONSET

- Inadequate trophoblast invasion
- Abnormal uterine arteries blood flow
- Abnormal umbelical arteries blood flow
- Intrauterine growth restriction (IUGR)

## LATE ONSET

- Normally grown baby
- Normal uterine spiral arteries
- Normal umbelical arteries blood flow
- Enlarged placental mass

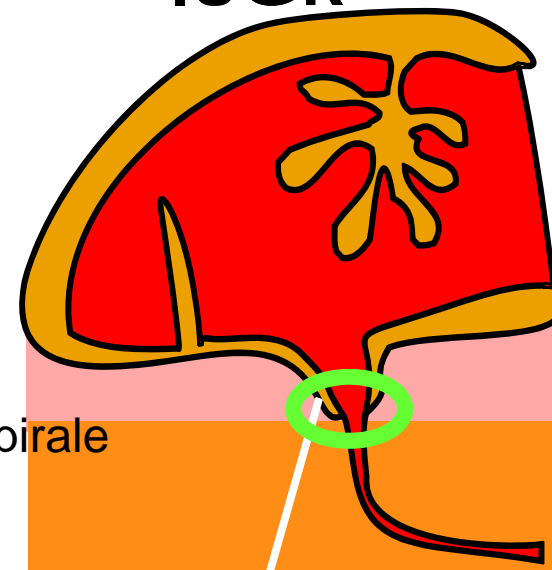
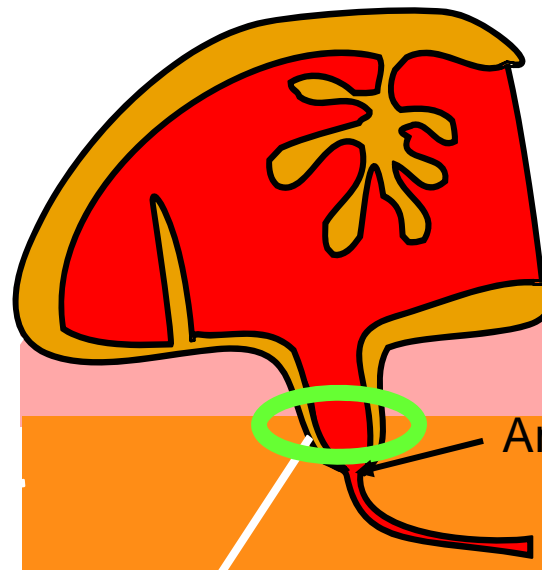
# Invasione trofoblastica delle arterie utero-placentari

**GRAVIDANZE  
NORMALI**

**PRE-ECLAMPSIA -  
IUGR**

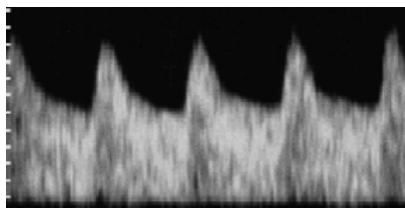
ENDOMETRIO

MIOMETRIO

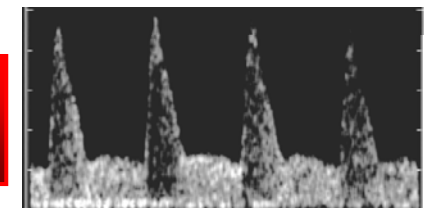


Invasione endometrio e  
terzo interno miometrio

Invasione limitata  
all'endometrio

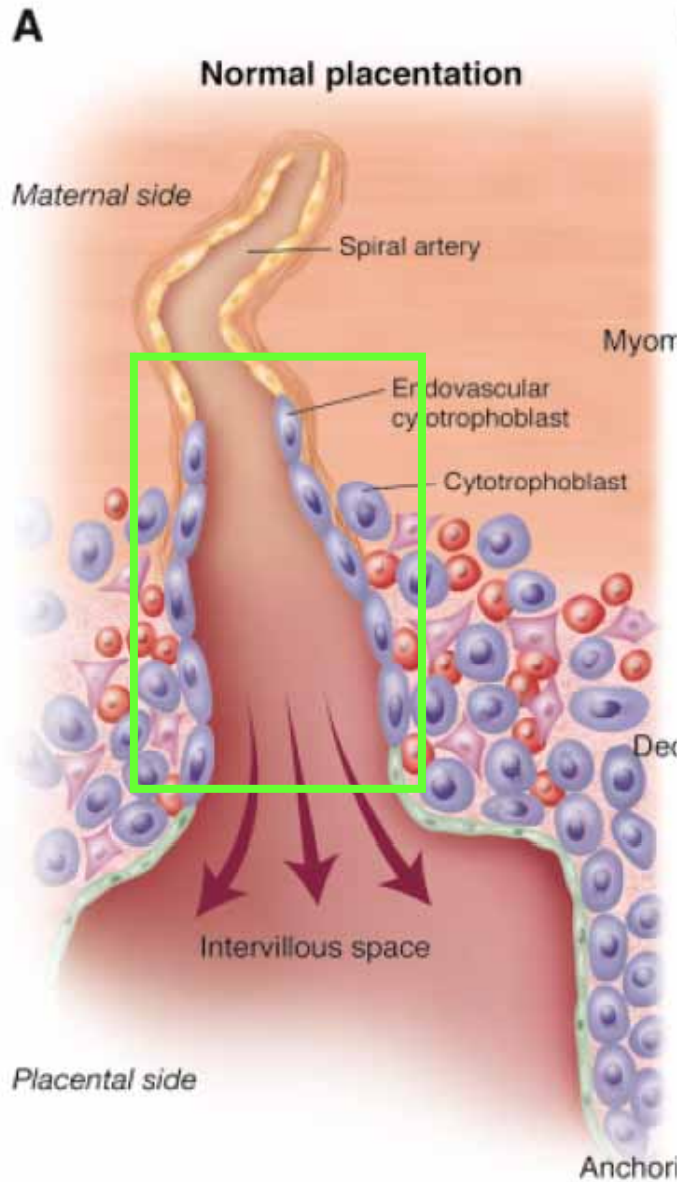


**RIDUZIONE DELLA PORTATA  
EMATICA UTERO-PLACENTARE**



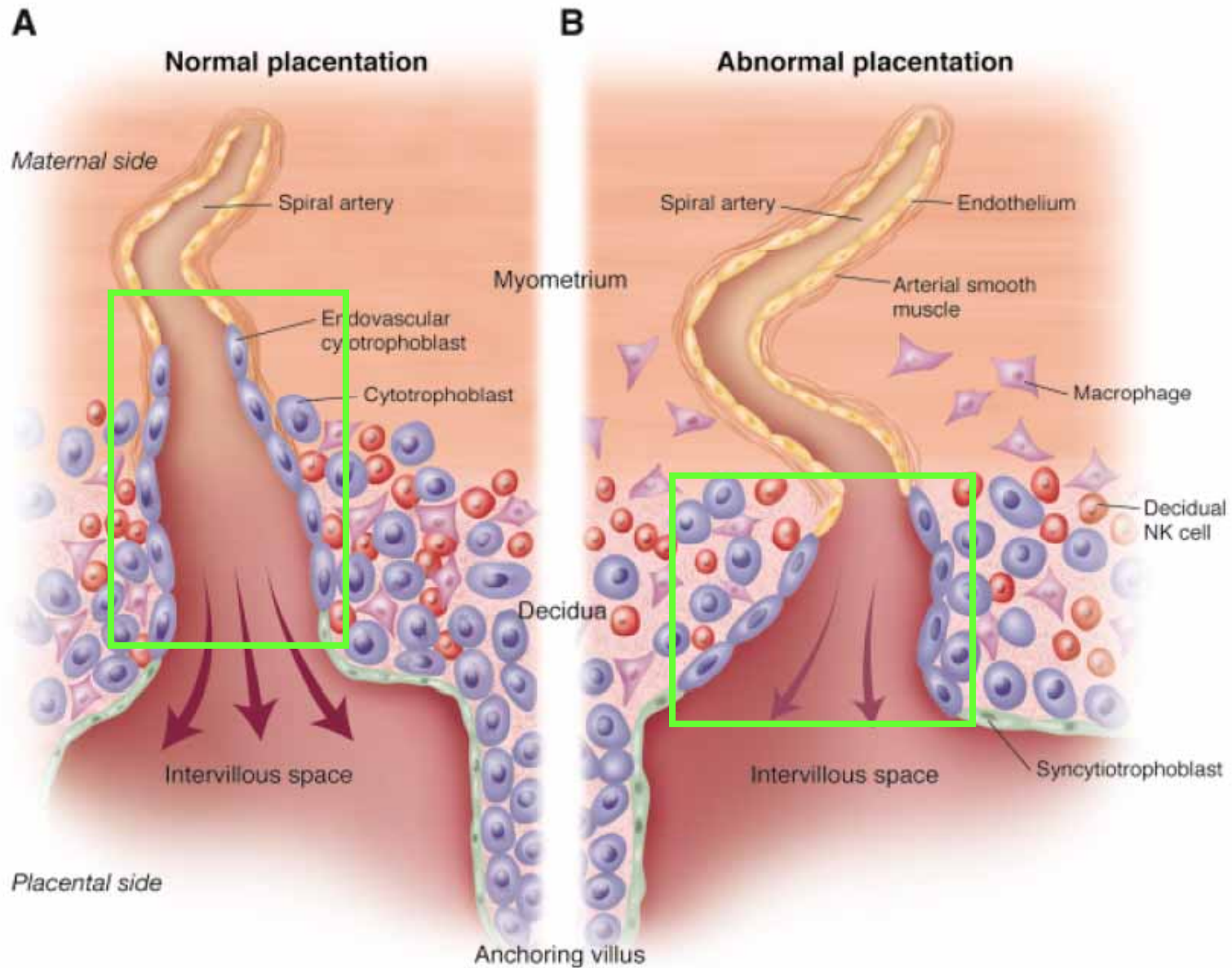
# Placentazione e PE

Redman e Sargent *Science* 2005,308:1592



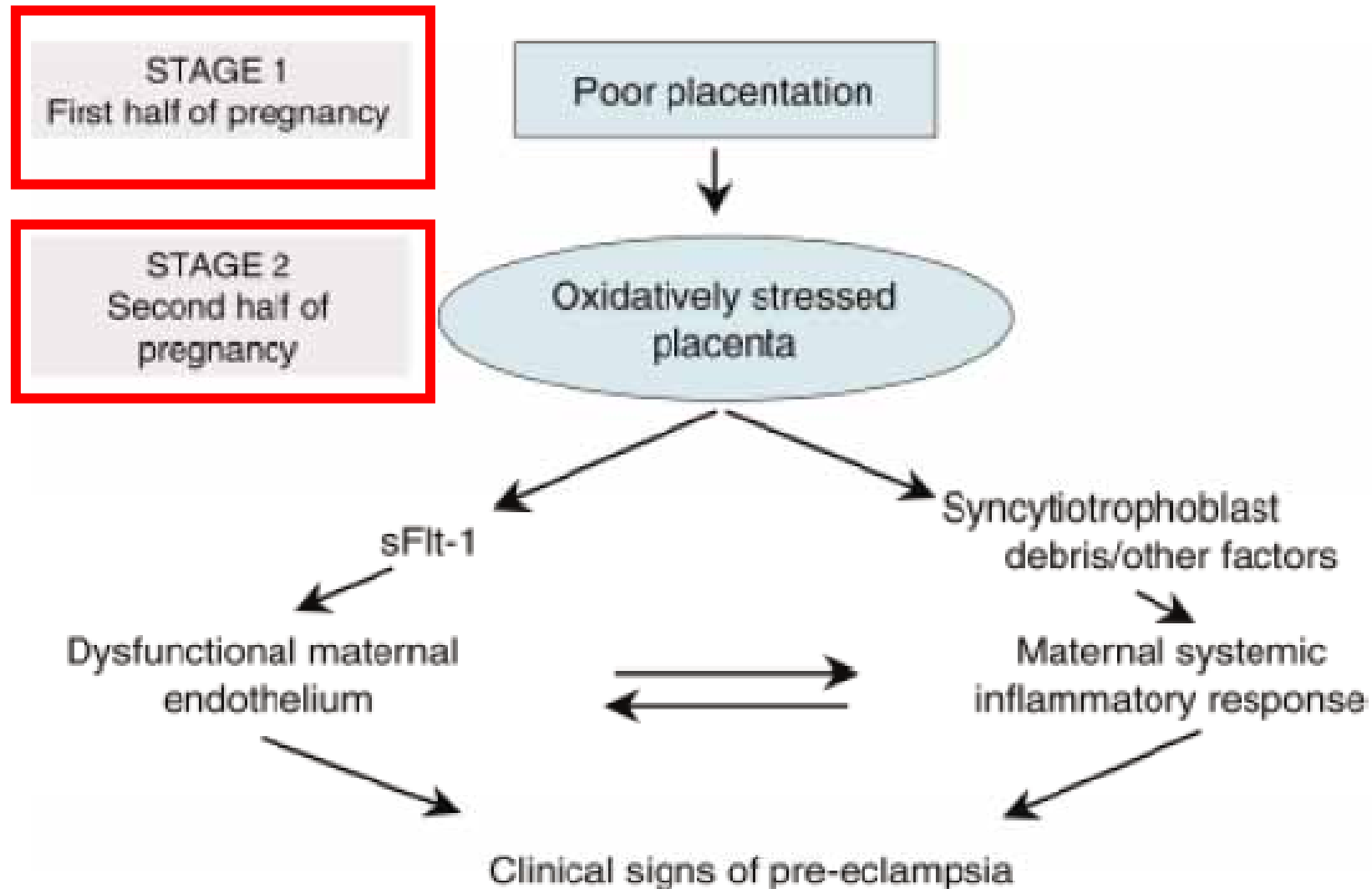
# Placentazione e PE

Redman e Sargent *Science* 2005,308:1592



# Placentazione e PE

Redman e Sargent *Science* 2005,308:1592



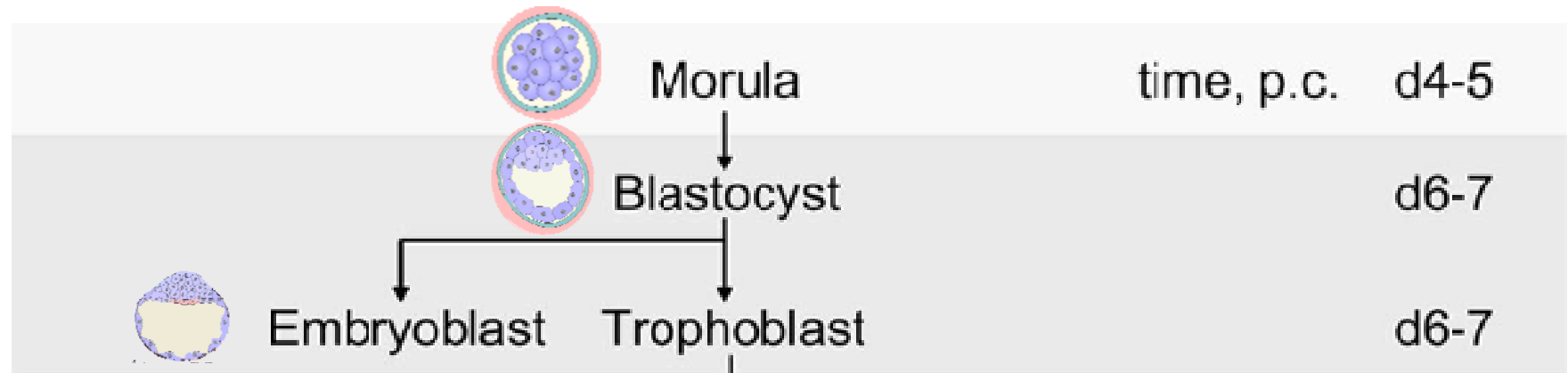
# I punti deboli della teoria corrente

La mancata invasione trofoblastica si ha solo dopo la 12<sup>a</sup> settimana (Jauniaux, *Am J Pathol* 2000,157:2111)

- Nel 1<sup>o</sup> trimestre sono già presenti nel sangue delle madre i markers sierici della PE

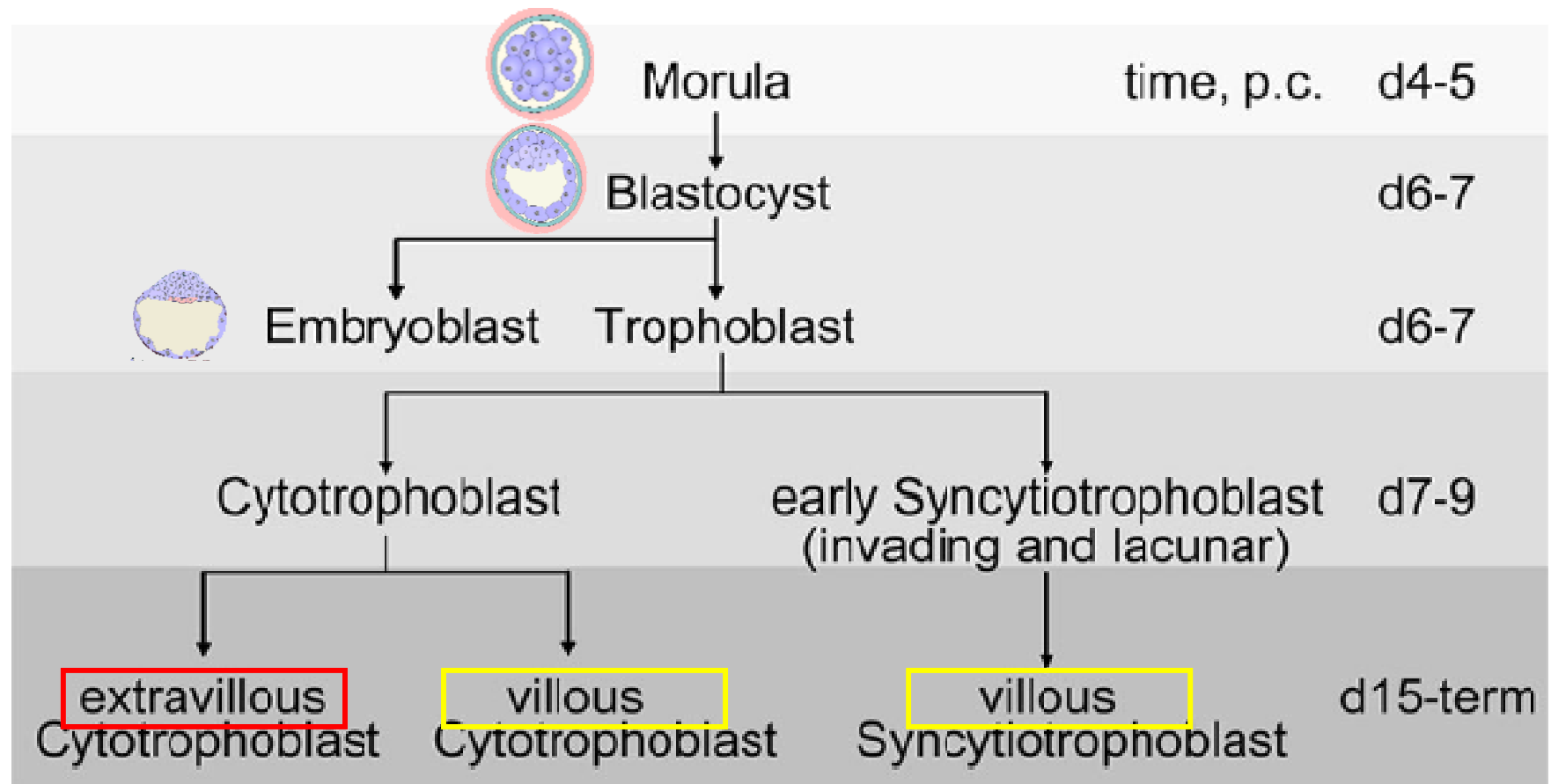
# Lo sviluppo precoce del trofoblasto

Huppertz *Hypertension* 2008,51:970



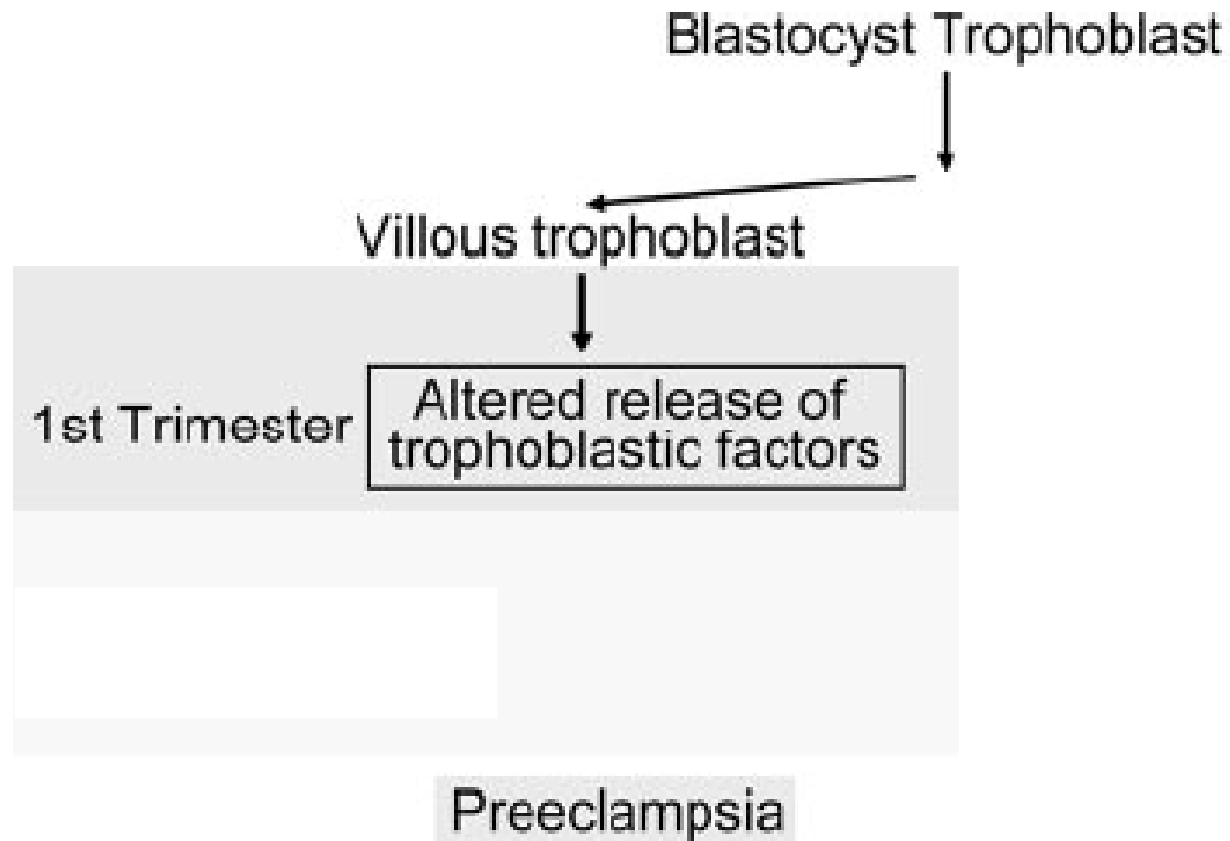
# Lo sviluppo precoce del trofoblasto

Huppertz *Hypertension* 2008,51:970



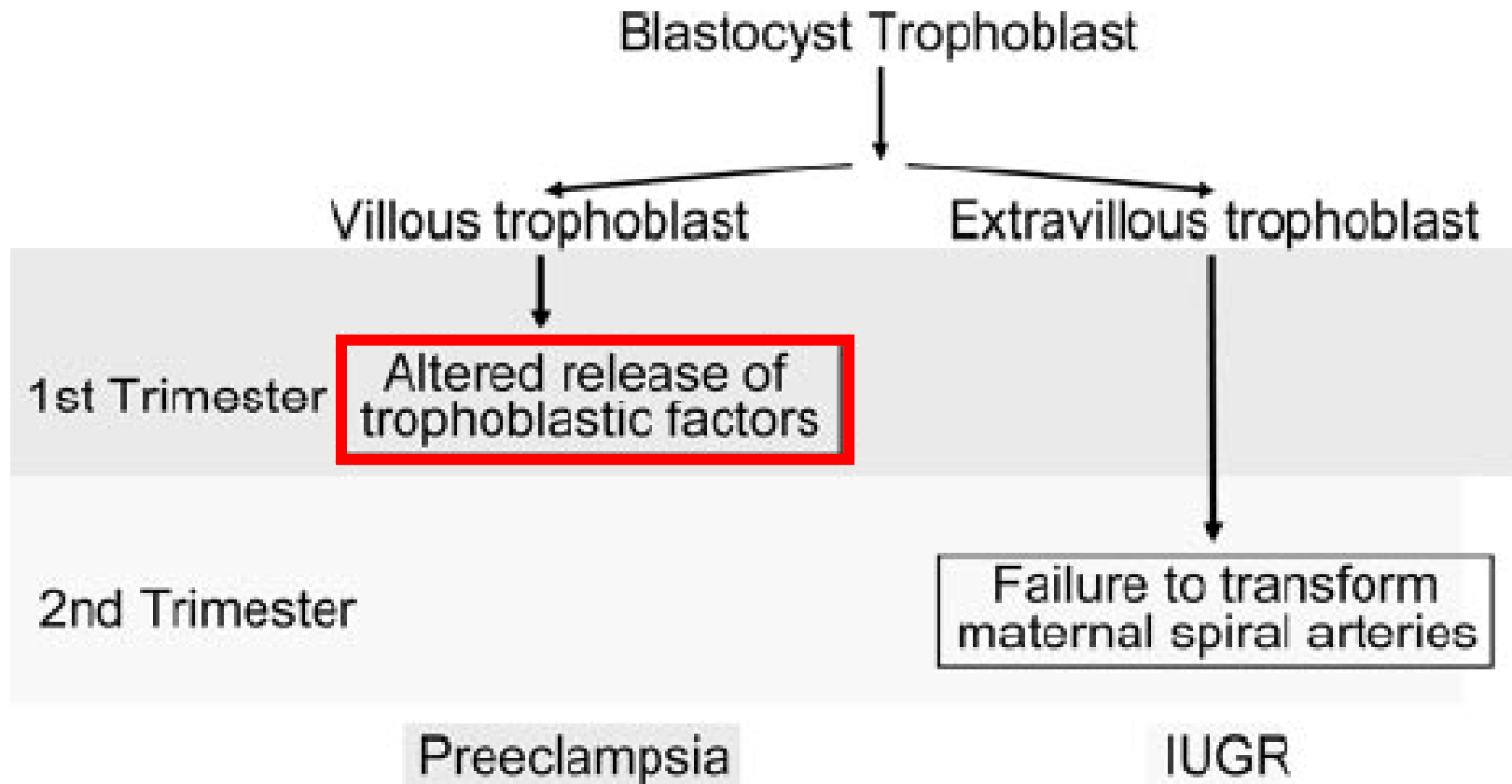
# Due vie differenti alla PE e all'IUGR

Huppertz *Hypertension* 2008,51:970



# Due vie differenti alla PE e all'IUGR

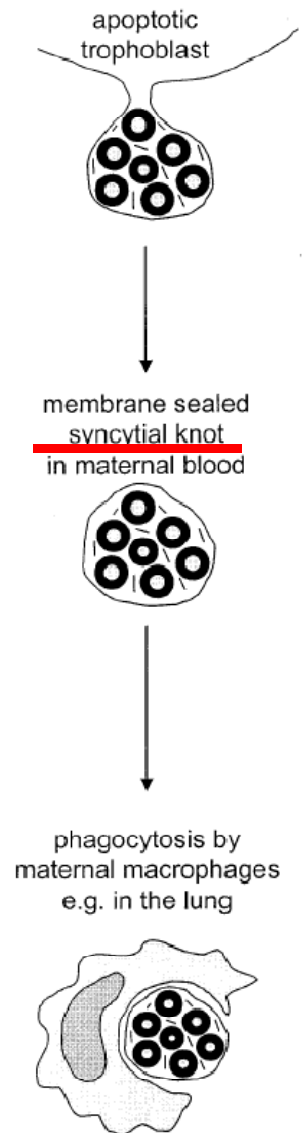
Huppertz *Hypertension* 2008,51:970



# Il passaggio di materiale trofoblastico nel sangue materno

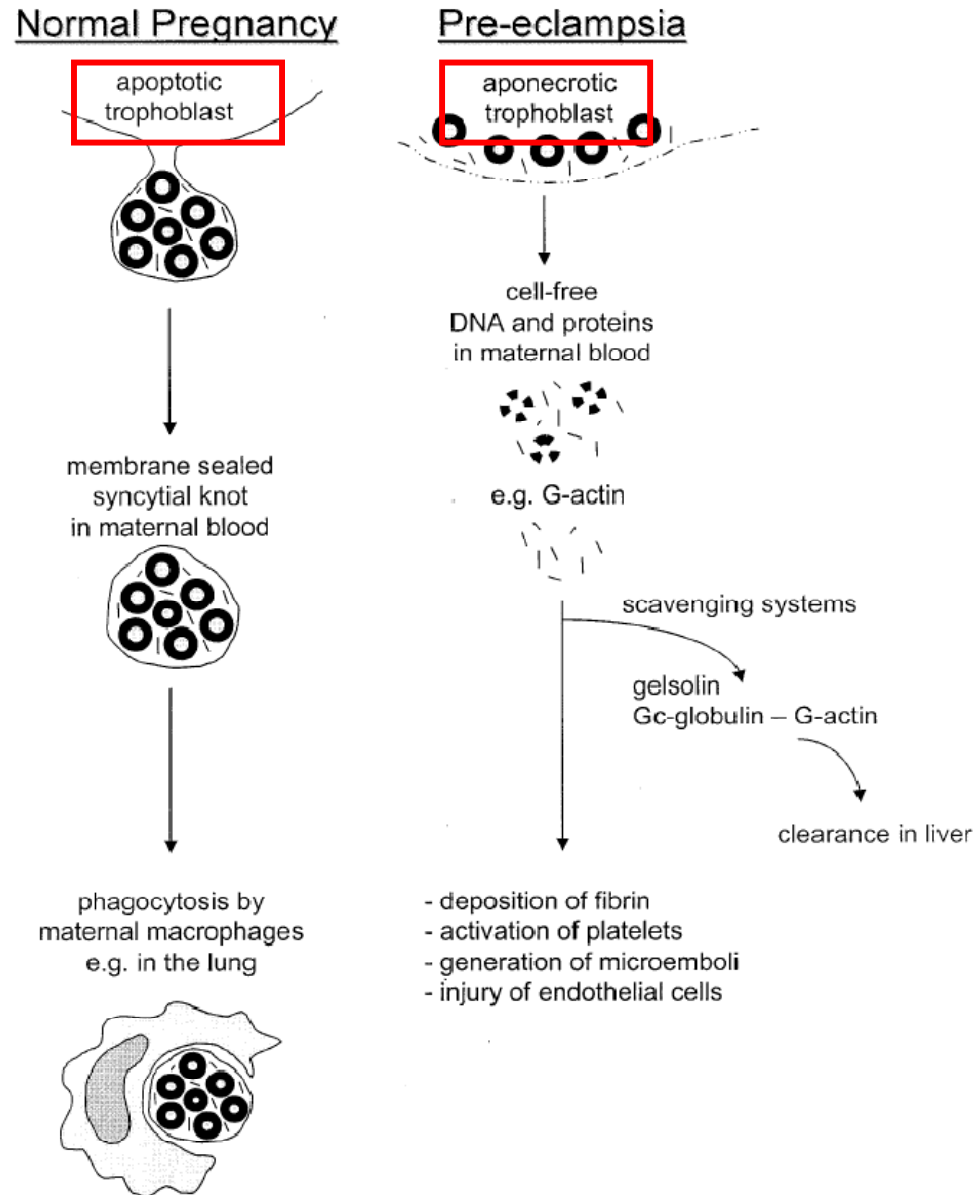
Huppertz e Kingdom *J Soc Gynecol Investig* 2004,11:353

## Normal Pregnancy



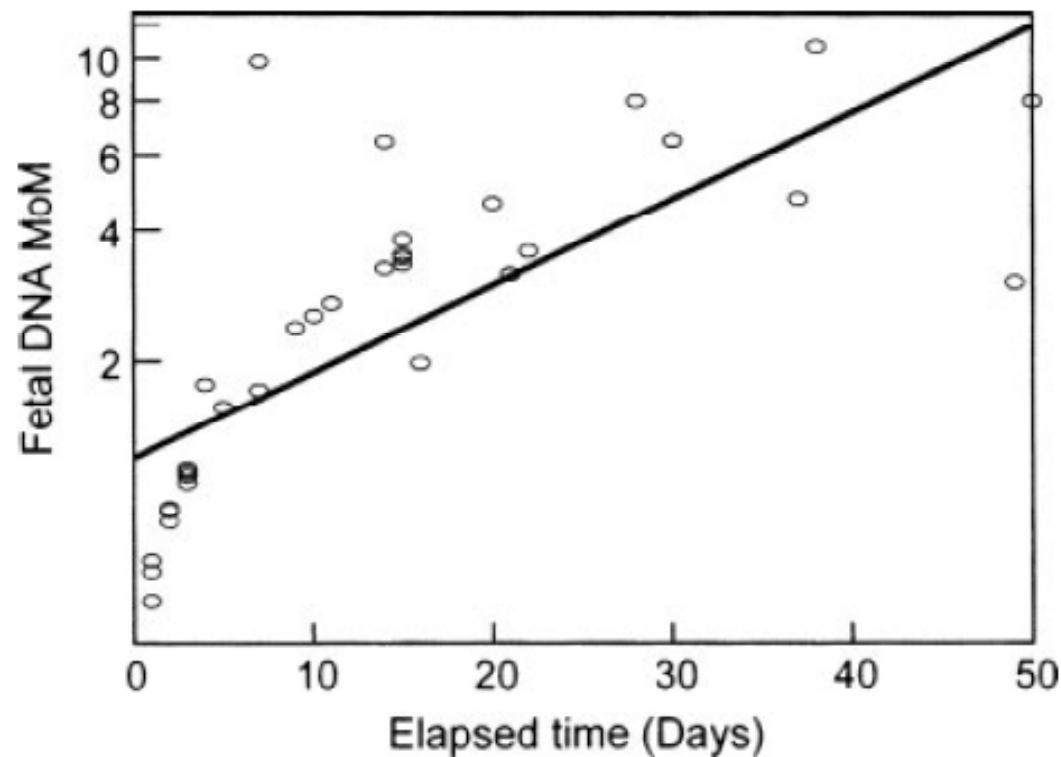
# Il passaggio di materiale trofoblastico nel sangue materno

Huppertz e Kingdom *J Soc Gynecol Investig* 2004,11:353



## Cell-free fetal DNA (SRY locus) concentration in maternal plasma is directly correlated to the time elapsed from the onset of preeclampsia to the collection of blood

Antonio Farina<sup>1,3\*</sup>, Akihiko Sekizawa<sup>3</sup>, Nicola Rizzo<sup>2</sup>, Manuela Concu<sup>1</sup>, Irina Banzola<sup>1</sup>, Paolo Carinci<sup>1</sup>, Giuliana Simonazzi<sup>2</sup> and Takashi Okai<sup>3</sup>



## Quantitative distribution of a panel of circulating mRNA in preeclampsia *versus* controls

Antonio Farina<sup>1,2\*</sup>, Akihiko Sekizawa<sup>2</sup>, Yuditiya Purwosunu<sup>2,3</sup>, Nicola Rizzo<sup>1</sup>, Irina Banzola<sup>1</sup>, Manuela Concu<sup>1</sup>, Danila Morano<sup>1</sup>, Federica Giommi<sup>1</sup>, Maurizio Bevini<sup>1</sup>, Mohamad Mabrook<sup>1</sup>, Paolo Carinci<sup>1</sup> and Takashi Okai<sup>2</sup>

Table 3—Distributions of the mRNA species

		hPL <sup>a*</sup>	Inhibin A <sup>b*</sup>	KISS-1 <sup>b*</sup>	PAI-1 <sup>b*</sup>	PAPP-A <sup>a</sup>	P-Selectin <sup>b***</sup>	VEGF <sup>b**</sup>
Controls	Median	2 754 862	34 334	165	3 071 068	30 794	139 574 988	593 525
	Min	1 071 068	22 929	25	648 739	11 243	85 735 286	320 502
	Max	9 401 681	34 574	1540	10 812 245	171 073	178 016 554	795 210
PE cases	Median	1 819 748	48 499	78	2 257 443	15 417	339 775 870	1 021 782
	Min	747 539	7323	24	917 167	10 108	37 301 973	350 040
	Max	3 889 796	181 513	222	2 292 317	38 556	1 212 735 894	5 250 922

Data are expressed as

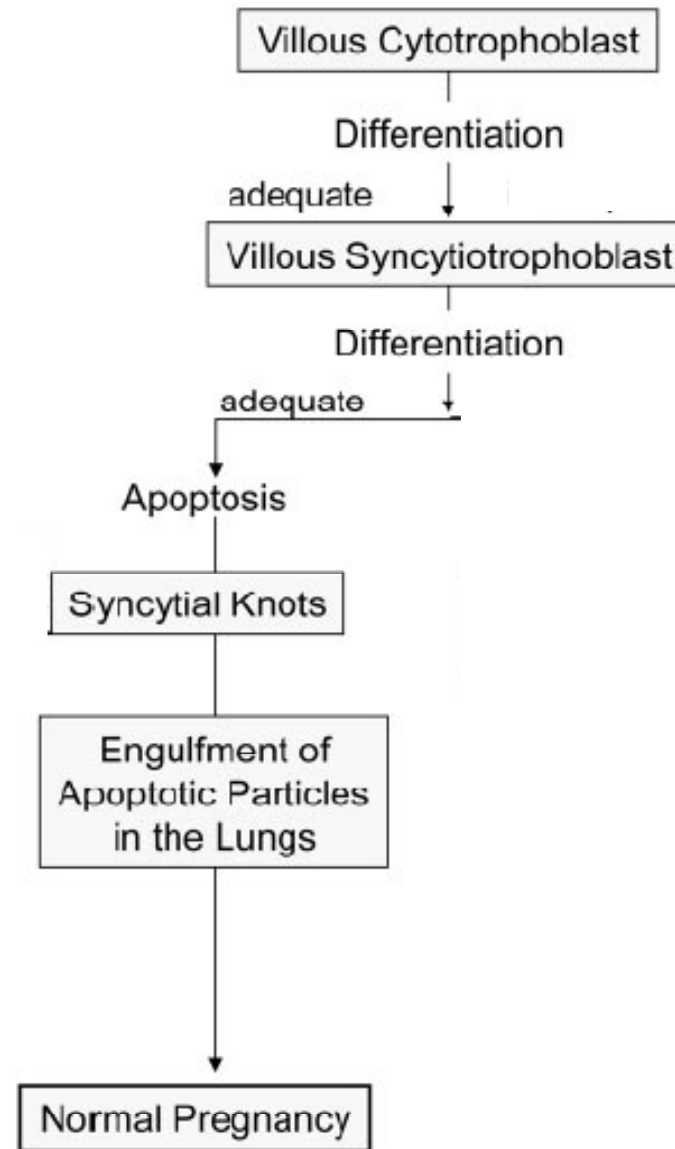
<sup>a</sup> median copies/mL (min-max) and

<sup>b</sup> relative concentration (RC).

\* *p*-value <0.05; \*\* *p*-value <0.01; \*\*\* *p*-value <0.001.

# La nuova ipotesi sulla origine placentare della PE

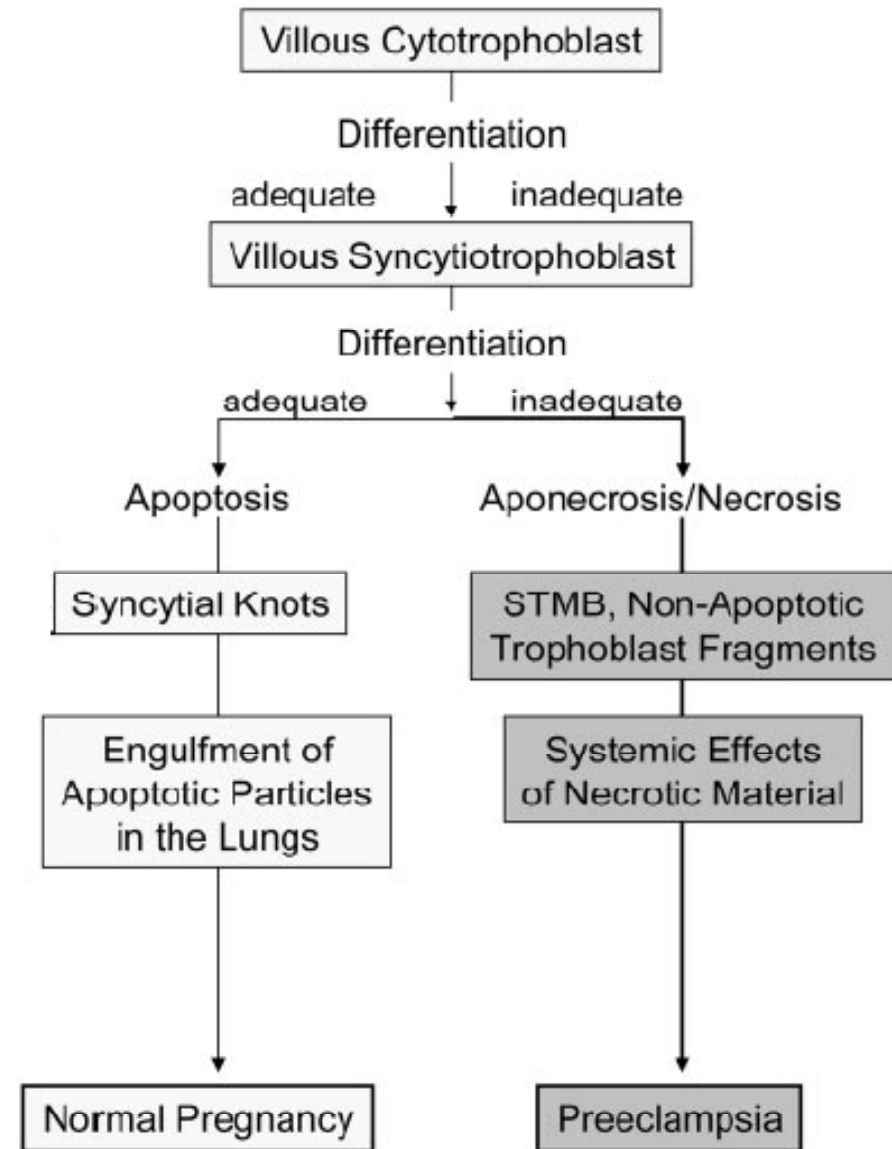
Huppertz *Hypertension* 2008,51:970



# La nuova ipotesi sulla origine placentare della PE

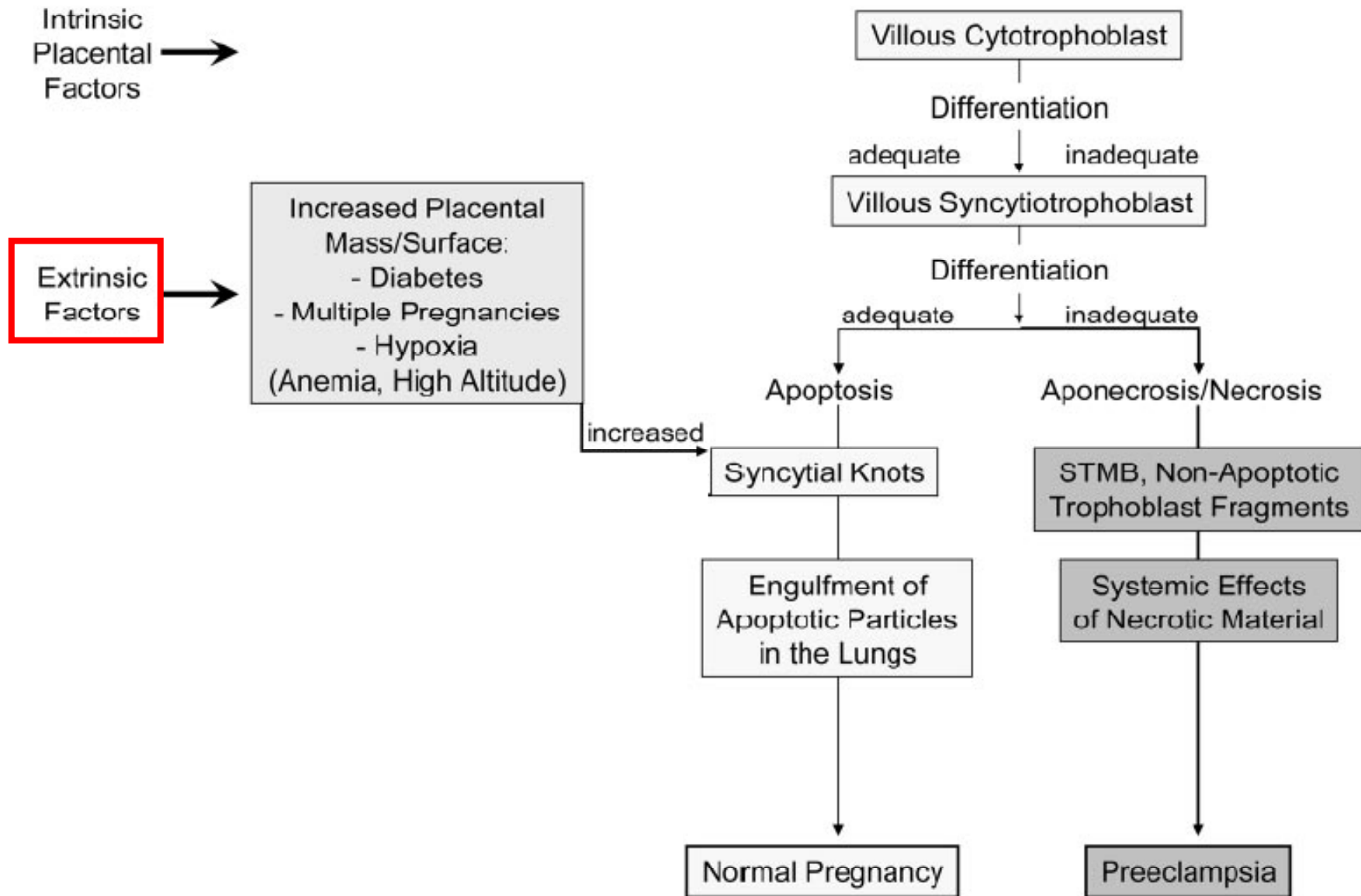
Huppertz *Hypertension* 2008,51:970

Intrinsic Placental Factors →



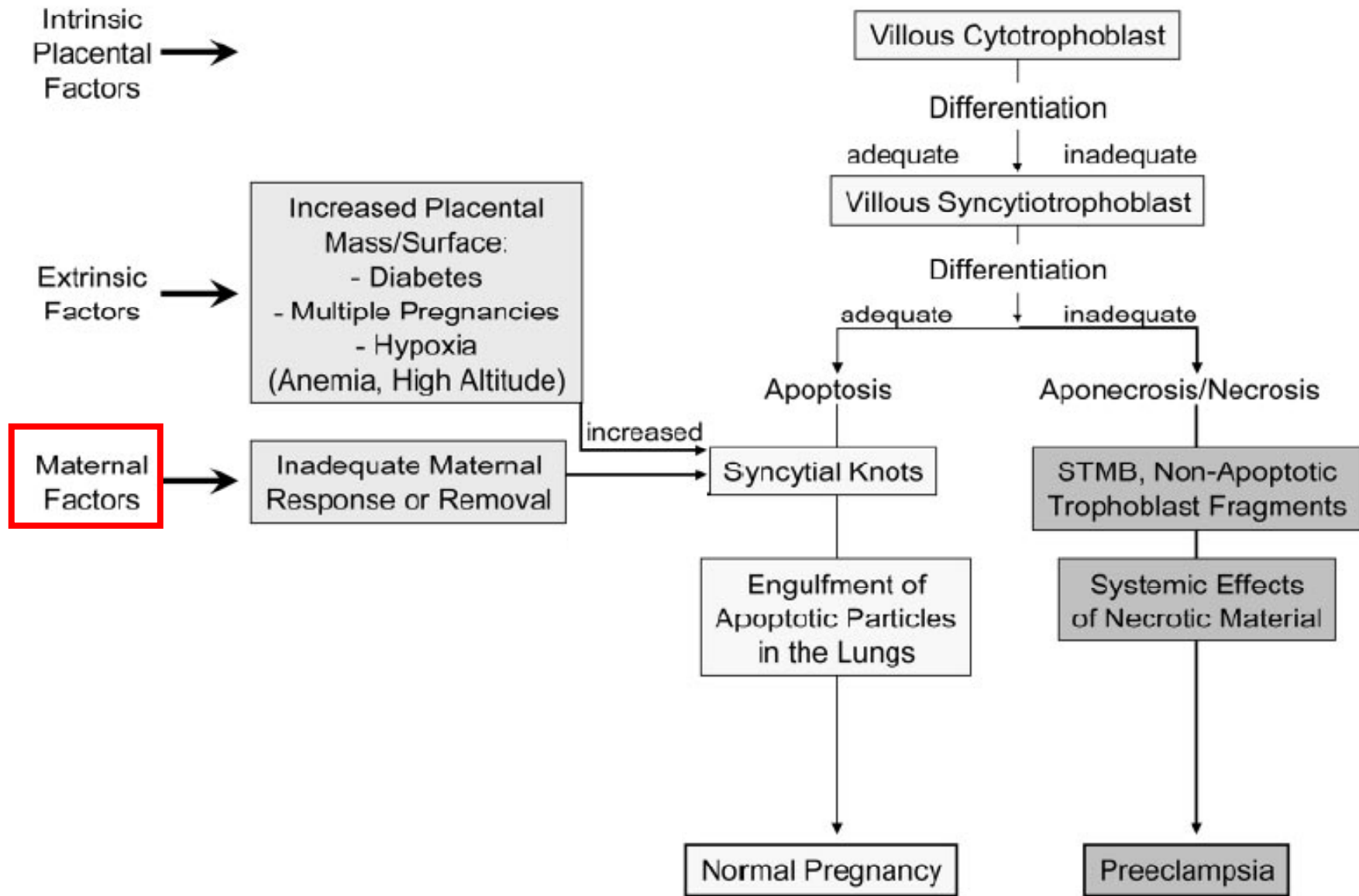
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Huppertz *Hypertension* 2008.51:970



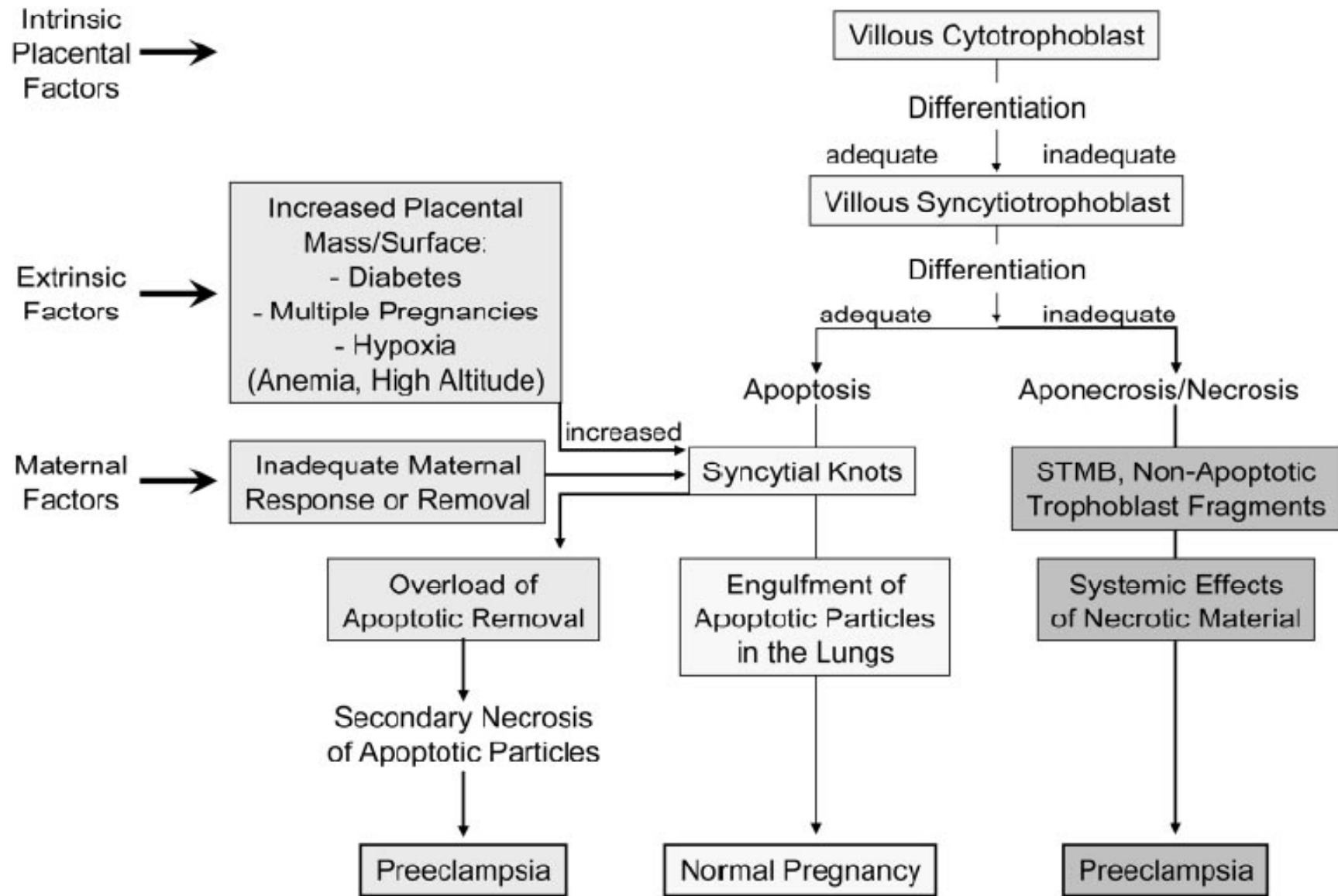
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Huppertz *Hypertension* 2008.51:970



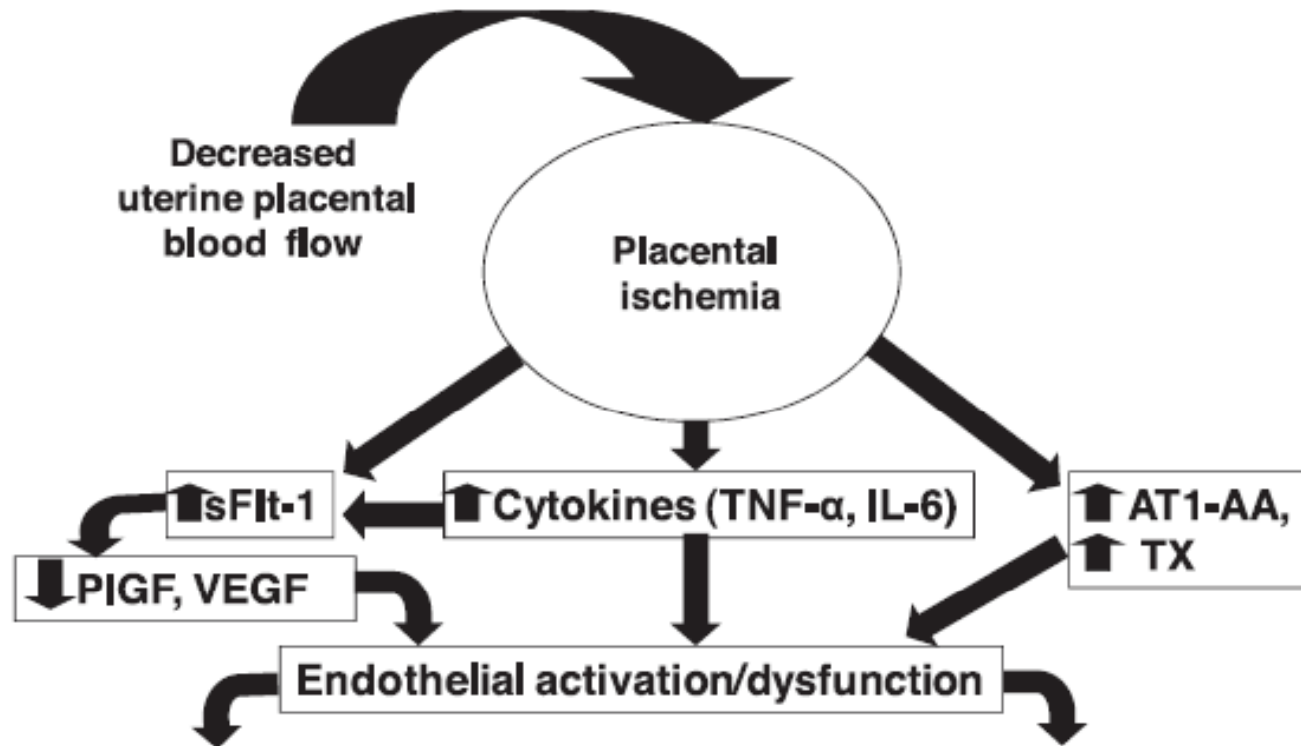
# La nuova ipotesi sulla origine placentare della PE

Huppertz *Hypertension* 2008.51:970



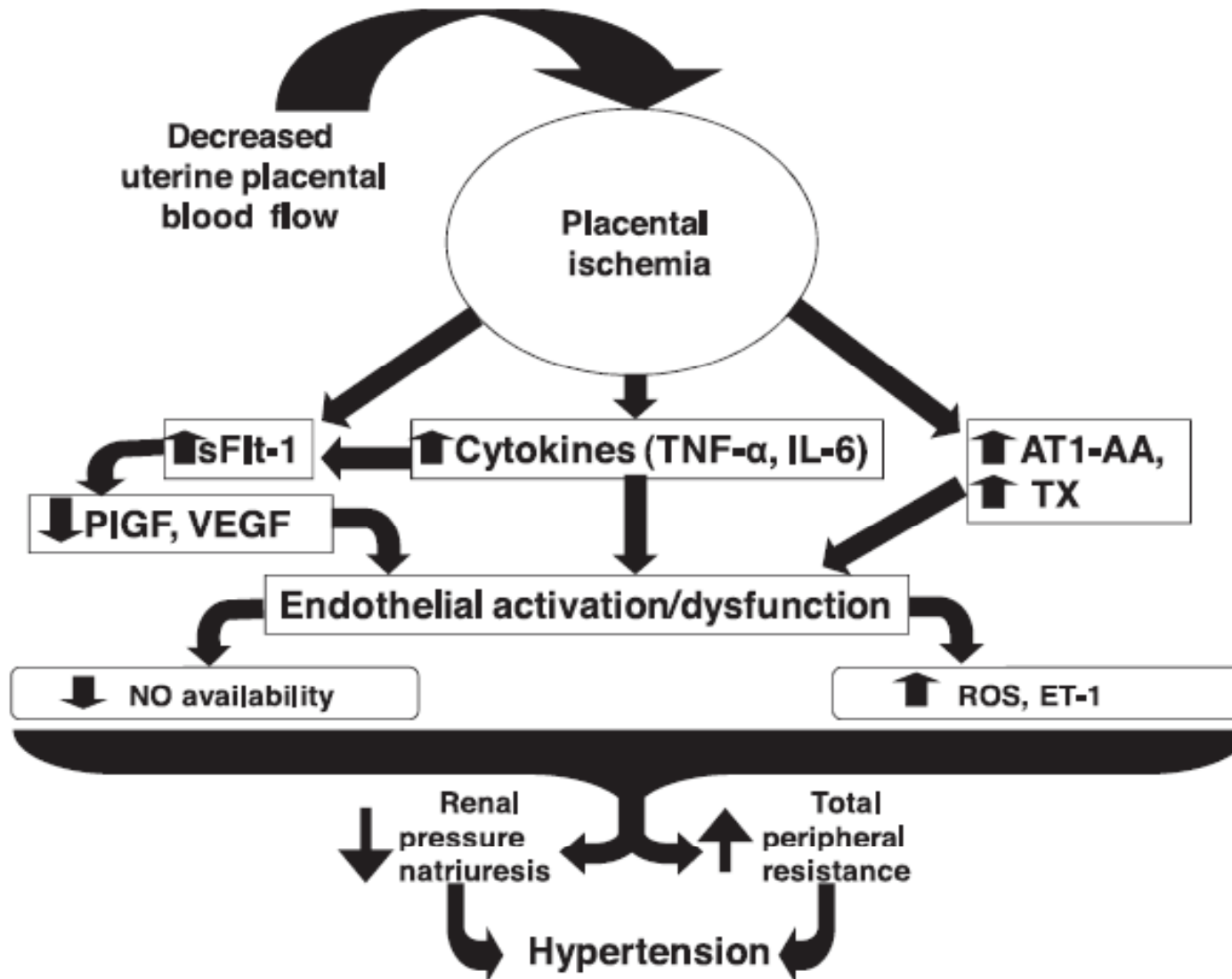
# Dalla ischemia placentare alla disfunzione endoteliale

Gilbert *Am J Physiol Heart Circ Physiol* 2008,294:H541



# Dalla ischemia placentare alla disfunzione endoteliale

Gilbert *Am J Physiol Heart Circ Physiol* 2008,294:H541



# Markers riportati come predittivi di PE

- Invasione trofoblastica anormale
- Placentari
- Apoptosi
- Cellule fetali e DNA fetale
- Stress ossidativo
- Disfunzione endoteliale
- Funzione piastrinica
- Attività fibrinolitica
- Funzione renale

# Markers riportati come predittivi di preeclampsia

## **Invasione trofoblastica anormale**

- Vascular Cell Adhesion Molecule-1 (VCAM-1)
- Intercellular Adhesion Molecule-1 (ICAM-1)
- E-Selectina
- Periostina
- P-Selectina
- VEGF
- VEGFR-1 (FLT1)
- Placental Growth Factor (PlGF)
- Insulin-like growth factor binding protein 1 (IGFBP-1)
- IGF-1
- Placental Protein 13 (PP-13)
- Endoglina solubile (antiangiogenica)

# Markers riportati come predittivi di preeclampsia

## **Fattori Placentari**

- Inibina
- CRH placentare
- Leptina
- Placental Growth Factor (PIGF)

## **Cellule fetali e DNA fetale**

## **Markers apoptotici**

- Tumor necrosis factor alpha (TNF-alpha)
- TNF-alpha recettore solubile (sTNFp55)
- Recettore per l'interleuchina-2
- Recettore Fas
- Proteina C-reattiva
- TGF-beta

## Markers riportati come predittivi di preeclampsia

### **Markers di disfunzione endoteliale**

- Fibronectina
- Una variante della fibronectina detta ED 1+ specifica dell'endotelio vascolare
- Endotelina-1
- Adrenomedullina
- Ossido nitrico (NO) ma solo quello inattivo legato alle albumine (S-nitroalbumina)
- Gelatinase-Associated Lipocalin (NGAL)

### **Markers di stress ossidativo**

- Omocisteina
- Trigliceridi
- Anticorpi antifosfolipidi

## Markers riportati come predittivi di preeclampsia

### **Funzione Piastrinica**

- Rapporto trombossani A2/prostaciline

### **Attività fibrinolitica**

- PAI-1
- PAI-C (complesso attivatore del plasminogeno-PAI-1 o PA-PAI-1)

### **Funzione renale**

Rapporto kallireina urinaria/creatinina

Calcio urinario

Collagene Type I (telopeptide/propetide carbossiteminale)

# Flt1 solubile

		<i>Sensibilità ad un FPR di :</i>		
		<i>5%</i>	<i>10%</i>	<i>20%</i>
Trimestre 1	Banzola I,2007	28	<b>30</b>	35
Trimestre 2	Abdalla ED,2008	90	<b>96</b>	98
Trimestre 2	Moore Simas A 2007(<34 w)*	75	<b>75</b>	100
Trimestre 2	Tiffany A,2007 (<34 w)	50	<b>50</b>	50
Trimestre 2	Moore Simas A 2007(<34 w)	50	<b>50</b>	50
Trimestre 2	Kim SY,2007*	40	<b>42</b>	60
Trimestre 2	Crispi F, 2008	36.8	<b>52.6</b>	78.9
Trimestre 2	Espinoza J,2007	5	<b>10</b>	18

# PIGF

		<i>Sensibilità ad un FPR di :</i>		
		<i>5%</i>	<i>10%</i>	<i>20%</i>
1 trimestre	Akolekar 2008 (early onset)	27.6	<b>51.7</b>	-
1 trimestre	Crispi F, 2008	0	-	5.3
1 trimestre	Sibai B, 2008 >37 w	-	<b>0</b>	-
1 trimestre	Sibai B, 2008 <27 w)	-	<b>5.3</b>	-
2 trimestre	Akolekar 2008 (late onset)	19.4	<b>21.1%</b>	-

## PAPP-A, Endotelina TNF-R1 al 1 trimestre

		<i>Sensibilità ad un FPR di :</i>		
		<i>5%</i>	<i>10%</i>	<i>20%</i>
PAPP-A	Akolekar 2008 (early onset)	51.7	<b>69</b>	-
PAPP-A	Akolekar 2008 (late onset)	29.6	<b>47.9</b>	-
PAPP-A	Poon LCY 2009 (early onset)	21.9	-	-
PAPP-A	Poon LCY 2009 (late onset)	6.5	-	-
Endotelina	Shaarawy M, 2000	30	<b>40</b>	60
TNF-R1	Leal AM 2009	30	<b>50</b>	60

# Endogлина 1

		<i>Sensibilità ad un FPR di :</i>		
		<i>5%</i>	<i>10%</i>	<i>20%</i>
1 trimestre	Baumann MU 2008 (late onset)	18	<b>22</b>	38
2 trimestre	Stepan H 2008 (early onset)	60	<b>60</b>	60

# DNA fetale o totale nel sangue materno al 2 trimestre

	<i>Sensibilità ad un FPR di :</i>		
	<i>5%</i>	<i>10%</i>	<i>20%</i>
Farina A et al 2004 (DNA Totale)	46	<b>50</b>	-
Farina A et al,2004 (DNA Fetale)	33	<b>50</b>	65

## PAI-1 e P-Selectina al 2 trimestre

		<i>Sensibilità ad un FPR di :</i>		
		<i>5%</i>	<i>10%</i>	<i>20%</i>
PAI-1	Baumann MU 2008 (late onset)	18	<b>22</b>	38
PAI-1	Stepan H 2008 (early onset)	60	<b>60</b>	60
P-Selectina	Chavarria ME 2008	75	<b>78</b>	-

## Gene expression in chorionic villous samples at 11 weeks' gestation from women destined to develop preeclampsia

Antonio Farina<sup>1\*</sup>, Akihiko Sekizawa<sup>2</sup>, Paola De Sanctis<sup>1</sup>, Yuditiya Purwosunu<sup>2,3</sup>, Takashi Okai<sup>2</sup>, Dong Hyun Cha<sup>4</sup>, Jin Hee Kang<sup>4</sup>, Claudia Vicenzi<sup>1</sup>, Annalisa Tempesta<sup>1</sup>, Noroyono Wibowo<sup>3</sup>, Luisella Valvassori<sup>1</sup> and Nicola Rizzo<sup>1</sup>

Table 3—Median (Min–Max) mRNA relative concentrations for cases and controls

mRNA species	PE <i>n</i> = 5	Controls <i>n</i> = 25	<i>p</i> -value <sup>a</sup>
Flt-1	84 249 (15 383.10–182 662.80)	21 710 (1056.70–86 196.00)	0.038
Eng	164 208 (123 381–2 865 316)	4150 (209.20–443 766.10)	<0.001
VEGFA	17.3 (9.30–87.80)	6.45 (1.70–50.50)	0.016
PlGF	1.57 (0.60–12.90)	12.50 (0.90–187.60)	0.014
TGF- $\beta$ 1	876 (206.8–7543.10)	143 (16.80–1347.40)	0.008
HO-1	0.50 (0.07–3.15)	2 (0.16–55.91)	0.047
SOD	166 (8.40–345.00)	237 (13.20–1460.90)	0.041

The gene expression is normalized for GAPDH.

<sup>a</sup> Mann–Whitney U test.

# Prediction of preeclampsia by analysis of cell-free messenger RNA in maternal plasma

Yuditiya Purwosunu, MD; Akihiko Sekizawa, PhD; Shiho Okazaki, PhD; Antonio Farina, PhD; Noroyono Wibowo, PhD; Masamitsu Nakamura, MD; Nicola Rizzo, PhD; Hiroshi Saito, PhD; Takashi Okai, PhD

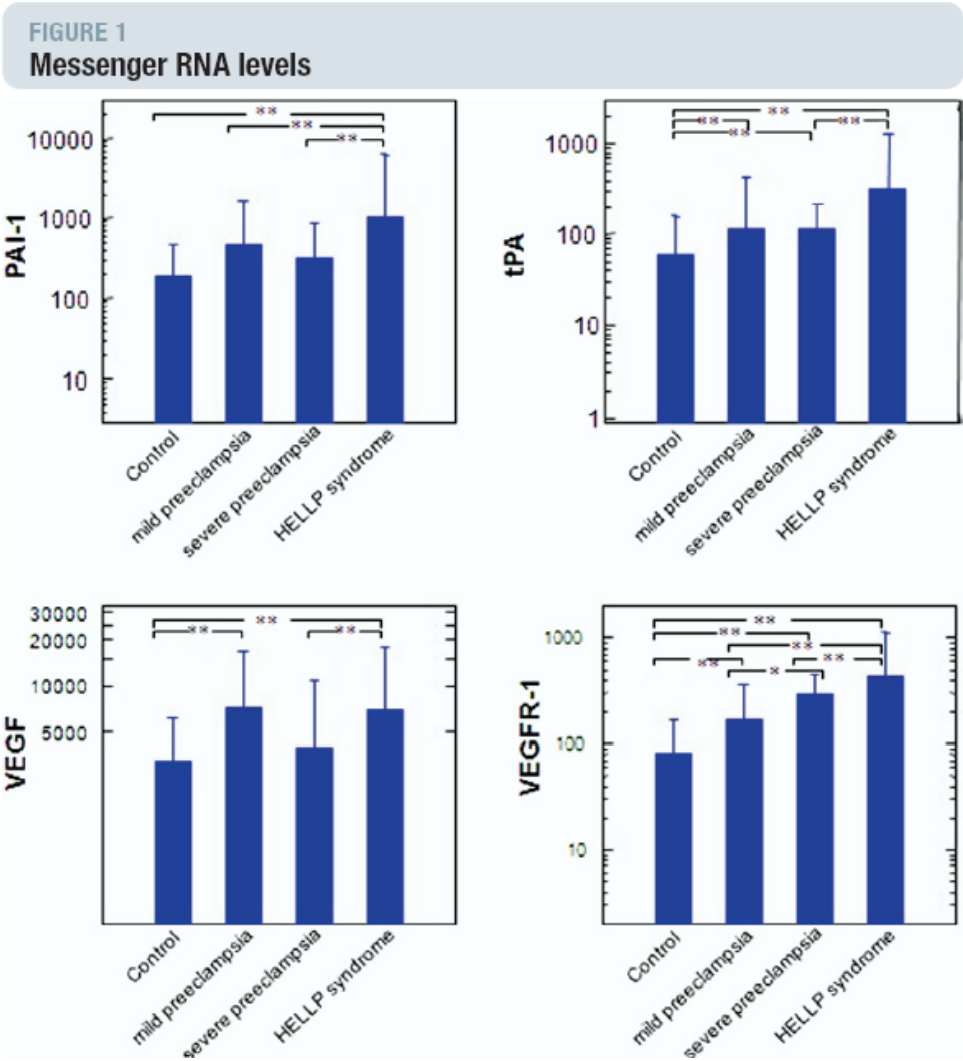


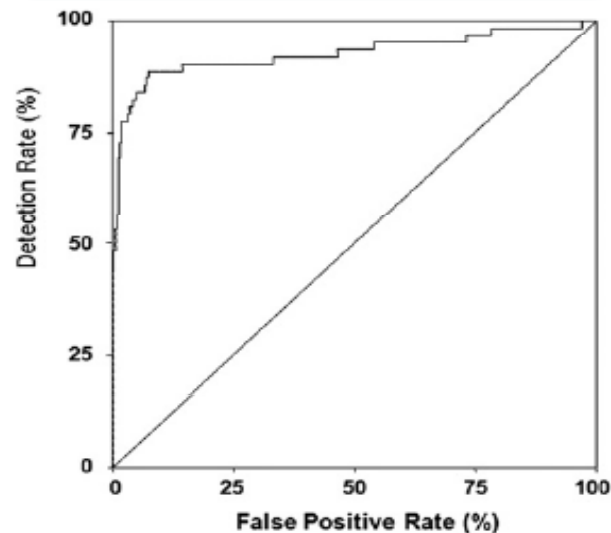
TABLE 5

Output of multivariable ROC curve with the use of the discriminant score of the development of preeclampsia as a test variable, according to the severity of the preeclampsia

Variable	Area under the curve	SEM	P value	95% CI for area under the curve		Detection rate at 5% false-positive rate (%)	95% CI for detection rate (%)	
				Lower	Upper		Lower	Upper
Mild preeclampsia (n = 26)	0.837	0.055	< .001	0.728	0.945	65.4	44.3	82.0
Severe preeclampsia (n = 24)	0.989	0.005	< .001	0.980	0.998	95.8	76.8	99.7
HELLP syndrome (n = 12)	0.997	0.004	< .001	0.991	1.000	100	69.8	100

Purwosunu. Prediction of preeclampsia by analysis of cell-free messenger RNA in maternal plasma. *Am J Obstet Gynecol* 2009.

FIGURE 2  
Multivariable ROC curve



Multivariable receiver operating characteristic (ROC) curve that was obtained with the discriminant score as a test variable for the prediction of preeclampsia.

# Conclusioni

- L'esperienza non ha fornito finora dati robusti per la applicazione prospettica di un test ai fini dello screening
- Appare più convincente il tentativo di produrre in futuro modelli predittivi che implicano la utilizzazione contemporanea di più markers di diverso genere

Fine