Perinatal Medicine 2019
9-11 May 2019, Hilton Hotel • İzmir, Turkey

# First trimester screening of preeclampsia; sFlt-1/PIGF-ratio

Doç. Dr.Halil Aslan

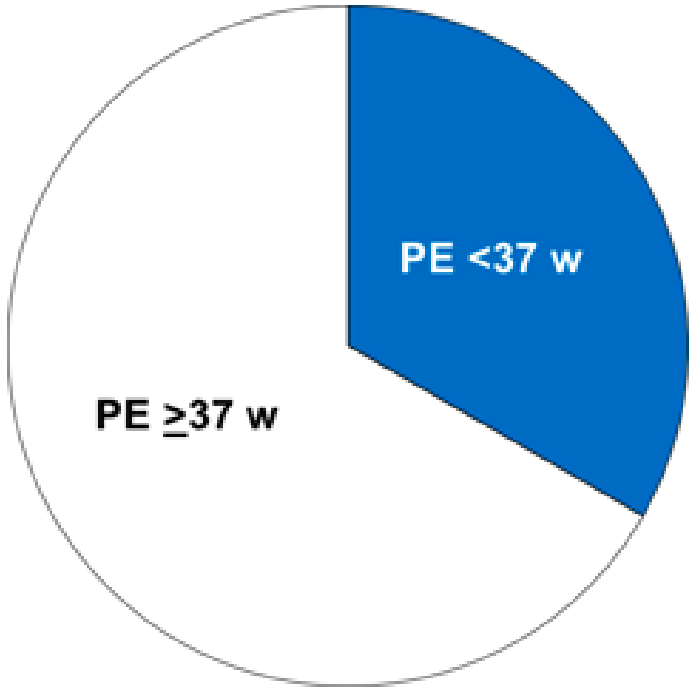
# Ağır bir obstetrik komplikasyon: Preeklampsi

| Maternal | Normal outcome (n=225,656) | Pre-eclampsia (n=10,379) |
|---|---|---|
| Induction of Labour | 21.5% | 52.3% |
| CS (labour) | 16.1% | 17.8% |
| CS (no labour) | 13.1% | 22.0% |
| APH | 0.8% | 1.5% |
| Severe PPH | 0.7% | 1.6% |
| Acute renal failure | 0.1% | 0.5% |
| ITU admission | 0.1% | 2.0% |
| Composite morbidity | 1.6% | 6.4% |

| Perinatal | Normal outcome (n=230,370) | Pre-eclampsia (n=10,952) |
|---|---|---|
| Fetal Death | 0.59 | 0.74% |
| Preterm birth (20-32) | 1.3 | 4.4% |
| Preterm birth (33-36) | 4.7 | 15.2% |
| SGA | 9.4 | 14.8% |
| 5 min Apgar <7 | 1.5 | 2.6% |
| NNU admission | 2.3 | 7.2% |
| Comp morbidity / mortality | 3.3 | 9.2% |

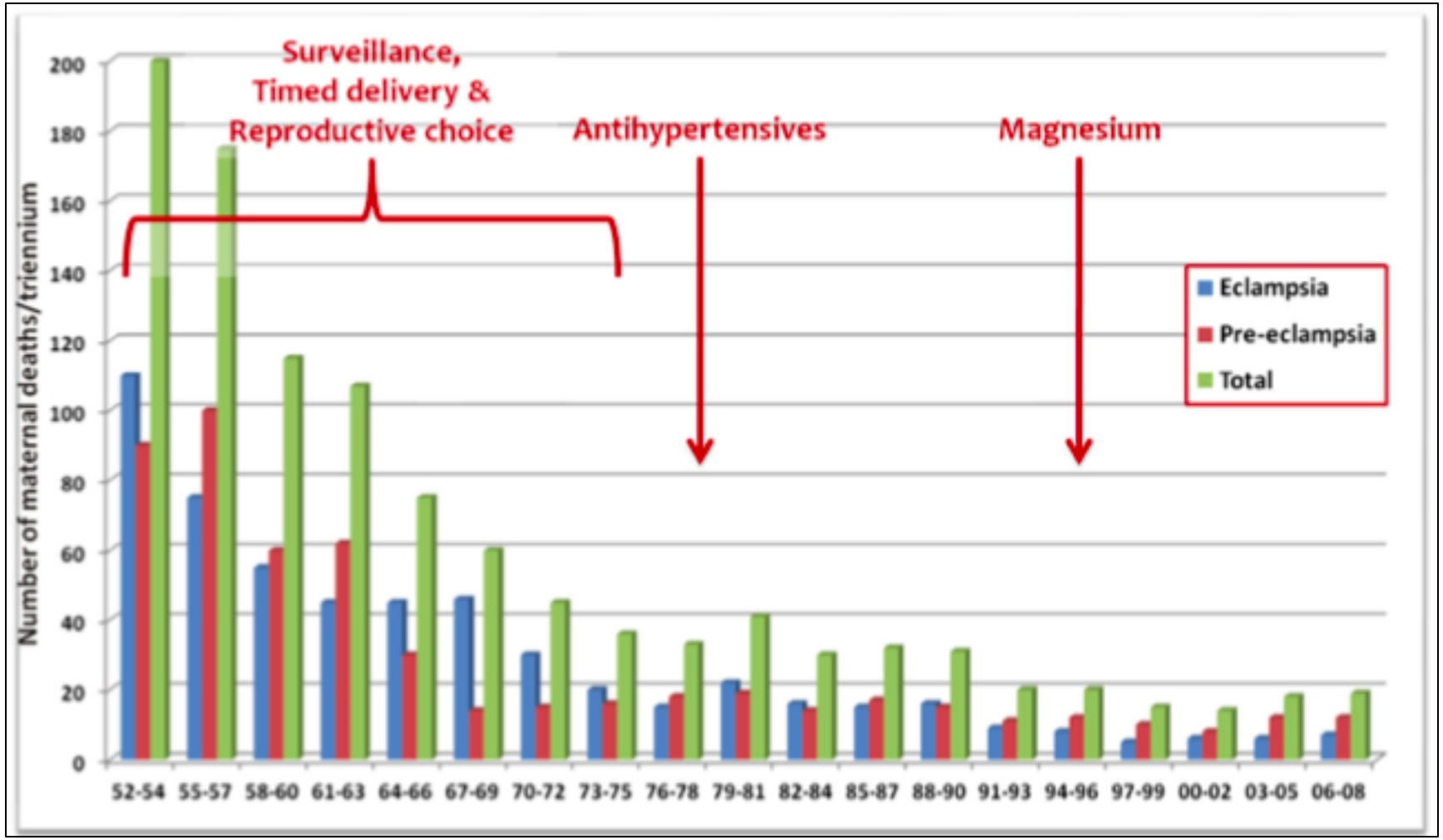
Roberts ve ark 2005

50 000-75 000 maternal ölüm /yıl

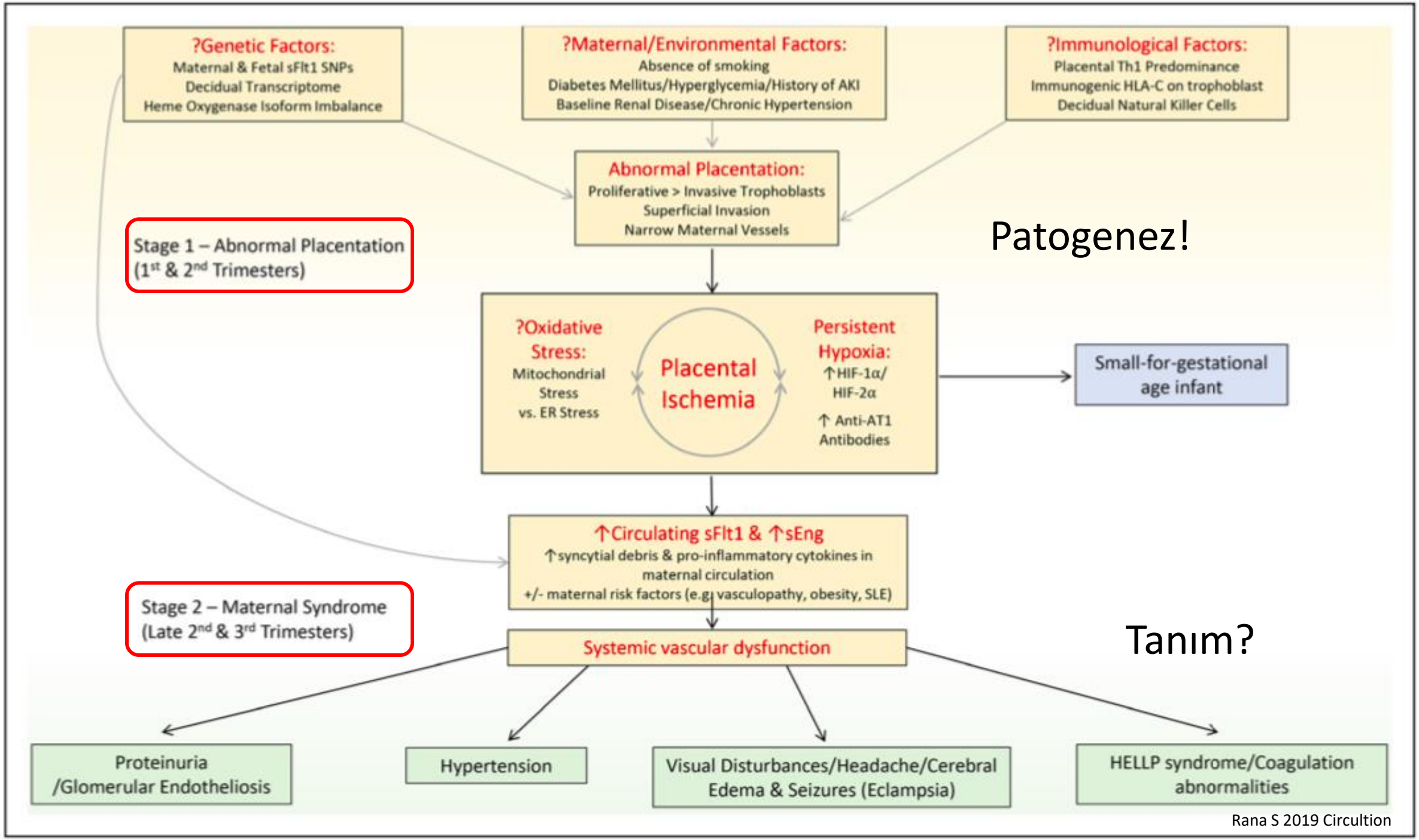



<32 hf preterm doğumların %20

# Preeklampsi-eklampsiye bağlı ölümler




Von Dadelszen P 2014 Curr Hypertens Rep




Rana S 2019 Circultion

The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

# COMMITTEE OPINION

Number 638 • September 2015

**Committee on Obstetric Practice**

*This document has been endorsed by the Society for Maternal–Fetal Medicine. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.*

## First-Trimester Risk Assessment for Early-Onset Preeclampsia

**ABSTRACT:** Hypertensive disorders with adverse sequelae (including preterm birth, maternal morbidity and mortality, and long-term risk of maternal cardiovascular disease) complicate 5–10% of pregnancies. Early identification of pregnant women at risk of developing early-onset preeclampsia would theoretically allow referral for more intensive surveillance or application of preventive therapies to reduce the risk of severe disease. In practice, however, the effectiveness of such triage would be hindered by the low positive predictive value for early-onset preeclampsia reported in the literature. In spite of the modest predictive value of first-trimester preeclampsia risk assessment and the lack of data demonstrating improved clinical outcomes, commercial tests are being marketed for the prediction of preeclampsia in the first trimester. Taking a detailed medical history to evaluate for risk factors is currently the best and only recommended screening approach for preeclampsia; it should remain the method of screening for preeclampsia until studies show that aspirin or other interventions reduce the incidence of preeclampsia for women at high risk based on first-trimester predictive tests.

# Preeklampsi Risk Faktörleri

**High risk factors**

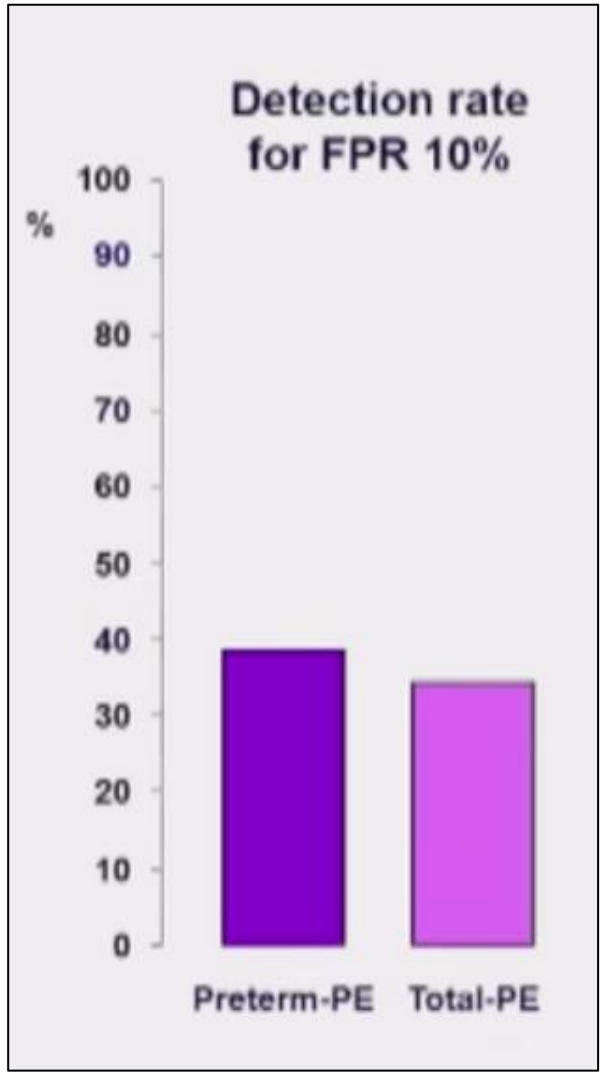
- Previous preeclampsia
- Chronic renal disease
- Chronic hypertension
- Diabetes mellitus
- SLE or APS

World Health Organization

NICE National Institute for Health and Care Excellence

**Moderate risk factors**

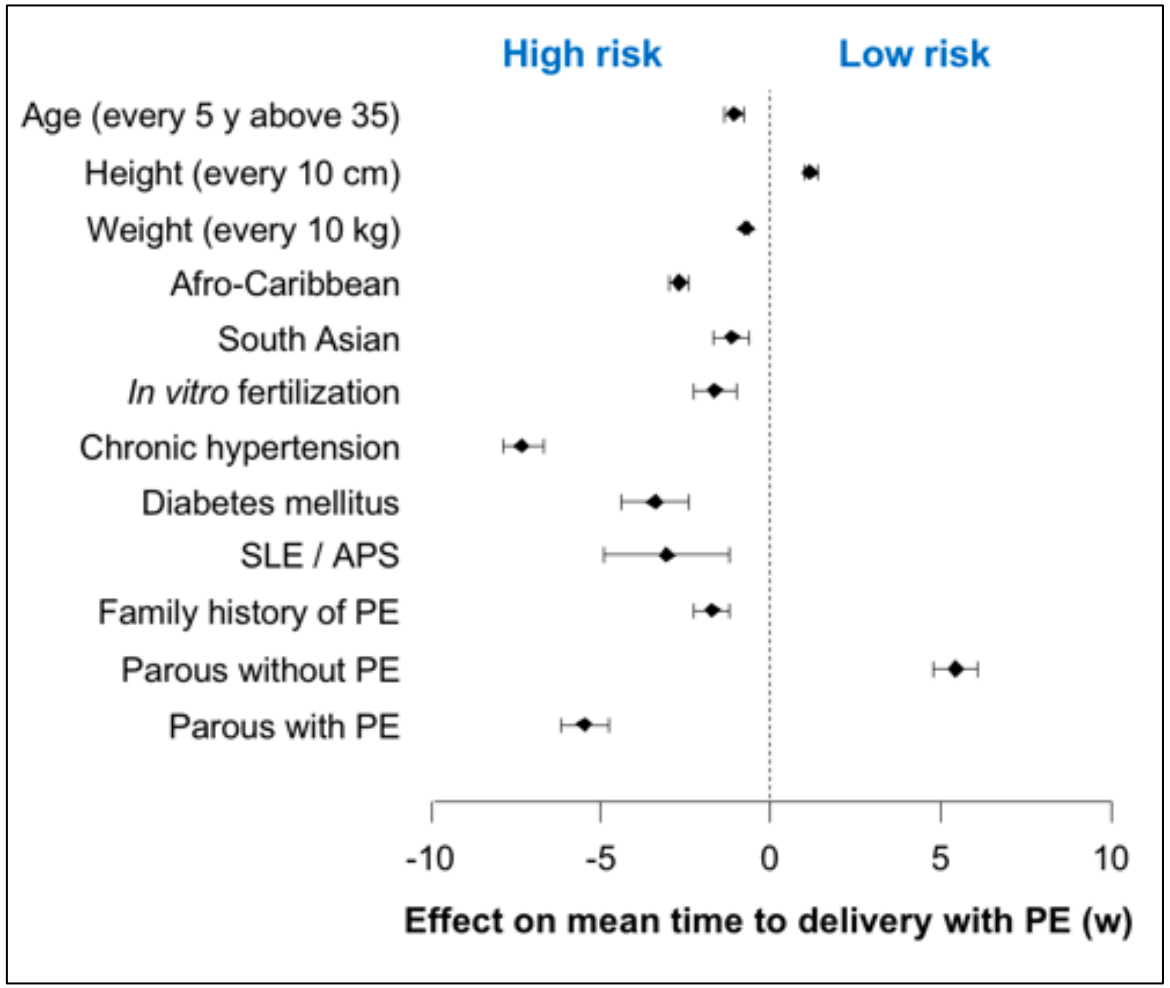
- First pregnancy
- Age ≥ 40 yrs
- Body mass index ≥ 35 kg/m²
- Inter-pregnancy interval > 10 yrs
- Family history of preeclampsia

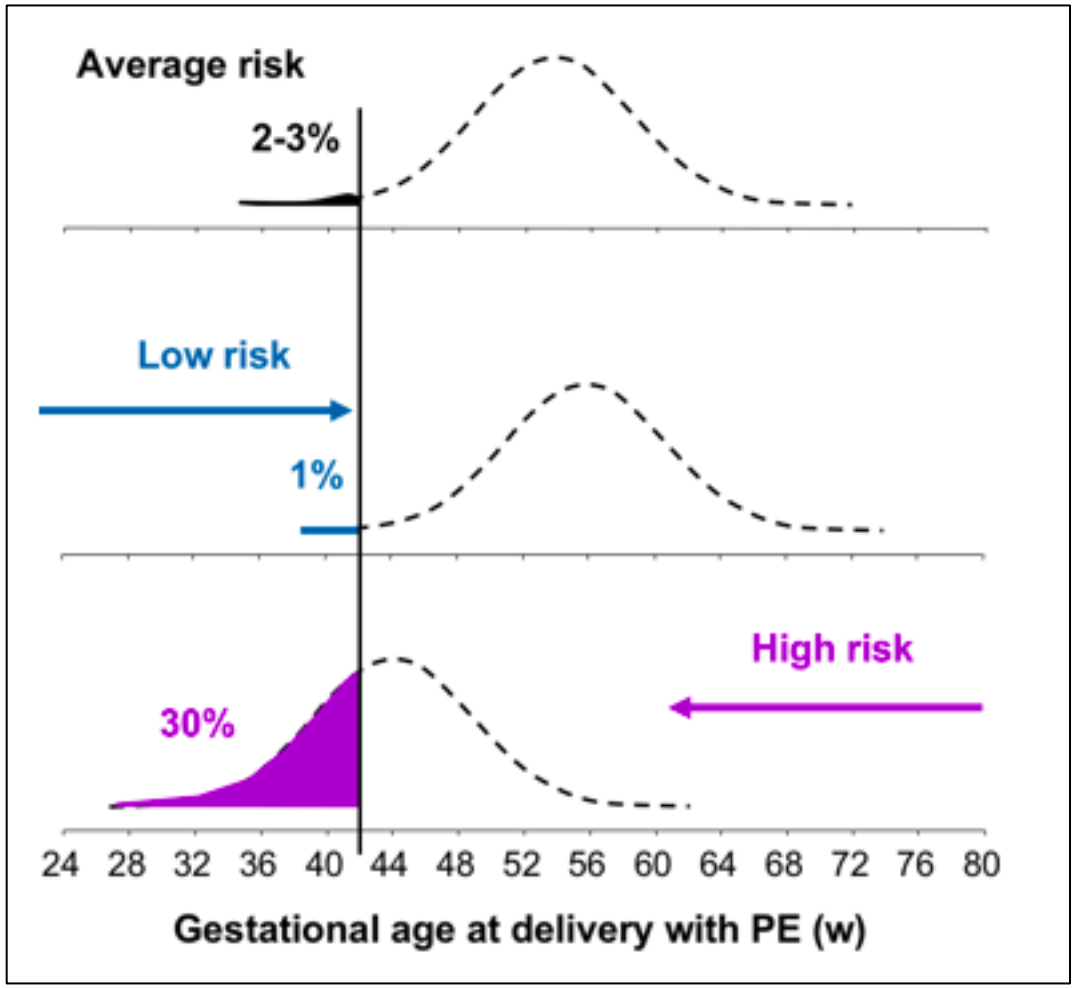


OBSTETRICS

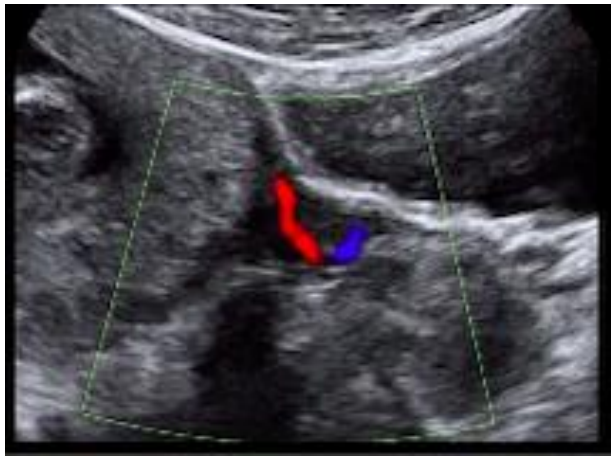
# Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation

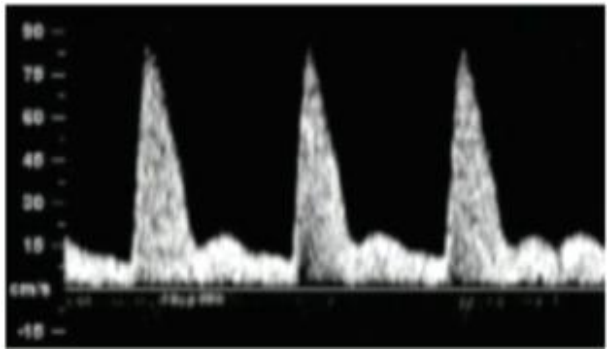
Neil O'Gorman, MD; David Wright, PhD; Argyro Syngelaki, RM; Ranjit Akolekar, MD; Alan Wright, PhD; Leona C. Poon, MD; Kypros H. Nicolaides, MD



# Uterin Arter PI (UtA PI)

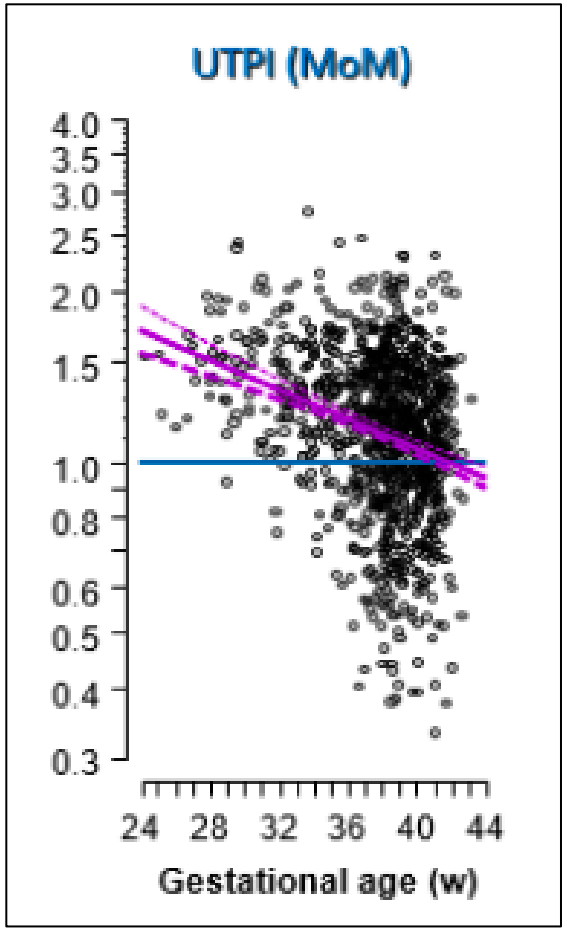




**Birinci trimester Transabdominal usg**

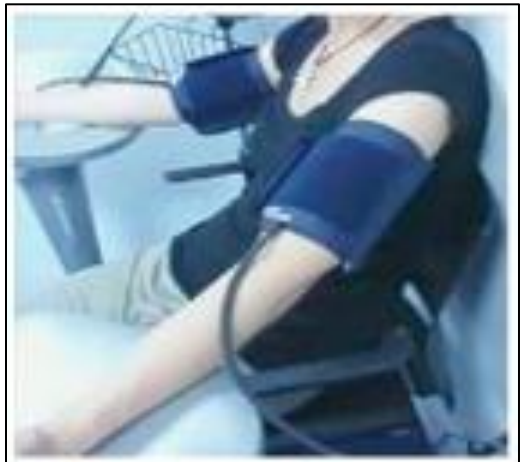
Uterin arterlerin bulunması:
- Renkli Doppler Cx sagittal kesit
- Orta hattan yanalara doğru, IO seviyesinde

Örnekleme aralığı: 2mm damarı tamamen kaplamalı
İnsonasyon açısı: < 30
PSV: > 60 cm/sn
Ortalama PI: sağ+sol/2




Plasencia W 2007 Ultrasound Obstet Gynecol

# Ortalama arter Basıncı (MAP)

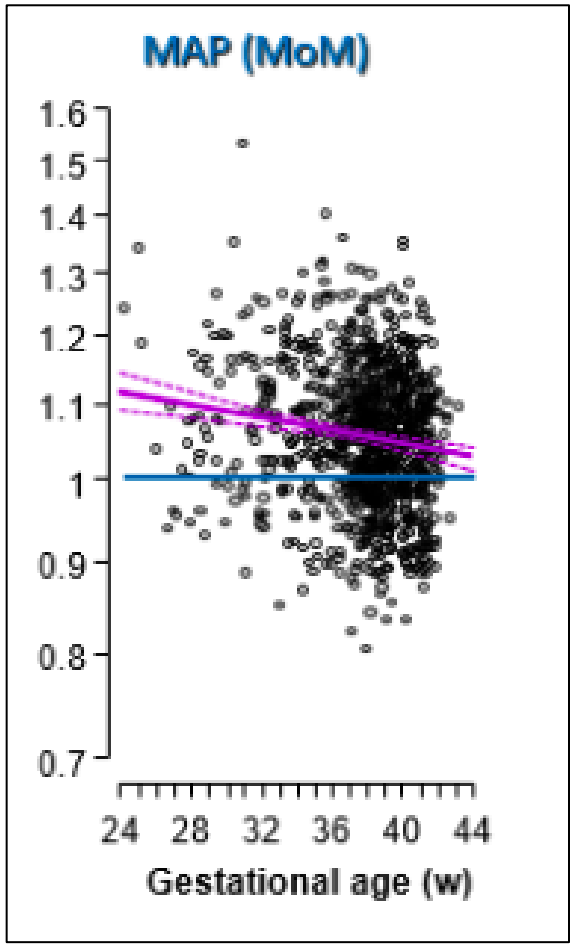


**Cihaz:** Düzenli kalibrasyon yapılan otomatik cihazlar

**Yöntem:** 5 dk istirahat sonrası kollar kalp seviyesinde

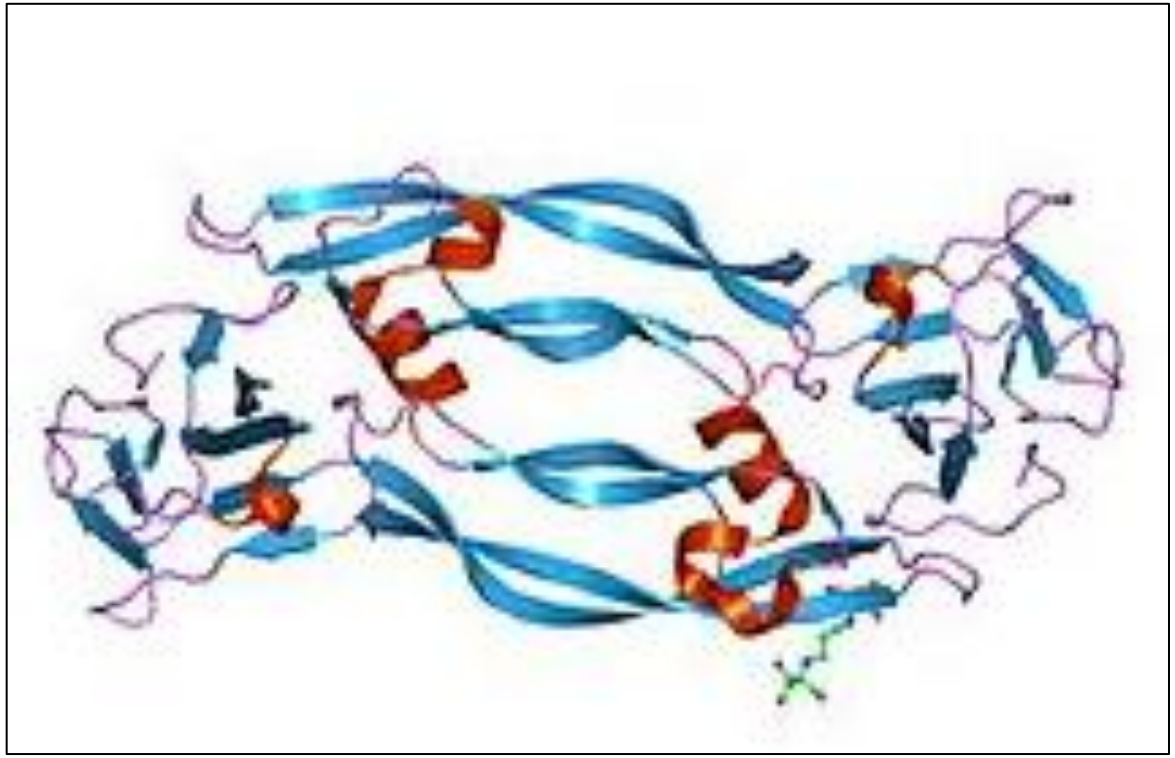
**Manşon boyutu:** Kolun kalınlığına göre küçük <22 cm, normal 22-32 cm, büyük 33-42 cm

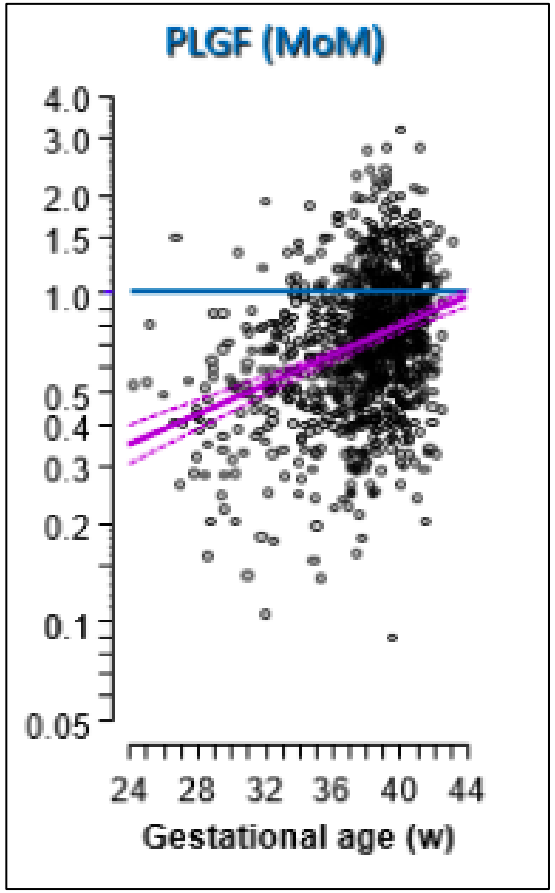
**Ölçüm:** Her iki kolda 2 ölçüm ve ortalaması alınır




Poon LC 2012, Fetal Diagn Ther

# Placental Growth Factor (PlGF)

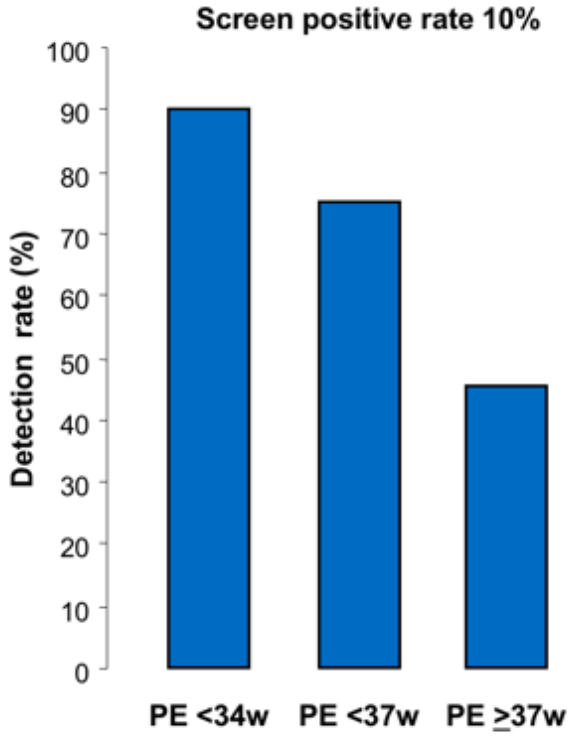





Tsiakkas A 2015 Ultrasound Obstet Gynecol

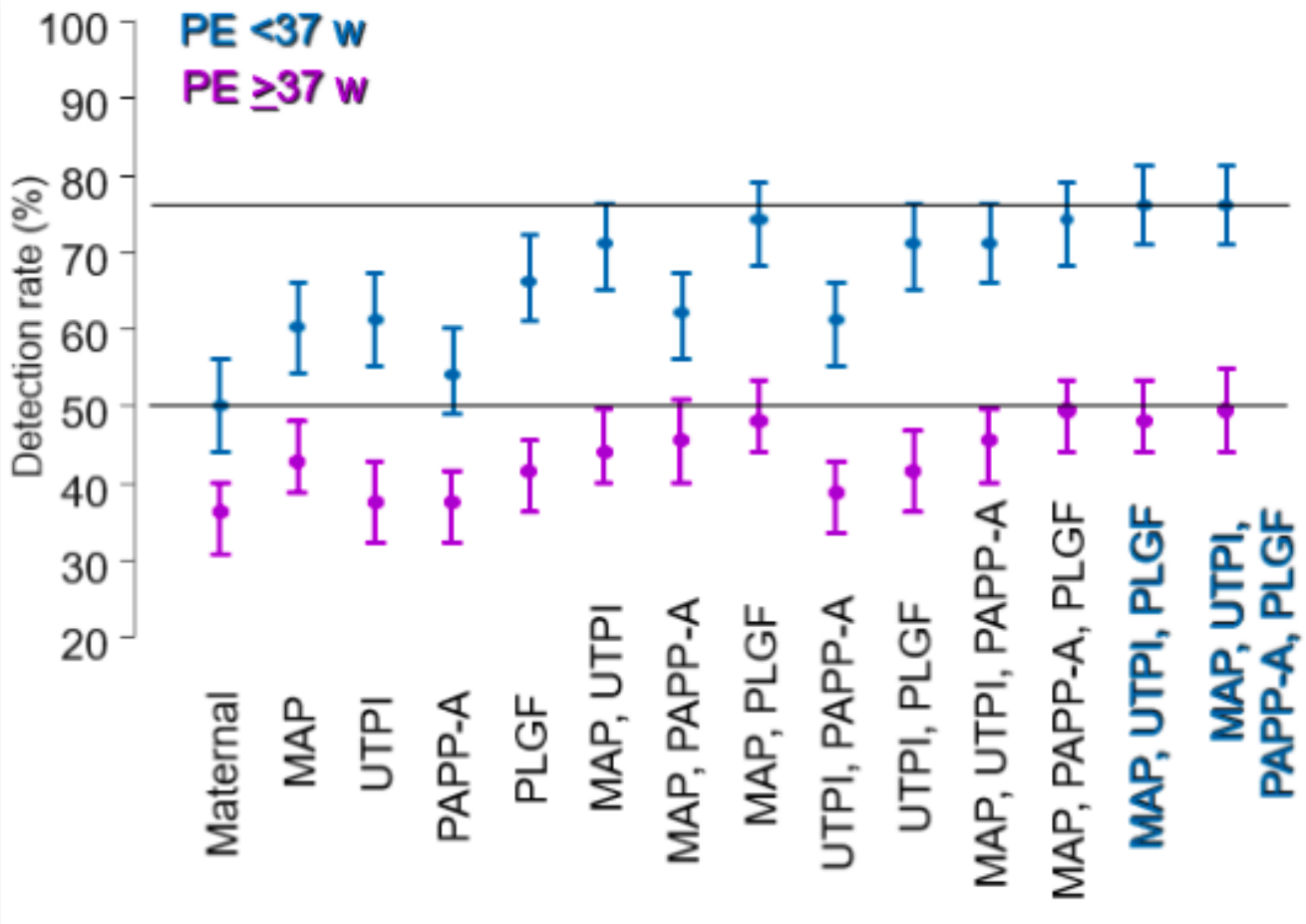
# Maternal risk faktörleri

+


| Method of screening | Detection rate | | |
|---|---|---|---|
| | PE <34 w | PE <37 w | PE ≥37 w |
| Maternal factors | 58% | 50% | 38% |
| Maternal factors plus: | | | |
| MAP | 65% | 60% | 43% |
| MAP, UTPI | 80% | 70% | 44% |
| MAP, PLGF | 85% | 73% | 47% |
| MAP, UTPI, PLGF | 90% | 75% | 47% |

Fetal Medicine Foundation 2014




| Method of screening | DR % |
|---|---|
| History | 48 |
| + MAP | 55 |
| + MAP, UTPI | 70 |
| + MAP, UTPI, PAPP-A | 71 |
| **+ MAP, UTPI, PLGF** | **76** |
| + MAP, UTPI, PLGF, PAPP-A | 76 |

**Risk cut-off 1 in 100**

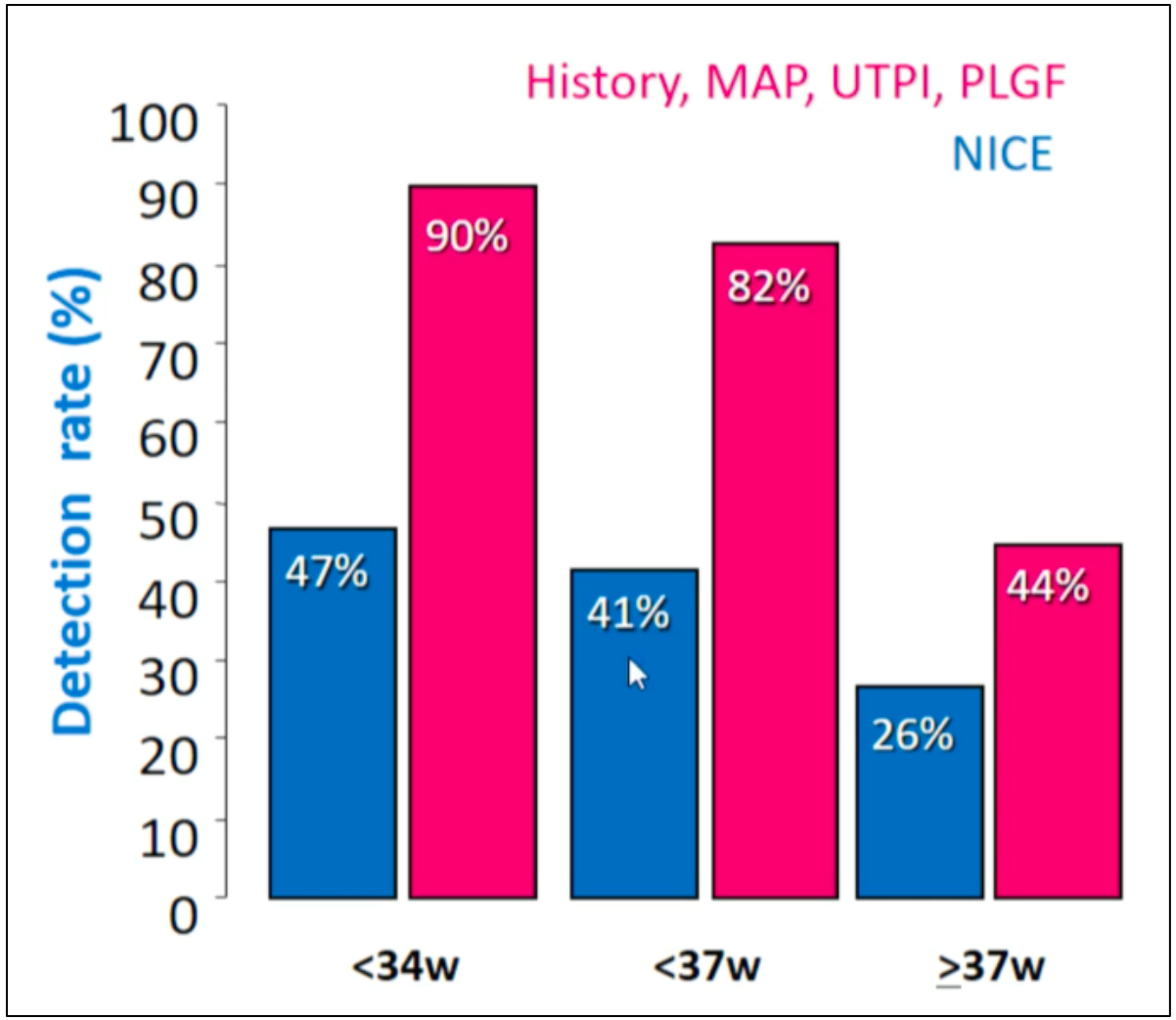
# Risk tabanlı vs öykü+biofizik+biokimyasal tarama

**High risk factors**

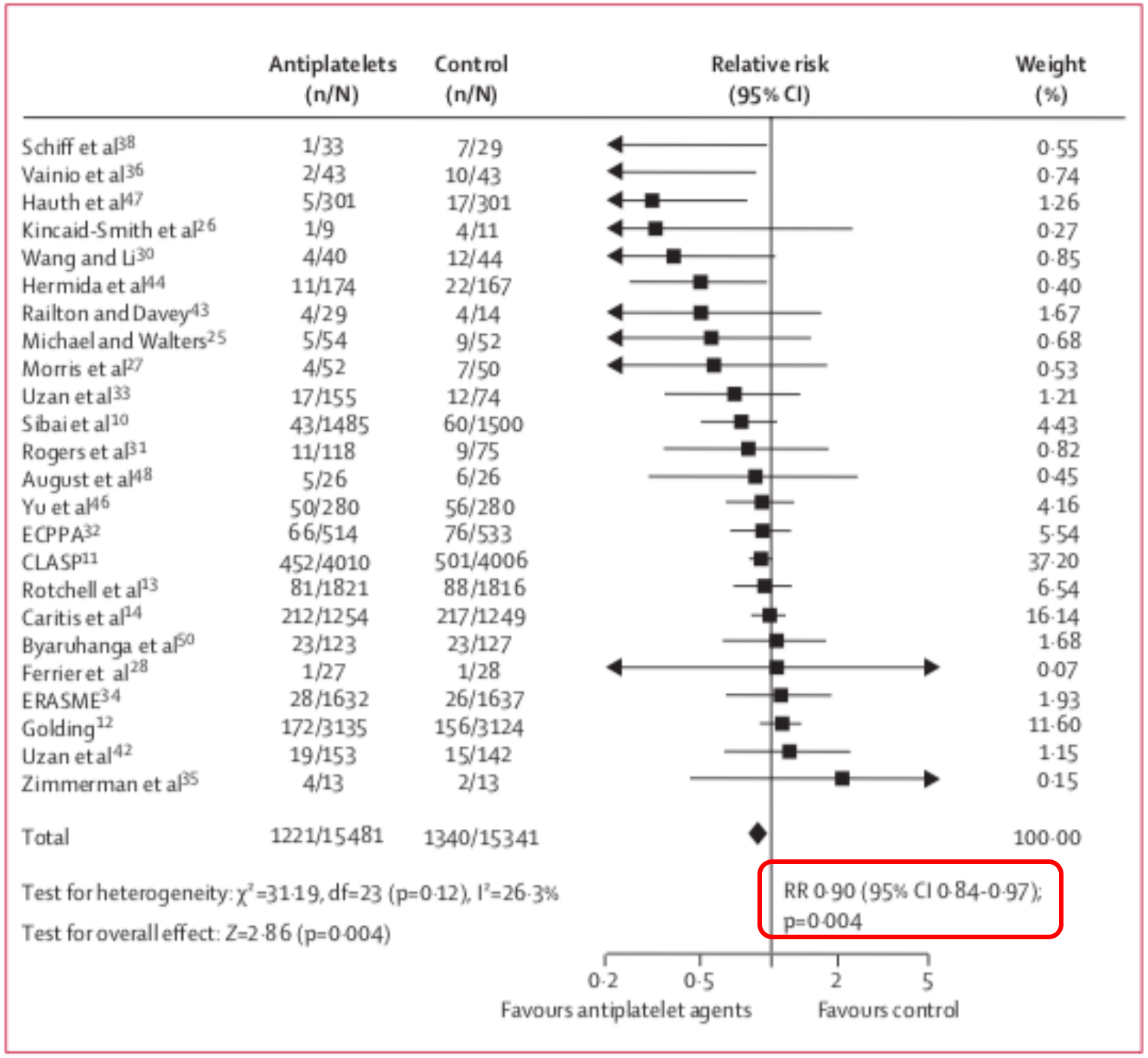
- Previous preeclampsia
- Chronic renal disease
- Chronic hypertension
- Diabetes mellitus
- SLE or APS

**Moderate risk factors**

- First pregnancy
- Age ≥ 40 yrs
- Body mass index ≥ 35 kg/m²
- Inter-pregnancy interval > 10 yrs
- Family history of preeclampsia




NHS 2014




**Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data**

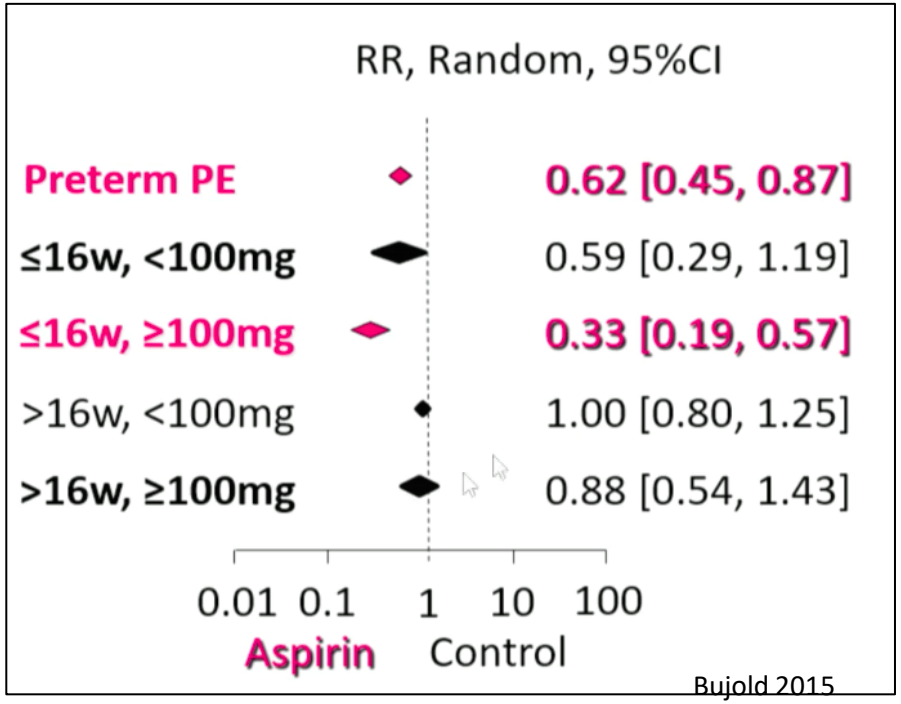
*Lisa M Askie, Lelia Duley, David J Henderson-Smart, Lesley A Stewart, on behalf of the PARIS Collaborative Group**

- 32217 gebe, 31 RKT
- RR preeklampsi

0.90 (%95 CI 0.84-0.97)

- RR <34 hf doğum

0.90 (%95 CI 0.83-0.98)



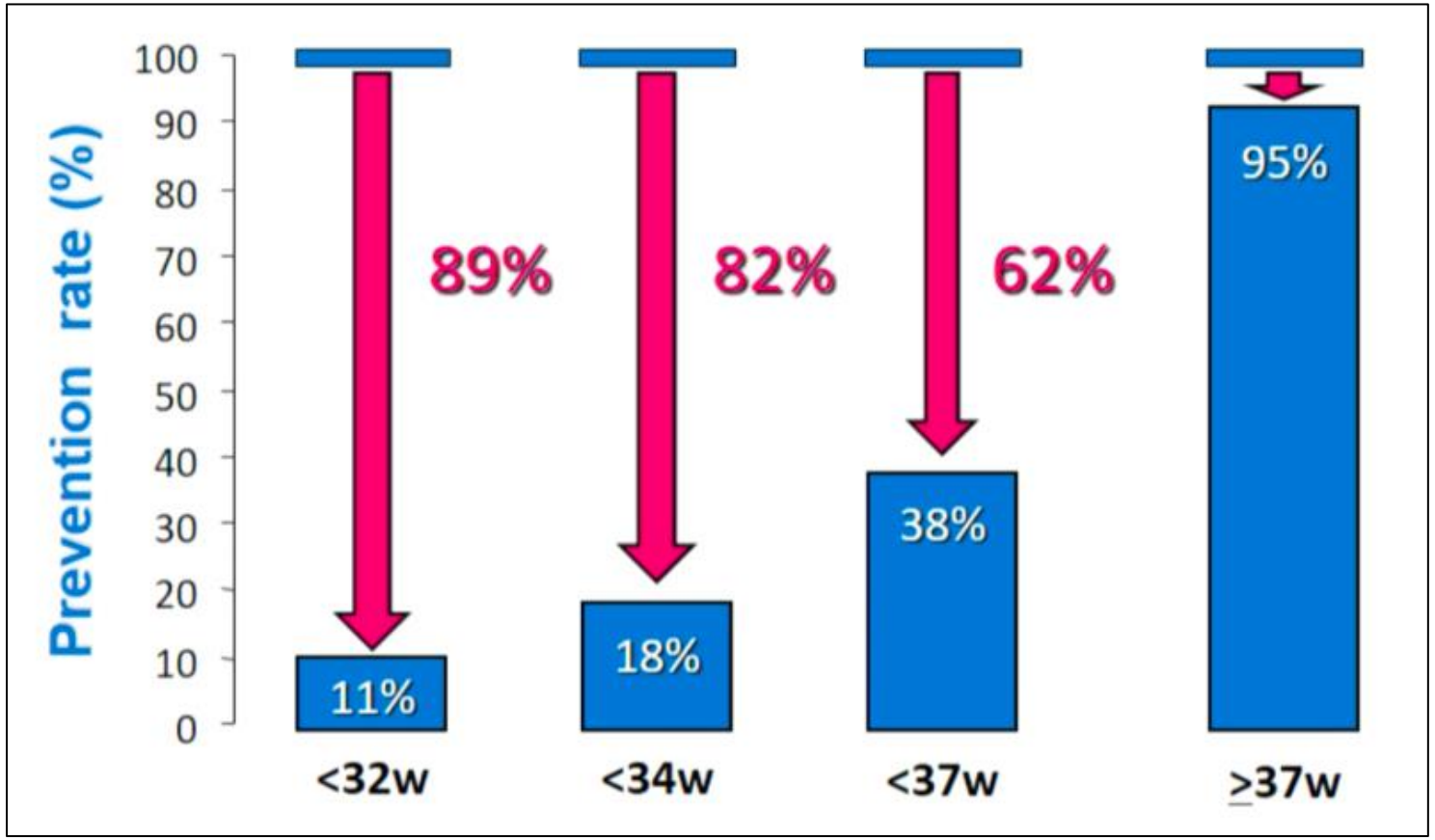

Bujold 2015

# ASPRE

- 6 ülke, 26 941 gebe
- < 37 hf preeklampsi yüksek riskli 1971 gebe %11
- 1620 gebe >1:100
  - Doz: 150 mg, gece
  - Başlangıç: 12 hf
  - Bitiş: 36 hf

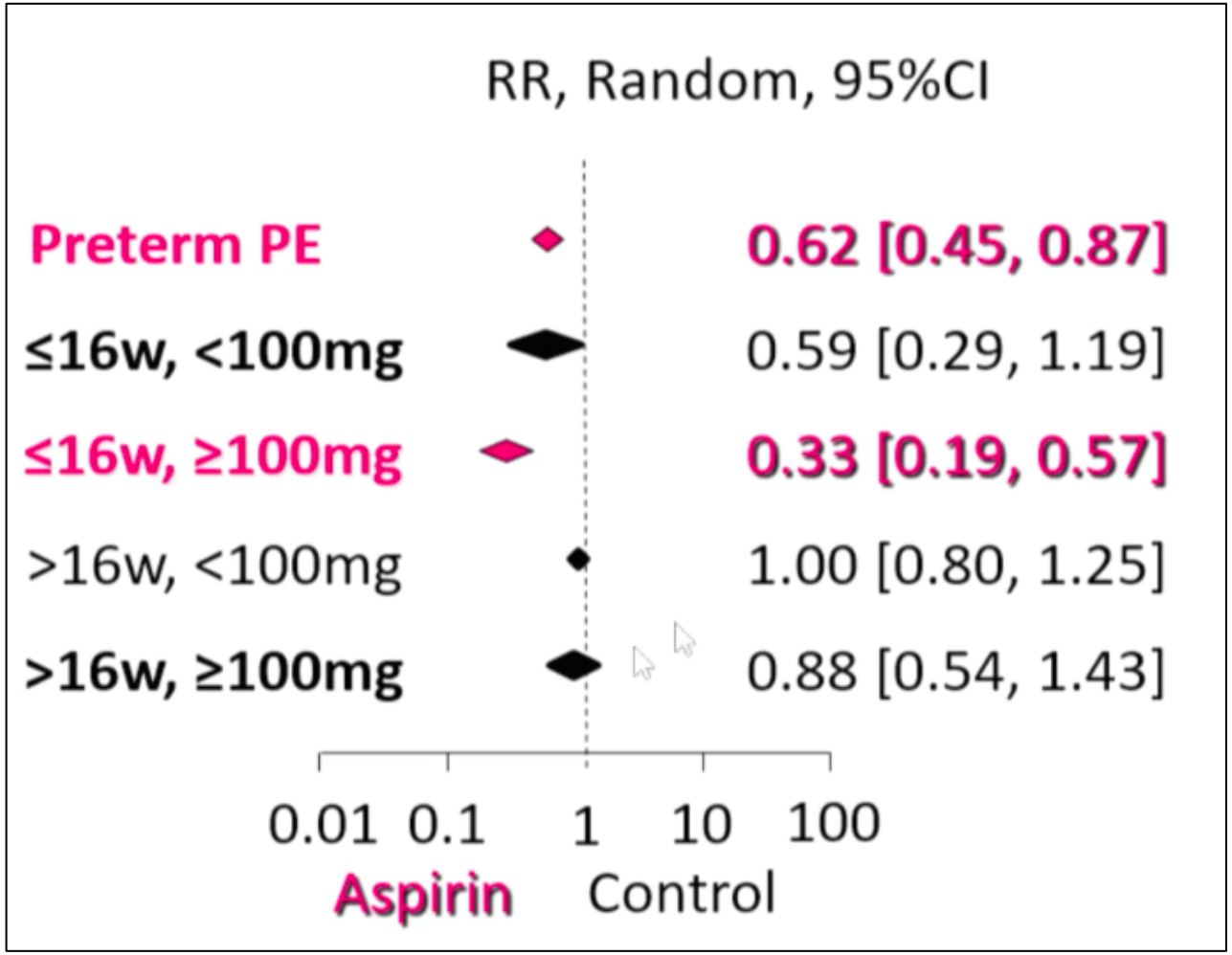
Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia

Daniel L. Rolnik, M.D., David Wright, Ph.D., Liona C. Poon, M.D., Neil O'Gorman, M.D., Argyro Syngelaki, Ph.D., Catalina de Paco Matallana, M.D., Ranjit Akolekar, M.D., Simona Cicero, M.D., Deepa Janga, M.D., Mandeep Singh, M.D., Francisca S. Molina, M.D., Nicola Persico, M.D., Jacques C. Jani, M.D., Walter Plasencia, M.D., George Papaioannou, M.D., Kinneret Tenenbaum-Gavish, M.D., Hamutal Meiri, Ph.D., Sveinbjorn Gizurarson, Ph.D., Kate Maclagan, Ph.D., and Kypros H. Nicolaides, M.D.



# ASPRE

- Hasta uyumu >90 erken başlangıçlı Preeklampsi %75 azalıyor
- Asprin etkisi yaş, sigara, gibi maternal özelliklere göre değişmiyor. Kronik HT istisna
- Yenidoğan YB kalış süresini %70 azaltıyor
- >100 mg ve <16 hf preterm preeklampsi %67 oranında azalır
- Dekolman plasenta ve antepartum kanamayı azalttığı düşünülüyor




Rolnik DL 2007

# Two Stage Theory of Preeclampsia

genetic factors

immunological factors

environmental factors

Abnormal placentation

Placental hypoperfusion

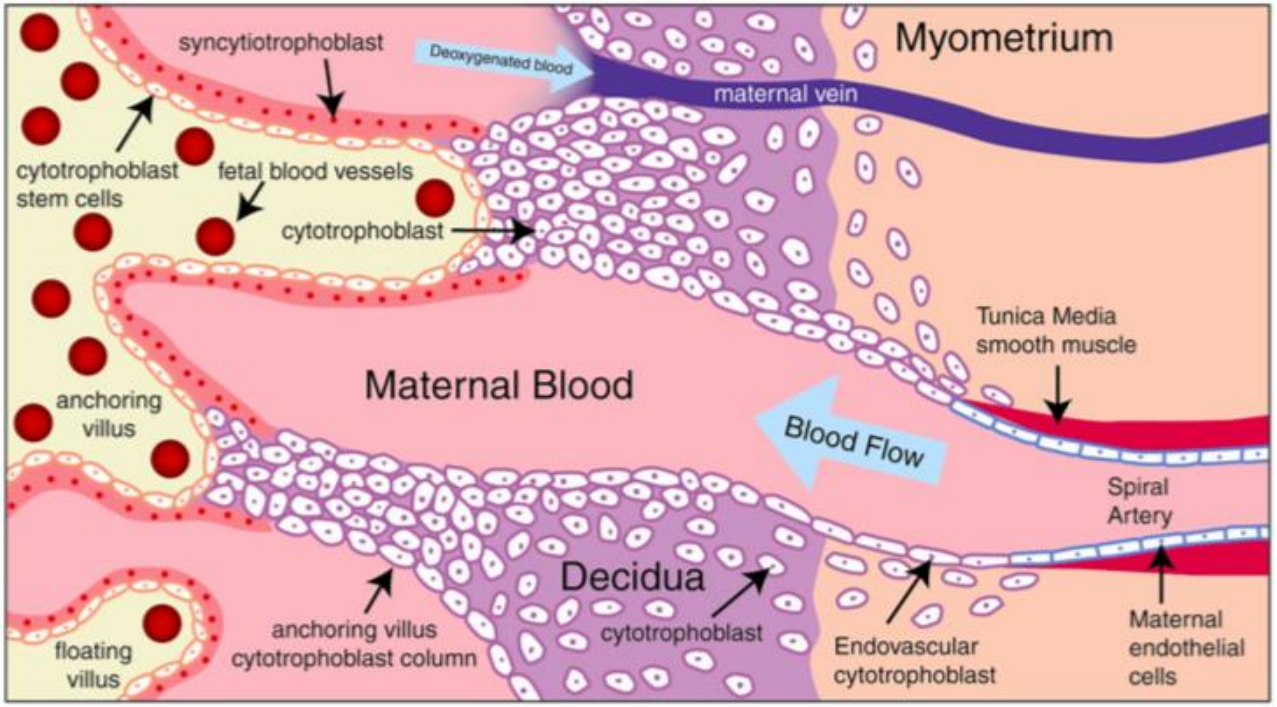
Placental factors ↑ (sFlt1 ↑)

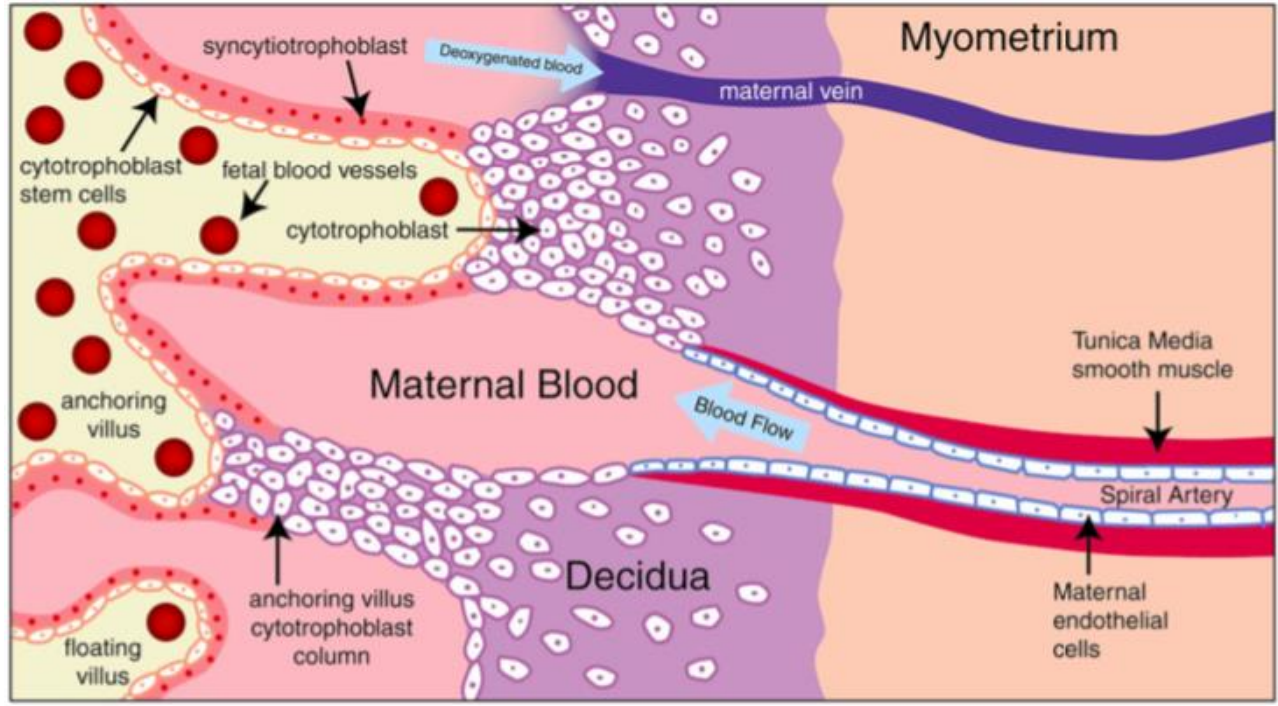
endothelial dysfunction

Systemic vascular dysfunction

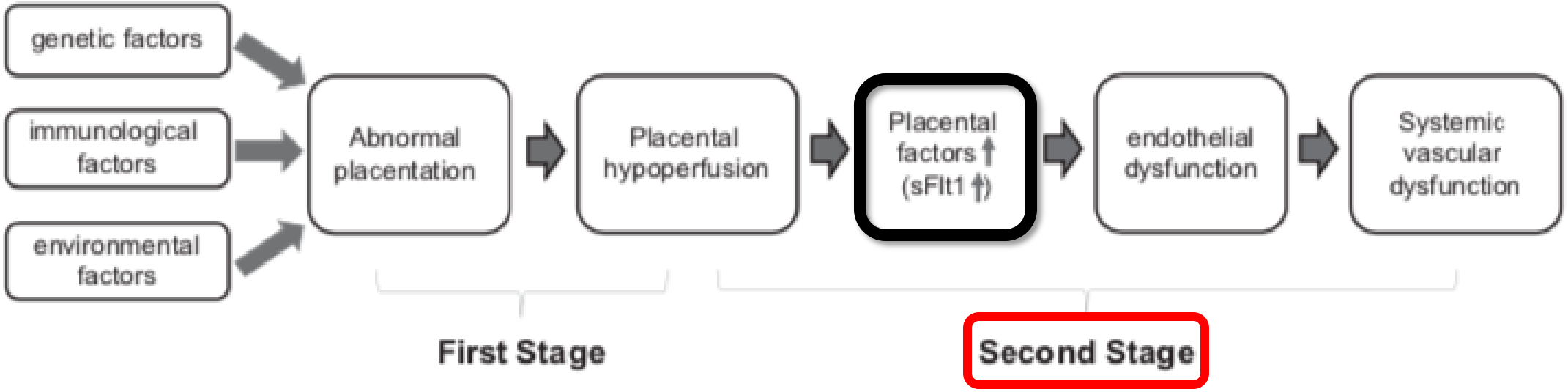
**First Stage**

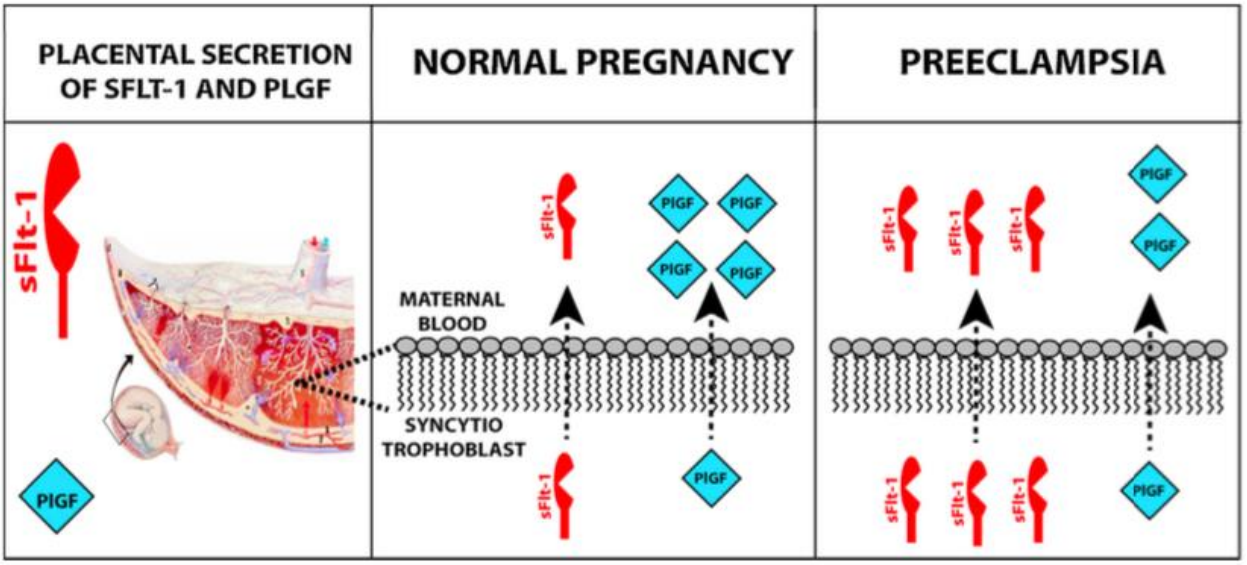
**Second Stage**

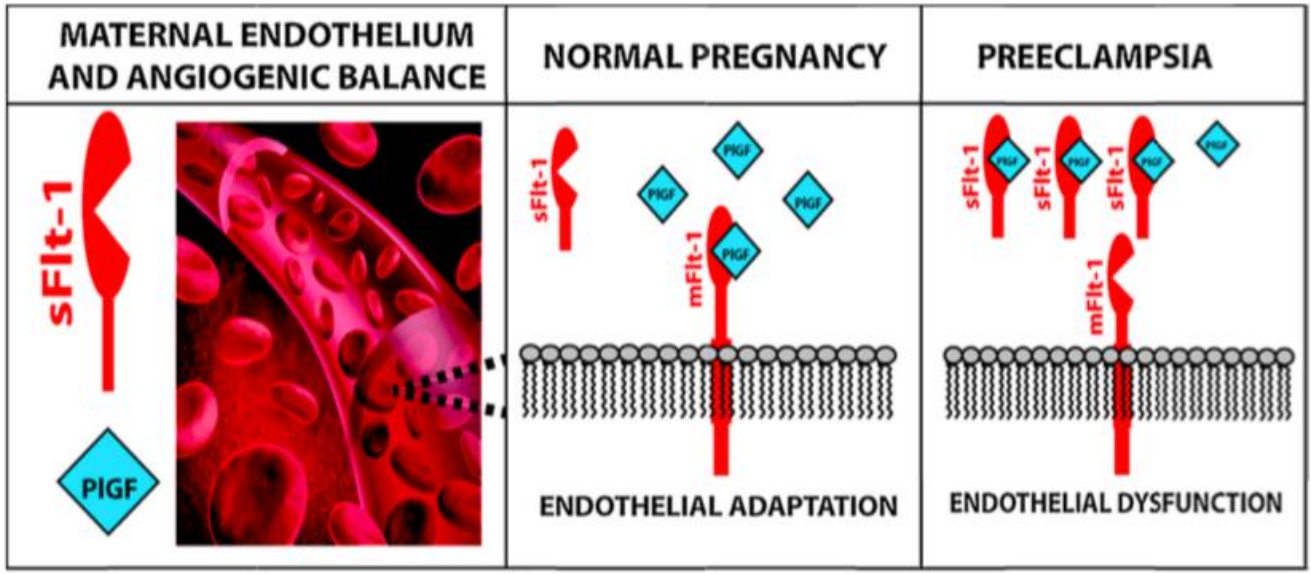


# Two Stage Theory of Preeclampsia

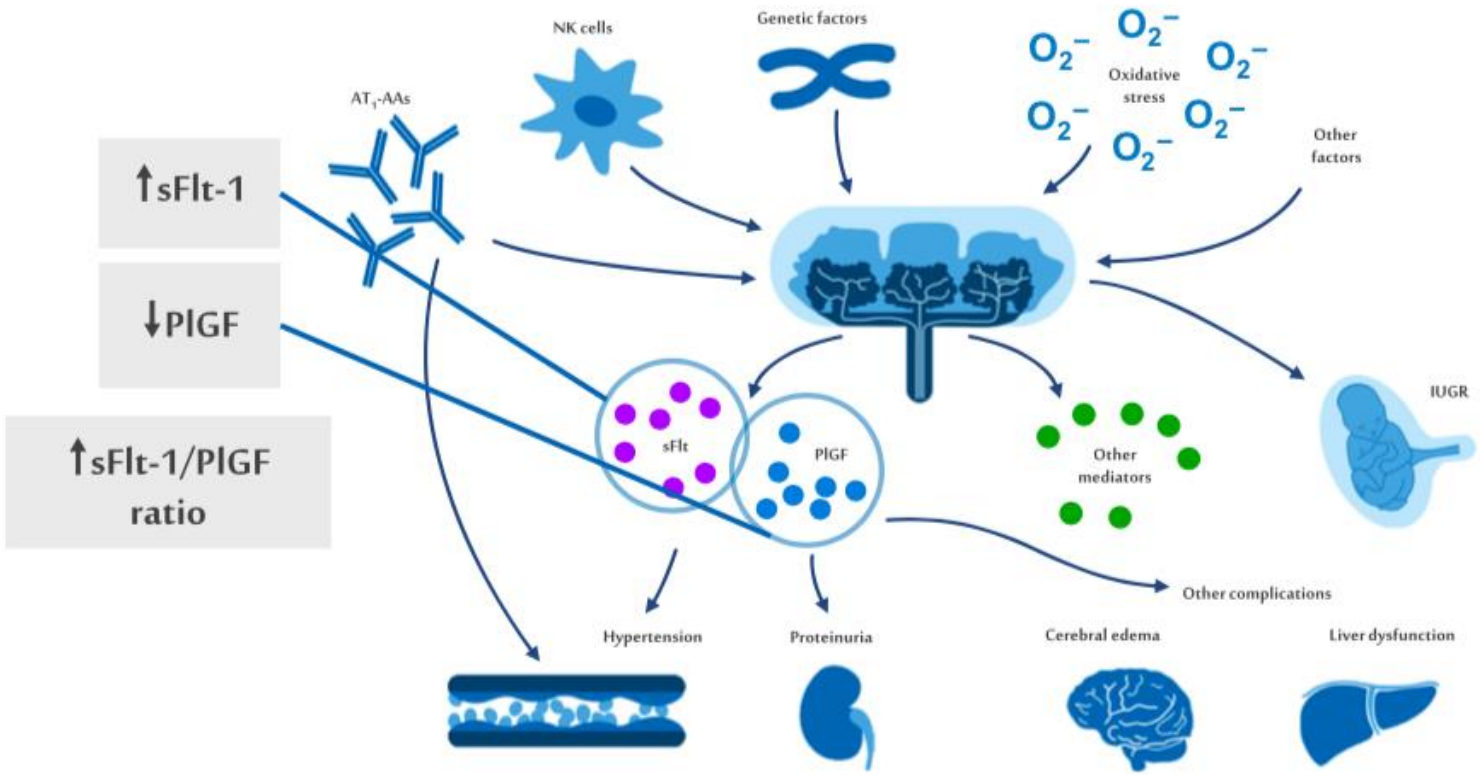



Lecarpantier E 2016

# Plasental Yetmezlik




1. Preeklampsi
2. İntrauterin büyüme Gelişme Kısıtlılığı
3. Dekolman Plasenta

   a. Defektif derin trofoblastik invazyon, spiral arter remodelizasyon kusuru ve yetersiz plasental perfüzyon
   b. Anjiojenik faktör imbalansı

-Anti-anjiojenik faktörler (sFlt-1)
-Pro-anjiojenik faktörler (VEGF, PlGF)

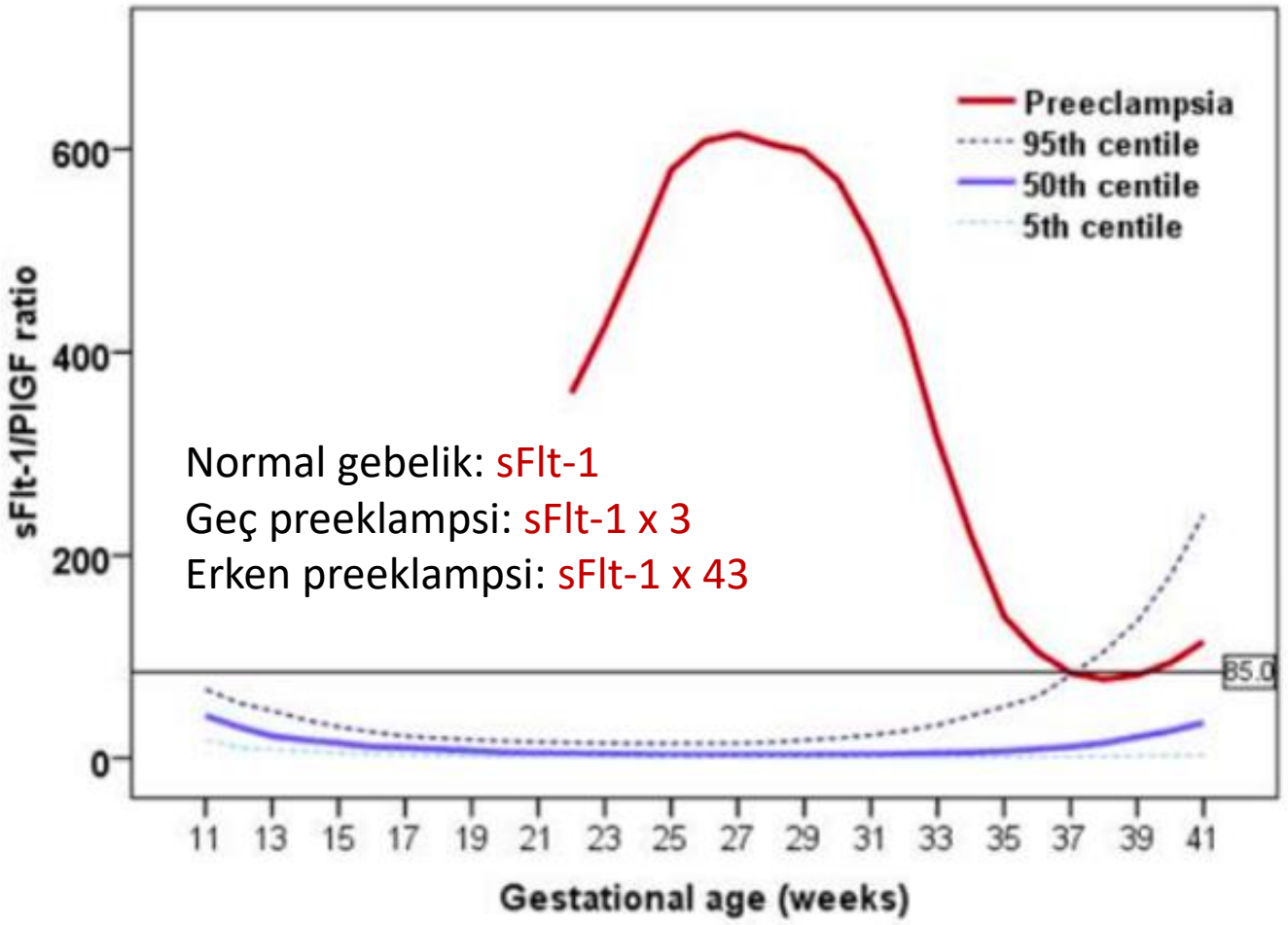
Hemoksijenaz defekti, plasental hipoksi, genetik faktörler, Corin eksikliği, Anjiotensin oto Ab, oksidatif stress, enflamasyon, NK sinyal değişikliği, COMT eksikliği, Aktive C, Aberan vazopressin üretimi

Petersen S 2017 Curr Hypertens Rep

# Soluble FMS like tyrosine kinase 1/ Placental growth factor

## sFlt-1/PlGF

MCSFR
ONCOGENE FMS; FMS
c-FMS
CD115 ANTIGEN; CD115
V-FMS MCDONOUGH FELINE SARCOMA VIRAL ONCOGENE HOMOLOG, FORMERLY




- Preeklampsi Öngörüsü 1. trimester?
- Preeklampsi şüphesinde tanı amaçlı
- Yönetim ve prognoz belirlemede
- Yeni tx etkinliklerinin izlenmesinde

# sFlt-1/PlGF

| Proposed Application | Comments |
|---|---|
| Prediction of PD and stratification of care | →First trimester (11–14 weeks): for the selection of women potentially benefit from the use of preventive measures such as low dose aspirin (only PlGF);<br>→Second and third trimester: for the precise stratification of patients that should receive intensive following-up in a specialized center. |
| Early diagnosis of PD | sFlt-1/PlGF ratio increases significantly 5 to 8 weeks before the appearance of clinical manifestations. |
| Differential diagnosis | →Uncertain cases;<br>→Atypical cases. |
| Management of PE | Categorize those cases susceptible to receive an expectant management. |
| Cost-efficiency | Avoidance of other diagnostic tests or reducing admissions for false PD suspicion. |
| Treatment | Development of new treatments based on the angiogenic balance regulation and monitorization of its efficacy (especially sFlt-1). |

# sFlt-1/PlGF

| sFlt-1/PlGF result (EP/LP) | Interpretation | Time to delivery (EP) | What should be done? |
|---|---|---|---|
| Low: <38 | Rule out PE:<br>1 week: NPV ≈99%<br>4 weeks: NPV ≈95% | Unmodified | Reassuring the patient<br>No further determinations are needed unless new suspicion arises |
| Intermediate: 38–85/38–110 | Rule in PE:<br>4 weeks: PPV ≈40% | 20% remain pregnant after 1 month | Follow-up visit and retest in 1–2 weeks<br>Maternal education about signs and symptoms of PE |
| High: >85/>110 | Diagnosis of PE (or PD-related disorder) is highly likely | 15% remain pregnant after 2 weeks | Follow-up visit and retest in 2–4 days<br>EP: consider referral to higher-level center<br>LP: consider lowering the threshold for labor induction |
| Very high: >655/>201 | Short-term complications and need to deliver are highly likely | 30% remain pregnant after 2 days | Close surveillance<br>EP: corticoids to the mother for fetal maturation |

Herraiz I Fetal Diagn Ther 2017

# First and Second Trimester Serum sFlt-1/PlGF Ratio and Subsequent Preeclampsia: A Systematic Review

Arif M. Yusuf, MD;[1] Alyssa Kahane, BSc;[2,3] Joel G. Ray, MD, MSc[2,4,5]

## Abstract

**Objective:** Angiogenic biomarkers may be predictive of preeclampsia before clinical symptoms. The objective of this review was to determine the relationship between first and second trimester soluble fms-like tyrosine kinase-1/ placental growth factor (sFlt-1/PlGF) ratio and preeclampsia.

**Methods:** A search algorithm using appropriate medical subject headings was developed. PubMed, EMBASE, and Cochrane were searched for publications from inception to July 4, 2017. Observational studies, including prospective and retrospective cohorts, that measured serum sFlt-1/PlGF ratio at ≤24 weeks' gestation were included. Study characteristics, study design, timing of blood samples, and outcome data were systematically extracted. Study cohorts were grouped into women with low-risk and high-risk factors for preeclampsia.

**Results:** Fifteen studies were included for analysis, including 11 779 pregnancies. In studies of women with low-risk features, four subgroups from seven studies demonstrated higher sFlt-1/ PlGF ratios in women who developed preeclampsia versus those who did not. In studies of women with high-risk features, six subgroups from nine studies demonstrated a higher sFlt-1/PlGF ratio in women who later developed preeclampsia. Elevated sFlt-1/PlGF ratios were especially seen in women who had early-onset or severe preeclampsia.

**Conclusion:** The serum sFlt-1/PlGF ratio measured at ≤24 weeks' gestation may be elevated in select women who later develop preeclampsia, but inconsistently so.



- 15 çalışma, sFlt1/PlGF < 25 hf
- 1. trimester sFlt1/PlGF erken başlangıçlı preeklampsi ve ağır preeklampside artma eğiliminde ancak tutarlı sonuçlar yok

# Teşekkürler

**Table 1.** Prevalence of preeclampsia in aspirin and placebo-treated high-risk cohorts in the ASPRE trial

| | Aspirin ($n = 798$) | Placebo ($n = 822$) | Risk reduction ($P$) |
|---|---|---|---|
| Preeclampsia with delivery <32 weeks | 3 (0.4%) | 15 (1.8%) | 78% ($P < 0.01$) |
| Preeclampsia with delivery <37 weeks | 13 (1.6%) | 35 (4.3%) | 63% ($P < 0.01$) |
| Preeclampsia with delivery ≥37 weeks | 53 (6.6%) | 59 (7.2%) | 5% ($P =$ n/s) |
| All preeclampsia | 66 (8.3%) | 94 (12.5%) | 34% ($P = 0.03$) |