Anjiyogenetik Faktörler ve Preeklampsi

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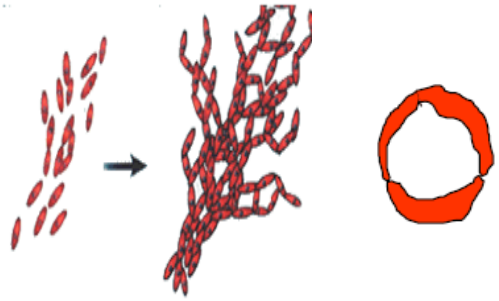
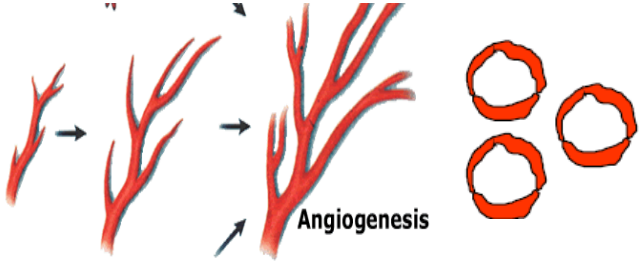
Istanbul Universitesi Cerrahpaşa Tıp Fakültesi Kadın Hastalıkları ve Doğum ABD

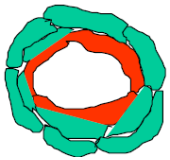
Tanımlar



- **Vaskulogenez**
  Vaskuler kök hücrelerden kapiller damar oluşumu



- **Anjiyogenez**
  Mevdut damarlardan yeni damar oluşumu



- **Arteriyogenez**
  Olgun (kalın duvarlı) damar oluşumu

FİZYOLOJİK

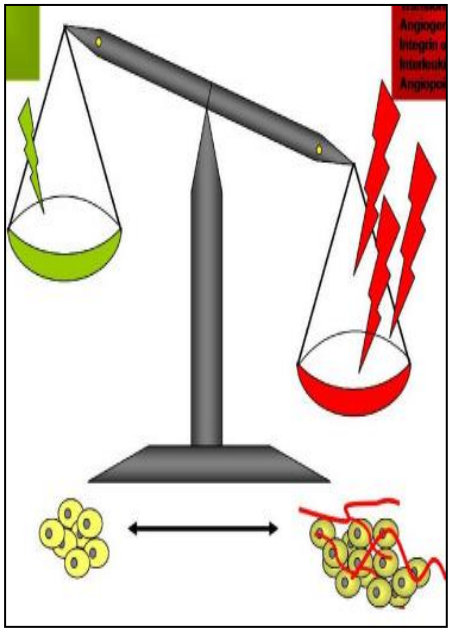
- Embriyogenez, Plasenta
- Yara iyileşmesi
- Ovaryal ve Endometriyal siklus
- Saç uzaması

PATOLOJİK

- Malignite
- Hemanjiyom
- Makula dejener
- Kr İnflamasyon
- Ateroskleroz
- Romatoid artrit
- Diyabetik retinopati
- İskemi

- **Anjiyogenez / Aktive ve İnhibe edici faktörler Denge**

- **Anjiyogenetik Faktörler**
  - *Vascular Endothelial Growth Faktörler (VEGF)*
  - *Angiopoietinler (Ang)*
  - *Ephrin*
  - *Fibroblast Growth Faktör (FGF)*
  - *Platelet-Derived Growth Faktörler (PDGF)*
  - *Transforming Growth Faktörler β* (TGFβ)
  - *Notch*

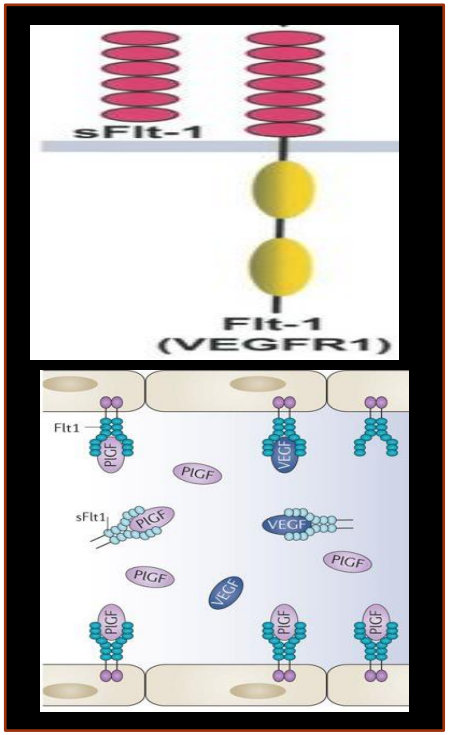


- **Anti-Anjiyogenetik Faktörler**
  - *Angiostatin,*
  - *Endostatin,*
  - *Interferon,*
  - *Platelet factor 4,*
  - *Thrombospondin, (TSP1)*
  - *Prolactin 16 kD fragment*
  - *Tissue inhibitor of metalloproteinase-1,2, 3*

Sistemler

- Vascular endothelial growth factor (VEGF)

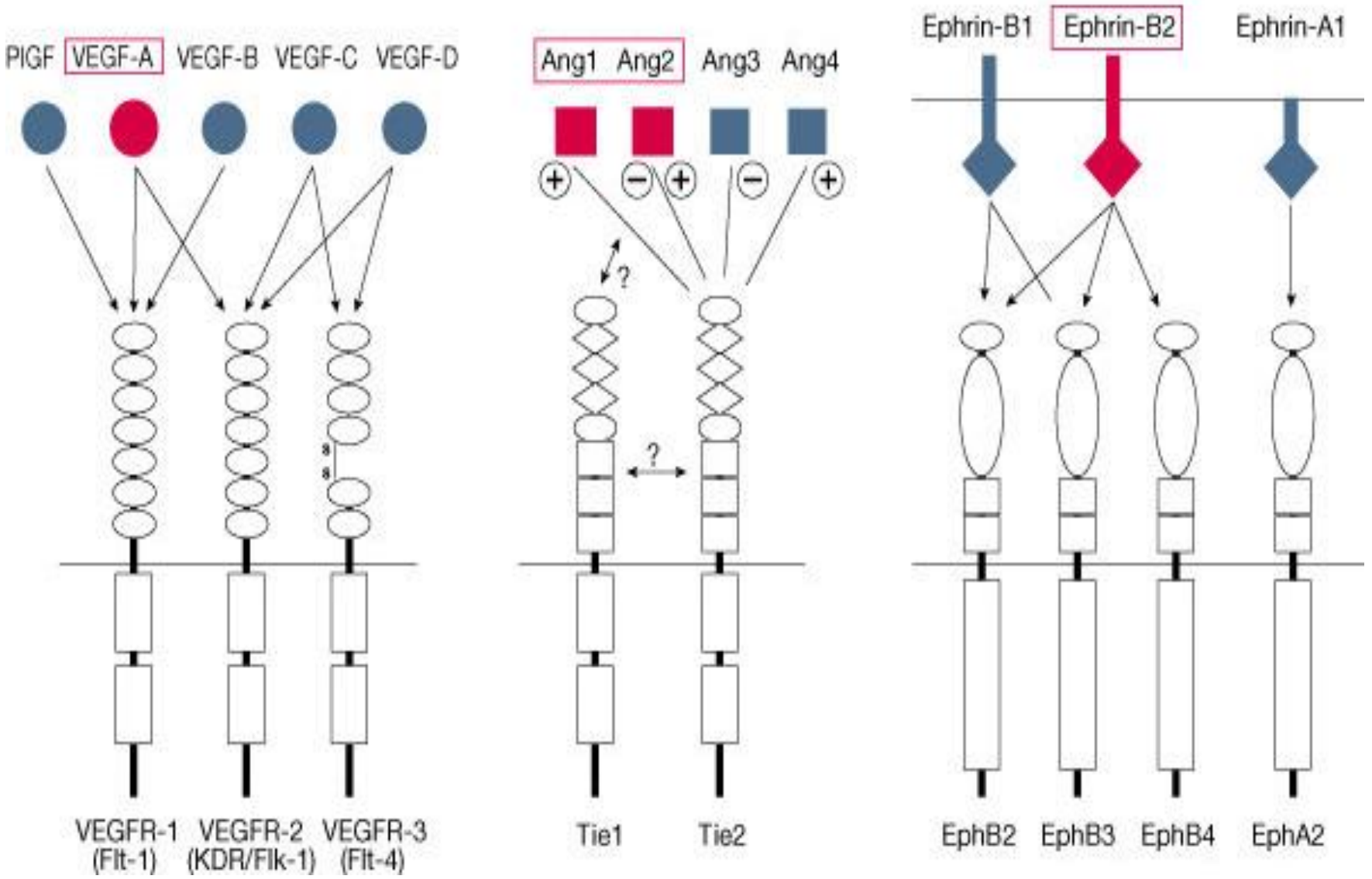
	Reseptör	
VEGF A	VEGFR-1 (flt-1)	**sflt-1**
VEGF B	VEGFR-2 (flk-1/KDR)	
VEGF C	VEGFR-3 (flt-4)	
VEGF D		
PIGF		



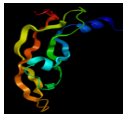
- Angiopoietin (Ang)

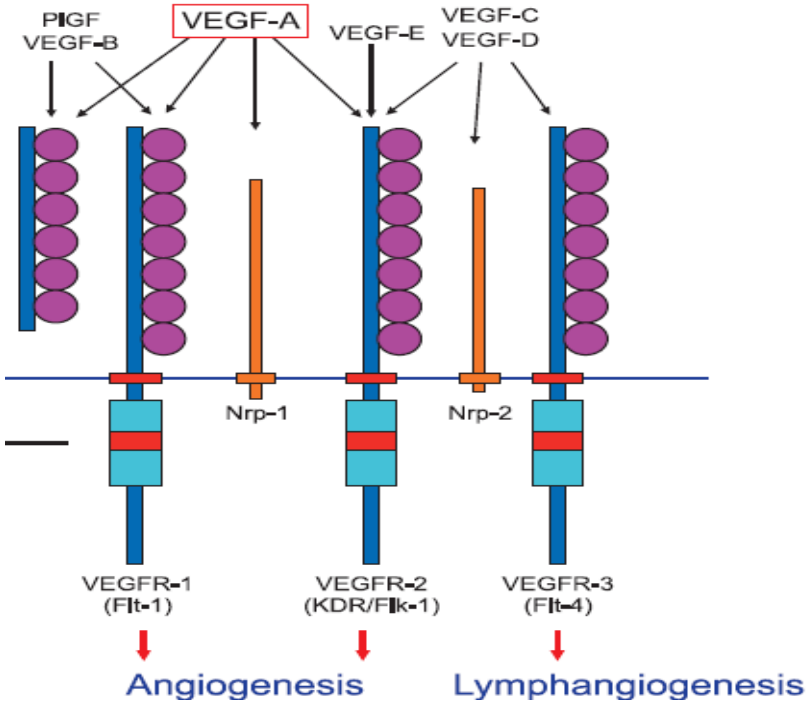
Ang1	TIE1
Ang2	TIE2
Ang3	
Ang4	

- Ephrin — Eph B
- Transforming growth factor-β — Endoglin (ENG) — **sENG**


PIGF
VEGF-A
VEGF-B
VEGF-C
VEGF-D
VEGFR-1 (Flt-1)
VEGFR-2 (KDR/Flk-1)
VEGFR-3 (Flt-4)
Ang1
Ang2
Ang3
Ang4
?
?
Tie1
Tie2
Ephrin-B1
Ephrin-B2
Ephrin-A1
EphB2
EphB3
EphB4
EphA2

Vascular Endothelial Growth Faktörler



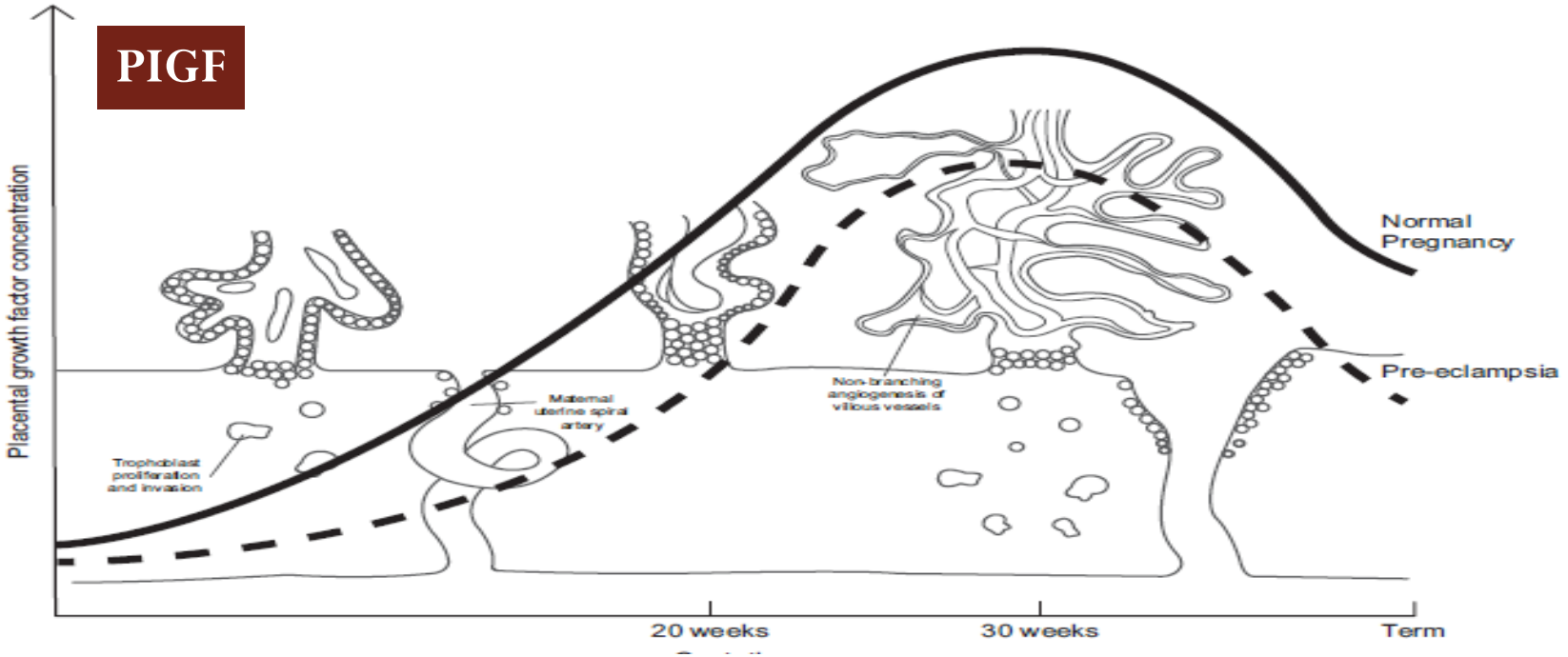


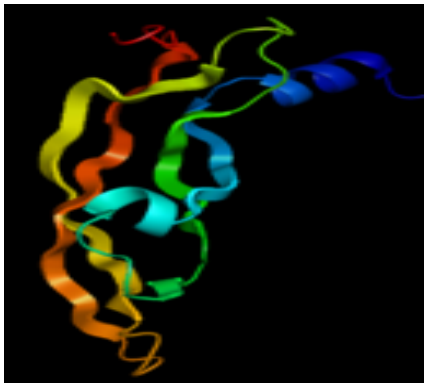
- Hipoksi
- EGF
- FGF
- IGF-1
- IL-6
- IL1

→ Uyarır

- Pek çok hücre sentezliyor
- Endotel, Damar Fonksiyonu
  - Permabilite
  - Vazadilatasyon / Nitrit oksit (NO)
  - Endotel hücre surviv
  - Tromboz inhibisyon

- Böbrek glomerul filtrasyon
- Oosit matürasyon, Corpus luteum
- Endometrium
- Kemik gelişim
- Nöroprotektif etki
- Akçiğer gelişimi
- Hematopoiesis





- Plasenta (Damar Yumak)

VEGF, PIGF / plasenta anjiyogenez ve Maternal arter remodeling

- VEGF-A, FLT-1, KDR yoğun / PIGF orta /gebeliğin 1. yarısı
- >25 gh PIGF ve sFLT-1 artar (non-baranching angiogenesis)

Endotel

- $6x10^{11}$ endotel hüc, 500 m2, 1.5-2 kg
- Sessiz ve hücre döngüsü yıllar
- Damar fonksiyonu (Vasküler Hemostaz)
- Damar tonusu
- Mekanik bariyer, geçirgenlik
- Pıhtılaşma

- Endotel aktivasyonu/ Disfonksiyonu
  - Anjiyogenetik faktörler
  - Sitokinler
  - İnflamatuvar faktörler, hücreler
  - Diğer

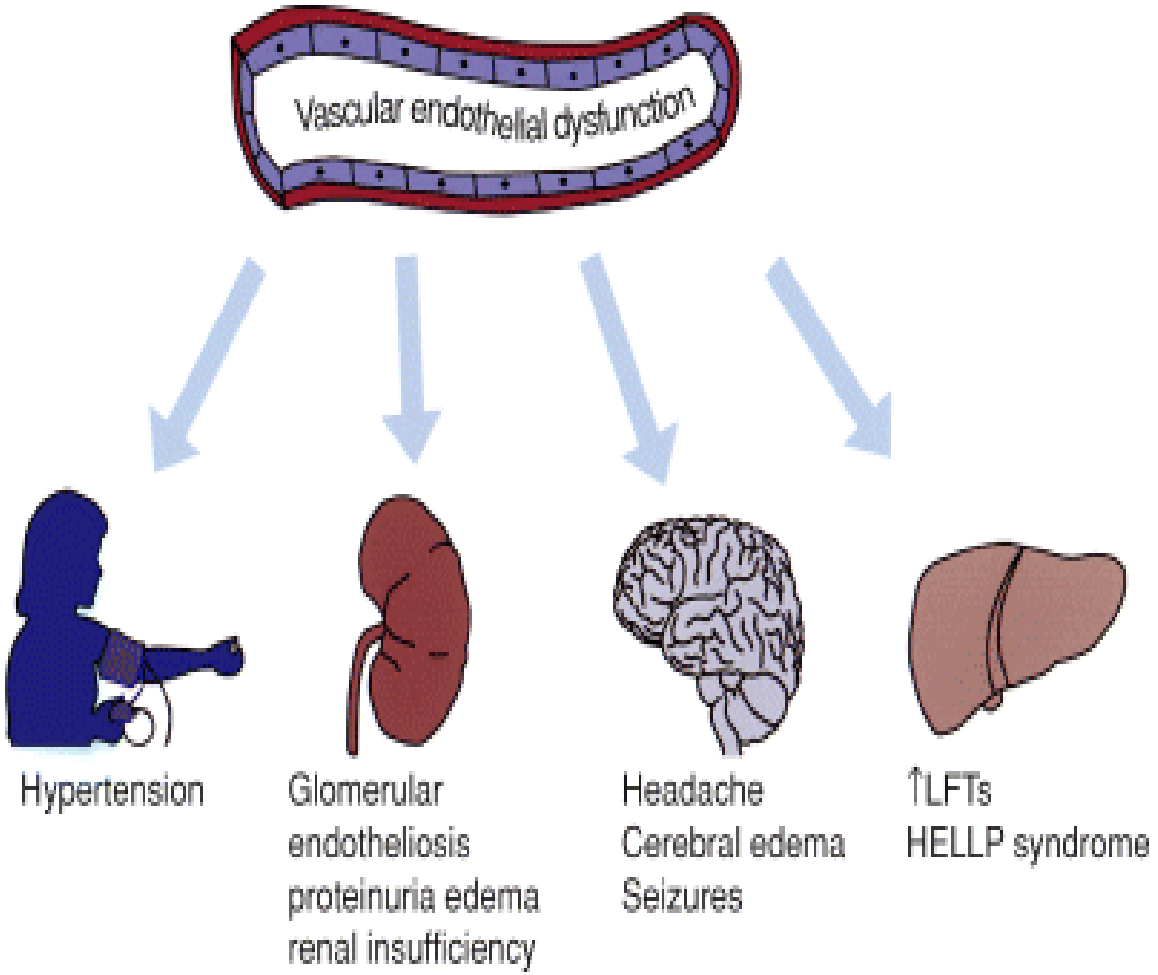
ENDOTEL DİSFONKSİYONU

- **Vasomotor Tonus Bozulma**
- **Tromboz Eğilim**
- **Pro-İnflamatuar Durum**
- **Arter Duvar Proliferasyon**

Preeklampsi

- **Maternal Sendrom**

  Klinik bulgular ENDOTEL DİSFONKSİYONU ile açıklanabilir



- **Vazodilatatör**
  - PGI_2
  - NO
  - EDHF
  - ANP
- **Vazokonstriktör**
  - TxA_2
  - Endothelin
  - VEGF
  - Aldosterone
  - Catecholamine
- **Endotel Belirteçleri**
  - Fibronectin
  - VCAM-1
  - E-Selectine
  - Von Willebrand
  - Plasminogen activ.
  - ANP
  - B-tromboglobuline
  - T-ATIII Complex

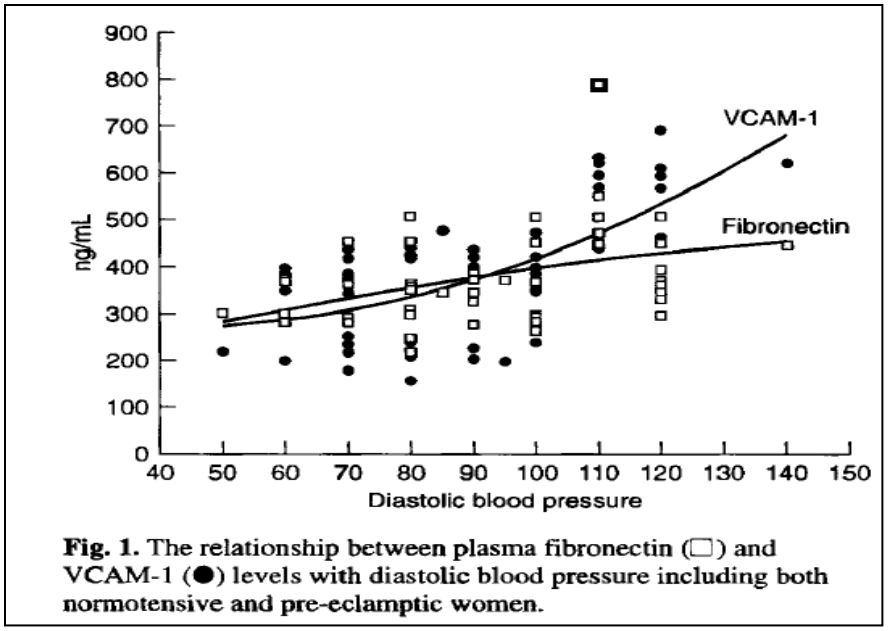
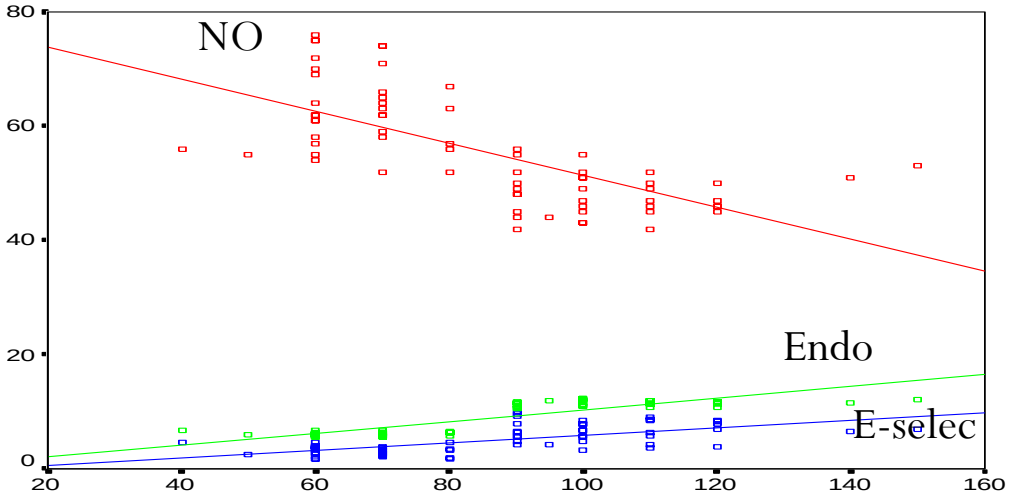


Fig. 1. The relationship between plasma fibronectin (□) and VCAM-1 (●) levels with diastolic blood pressure including both normotensive and pre-eclamptic women.

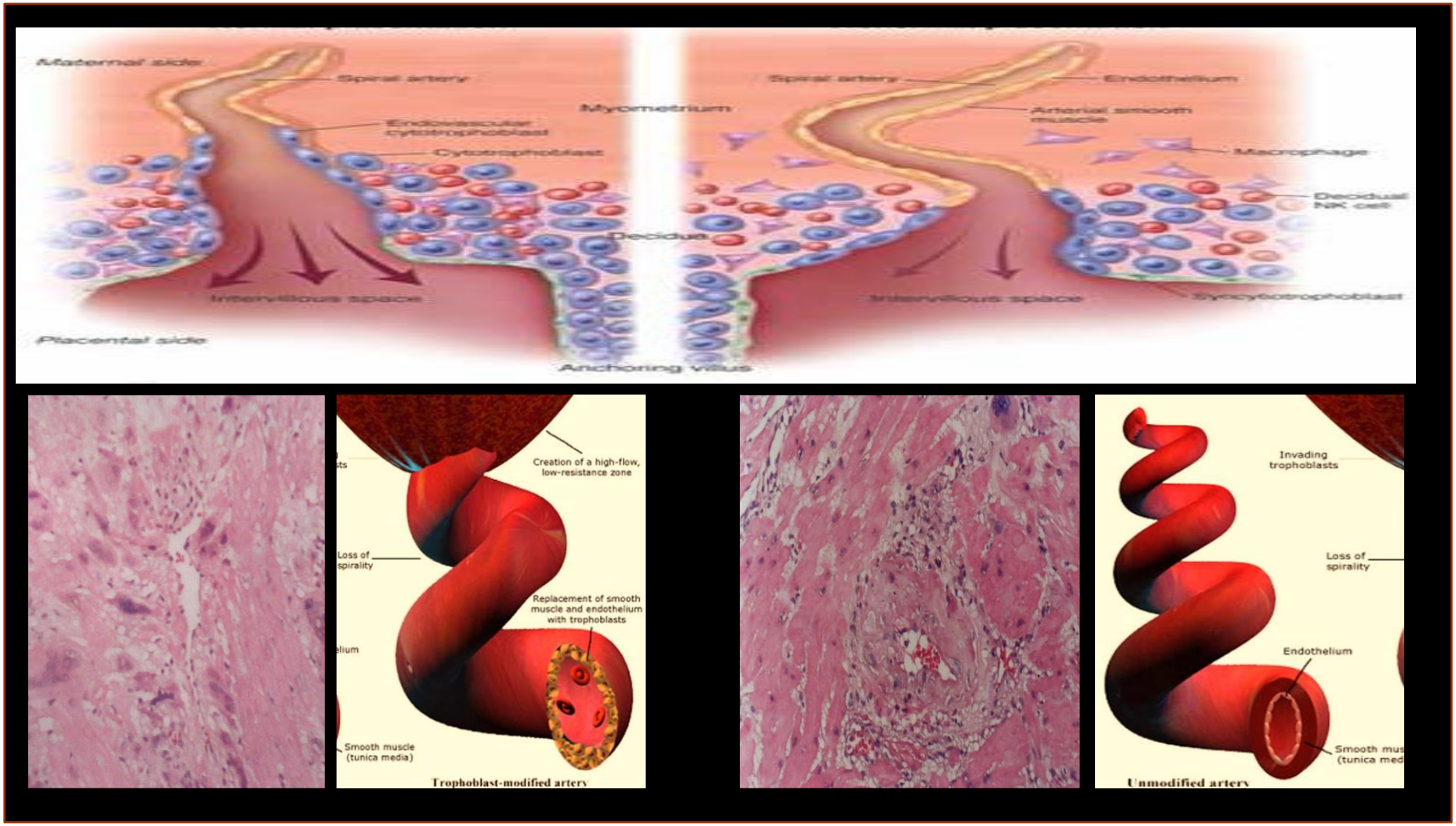
Madazlı et al. BJOG, 2000



Madazlı et al. EJOGRB, 2003

Plasenta- Plasentasyon

- Yetersiz Trofoblastik İnvazyon



Remodeling of a myometrial segment in normal pregnancy vs preeclampsia in placental bed biopsy studies

Study	Normal pregnancy, n/N (%)[a]	Pregnancy with preeclampsia, n/N (%)[b]
Gerretsen et al[25]	22/23 (96)	1/30 (3)
Khong et al[5]	18/18 (100)	3/14 (21)
Frusca et al[26]	13/14 (93)	6/24 (25)
Meekins et al[27]	16/21 (76)	3/24 (12)
Sagol et al[28]	16/20 (80)	7/17 (41)
Kim et al[7]	55/59 (93)	9/31 (29)
Kim et al[8]	89/103 (86)	18/43 (19)
Guzin et al[29]	16/20 (80)	11/32 (33)

[a] Mean, 88% (range, 76–100%); [b] Mean, 27% (range, 3–41%).

Brosens. Classification of defective deep placentation. Am J Obstet Gynecol 2011.

	Normotensive (n = 25)	Mild pre-eclampsia (n = 16)	Severe pre-eclampsia (n = 16)	Eclampsia (n = 3)	Severe group (n = 19)*
Fibronectin (ng/mL)	336 (67)	362 (75)	470 (114)	428 (46)	464 (106)†
VCAM-1 (ng/mL)	325 (102)	353 (86)	525 (100)	632 (56)	542 (102)†
Pathologic bed biopsy	0/17 [0]	2/5 [40]	9/13 [69]	3/3 [100]	12/16 [75]

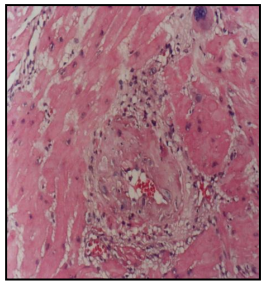
Madazlı et al. BJOG, 2000

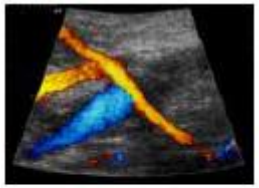
İki Evreli Oluşum Teorisi

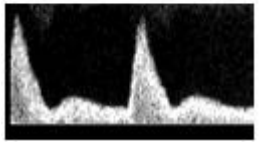
?

Genetik Yatkınlık / İmmün Maladaptasyon / Trofoblast Defekt

- Evre I







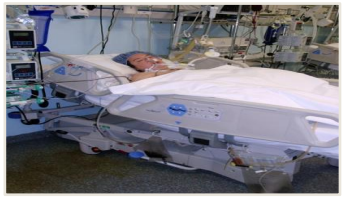
Plasenta – Yetersiz Trofoblastik İnvazyon

- **Anjiyogenetik Faktörler**
- **Sitokinler**
- **Oksidatif Stres**
- **Mikropartiküller**
- **Lokosit, Kompleman aktivasyon**

?

- Evre II

Endotel Disfonksiyonu



Preeklampsi

Sorun I

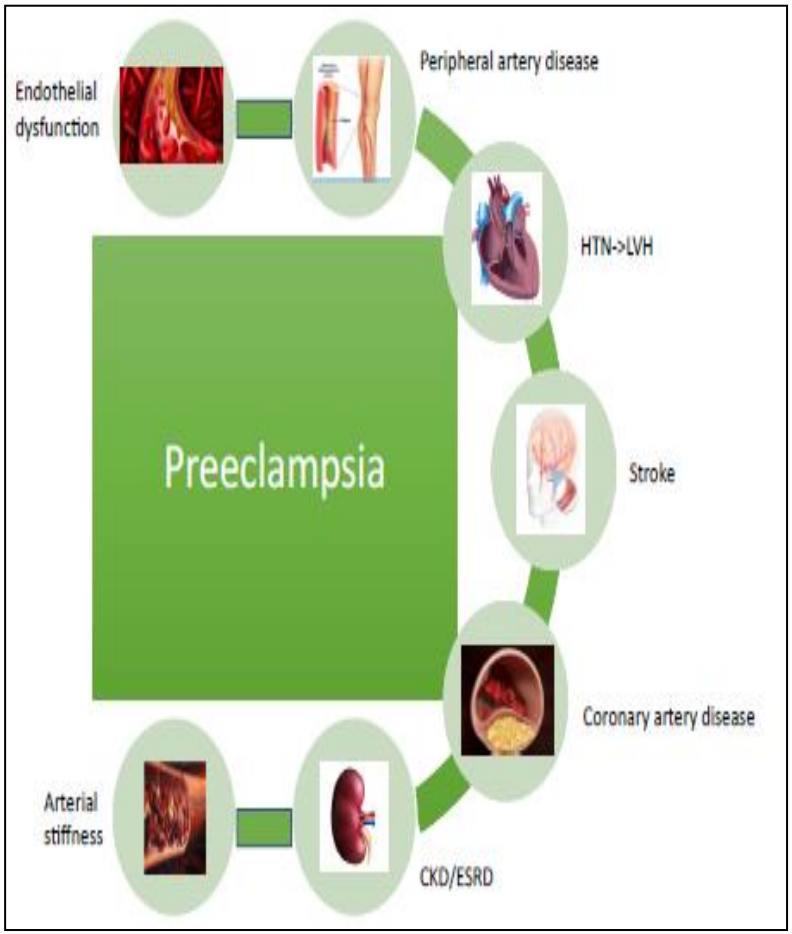
- Plasentasyon Sorunu Olan Olguların Tamamında Preeklampsi Gelişmiyor / FGK var, Preeklampsi yok

- Yetersiz Trofoblastik İnvazyon Tek başına Preeklampsi Maternal Sendromun Gelişmesi için Yeterli Değil

Sorun II

- Erken ve Geç Başlangıçlı Preeklampsi , İki Farklı Patoloji / Tek bir preeklampsi yok

- Geç Başlangıçlı Preeklampside Yetersiz Trofoblastik İnvazyon Yok



- **Gebelik öncesi**
  - Diyabet,Hipertansiyon,Obesite, Kolestrol, trigliserit↑

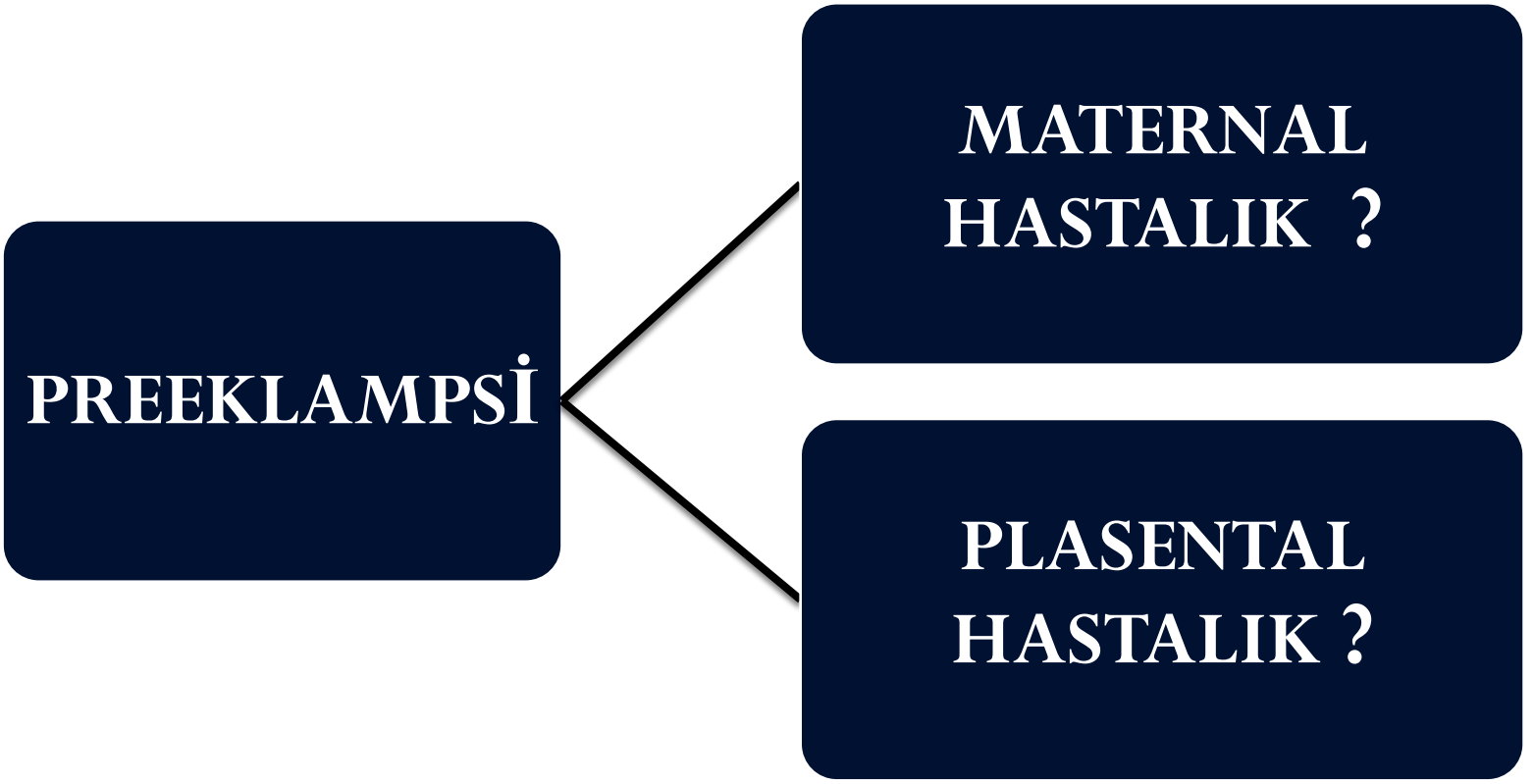
- **Postpartum /Uzun vade**

	RR
Hipertansiyon	1.87; 0.94–3.73
İskemik Kalp has	2.31; 1.95–2.78
Serebro-vaskuler	2.03; 1.54–2.67
Konjestif Kalp hast	3.46; 1.97–6.10
Ölüm	2.29; 1.73–3.04

Rana et al. Circ Res.2019

- Gebelik Maternal Kardiyovasküler Sisteme Yük
- Uyum Sağlıyamaz veya Fren Mekanizmaları Zayıf

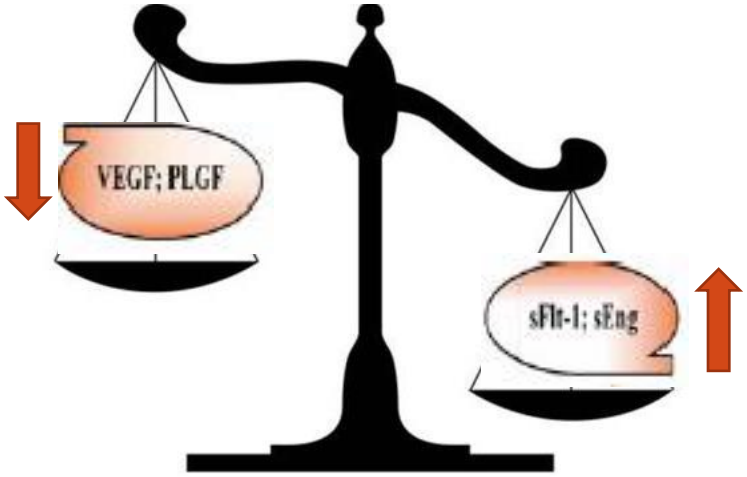
→ **Preeklampsi**

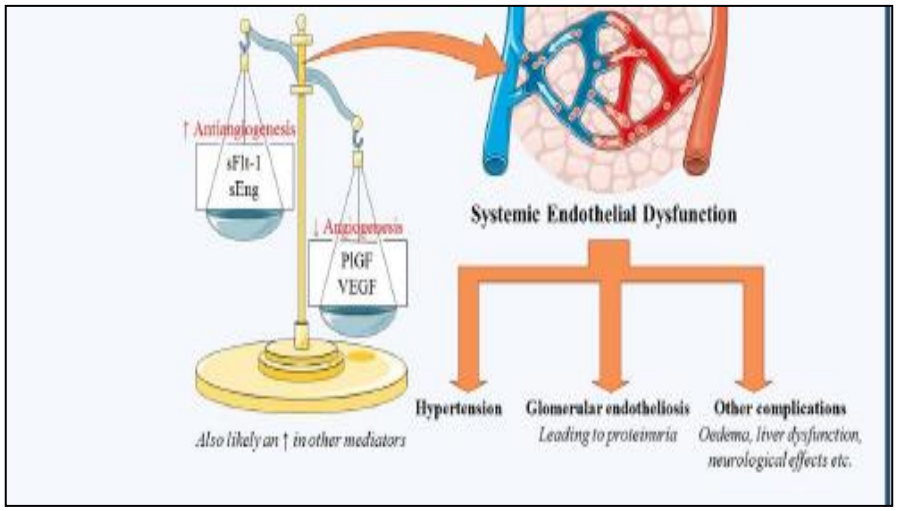

PREEKLAMPSİ
MATERNAL HASTALIK ?
PLASENTAL HASTALIK ?

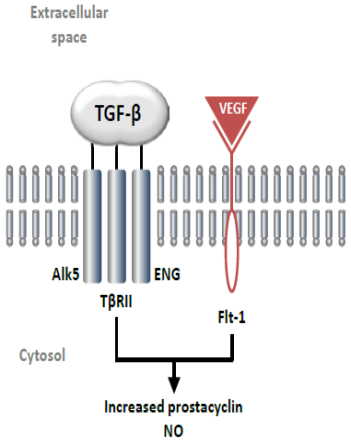
Anjiyogenetik Faktörler

- Patogenez
- Öngörü
- Preeklampsi Şüphesi
- Yönetim ve Prognozu Belirleme
- Uzun vade sorunlar
- Tedavi

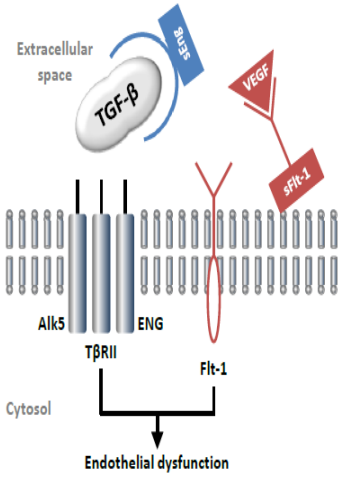
Patogenez /Anjiyogenik Dengesizlik



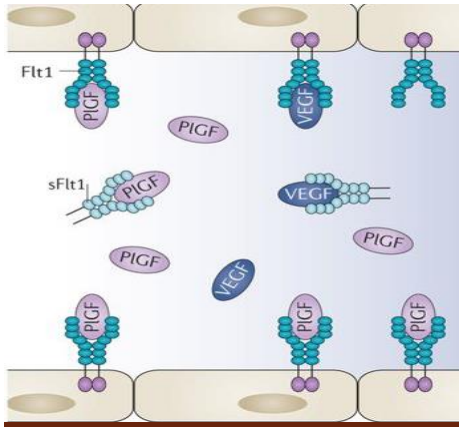




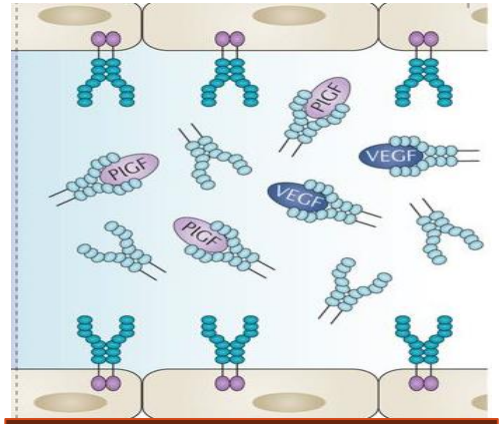
Normal



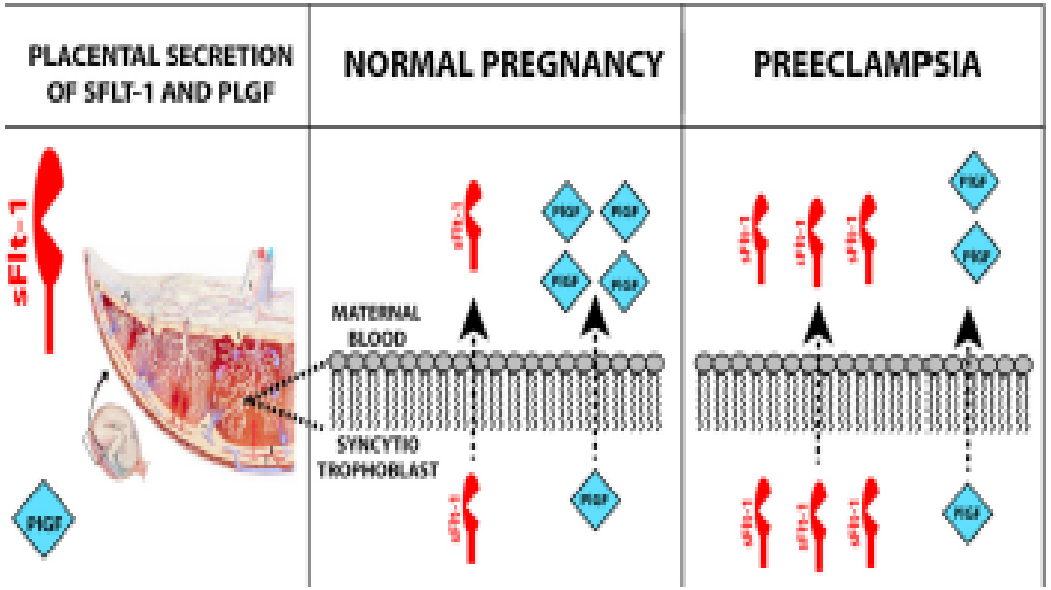
Preeklampsi

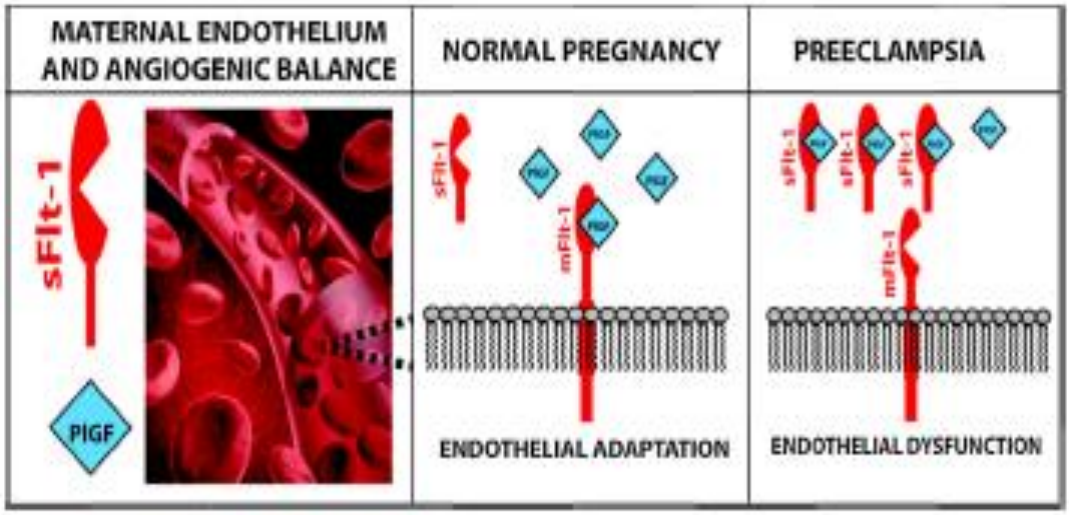


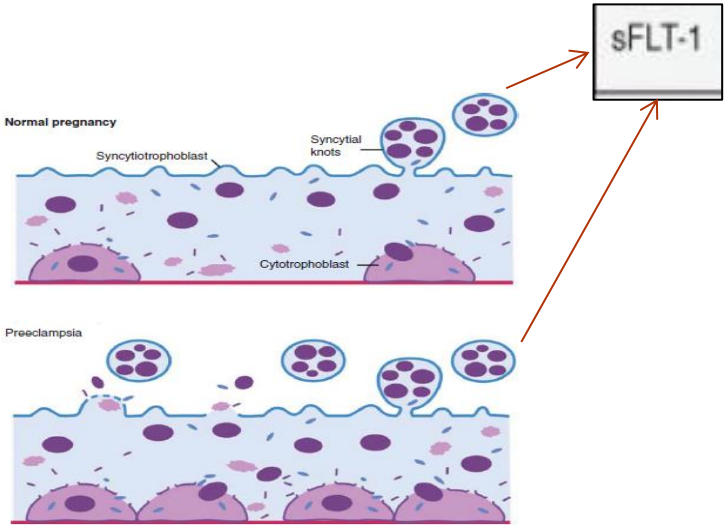
sFlt1:PIGF ↓
Sağlıklı Endotel
Normal Gebelik

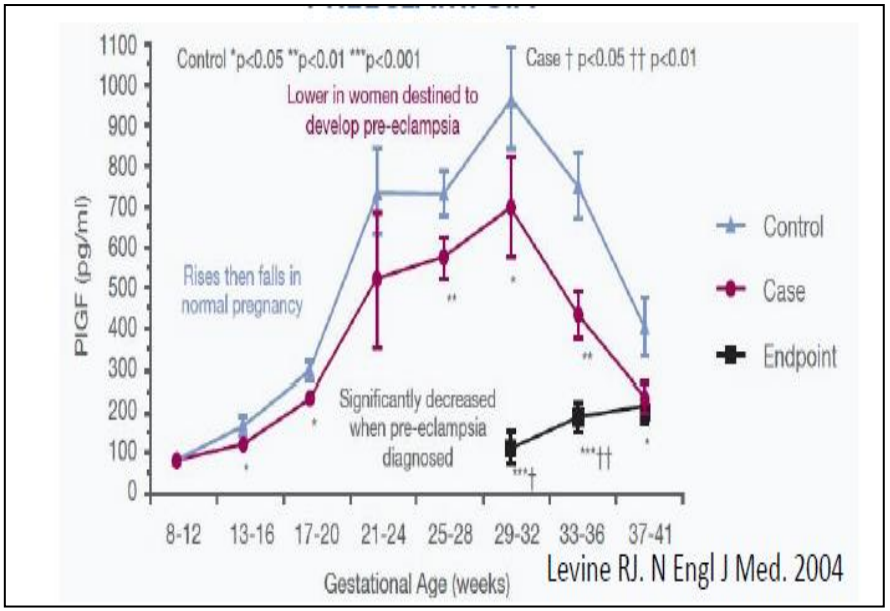


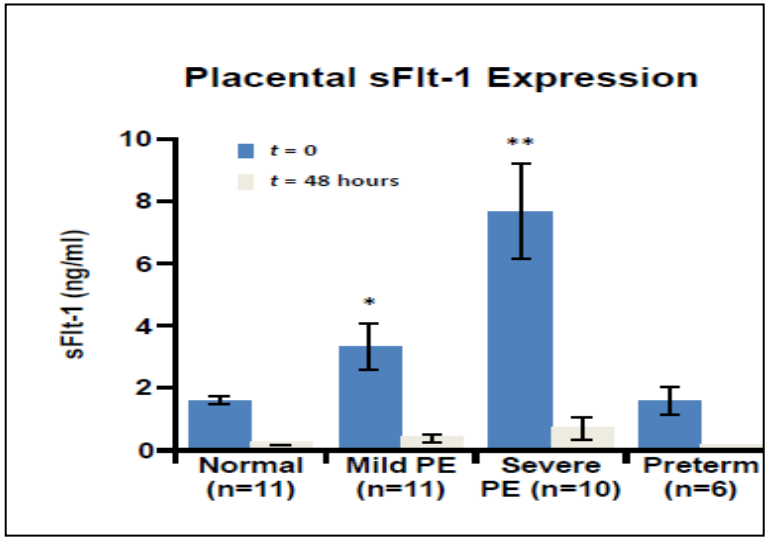
sFlt1:PIGF ↑
Endotel Disfonksiyon
Preeklampsi

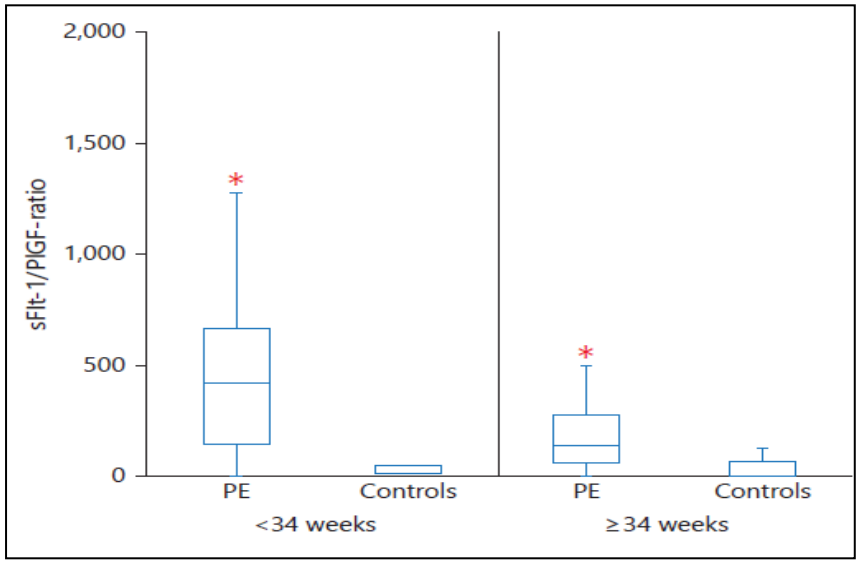

PLACENTAL SECRETION OF SFLT-1 AND PLGF
NORMAL PREGNANCY
PREECLAMPSIA
sFlt-1
PlGF
MATERNAL BLOOD
SYNCYTIO TROPHOBLAST


MATERNAL ENDOTHELIUM AND ANGIOGENIC BALANCE
NORMAL PREGNANCY
PREECLAMPSIA
sFlt-1
PlGF
mFlt-1
ENDOTHELIAL ADAPTATION
ENDOTHELIAL DYSFUNCTION

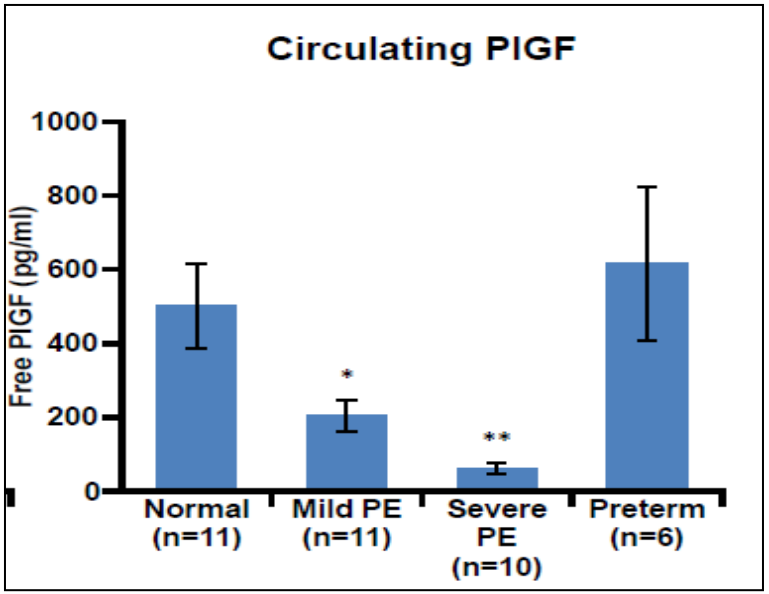

sFLT-1
Normal pregnancy
Syncytiotrophoblast
Syncytial knots
Cytotrophoblast
Preeclampsia







Ohkuchi A, Hypertens Res 2010;33:422–427.



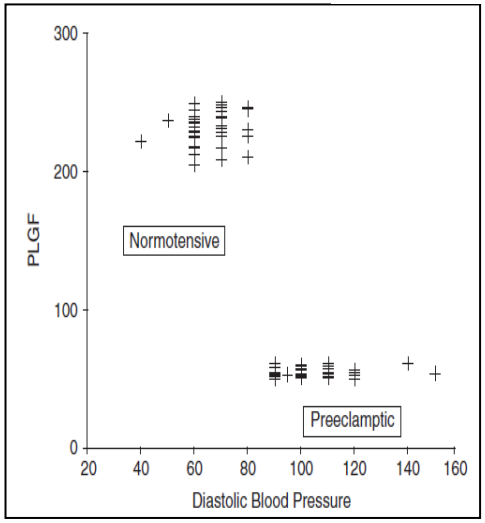
*P < 0.05 and **P < 0.01 as compared with normotensive controls.PE, preeclampsia

Maynard SE, et al. J Clin Invest 2003;111: 649–658

Maternal plasma levels of cytokines in normal and preeclamptic pregnancies and their relationship with diastolic blood pressure and fibronectin levels

Riza Madazli [a]; Seval Aydin; Seyfettin Uludag; Ocak. Vildan; Necati Tolun

Acta Obstet Gynecol Scand 82 (2003)



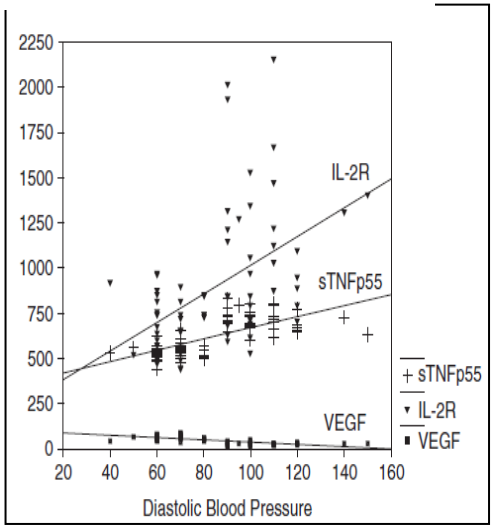


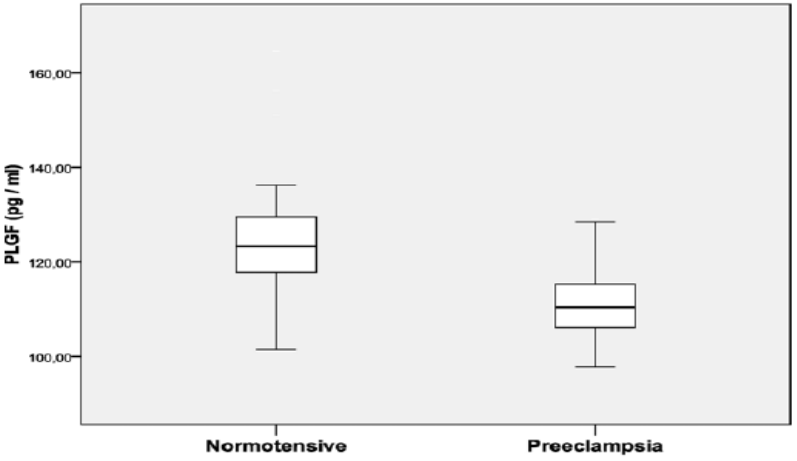
Table II. Plasma cytokine concentrations (pg/ml) of normotensive and preeclamptic pregnancies

	Normotensive ($n=33$)	Preeclampsia ($n=35$)	Significance
PLGF	231 ± 12.3	54.9 ± 2.9	<0.001
VEGF	64.8 ± 13.1	28.5 ± 7.9	<0.001

First-trimester maternal serum metastin, placental growth factor and chitotriosidase levels in pre-eclampsia

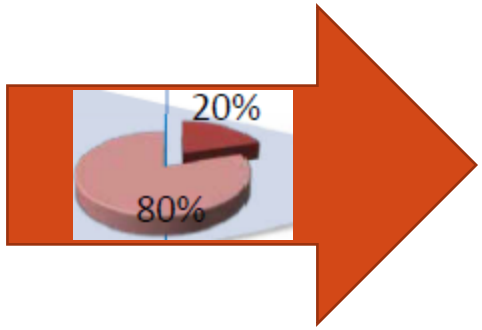
Riza Madazli *, Berk Bulut, Abdullah Tuten, Burcu Aydin, Gökhan Demirayak, Mine Kucur

European Journal of Obstetrics & Gynecology and Reproductive Biology 164 (2012) 146–149



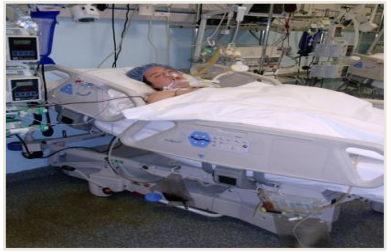
Preeklampsi Şüphe

- Kan basıncı yüksekliği
- Kr hipertansiyon KB yükselme
- Proteinüri
- Baş ağrısı, epigastrik ağrı, Görme şikayetleri
- Ödem, Aşırı kilo artışı
- Trombositopeni, Karaciğer enzim yüksekliği



- **Preeklampsi**

sFlt1/PIGF
PIGF

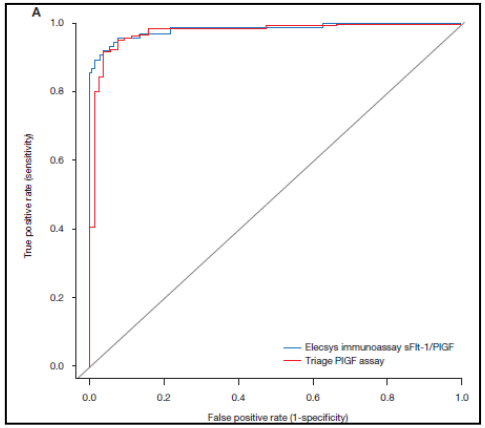


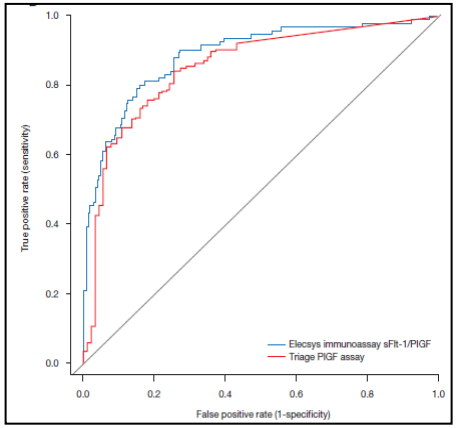
	PROGNOSİS *(Zeisler et al. N Engl J Med, 2016)*	**PELICAN** *(Chappel et al, Circulation, 2013)*	**Alvares ve ark** *(Clin Chem Lab Med,2014)*	
Çalışma	14ülke (30 merkez)	UK,Irl (7 merkez)	İspanya	
Olgu /Hafta	1050 /24-36 hft	424 / 20-36hft	62 /20-34 hafta	
Test	sFlt1/PIGF	PIGF	sFlt1/PIGF	
Sınır değer	38	<100 pg/ml	<23	<85
Sonuç	4hf içinde PE	2 hf içinde PE	3 hf içinde PE yok	
Sens	66	96	92	56
Spesf	83	56	81	97
PPV	37	44	76	93
NPV	95	98	94	76

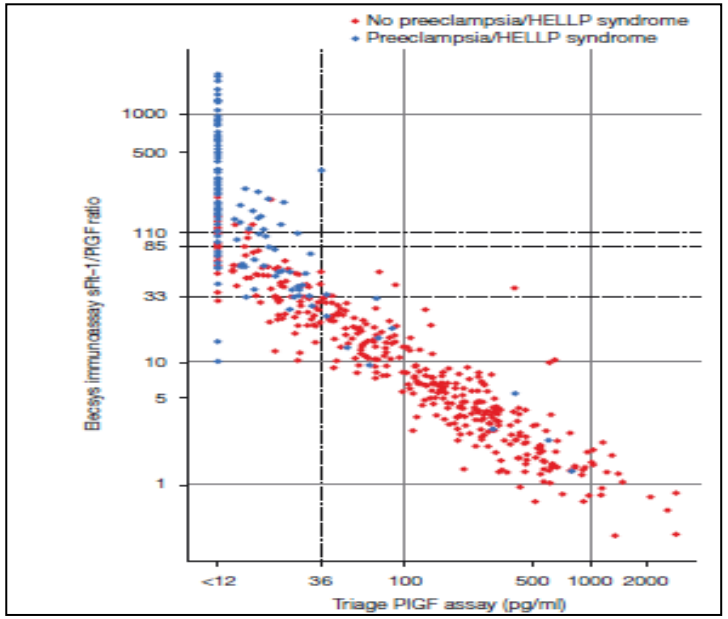
A comparison of the diagnostic utility of the sFlt-1/PlGF ratio versus PlGF alone for the detection of preeclampsia/HELLP syndrome

Stepan et al., Hypertension Pregnancy, 2016

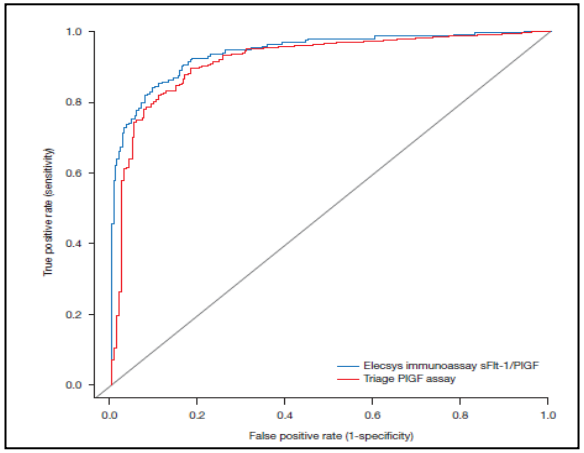
	Total	Early gestation *n* = 257	Late gestation *n* = 312
Controls	391	174	217
Preeclampsia/ HELLP syndrome*	178*	83	95







Assay		Early gestation (<34 weeks)	Late gestation (≥34 weeks)
Elecsys immunoassay sFlt-1/ PlGF ratio	Sensitivity	94.0% (86.5–98.0) [cutoff 33]	89.5% (81.5–94.8) [cutoff 33]
	Specificity	99.4% (96.8–99.9) [cutoff 85]	95.4% (91.7–97.8) [cutoff 110]
Triage PlGF [cutoff 36 pg/ml])	Sensitivity	96.4% (89.8–99.3)	90.5% (83–96)
	Specificity	88.5% (82.8–92.8)	64.5% (57.8–70.9)



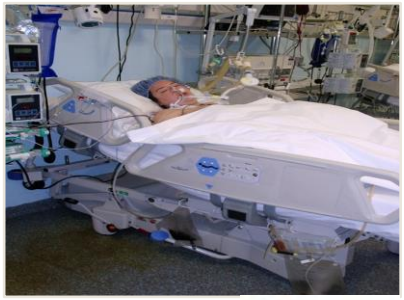
Opinion

Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice

Ultrasound Obstet Gynecol 2015; 45: 241–246

sFlt-1/PlGF (EB-P / GB-P)	Yorum	Doğuma geçen süre (EB-P)	Yönetim
Düşük <38	PE gelişmeyecek (1 hf %99, 4hf %95)		Rutin Takip
Orta 38-85 / 38-110	4 hf içinde PE gelişme %40	1 ay sonra %20 gebelik devam	1-2 hft test tekrar Maternal eğitim
Yüksek >85 / >110	PE	2 hafta sonra %15 gebelik devam	2-4 gün test tekrar / PE yönetim
Çok Yüksek >655 / >201	Komplikasyon↑ ve doğum gerekli	2 gün sonra %30 gebelik devam	Çok yakın takip (Ağır preeklampsi)

Yönetim ve Prognoz Belirleme



sFlt1/PIGF
PIGF

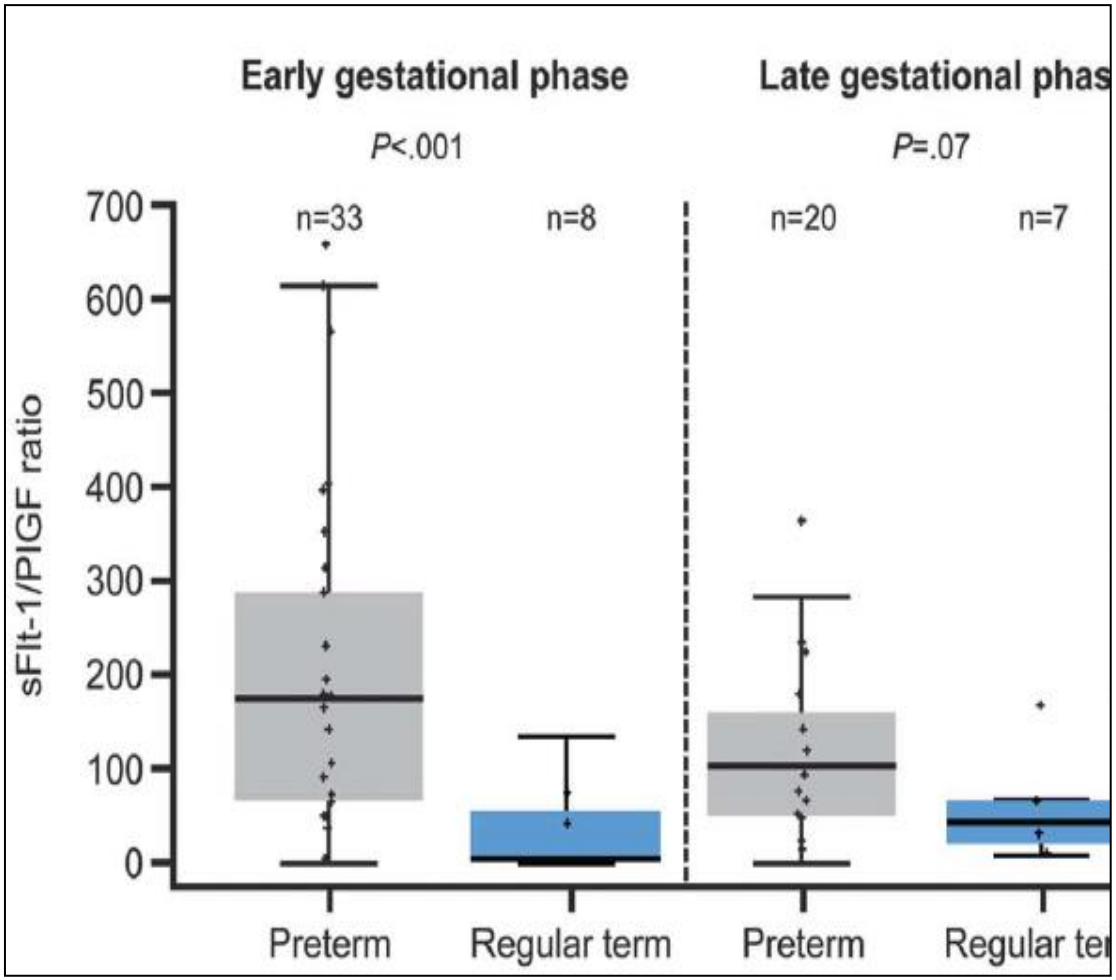
- **Doğum Kararı**
- **Olumsuz Sonuçların öngörüsü**
- **Yönetime Yararı**

- **sFlt/PIGF**
  - **EB-Pre >655**
  - **GB-Pre>201**
- **PIGF**
  - **<100 pg/ml**
  - **<12 pg/ml**

Soluble fms-Like TyrosineKinase-1-to-Placental Growth Factor Ratio and Time to Delivery in Women WithSuspected Preeclampsia

Zeisler et al., Obstet Gynecol, 2016

- PROGNOSİS çalışması



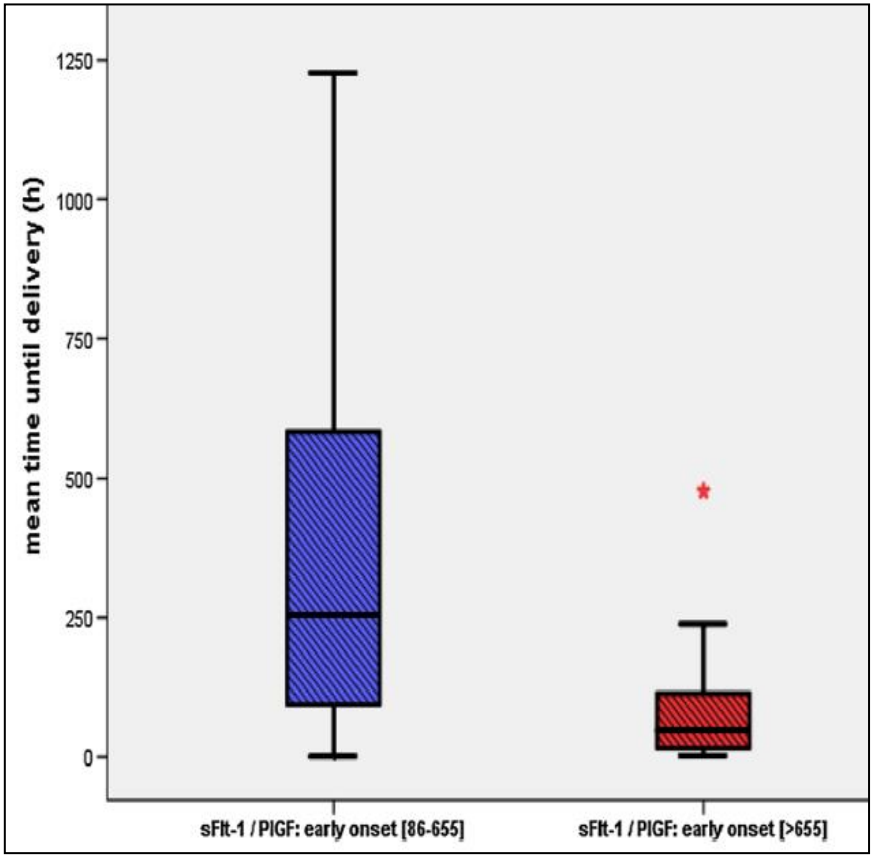
	Gest. Phase	Median sFlt-1/PIGF ratio (IQR)	N
Preterm delivery	Early	177 (68.4–289)	33
	Late	105 (52.6–154)	20
Regular term delivery	Early	5.7 (3.0–49.6)	8
	Late	44.4 (22.7–68.2)	7

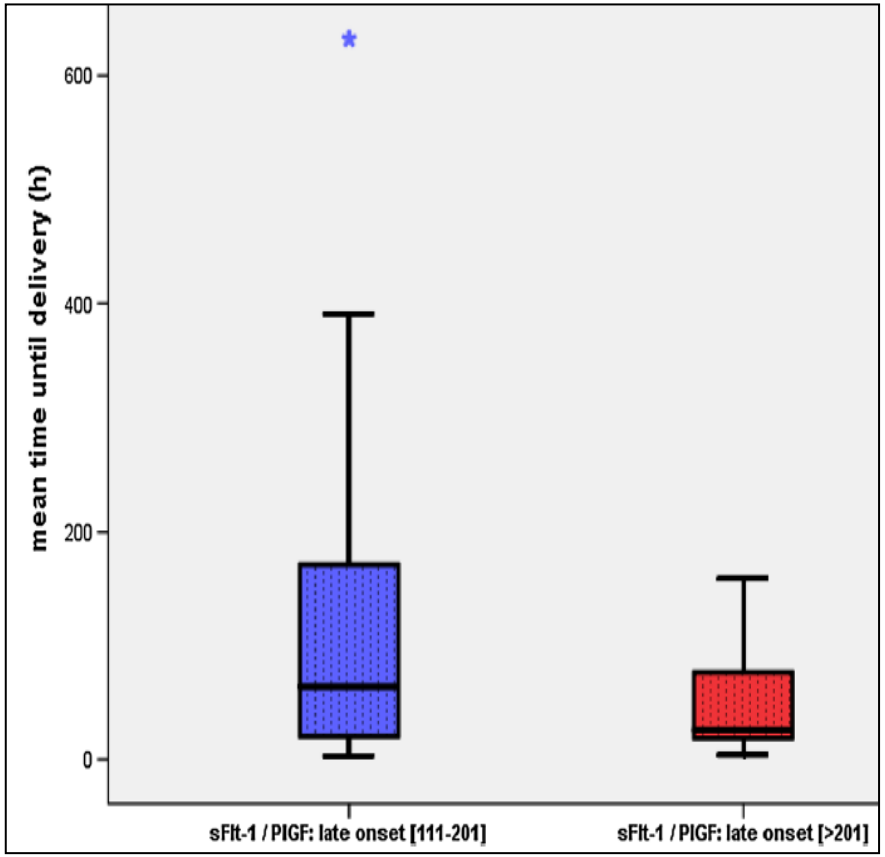
sFlt-1/PlGF ratio for the prediction of the time of delivery

Graupner et al.,Arch Gynecol Obstet,2018

- 995 PE /Almanya,Münih
- sFlt/PIGF / EB>655, GB>201

- Etkili / Karar vermede tek başına kullanılmamalı



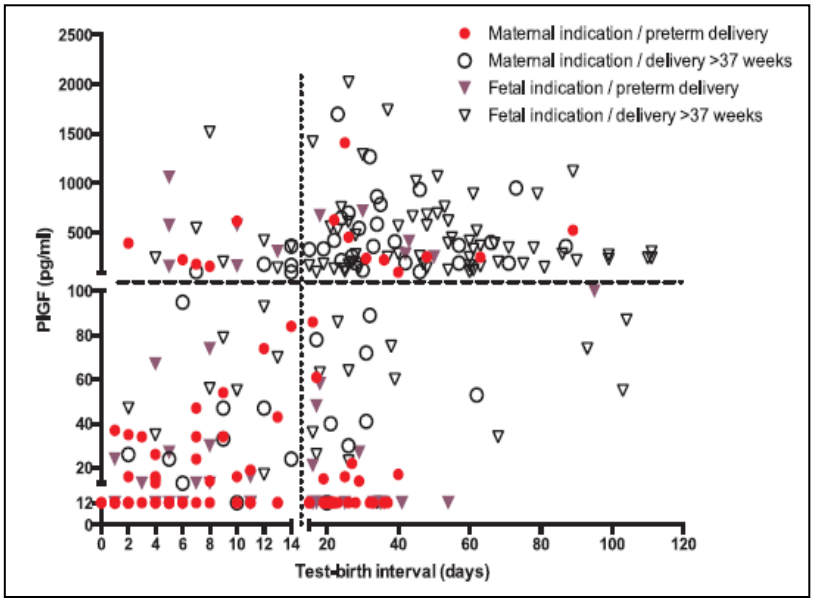


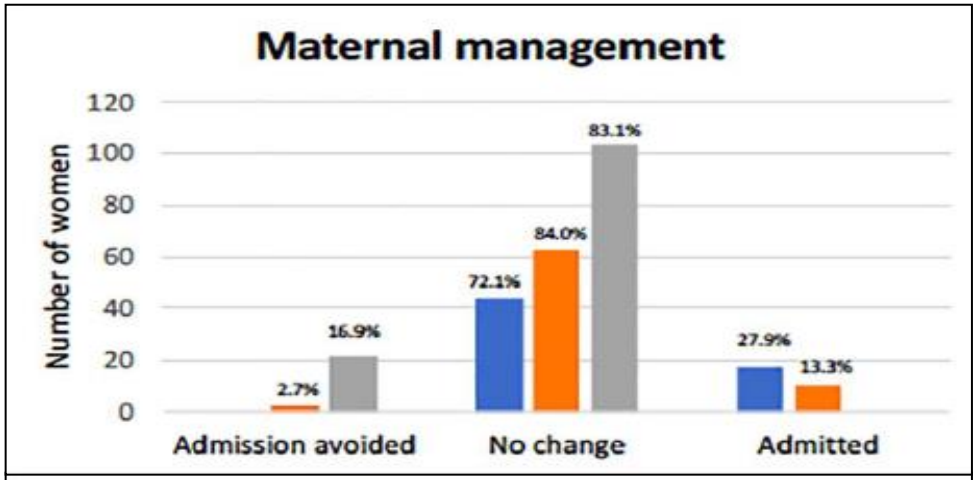
A clinical evaluation of placental growth factor in routine practice in high-risk women presenting with suspected pre-eclampsia and/or fetal growth restriction

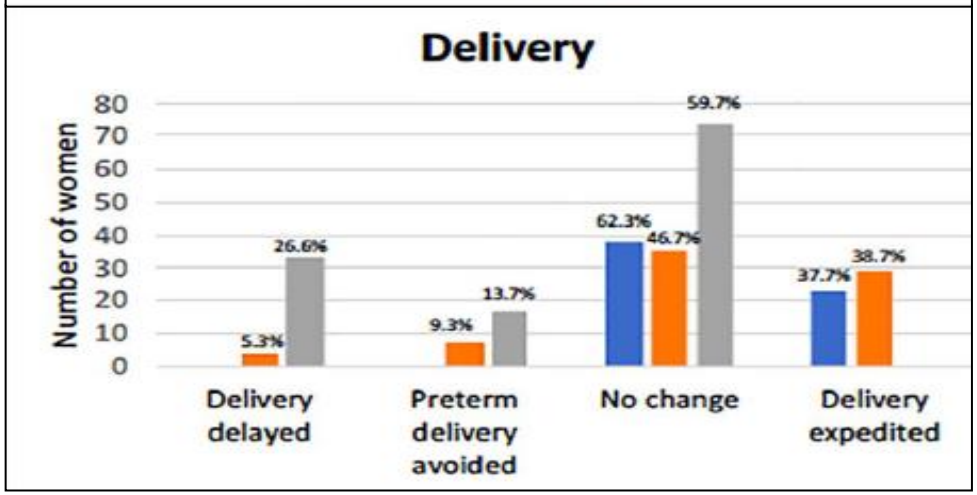
Ormesher et al.,Pregn Hypert,2018

- 260 PE /UK, Manchester
- PIGF <12, 12-100, >100 pg/ml

- Etkili / Karar vermede tek başına kullanılmamalı







Intermediate PlGF (12-100pg/ml) [n=75]

Low PlGF (<12pg/ml) [n=61]

Normal PlGF (>100pg/ml) [n=124]

Angiogenic Factor Estimation as a Warning Sign of Preeclampsia-Related Peripartum Morbidity Among Hospitalized Patients

Perdigao et al., Hypertension, 2019

- 375 PE / ABD, Chicago
- Antenatal Olumsuz Sonuçlar ve Postpartum HT ↑

Table 3. Increasing Risk of Antepartum Complications With Increasing Level of sFlt1/PlGF Ratio Among Patients With an HDP

Angiogenic Factors	Tertile 1			Tertile 2			Tertile 3		
	Adverse Outcomes, N (%)	Odds Ratio (95% CI)	*P* Value	Adverse Outcomes, N (%)	Odds Ratio (95% CI)	*P* Value	Adverse Outcomes, N (%)	Odds Ratio (95% CI)	*P* Value
Univariate									
sFlt1	5 (4.24)	1.0 [REF]	…	10 (8.40)	2.07 (0.69–6.26)	0.20	30 (25.42)	7.71 (2.87–20.67)	<0.0001
PlGF*	10 (8.47)	1.0 [REF]	…	7 (5.74)	0.66 (0.24–1.79)	0.41	28 (24.78)	3.56 (1.64–7.73)	0.001
sFlt1/PlGF	6 (4.92)	1.0 [REF]	…	8 (7.08)	1.47 (0.50–4.39)	0.49	31 (26.27)	6.89 (2.75–17.24)	<0.0001

Table 7. Increasing Risk of Postpartum Hypertension With Increasing Level of sFlt1/PlGF Among Who Patients Have Antepartum Hypertension

Angiogenic Factors	Tertile 1			Tertile 2			Tertile 3		
	PPHTN N (%)	Odds Ratio (95% CI)	*P* Value	PPHTN N (%)	Odds Ratio (95% CI)	*P* Value	PPHTN N (%)	Odds Ratio (95% CI)	*P* Value
Univariate									
sFlt1	99 (83.90)	1.0 [REF]	…	107 (89.92)	1.71 (0.79–3.71)	0.17	115 (97.46)	7.36 (2.11–25.60)	0.002
PlGF*	97 (82.20)	1.0 [REF]	…	112 (91.80)	2.43 (1.09–5.40)	0.03	110 (97.35)	7.94 (2.30–27.43)	0.001
sFlt1/PlGF	99 (81.15)	1.0 [REF]	…	105 (92.92)	3.05 (1.30–7.14)	0.01	115 (97.46)	8.91 (2.60–30.55)	0.001

Placental Growth Factor informed management of suspected pre-eclampsia or fetal growth restriction: The MAPPLE cohort study

Sharp et al.,Pregn Hypert,2018

- 396 PE /UK, Almanya, Avusturya, Avustralya
- MAPPLE / PELICAN

- Maternal Olumsuz sonuçlar anlamlı fark yok %11.9% vs %10.1(RR, 1.17; 95% CI 0.76–1.82)

Maternal and fetal outcomes in women in MAPPLE (revealed PlGF testing) and PELICAN (concealed PlGF testing) cohort studies presenting prior to 35 weeks' gestation presented by PlGF results at enrolment.

	MAPPLE (revealed) PlGF < 12	PELICAN (concealed) PlGF < 12	MAPPLE (revealed) PlGF 12–100	PELICAN (concealed) PlGF 12–100	MAPPLE (revealed) PlGF > 100	PELICAN (concealed) PlGF > 100
Maternal	n = 116	n = 69	n = 137	n = 97	n = 143	n = 121
Final diagnosis of pre-eclampsia (n, %)	51 (48.6)	67 (97.1)	69 (53.1)	72 (74.2)	73 (56.2)	37 (30.6)
Women with any maternal adverse outcome (n, %)	25 (21.6)	12 (17.4)	16 (11.7)	8 (8.2)	6 (4.2)	9 (7.4)

- Yönetimde Etkinliği Gösterilemedi

Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial

Kate E Duhig, Jenny Myers, Paul T Seed, Jenie Sparkes, Jessica Lowe, Rachael M Hunter, Andrew H Shennan, Lucy C Chappell*, on behalf of the PARROT trial group†*

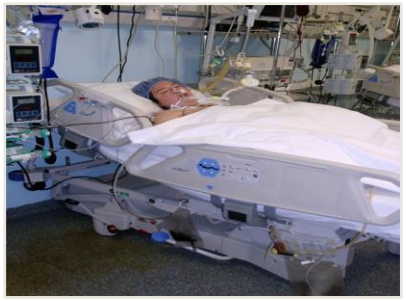
www.thelancet.com **Published online April 1, 2019**

	Revealed PlGF (intervention; n=573)	Concealed PlGF (n=446)
PlGF, pg/mL		
<12	130 (23%)	106 (24%)
12–100	213 (37%)	173 (39%)
>100	230 (40%)	167 (37%)
Time to diagnosis of pre-eclampsia in those diagnosed, days	1·9 (0·5–9·2)	4·1 (0·8–14·7)
Number of women with adverse outcomes, defined by the fullPIERS consensus*	22 (4%)	24 (5%)

Number of women with maternal adverse events	0	4 (1%)
Maternal death	0	0
Maternal stroke	0	2 (<1%)
Maternal cardiac arrest	0	1 (<1%)*
Eclampsia	0	2 (<1%)
Number of babies with perinatal serious adverse events	10 (2%)	7 (2%)
Intrauterine fetal death		
Before viability†	3 (1%); 2	3 (1%); 3
Viable (no fetal dysmorphism)	1 (<1%); 1	3 (1%); 2‡
Viable (fetal dysmorphism noted)	3 (1%); 1	0
Neonatal deaths	3 (1%); 3	1 (<1%); 1

- 11 Merkez UK (NICE)/1019 gebe
  - Tanı Süre
    1.9 g vs 4.1g
    (AOR 0·36)
  - Maternal ağır sonuç
    %4 vs %5
    (AOR 0·32)
  - Perinatal olumsuz sonuç
    anlamlı fark yok

- PIGF Preeklampsi Yönetimde Etkin



- sFlt/PIGF ↑
  - EB-Pre >655
  - GB-Pre>201
- PIGF ↓
  - <100 pg/ml
  - <12 pg/ml

- Gebeliğin yönetiminde
- Doğum Kararı verilmesinde
- Prognostik Faktör olarak

→ Etkili

- Henüz Tek Başına Preeklampsi (Ağır) Yönetimde Kullanılması Önerilmiyor

Uzun Vade Sorunlar

- Kalp Hastalığı↑
- Böbrek Hastalığı ↑

→ Anjioyogenik Faktörler İlişki ?

Placental Growth Factor as an Indicator of Maternal Cardiovascular Risk After Pregnancy

Benschop et al Circulation. 2019

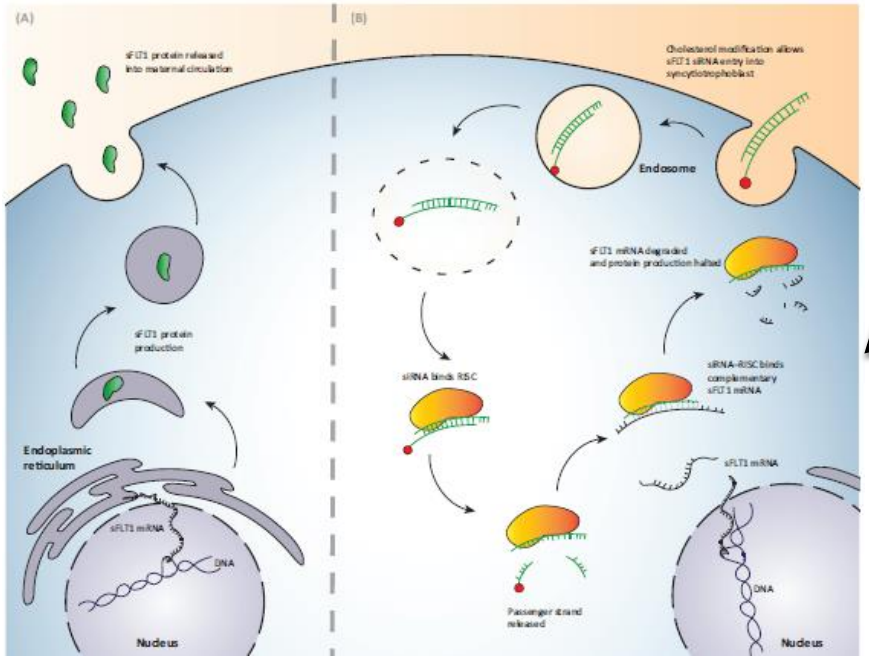
- Midpregnancy PIGF ↑ 5475 gebe Hollanda / 6yıl
  - Aort kök çap ↓(−0.24 mm, −0.39 - −0.10)
  - Sol atrial çap ↓ (−0.75 mm,−0.95 - −0.56)
  - Sol ventrikül kitle ↓ (−3.9 g, −5.5 - −2.3)
  - Sistolik kan basıncı↓ (−1.1 mm Hg, −1.7 to −0.46)

Tedavi

- Rekombinant VEGF, PIGF
- RNA interference (Small interfering RNA (siRNA)
- Aferez
- Metformin
- Protein Pompa İnhibitorleri
- Statin
- Sildenafil

Rekombinant VEGF, PlGF

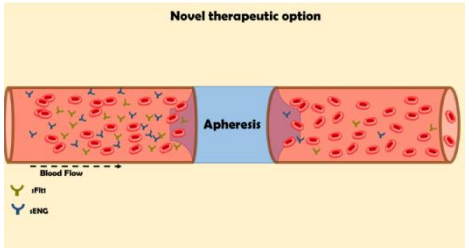
- Deneysel
- Maternal VEGF gene / EB-FGK EVERREST çalışma (Ad.VEGF-Uterin Arter)



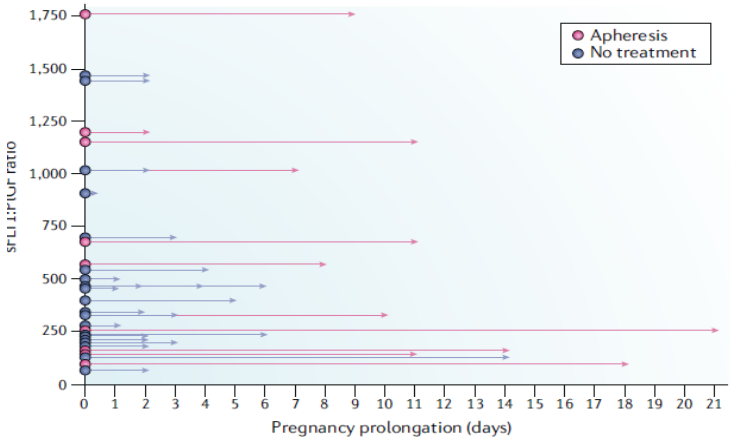
Small interfering RNA (siRNA)

- sFLT1 mRNA parçalıyor, üretimi ↓
- Tek doz iv sFLT1 siRNAi / sFlt1 protein %50 ↓, proteinüri ve BP azaldı boboon modelinde *(Turanov et al.Nat. Biotechnol.2018)*

Aferez



sFLT1↓



- 11 EB-Preek gebe / Aferez
  - Aferez + / ort 8 gün
  - Aferez - / ort 3gün

  (Thadhani et al. J Am Soc Nephrol. 2016)

Protein Pompa İnhibitorleri

Esomeprazole

- Hücre kültür sFLT1 üretimini↓ ve Fare hipertansiyon düzeltiyor

- Randomize kontrollü klinik çalışma (EB-Preek) / Gebeliğin uzaması ve sFLT1azalması etkili değil

  (Cluver, et al, Am. J. Obstet. Gynecol, 2018)

Statin

- Plasenta sFLT1↓, NO↑
- Klinik çalışmalar / Preeklampsi ted etkili olabilir
  (Chaiworapongsa et al, J. Matern. Fetal Neonatal Med. 2017)

Metformin

- HIF1α↓ve plasenta sFlt-1 ve sENG sekresyonu ↓
  (Brownfoot et al. Am J Obstet Gynecol 2016)

Sildenafil

Sildenafil citrate (Viagra)

- Phosphodiesterase 5 inhibitor / NO↑, sFLT1↓
- Küçük klinik çalışma etkili
  (Trapani et al Obstet.Gynecol. 2016).
- STRIDER çalışması / EB-FGK tedavisi / Durduruldu – Fetal Akçiğer hast ve fetal kayıp çalışma grubu ↑
  (Hawkes, N. BMJ ,2018)

Teşekkürler