



BULLETIN

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Angiogenetic Factors in Preeclamptic Emergencies: Preclinic Alarm Biomarkers?

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December, 14-16, 2017 Saint-Petersburg

INTERNATIONAL CONGRESS

**Great Obstetrical and Neonatal Syndromes -
Pathophysiology and Clinical practice**



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Definition

PRE-ECLAMPSIA

- Hypertension and new onset Proteinuria after the twentieth week of gestation

SEVERE PRE-ECLAMPSIA

- Severe Hypertension ($\geq 160/110$ mmHg)
- Multi-organ involvement (Oliguria, Headache, Paraesthesia, Reducing Visual Acuity, Epigastric pain, Right Hypochondrium pain, HELLP Syndrome)
- Fetal growth restriction

ECLAMPSIA

- Generalized tonic-clonic convulsions
- Coma state
- Exitus

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- Comatose state
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Birth is the only therapeutic treatment

Overview

Epidemiology:

- Incidence: 5-8% of all pregnancies (8.5 million per year)
- Eclampsia 1%
- High rate in low-income countries due to poor access to standard healthcare

Risk Factors:

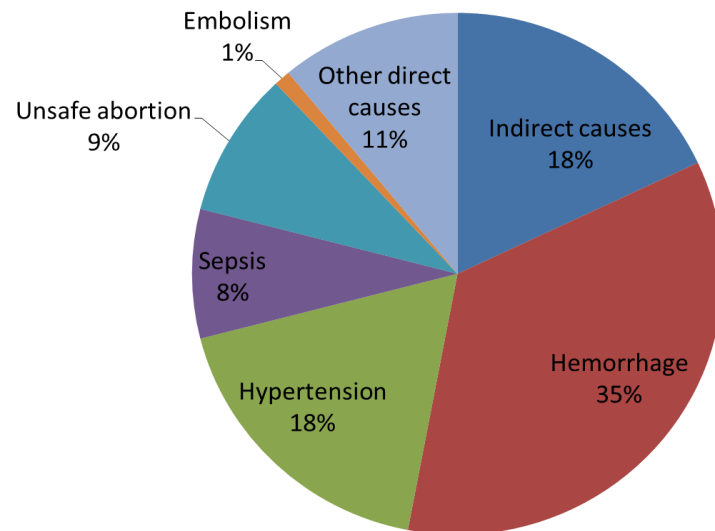
- Age < 18 e > 35 years
- First pregnancy or new partner
- Hypertension or pre-existing nephropathy
- Familiarity or previous PE
- Pregravidic diabetes
- Antiphospholipid antibodies syndrome

Mortality:

- 15-20% of maternal deaths (2nd cause)

The main causes of maternal mortality

Source: estimates OMS 2010 on data 1997-2007



Italy: 9 maternal deaths per 100,000 live births (rare)

Current diagnostic criteria:

- Blood pressure $\geq 140/90$ mmHg
- Proteinuria $\geq 0,3$ g/24 hours
- Headache
- Visus disorders
- Epigastric pain
- HELLP syndrome
- Convulsive crisis

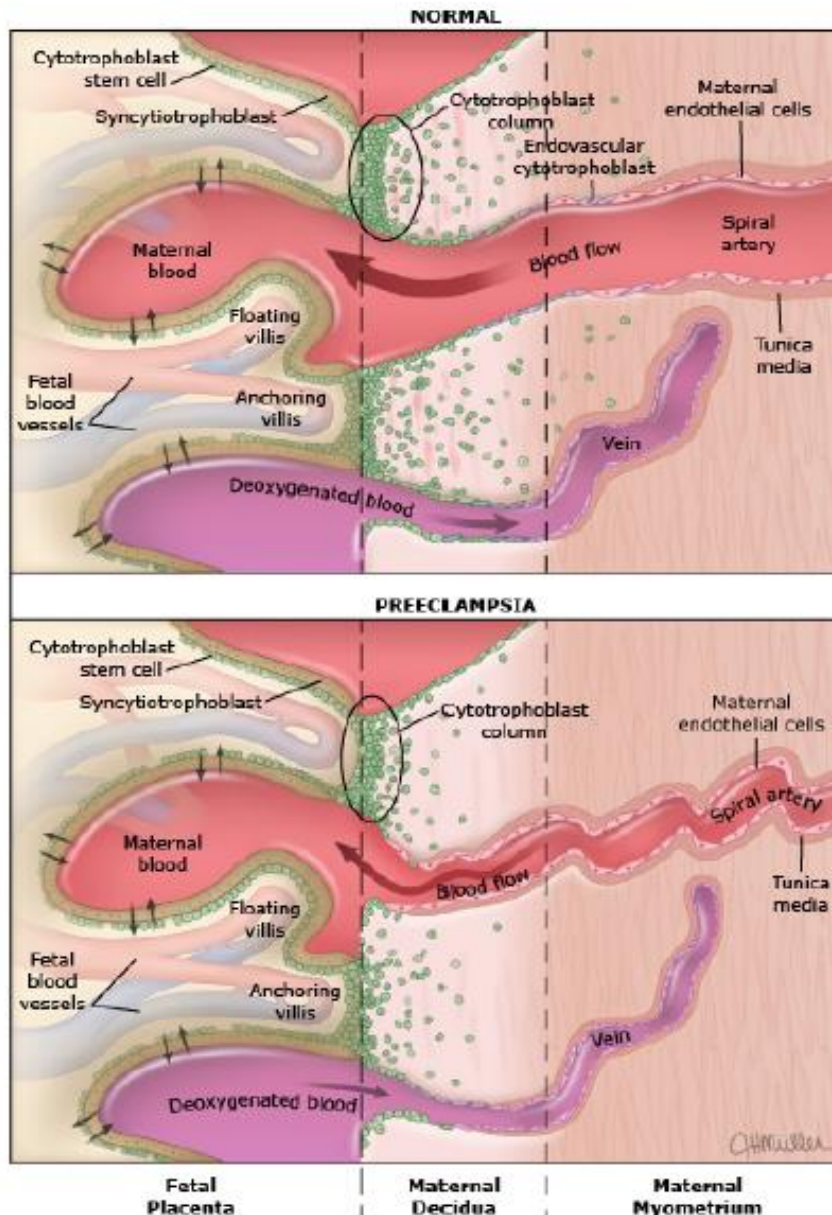


Delay or lack of diagnosis and treatment



Excessive or unnecessary medicalization of pregnancy

Pathogenesis



Two-stage theory of placental dysfunction:

- Lack of invasion of the spiral arteries by the trophoblast cells (pseudo-vasculogenesis) → placental hypoperfusion = *hypoxic insult*
- Oxidative stress and inflammatory framework with consequent release of cytokines and pro-inflammatory factors → *endothelial dysfunction*

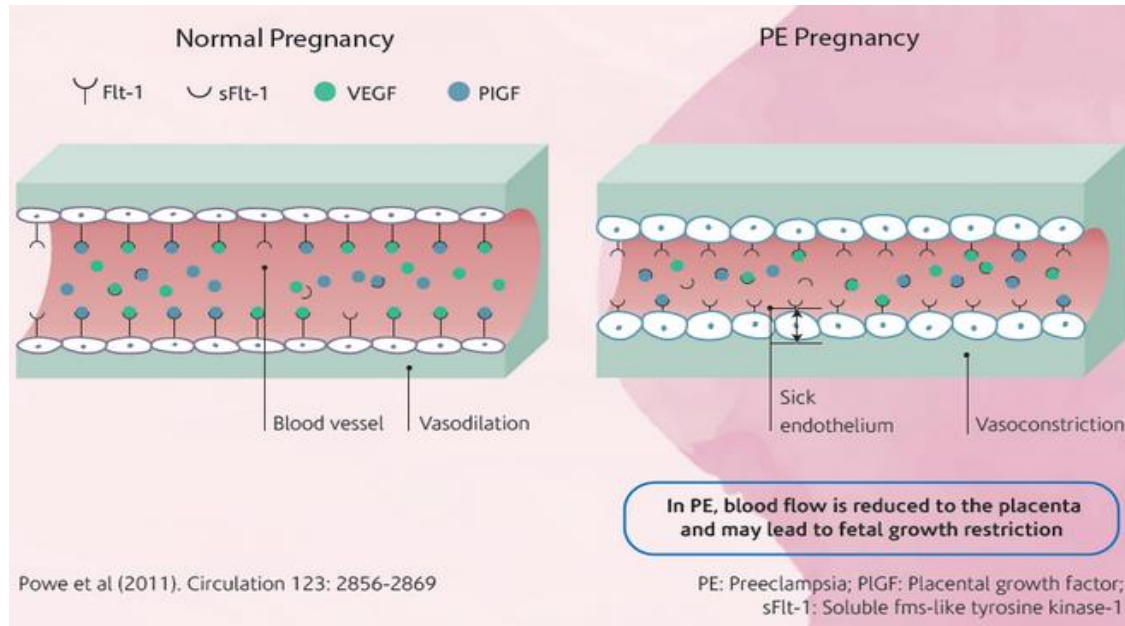
Angiogenic factors

PlGF :

- Family of the VEGF
- Produced primarily by the trophoblast
- Actions: angiogenesis, vasodilation, apoptosis inhibition
- Physiologically: gradual increase in I Trimester, rapid increase in II Trimester (peak 29 ° - 32 ° w), decrease in III Trimester.

sFlt-1:

- Soluble variant of the VEGFR-1 (Flt-1)
- Produced by the maternal endothelium
- Action: PlGF binding, reducing its free quote = anti-angiogenetic action
- Physiologically: constant during I and II trimester, III trimester gradually increase



Angiogenic factors

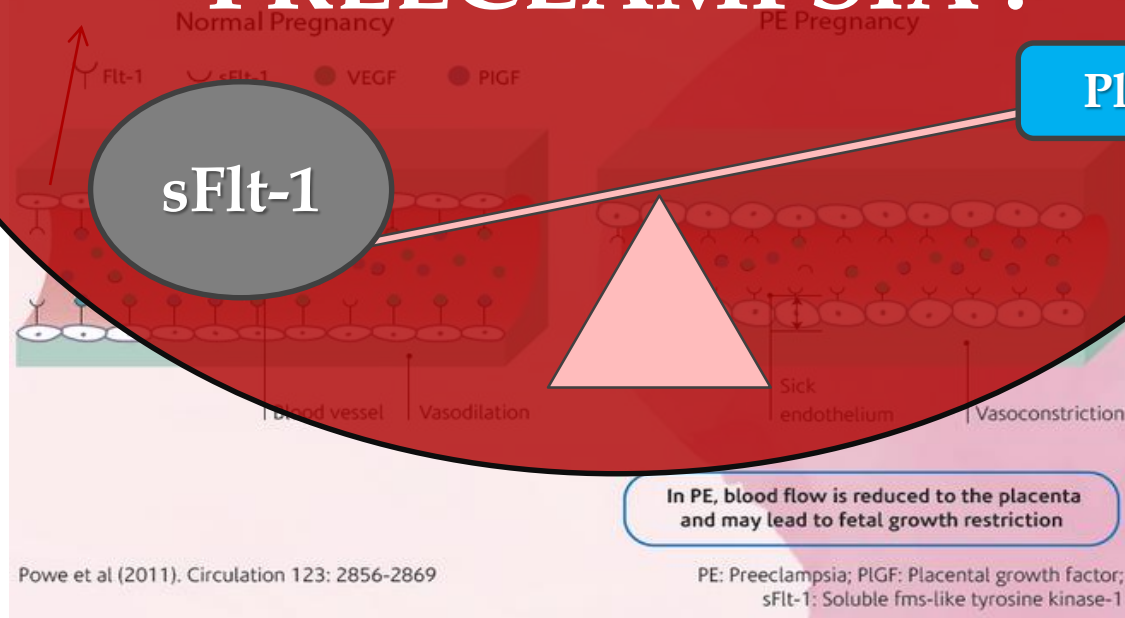
PlGF :

- Family of the VEGF
- Produced primarily by the trophoblast
- Actions: angiogenesis, vasodilation, apoptosis inhibition
- Physiologically: gradual increase in I quarter, rapid increase in II quarter (peak 29 ° - 52 ° w), decrease in III quarter

sFlt-1:

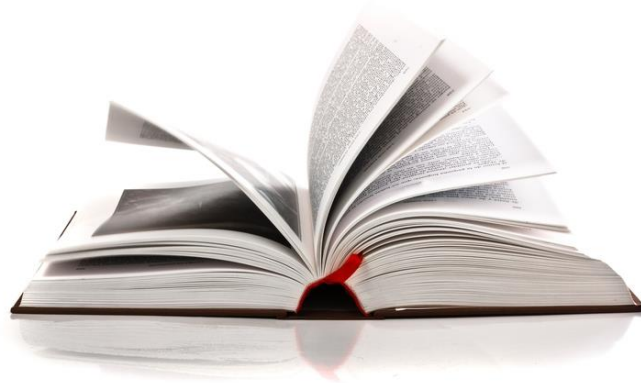
- Soluble variant of the VEGFR-1 (Flt-1)
- Produced by the maternal endothelium
- Action: PlGF alloy, reducing its free
- Physiologically: constant during I and II quarter, III quarter increases gradually.

IN PREGNANCY COMPLICATED BY PREECLAMPSIA :



State of the art

- Risk stratification
- Improved sensitivity and specificity of diagnosis
- The sFlt-1/PlGF ratio has a better predictive index than the two markers individually (Studio PROGNOSIS)
- Confirmation of diagnosis > 85(early) or > 110 (late)
 - Positive predictive value within 4 weeks 38-85 or 110
 - Negative predictive value at one week <38
- Support in the decision-making process of doctors (Studio PreOS)



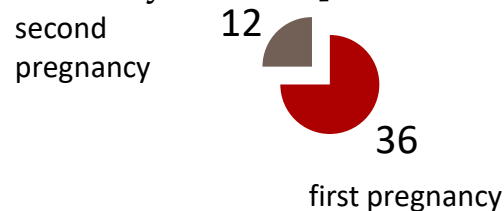
Our study

Design

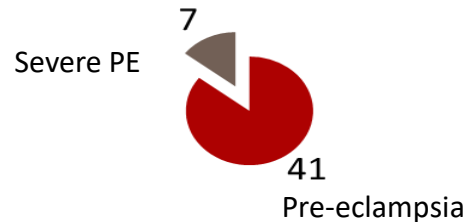
- Retrospective and prospective study on pregnant women with suspected or open preeclampsia clinical manifestations visited or admitted to Obstetrics-Gynecology Unit 2 of Pisa University Hospital from September 2010 to February 2017 with at least one plasma value of sFlt-1 and PlGF and who had given birth to this Unit.
- Data analysis organized in four clinical setting.

Sample

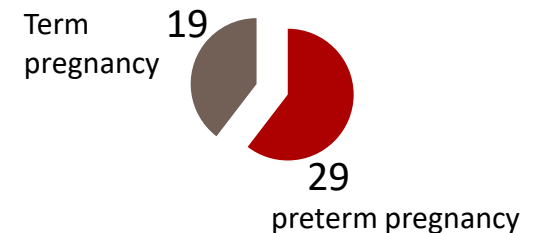
- 49 pregnant women > 20th weeks (one excluded) median age 35 years [CI 95% 34-36 years old]



NUMBER OF PREGNANCIES



CLINICAL FEATURES



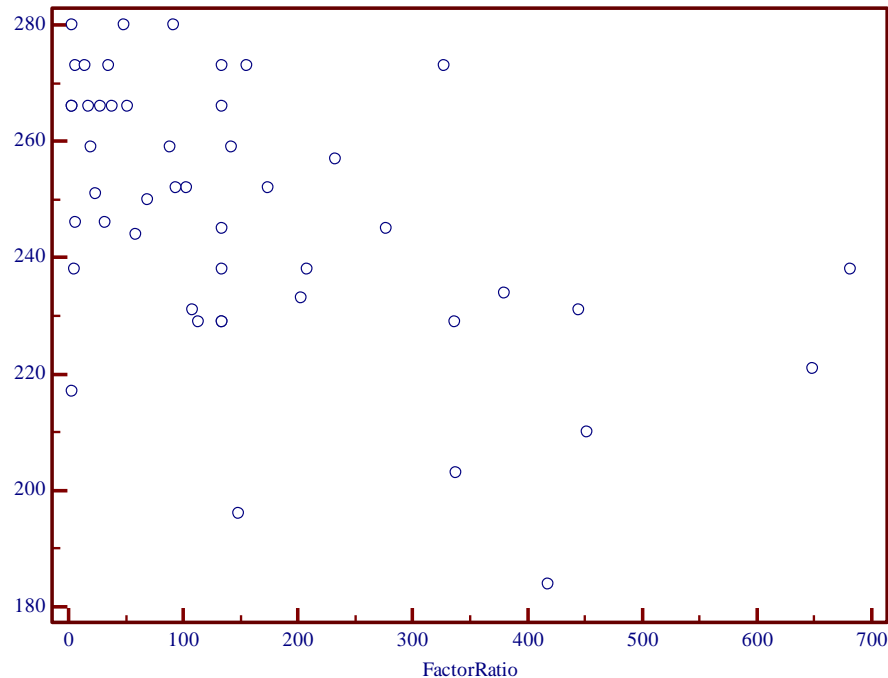
GA AT CHILDBIRTH

Goals

- Can angiogenic biomarkers in a single dosage be an early warning indicator in the expected critical clinical settings in a patient with preeclampsia or eclampsia?

First clinical setting: Can a single dose of sFlt-1/PlGF be a sign of pre-term delivery in women with pre-eclampsia?

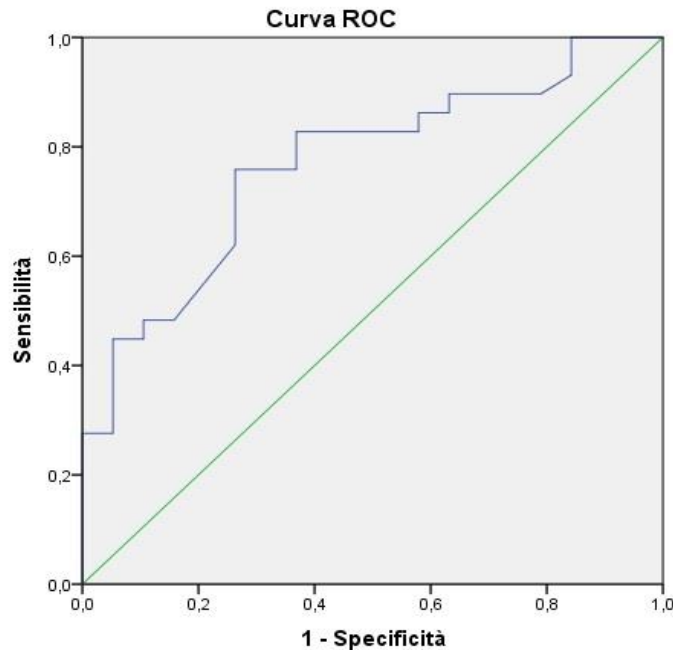
Linear regression:



Regression coefficient = - 0,71 (P-value < 0,0002)

Pearson correlation coefficient = 0,518 (good correlation)

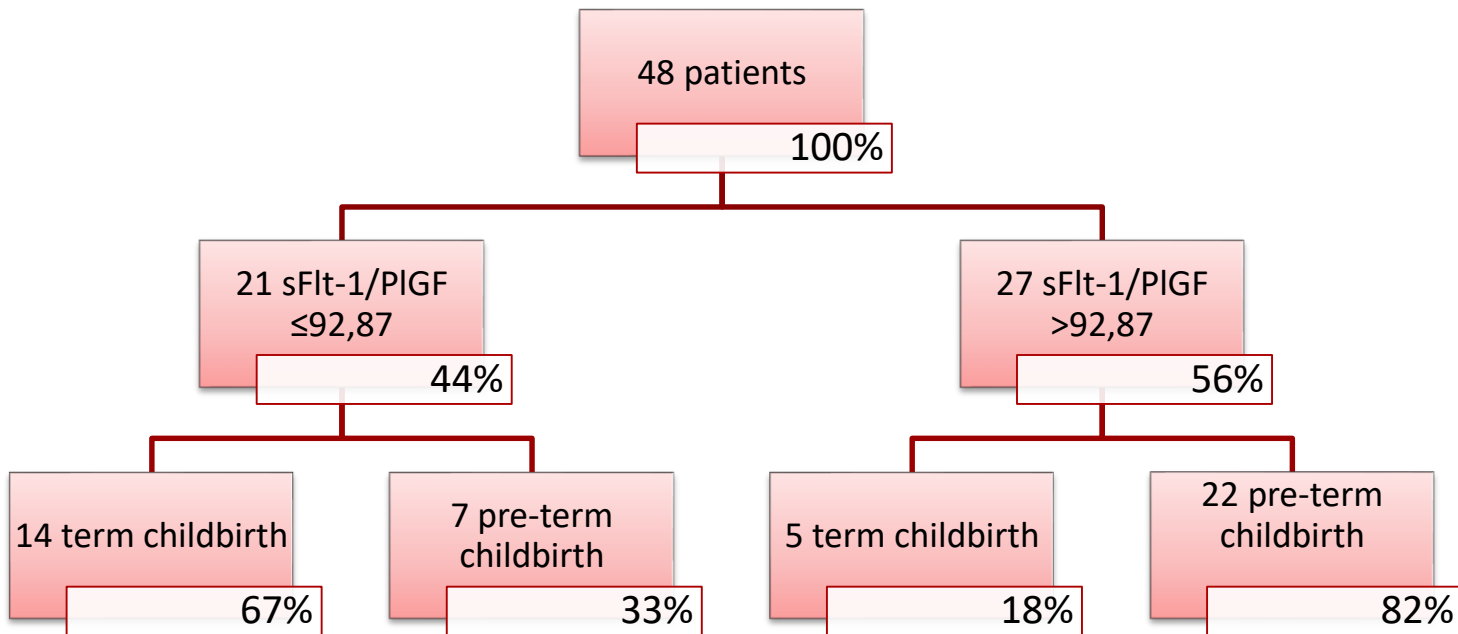
Test accuracy:



- Variable of the test:
sFlt-1/PlGF
- Variable of correlation:
preterm childbirth

	Sens. %	Spec. %
>68,63	75,86	63,16
>92,87	75,86	73,68
>113,18	62,07	73,68
>133,83	48,28	84,21

The value *sFlt-1 / PlGF* > 92.87 is indicative of pre-term delivery with a sensitivity of 76% and a specificity of 74%



	Pre-term (< 37 w)	At term (≥ 37 w)
sFlt-1/PlGF $> 92,87$	22	5
sFlt-1/PlGF $\leq 92,87$	7	14

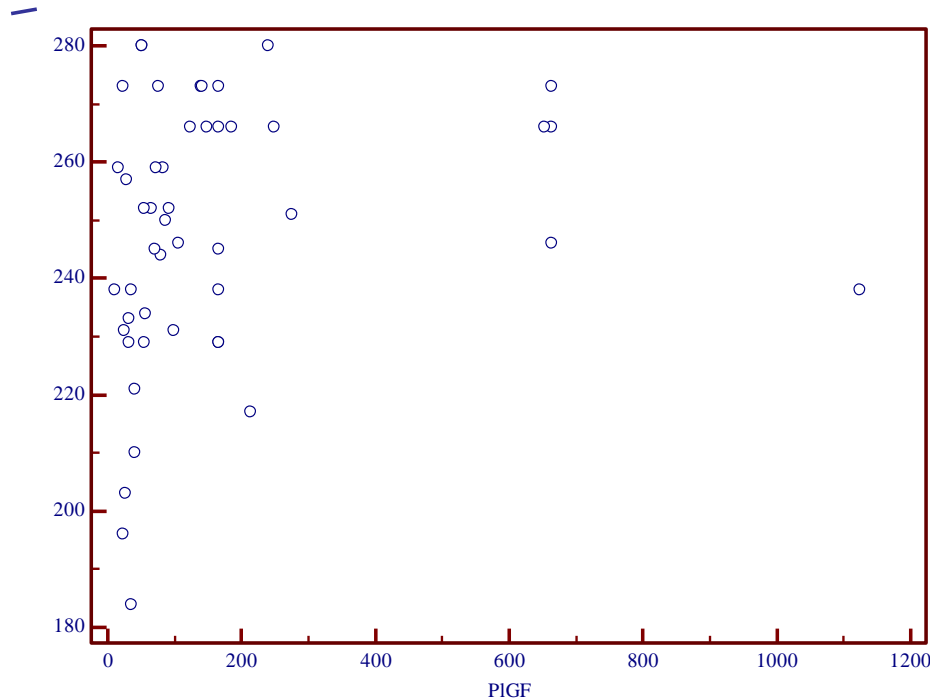
For values of $sFlt-1/PlGF > 92.87$ the patient will hesitate in a pre-term delivery.

[X^2 with continuity correction = 9,526 ($P < 0,002$)]

The association between $sFlt-1/PlGF > 92.87$ and pre-term delivery is strongly positive [OR=8,8]

Second clinical setting: sFlt-1/PlGF Ratio versus PlGF alone. What is the best index of a pre-term childbirth?

Linear regression:

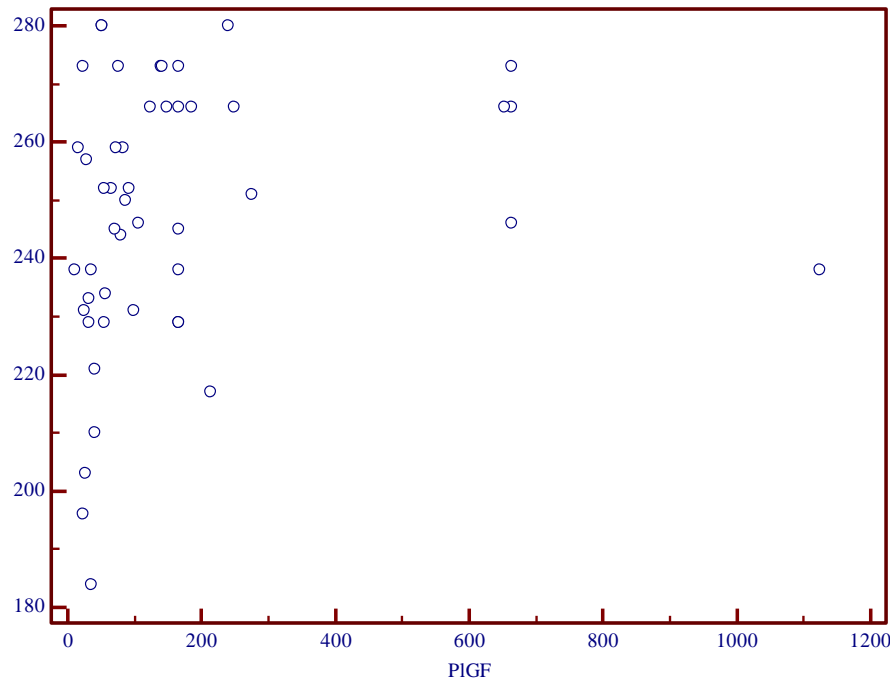


Pearson correlation coefficient = 0.196 (Very weakly correlation)

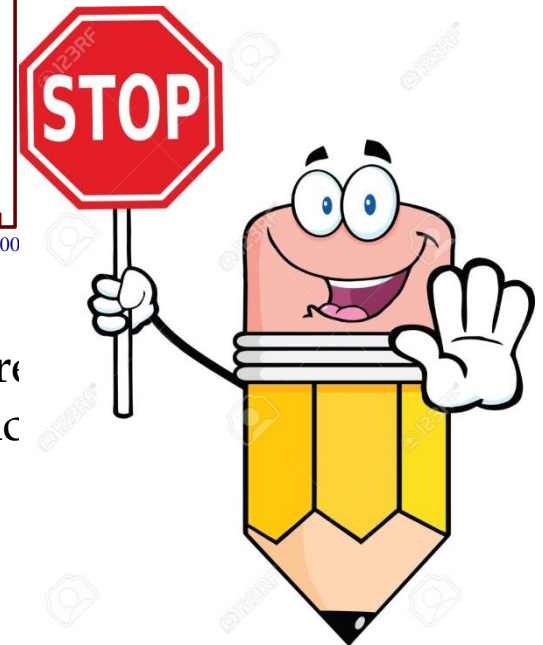
The regression coefficient is +0.20 ($P < 0.182$) (Not significant)

Second clinical setting: sFlt-1/PlGF Ratio versus PlGF alone. What is the best index of a pre-term childbirth?

Linear regression:



Pearson correlation coefficient = 0.196 (Very weakly correlated)
The regression coefficient is +0.20 ($P < 0.182$) (Not significant)



Third clinical setting: A single dosage of angiogenic biomarkers is predictive of severe preeclampsia or eclampsia?

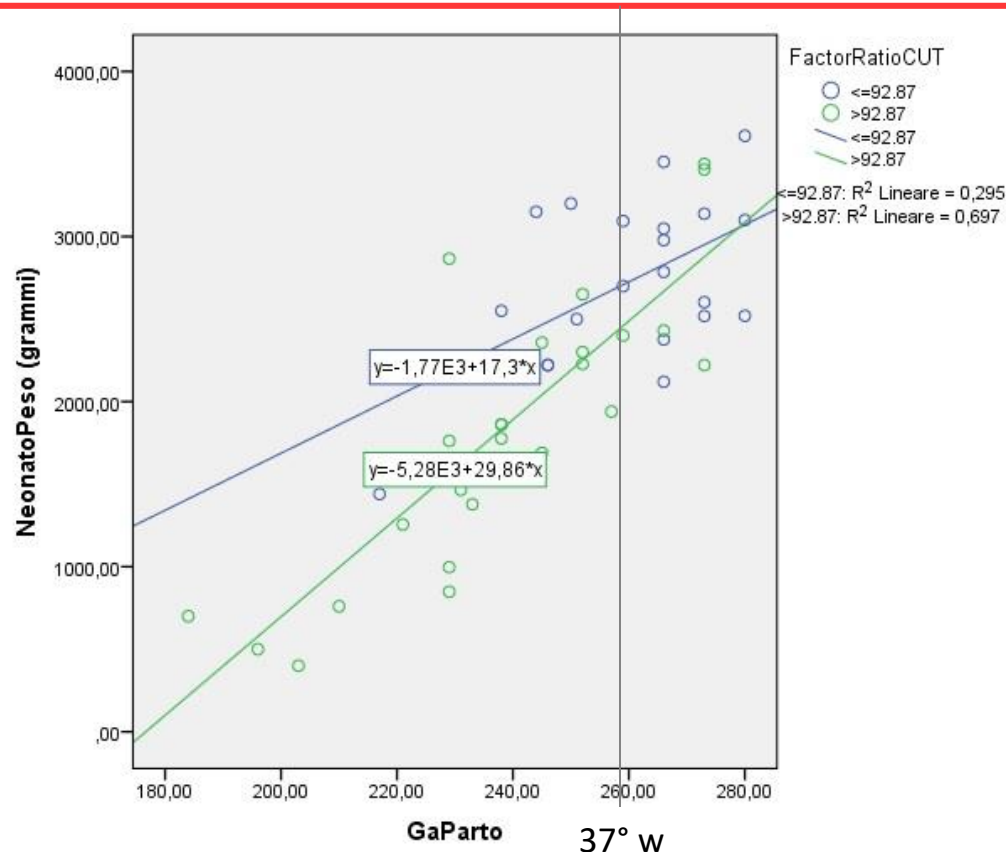
U di Mann-Whitney Test to independent samples

- The distribution of **sFlt-1/PlGF** ratio is the same between the two subpopulations with asymptotic significance $P < 0.627$.
- The distribution of **PlGF** is the same between the two subpopulations with asymptotic significance $P < 0.753$.

Case study extention?
Seriate dosage?



Fourth clinical setting: Does the sFlt-1/PlGF Ratio correlate with birth weight?

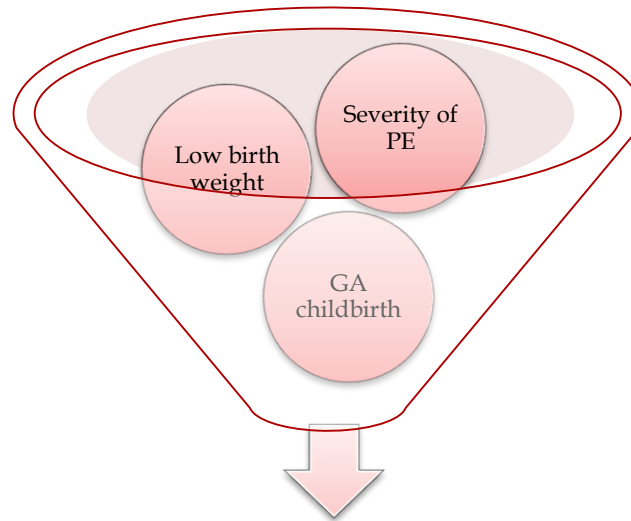


At the same gestational age:

Birth weight of newborns from mothers *sFlt-1/PlGF Ratio* > 92.87

Birth weight of newborns from mothers *sFlt-1 /PlGF Ratio* ≤ 92.87

Conclusions



- The elevated values of sFlt-1 / PlGF, even in single dosage, have proved to be indicative of placental insufficiency:
 - Childbirth before the expected date of birth (1st setting)
 - Low birth weight (4th setting)

This suggests that in these cases the waiting treatment does not benefit either the mother or the fetus, since the placental hypoxia and metabolic acidosis associated with prematurity, increase the risk of perinatal mortality/morbidity.
- The predictive role on maternal neurological severe complications is uncertain since the single dosage was not significant.

**Are angiogenic biomarkers alarm
indices?**



Are angiogenic biomarkers alarm indices ?

*The answer is definitely YES
for the fetus ... and also for the mother.*



Are angiogenic biomarkers alarm indices ?

The answer is : YES

Both for the fetus ... and also for the mother.



THANKS FOR YOUR ATTENTION