PERİNATOLOJİDE **GÜNCEL KONULAR**
01 Kasım 2014
İstanbul Üniversitesi Tıp Fakültesi 14 Mart Amfisi

İlk Üç Ayda Plasenta Yetmezliğinin Öngörüsü

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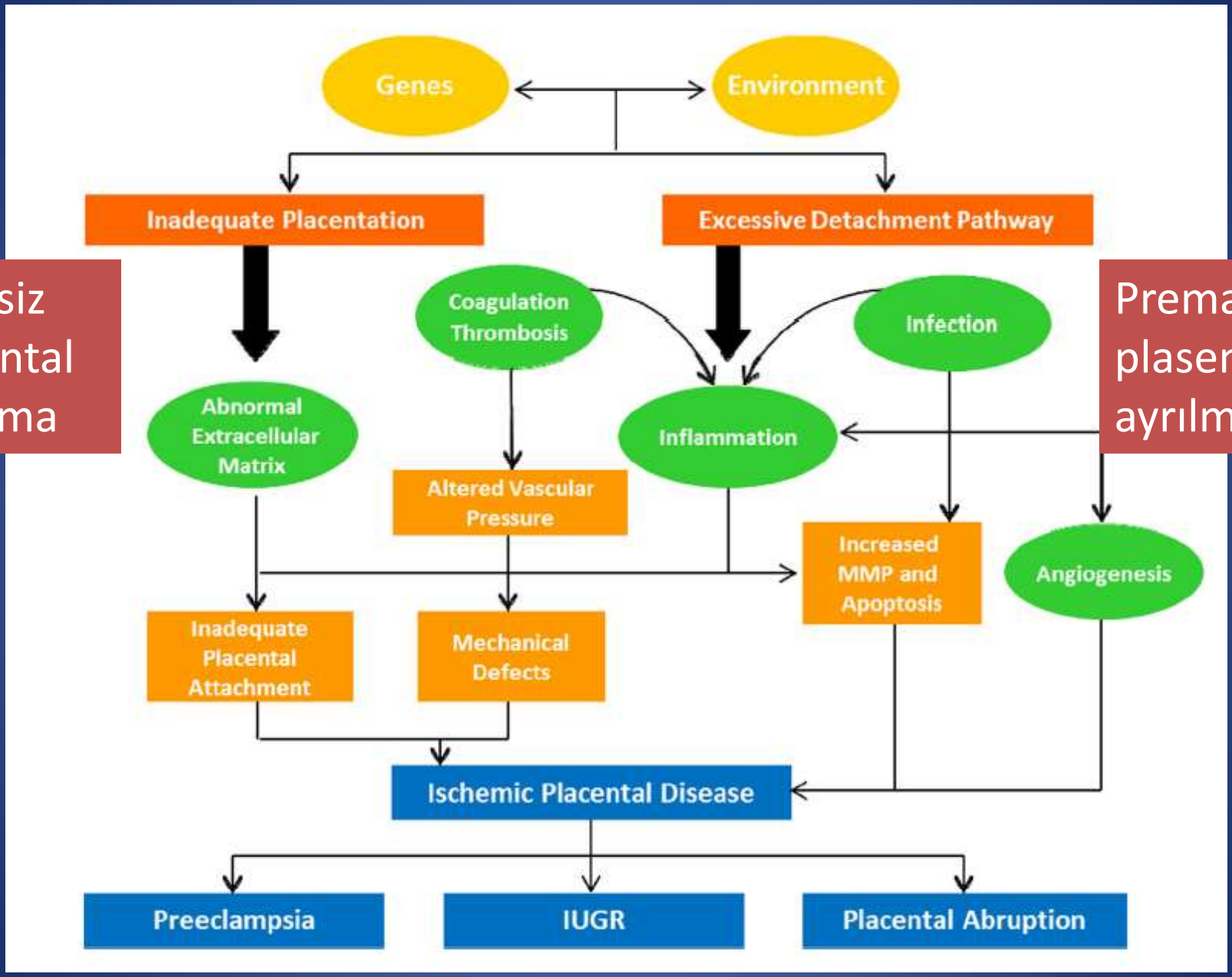
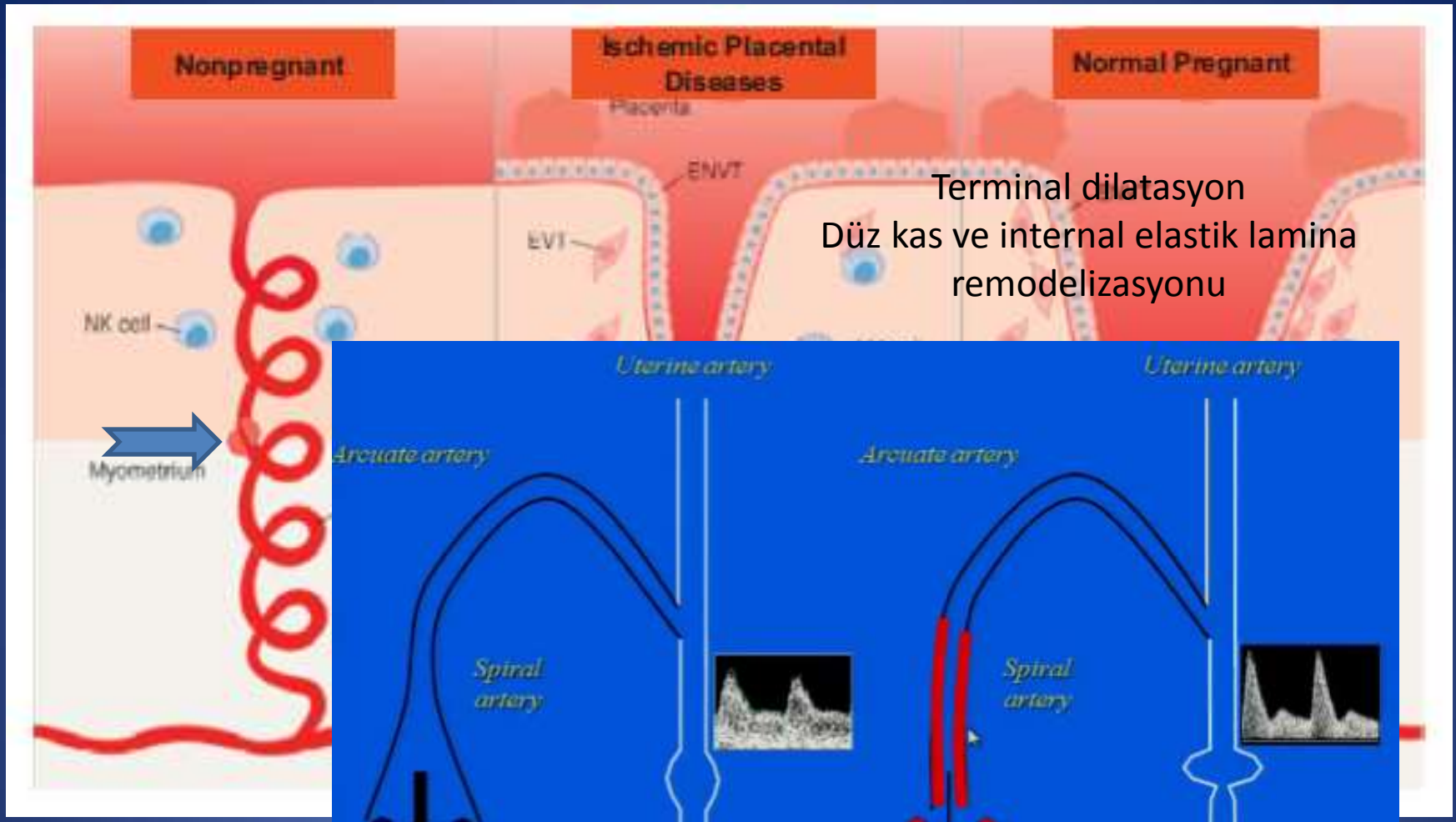
İstanbul Kanuni Sultan Süleyman EAH
Perinatoloji Kliniği

Yetersiz plasental yapışma

Prematür plasental ayrılma



Roberts JM,CooperDW.Pathogenesisandgeneticsofpre- eclampsia. Lancet. 2001



Ute

Sibai BM.Maternalanduteroplacentalhemodynamicsforthe classification andpredictionofpreeclampsia. Hypertension. 2008;

	Ischemic placental disease
Hypertension	+++
Cardiovascular disease/mortality	++
Metabolic syndrome	++
Cerebrovascular disease/stroke	+

Associations appear to be stronger when more than one manifestation of ischemic placental disease is present and/or if associated with preterm birth.

0.19

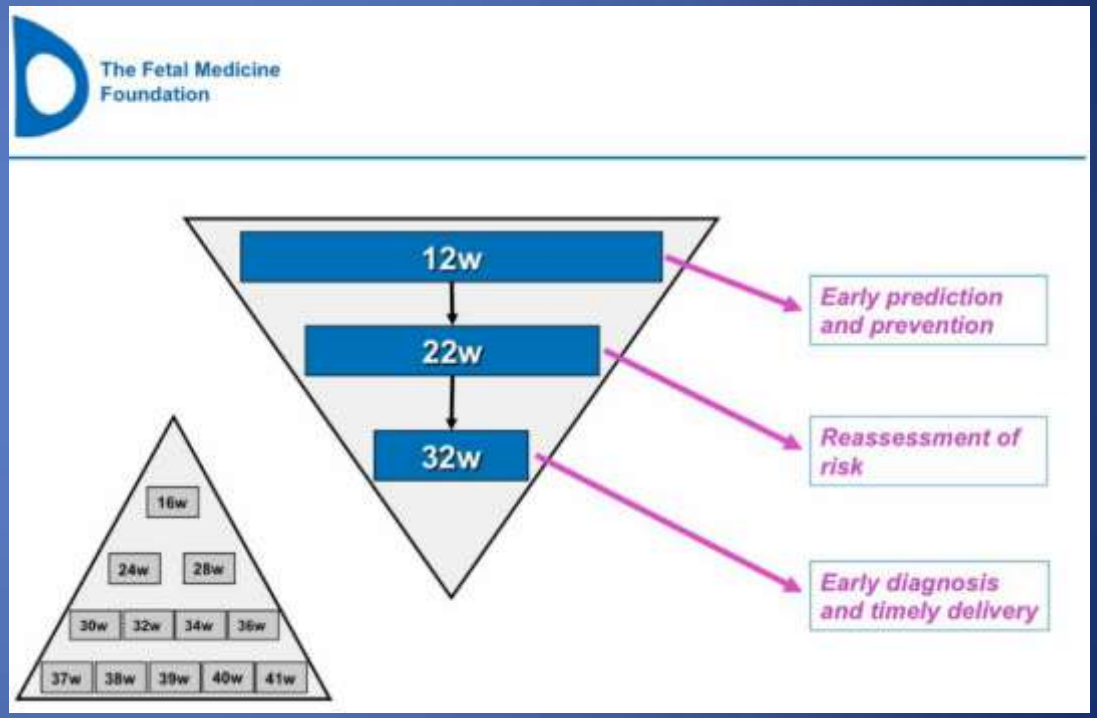
1. <34 hf endikasyonlu erken doğum gerektirirler.
2. Klinik özellikler,risk faktörleri,histoloji, Doppler usg belirgin benzerlik
3. Aralarında çapraz rekürrens vardır
4. Preterm preeklampsi ya da IUGG öyküsü olan annelerde ileride KVH riski artmıştır
5. Plasental yatak biopsileri oldukça benzerdir

Ananth CV,SmulianJC,VintzileosAM.IMaternFetalNeonatalMed. 2010

A model for a new pyramid of prenatal care based on the 11 to 13 weeks' assessment

Kypros H. Nicolaides[1,2]*

- Fetal anöploidiler
- Fetal yapısal anomaliler
- GDM fetal makrozomi
- Plasental Yetmezlik
  - Preeklampsi
  - IUGG (SGA)
  - Dekolman plasenta
  - Düşük ve ölü doğum
  - Erken doğum



İlk trimester plasental yetmezlik öngörüsü

- Maternal özellikler/öykü (Risk faktörleri)
- Doppler ultrasonografi
- Maternal serum biokimyasal belirteçleri
- Proteomik/Genomik incelemeler
- Preeklampsi
- IUGG
- Dekolman plasenta

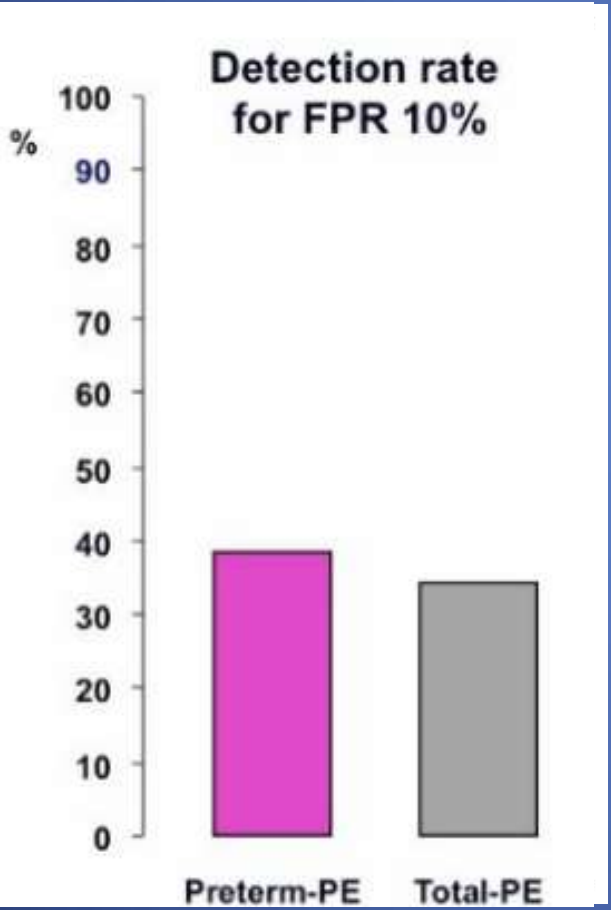
İlk trimester plasental yetmezlik öngörüsünde KULLANILMAYAN

- Provakatif biofizik testler (roll-over test, angiotensin II challenge)
- Serum ürik asit
- Kalıtsal trombofili testleri
- Antifosfolipid testi
- Maternal serum izole belirteç ve cffDNA
- Preeklampsi
- IUGG
- Dekolman plasenta

Risk faktörleri

Preeklampsi

Preconceptional
Chronic hyperten
Pregestational di
Connective tissue
Thrombophilia
Uncontrolled hyp
Polycystic ovary
Age older than 4
Obesity/insulin r
Maternal low bir
Maternal preterm
Preeclampsia in
Primipaternity
Pregnancies after
embryo donation
Limited sperm e
Partner who fath
woman
Smoking (reduce
Family history o
Pregnancy-relate
Multifetal gestati
Maternal infectio
Chromosomal ab

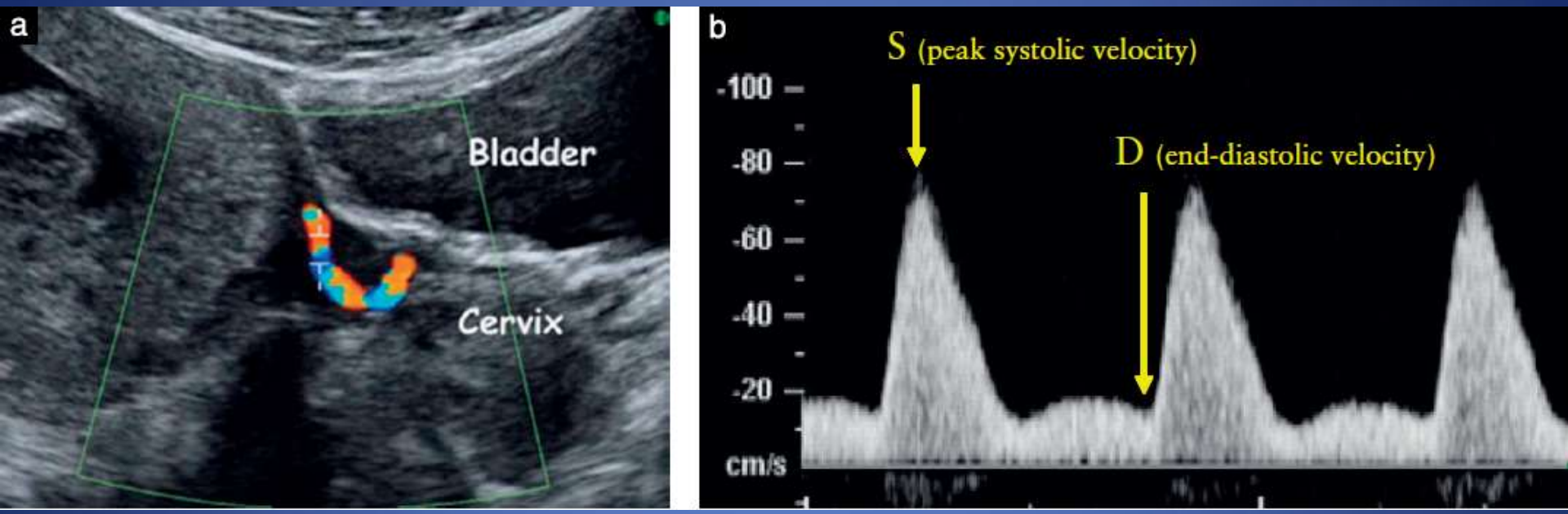


İUGG

Preconceptional or preexisting risk factors
Chronic hypertension/renal disease
Diabetes with vasculopathy
Autoimmune syndromes—antiphospholipid syndrome, lupus
Thrombophilia
Maternal hypoxemia (cyanotic heart disease, severe chronic anemia, chronic pulmonary disease)
Uterine anomalies—large submucous myomas, septate uterus, synechia
Low maternal age (teenagers)
Smoking
Substance abuse—alcohol, heroin, methadone, cocaine, therapeutic agents
Malnutrition
Environmental pollution (e.g. sulfur dioxide, nitrogen dioxide, carbon monoxide)
Family history of IUGR
Pregnancy-related risk factors in the first trimester
Fetal chromosomal abnormality (trisomy 13, 18 and 21, triploidy, uniparental disomy)
Fetal malformations (gastroschisis, omphalocele, diaphragmatic hernia, congenital heart defect)
Maternal infection—malaria, rubella, cytomegalovirus, herpes, toxoplasmosis
Multiple gestation

How to record uterine artery Doppler in the first trimester

A. KHALIL* and K. H. NICOLAIDES*

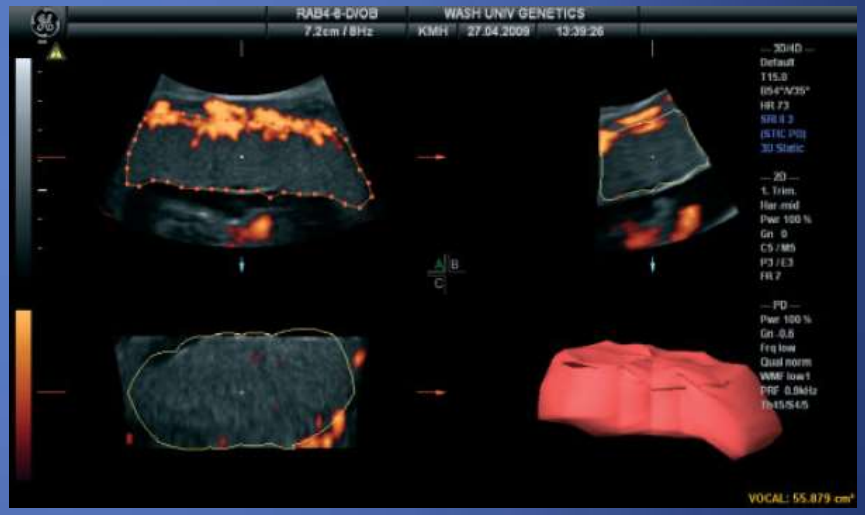


- Uteroservikal kanalın sagittal kesiti, ilgili alanı büyüt
- İnternal osu bulduktan sonra probu hafifçe yanlara kaydır renkli Doppler ile uterin arterleri bul
- Pulse Doppler ile insonasyon açısı $<30^{0}$ ve örneklem aralığı 2 mm olacak şekilde ölçüm yap
- En az üç ardışık dalgaformu kaydet , sag ve sol uAt ortalamasını al

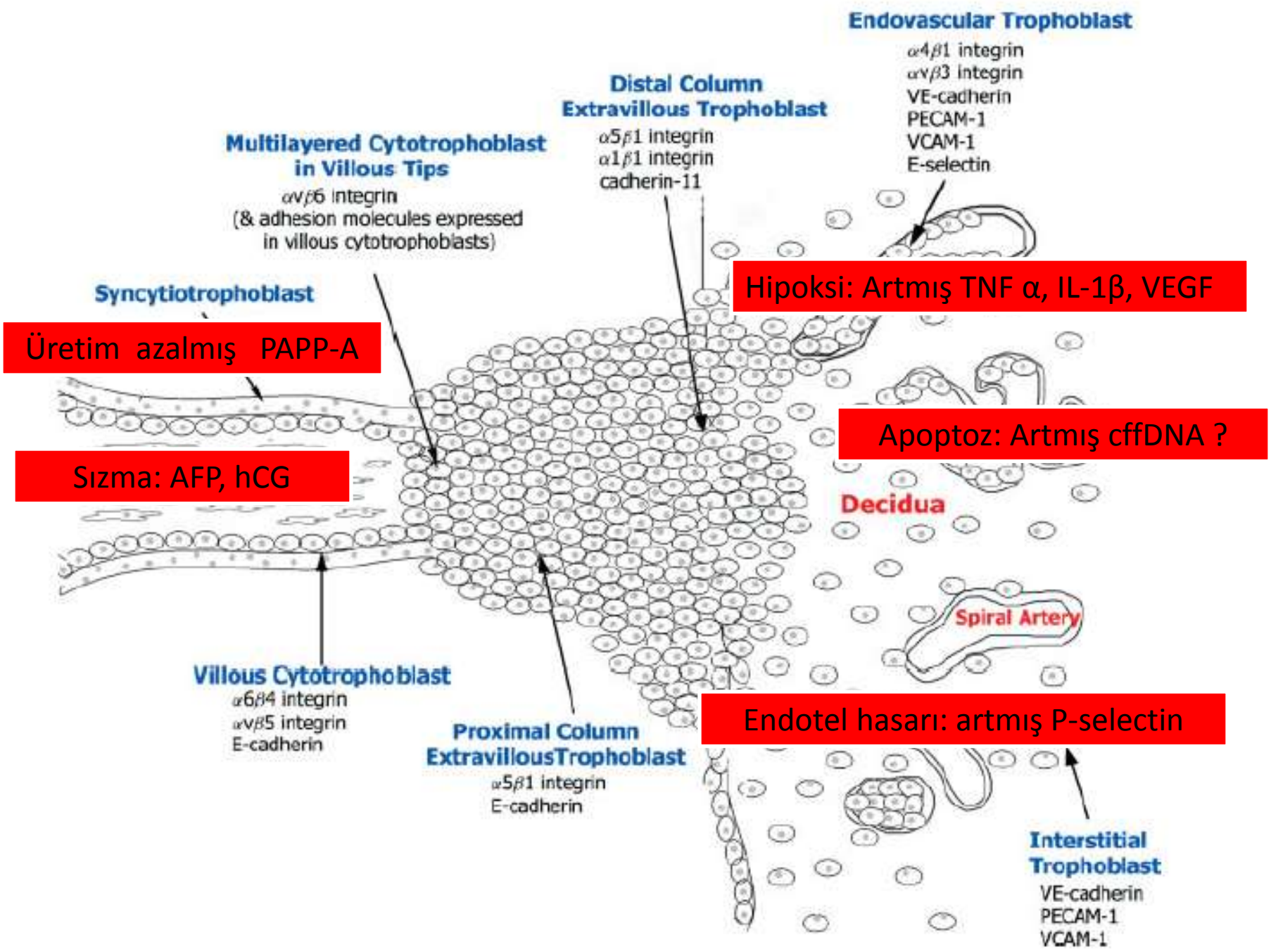
Ultrasound Obstet Gynecol 2013; 42: 478–479

Doppler usg

- Plasentanın büyüklüğü ve villöz ağacın içindeki vasküler akım paternlerinin gösterilmesi
- Azalmış yatak vaskülaritesi < 10. sentil <34 hf erken preek %60



Konje JC, Huppertz B, Bell SC, Taylor DJ, Kaufmann P. 2003.


Endovascular Trophoblast
α4β1 integrin
αvβ3 integrin
VE-cadherin
PECAM-1
VCAM-1
E-selectin
Distal Column
Extravillous Trophoblast
α5β1 integrin
α1β1 integrin
cadherin-11
Multilayered Cytotrophoblast
in Villous Tips
αvβ6 integrin
(& adhesion molecules expressed
in villous cytotrophoblasts)
Syncytiotrophoblast
Hipoksi: Artmış TNF α, IL-1β, VEGF
Üretim azalmış PAPP-A
Apoptoz: Artmış cffDNA ?
Sızma: AFP, hCG
Decidua
Spiral Artery
Villous Cytotrophoblast
α6β4 integrin
αvβ5 integrin
E-cadherin
Endotel hasarı: artmış P-selectin
Proximal Column
ExtravillousTrophoblast
α5β1 integrin
E-cadherin
Interstitial
Trophoblast
VE-cadherin
PECAM-1
VCAM-1

Maternal serum biokimyasal belirteçleri

- AFP
- hCG
- uE3
- İnhibin A
- PAPP-A
- ADAM-12
- sFlt-1
- PlGF
- sEng
- Aktivin A
- SP1
- HPL
- Leptin, TGF-B1, PAI 2
- Metabolomikler

II. Trimester

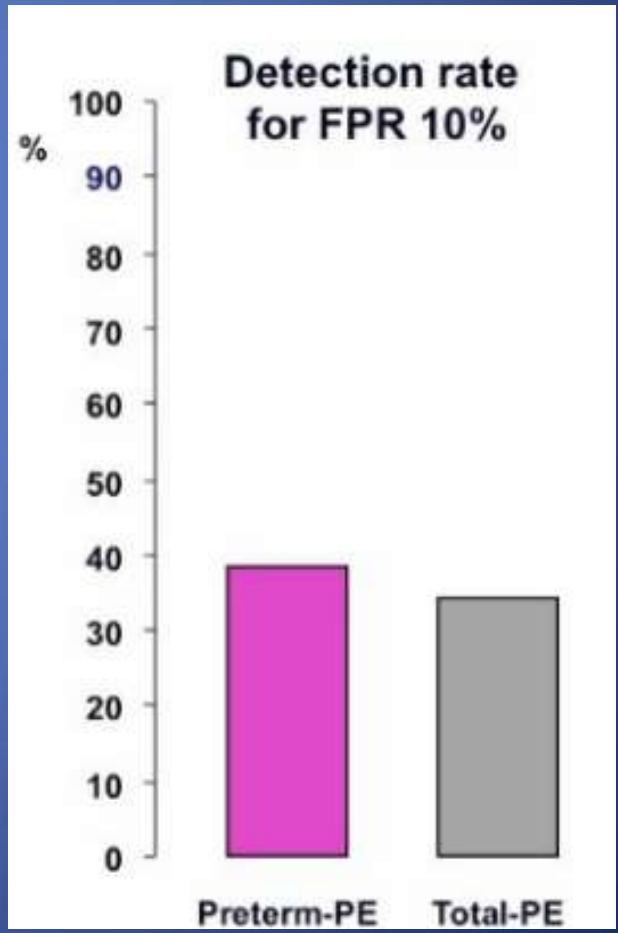
- P-selectin
- Plasental protein 13
- TNF-α
- SHBG
- Adiponektin

I. Trimester

İlk Trimester Preeklampsi Öngörüsü

- Risk faktörlerine dayalı öngörü

Yüksek risk faktörleri:
Önceki gebeliklerde hipertansif hastalık Kronik börek hastalığı Otoimmun hastalıklar; SLE ve ya APS Tip 1 ve ya 2 DM
Orta risk faktörleri:
İlk gebelik ≥40y Gebelikler arasında >10 yıl olması Ailede preeklampsi hikayesi Çoğul gebelik



İlk Trimester Preeklampsi Öngörüsü

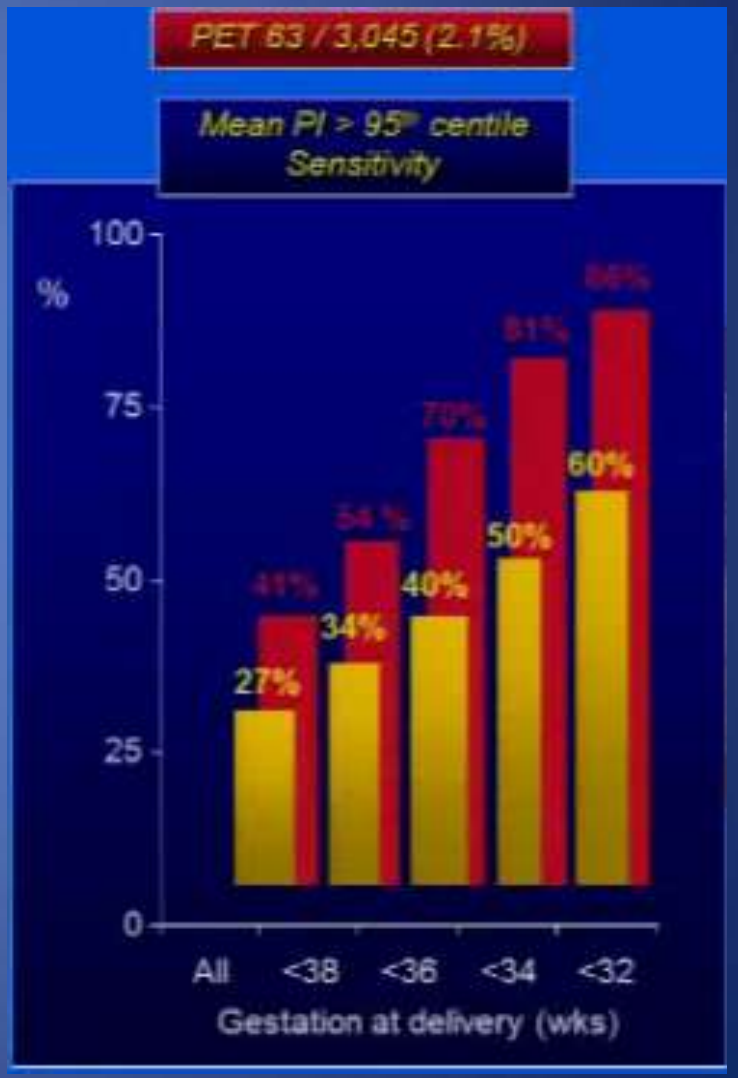
- UtA Doppler'e dayalı öngörü

- UtA Doppler:

erken preek %47, tüm preek %26 (%7.9 FPR) Düşük doz aspirin NNT: 173.

- Maternal faktör + UtA Doppler:

Erken preek <34 hf %81 (FPR %10)



İlk Trimester Preeklampsi Öngörüsü

- Biokimyasal belirteçlere dayalı öngörü:
- PAPP-A <0.4 MoM PPV: %15
- PlGF izole düşük öngörü kapasitesi
- Maternal risk + PlGF %45 saptama oranı (%5 FPR)
- sFlt-1, VEGF, anjiopoietin 1-2, ADAM 12, sEng, IGFBP-1, HbA1C, adiponektin
- Metabolomikler

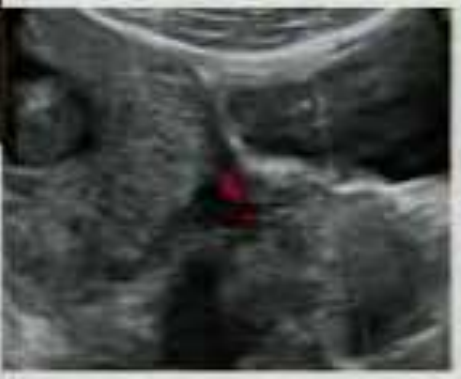
- Cell free fetalDNA'ya dayalı öngörü:

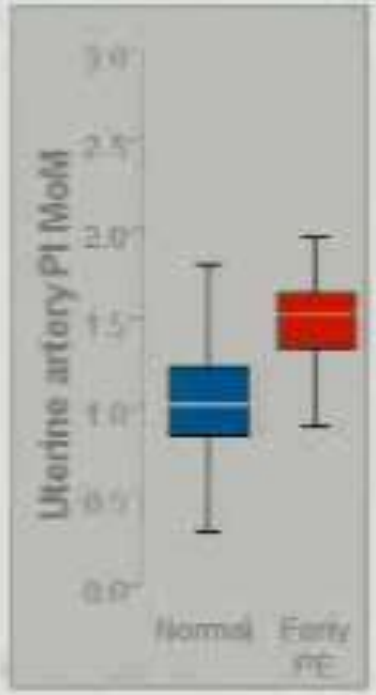
- UtA Doppler ile kombine edilmedikçe izole cffDNA preeklampsi birlikteliği yok

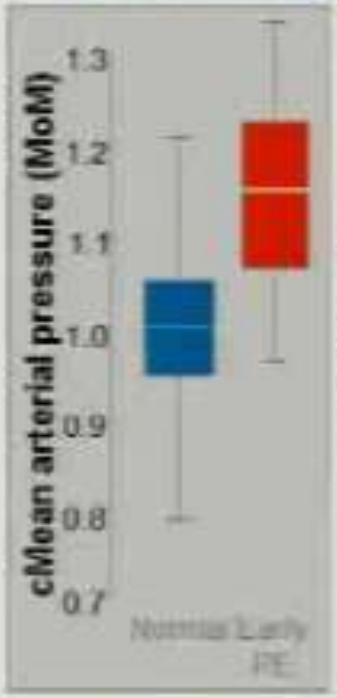
Nicolaides: Screening at 11-14 weeks gestation.

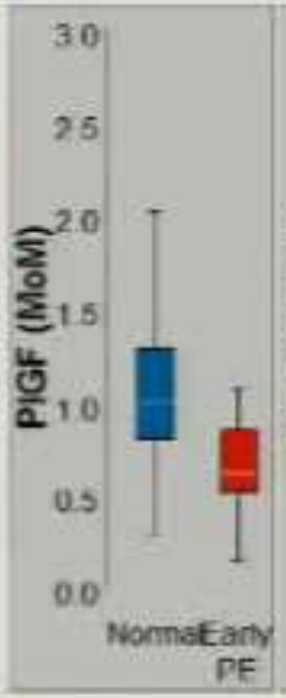
10,000 pregnancies: 600 patients developed Pre-eclampsia

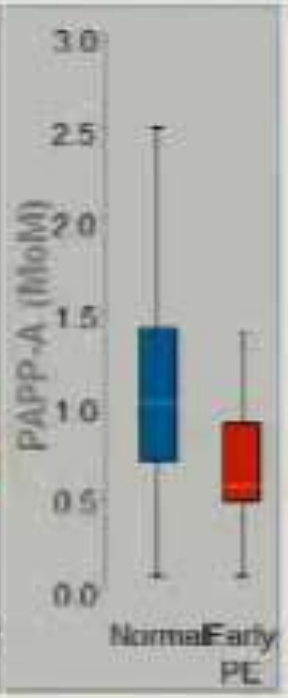
Early Pre-eclampsia (<34w): 45/50 predicted

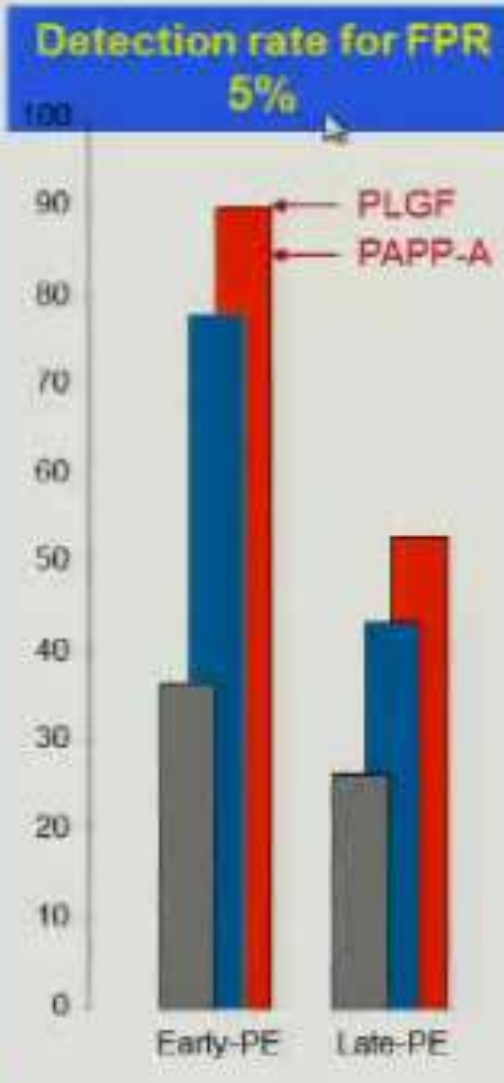












İlk Trimester İUGG/SGA öngörüsü

- IUGG ve SGA tanımları çalışma metodolojileri, preeklampsiyle birlikteliği, kötü obstetrik sonuçlarda yer almaları

- Risk faktörlerine dayalı öngörü:
- Tek başına uygulanabilir etkinlikte değil

HAYIR

Akolekar R, Casagrandi D, Skyfta E, Ahmed AA, Nicolaides KH Prenat Diagn. 2009

İlk Trimester İUGG/SGA öngörüsü

- Ultrasonografiye dayalı öngörü:

- İlk üç ay 2D plasenta şekil boyut
- İlk üç ay 3D power Doppler plasental yatak vaskülarite
- Plasenta volume ,plasenta morfoloji power Doppler

- İlk üç ay UtA PI: %67-85 saptama oranı (%25-58 FPR !!)
- 2014 metaanalizi öngörü %93 (%6.9 FPR)

Sifakis S, Akolekar R, Kappou D, Mantas N, Nicolaides KH Prenat Diagn. 2010

İlk Trimester İUGG/SGA öngörüsü

- Biokimyasal belirteçlere dayalı öngörü:
- İzole PAPP-A %15-33 (%20 FPR)
- PAPP-A + 2D usg
- PlGF, HPL, IGF, rezistin, ADAM-12, PP-13

- Biokimyasal belirteçlerin diğerleriyle kombinasyonu:
- PAPP-A , hCG, OAB, UtA Doppler %73 (%10 FPR)
- Ancak preeklampsiyle birlikte olmayan İUGG lerin saptama oranı %40 lara düşüyor

Plasencia W, Akolekar R, Dagklis T, Venduta A, Nicolaides KH Fetal DiagnTher. 2011

İlk Trimester Ölüdoğum Öngörüsü

- Düşük PAPP-A ve kronik HT ölüdoğum birlikteliği klinik kullanım için yeterli değil
- Maternal özellikler /öykü ve biokimyasal belirteçler klinik kullanımda yer almaktan çok uzak

HAYIR

Pilalis A, Souka AP, Antsaklis P, Daskalakis G, Papantoniou N Fet Ther 2011

İlk Trimester Erken Doğum öngörüsü

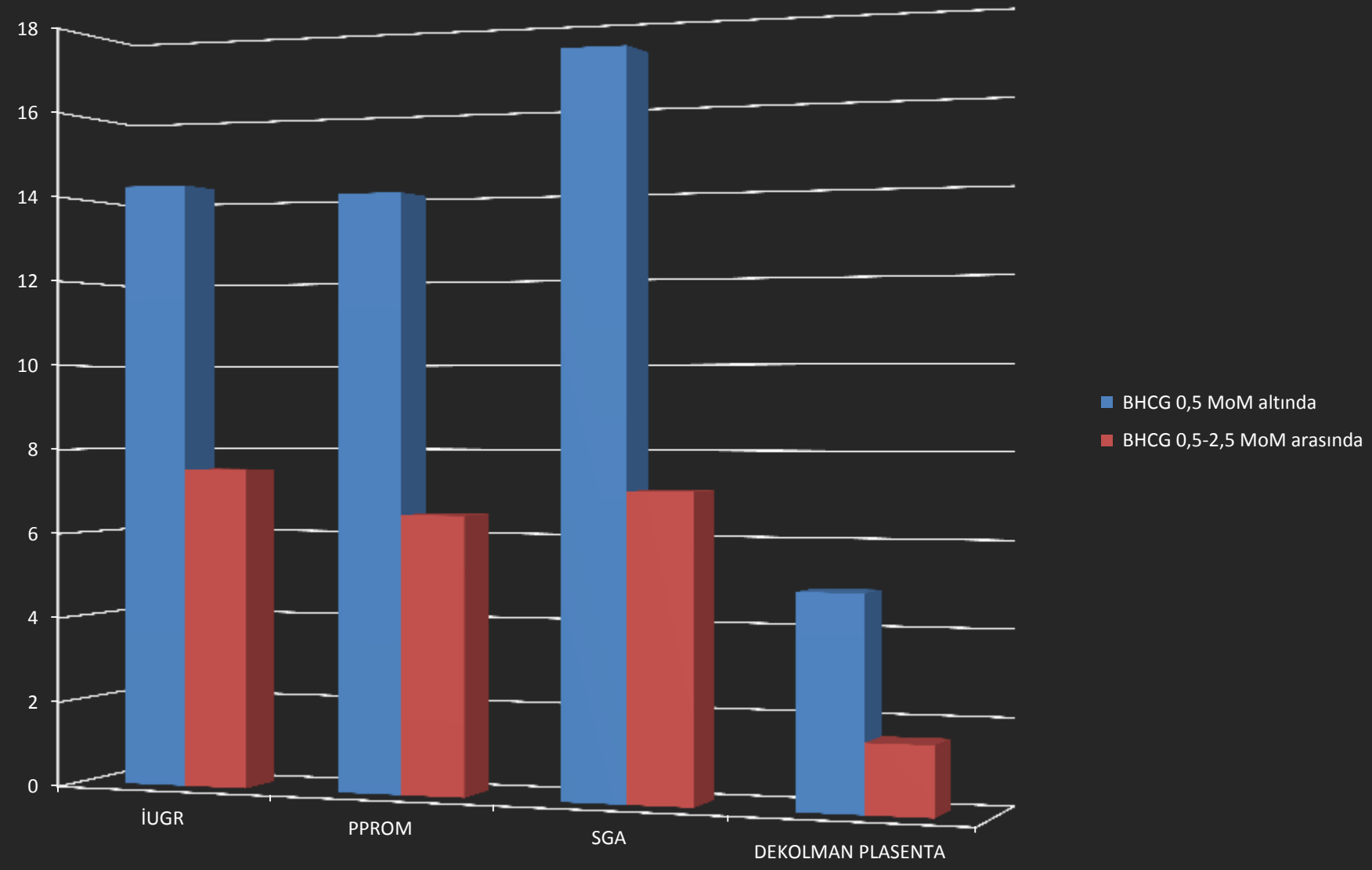
- Preterm doğum açısından İlk trimester serum belirteçleri veya servikal uzunluk ölçümü öykü ve demografik özelliklerden daha fazla katkı sağlamıyor

HAYIR

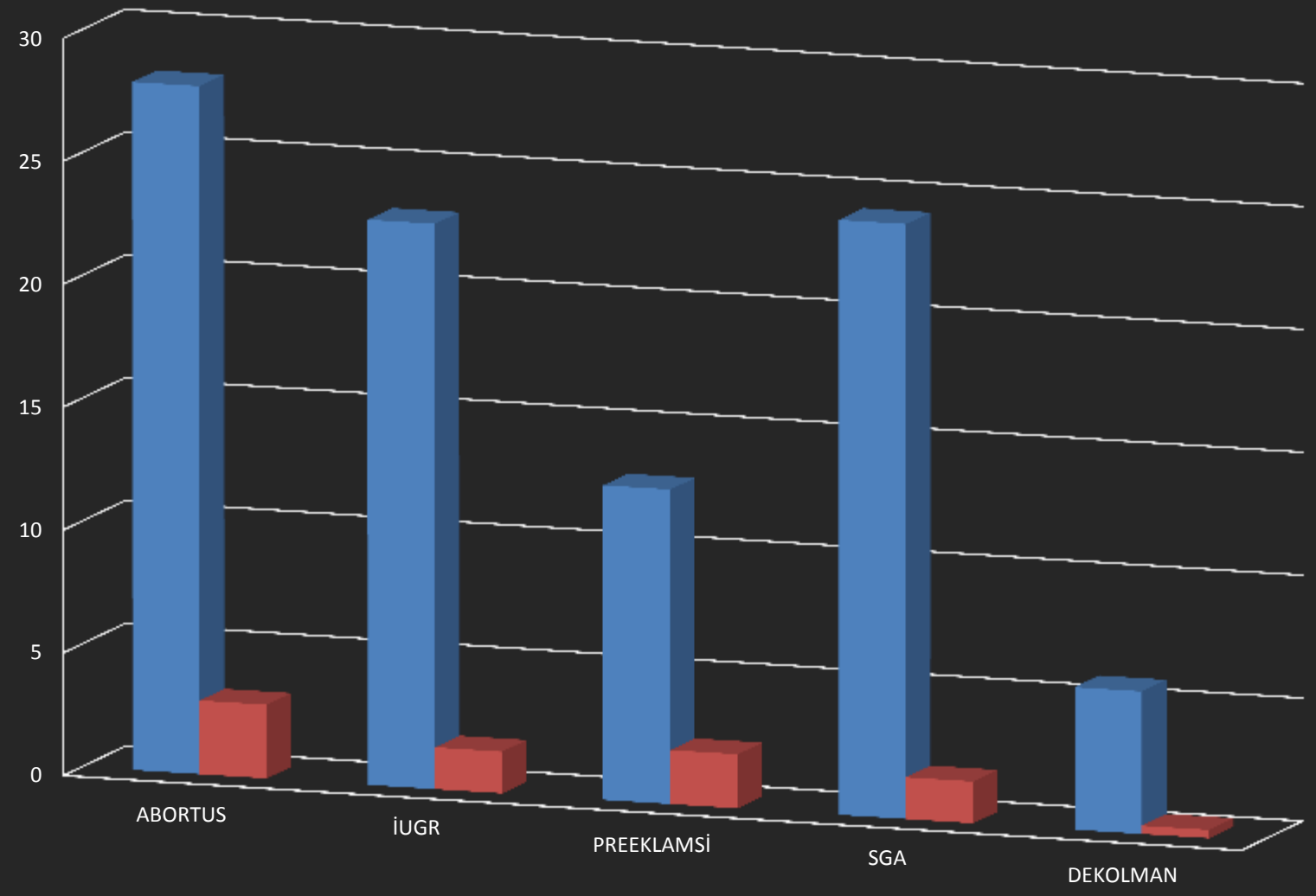
KSS Perinatoloji Deneyimi

- Çalışma temmuz 2012 –şubat 2014 tarihleri arasında Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesinde toplam 1104 olgu üzerinde yapılmıştır. Çalışma grupları ikili test PAPP-A veya beta-HCG sonuçları 0.5-2.5 MoM düzeyi arasında normal olan 516 olgu ve test sonuçları 0,49 MoM altında düşük anormal kabul edilen olan 250 olgu

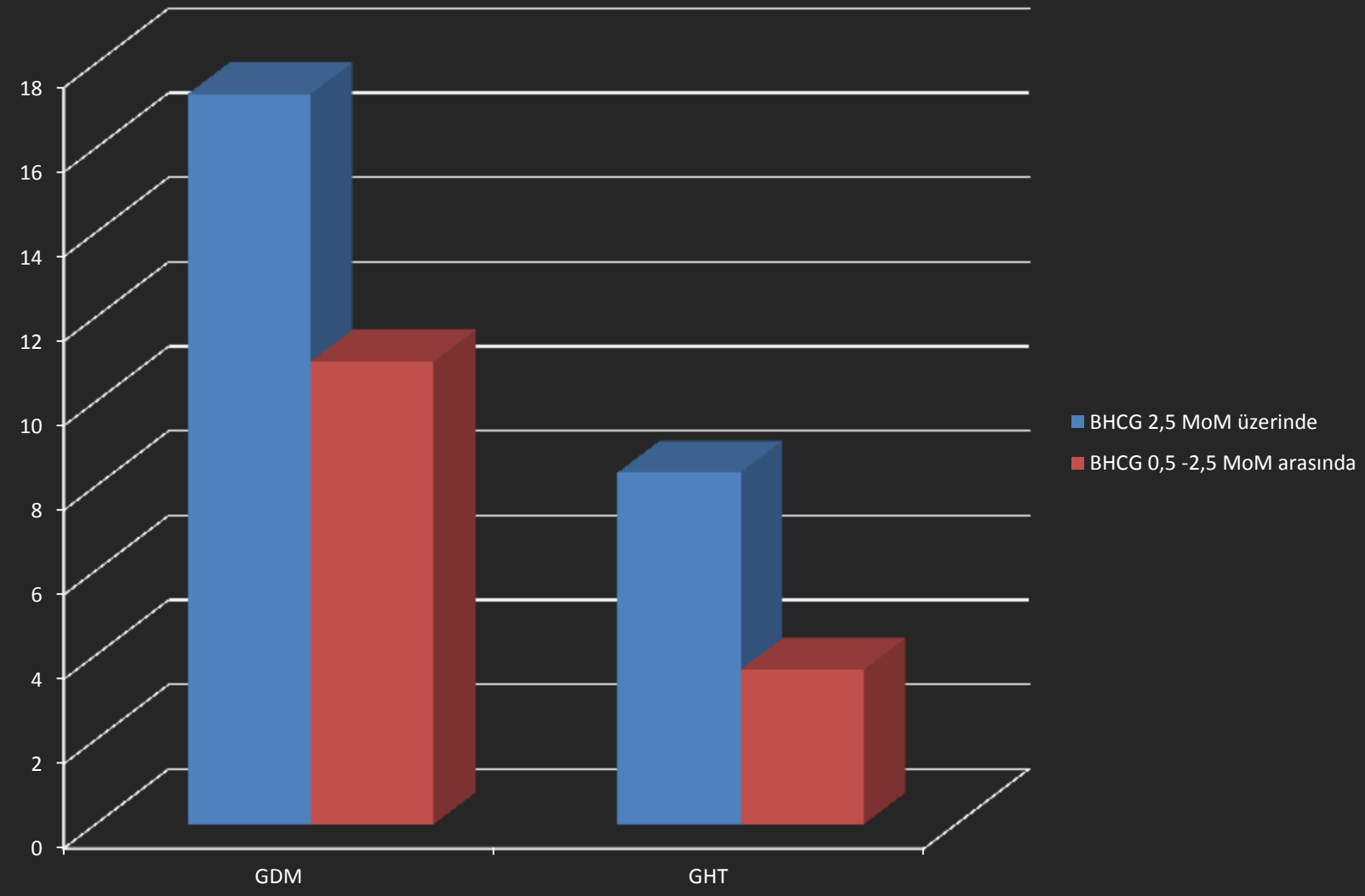
BhCG <0.5 MoM


18
16
14
12
10
8
6
4
2
0
İUGR
PPROM
SGA
DEKOLMAN PLASENTA
BHCG 0,5 MoM altında
BHCG 0,5-2,5 MoM arasında

PAPP-A <0.5 MoM



BhCG >2.5 MoM


18
16
14
12
10
8
6
4
2
0
GDM
GHT
BHCG 2,5 MoM üzerinde
BHCG 0,5 -2,5 MoM arasında

References	Type of study (population)	Gestational age (weeks)	Predictors	Findings
Van den Elzen et al.[13]	Prospective cohort ($n = 352$; women aged ≥35 years)	12–13	UtA PI > 1.67	UtA PI was associated with development of hypertensive disorders (RR = 4.2), SGA infants (RR = 2.4), and prematurity (RR = 3.1).
Harrington et al.[14]	Prospective cohort ($n = 652$)	12–16	UtA PI, RI, TAV, maximum systolic velocity, volume flow, UA PI, and UA RI	Bilateral UtA notching was associated with development of PE (OR = 42.02), SGA (OR = 8.61), and prematurity (OR = −2.38).
Martin et al.[15]	Prospective cohort ($n = 3324$; 63 later developed PE and 290 developed SGA)	11–14	UtA PI > 95%	UtA PI > 2.35 detected 50% of early PE (PPV = 4.5%, NPV = 99.8%) and 24% of preterm SGA (with no PE) (PPV = 3.9%, NPV = 99.3%).
Nicolaides et al.[16]	Nested case–control (10 later developed early PE and 423 controls)	11–13	Combination of UtA PI and maternal serum PP-13 levels	For a 10% FPR, the detection rate of early PE was 80% by (low) serum PP-13, 40% by (high) UtA PI, and 90% by both markers combined.
Plasencia et al.[17]	Prospective screening (107 later developed PE and 5041 were unaffected)	11–13	Combination of maternal history and UtA PI	For a 10% FPR, the detection rate of early PE was 50% by maternal history alone, 82% by UtA PI alone, and 82% by both combined.
Parra-Cordero et al.[18]	Nested case–control (18 later developed PE and 60 controls)	11–13	Combination of UtA PI and maternal serum of sVCAM-1 and sICAM-1 levels	The UtA PI was higher among those who developed PE; there were no differences in sVCAM-1 and sICAM-1 levels.
Spencer et al.[19]	Nested case–control (64 later developed PE and 240 controls)	11–13	Combination of UtA PI, maternal serum inhibin-A, and activin-A levels	For a 5% FPR, the detection rate of PE was 55% by UtA PI alone, 68% by UtA PI + (high) inhibin-A, and 63% by UtA PI + (high) activin-A.

Spencer et al.[20]	Prospective screening for aneuploidy and SGA (3539 SGA and 46,262 controls)	11–13	Combination of maternal history/characteristics, maternal serum PAPP-A, and free beta-hCG levels	The combination of maternal factors and (low) PAPP-A detected 12%, 14%, and 14% of those who developed SGA (below the 10th, 5th, and 3rd centiles, respectively).
Akolekar et al.[21]	Case–control (127 later developed PE and 609 controls)	11–13	Combination of maternal history/characteristics, UtA PI, maternal serum PlGF, and PAPP-A levels	For a 5% FPR, the highest detection rate of early PE (76%) was achieved by the combination of maternal history/characteristics + UtA PI + (low) PlGF with or without (low) PAPP-A.
Plasencia et al.[22]	Prospective screening (n = 3107; 93 later developed PE)	11–13; 21–24	Combination of maternal history/characteristics and change in UtA PI between first and second trimester	For a 5% FPR, the detection rate of early PE was 91% (change in UtA PI was steeper in pregnancies with normal outcome).
Poon et al.[23]	Prospective cohort (n = 8051; 156 later developed PE)	11–13	Combination of maternal history/characteristics, UtA PI and maternal serum PAPP-A levels	For a 5% FPR, the highest detection rate of early PE (66%) was achieved by the combination of maternal history/characteristics and UtA PI; detection rates were not improved by inclusion of PAPP-A.
Leal et al.[25]	Case–control (128 later developed PE and 569 controls)	11–13	Combination of maternal history/characteristics, UtA PI, and maternal serum TNF-R1 levels	For a 5% FPR, the highest detection rates (32% for PE and 24% for SGA) were achieved by the combination of maternal history/characteristics and UtA PI; inclusion of (high) TNF-R1 did not improve prediction.

Akolekar et al.[26]	Prospective screening (121 later developed PE, 87 with GH, and 208 controls)	11–13	Combination of maternal history/characteristics, UtA PI, maternal serum inhibin-A, and PAPP-A levels	For a 5% FPR, the highest detection rate of early PE (85%) was achieved by the combination of maternal factors, UtA PI, and (high) inhibin-A; inclusion of PAPP-A did not improve prediction.
Akolekar et al.[27]	Prospective screening (126 later developed PE, 88 with GH, and 207 controls)	11–13	Combination of maternal history/characteristics, UtA PI, and maternal serum Ang-2 levels	Ang-2 levels were not different among those who develop PE or GH as compared to controls.
Akolekar et al.[28]	Case–control (120 later developed PE, 87 with GH, and 207 controls)	11–13	Combination of maternal history/characteristics, UtA PI, and maternal serum pentraxin levels	Increased maternal serum pentraxin levels were observed only among those women who later developed early PE.
Akolekar et al.[29]	Case–control (126 later developed PE, 88 with GH, and 214 controls)	11–13	Combination of maternal history/characteristics, UtA PI, maternal serum PAPP-A, TNF-R1, and activin-A levels	Best prediction for early PE was achieved by a combination of maternal history/ characteristics, UtA PI, and (low) PAPP-A; inclusion of (high) TNF-R1 and (high) activin-A levels did not improve prediction.
Staboulidou et al.[30]	Nested case–control (165 who later developed PE and 301 cases of fetal aneuploidy)	11–13	UtA PI and maternal serum PAPP-A levels	In cases with low PAPP-A, UtA PI can differentiate between trisomy 21 (normal UtA PI) and impending early PE (high UtA PI).
Akolekar et al.[31]	Case–control (90 later developed PE and 180 controls)	11–13	Combination of maternal history/characteristics, UtA PI, maternal serum sFlt-1, free-VEGF, and PlGF levels	Maternal serum sFlt-1 and free-VEGF levels were not useful in the prediction of PE.

Ashoor et al.[32]	Prospective screening (127 later developed PE and 3592 controls)	11–13	UtA PI, MAP, maternal serum TSH, free T4, and free T3 levels	UtA PI and MAP were increased among those who developed early PE. In late PE (>34 weeks), TSH was increased and free T4 was decreased.
Sifakis et al.[33]	Case–control (50 later developed PE and 106 controls)	11–13	Combination of maternal history/characteristics, UtA PI, and maternal serum IGF-I levels	UtA PI was increased and IGF-I level was decreased among those who developed early PE.
Karagiannis et al.[34]	Prospecting screening for SGA in the absence of hypertension (1536 cases and 31,314 controls)	11–13	Combination of maternal history/characteristics, MAP, NT, UtA PI, maternal serum PAPP-A, free beta-hCG, PlGF, PP-13, and ADAM12 levels	In the SGA group, the UtA PI and MAP were increased and serum PAPP-A, free beta-hCG, PlGF, PP-13, ADAM12, and NT were decreased. For a 5% FPR, the combination of all above markers detected 61% of preterm SGAs (for a 10% FPR the detection rate was 73%).
Sifakis [35]	Case–control (60 later developed PE and 120 controls)	11–13	Combination of maternal history/characteristics, UtA PI, and maternal serum IGFBP-1 levels	UtA PI was increased and serum IGFBP-1 levels were decreased among those who developed PE (more drastic decrease in early PE).
Nanda et al.[36]	Case–control (90 later developed PE and 300 controls)	11–13	Combination of maternal history/characteristics, UtA PI, maternal serum PAPP-A, and adiponectin levels	Serum adiponectin levels were increased among those who developed early, but not late, PE. For a 5% FPR, the combination of maternal factors and UtA PI detected 57% of early PE cases.
Sifakis et al.[37]	Case–control (60 later developed PE and 120 controls)	11–13	Combination of maternal history/characteristics, UtA PI, maternal serum PAPP-A, and hPGH levels	UtA PI was increased and serum PAPP-A levels were decreased among those who developed PE (more drastic decrease in early PE); hPGH levels were not different between PE and controls.

Plasencia et al.[38]	Prospective screening (144 developed SGA and 2811 controls)	11–13	Combination of maternal history/characteristics, maternal serum PAPP-A, and placental volume by 3D ultrasound	Placental volume and serum PAPP-A levels were decreased among SGA pregnancies. Combination of maternal characteristics, serum PAPP-A, and placental volume detected 35% of the SGA cases (FPR = 10%).
Ertl et al.[39]	Case–control (150 developed SGA and 1000 controls)	11–13	Combination of maternal history/characteristics, maternal serum PAPP-A, and 25(OH)D levels	SGA pregnancies had lower PAPP-A and 25(OH)D levels.
Sifakis et al.[40]	Case–control (60 later developed PE and 120 controls)	11–13	Combination of maternal history/characteristics, UtA PI, maternal serum PAPP-A, and IGFBP-3 levels	In late PE, but not in early PE, serum IGFBP-3 was increased; in early PE, but not in late PE, UtA PI was increased and serum PAPP-A was decreased.
Wright et al.[41]	Prospective screening (1426 later developed PE and 57,458 controls)	11–13	Combination of maternal history/characteristics, UtA PI, and MAP	The combined model detected 80–90% of early PE cases (for FPRs 5% and 10%, respectively) and 35–57% of all PE cases (for FPRs 5% and 10%, respectively).
Akolekar et al.[42]	Prospective screening (1426 later developed PE and 57,458 controls)	11–13	Combination of maternal history/characteristics, UtA PI, MAP, maternal serum PAPP-A, and PlGF levels	The combined model detected 93–96% of early PE cases (for FPRs 5% and 10%, respectively) and 38–54% of all PE cases (for FPRs 5% and 10%, respectively).
Ferreira et al.[43]	Case–control (80 later developed PE and 240 controls)	11–13	UtA PI and maternal visfatin levels	The UtA PI and serum visfatin levels were higher among those who developed PE.
Poon et al.[44]	Prospective combined screening for both PE and SGA (1426 later developed PE, 3168 with SGA and no preeclampsia, and 57,458 controls)	11–13	Combination of two algorithms using maternal history/ characteristics, UtA PI, MAP, maternal serum PAPP-A, and PlGF levels	For a 10% FPR, the detection rates of early PE, late PE, preterm SGA, and term-SGA were 95%, 46%, 56%, and 44%, respectively.

Önleme

- Düşük doz Aspirin
- Kalsiyum
- Vitamin C ve E
- Balık yağı / omega 3
- Heparin
- Multivitaminler
- Statinler !!

TEŞEKKÜRLER