



# **Kombine Oral Kontraseptif Haplar - Estrojen**

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## Hedef / Süreç

- Yüksek kontraseptif etkinlik
- Güçlü siklus kontrolü
- Minimal yan etki

- **Estrojen (E)**

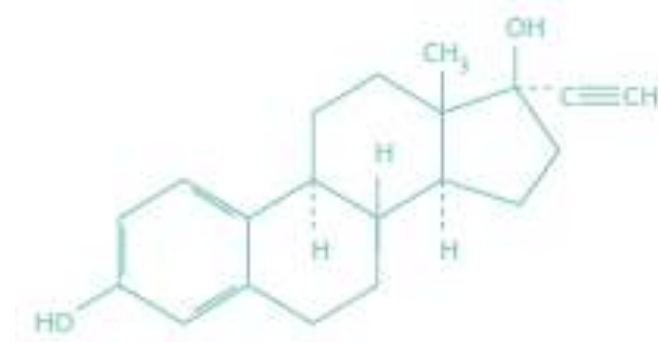
- ✓ EE dozu
- ✓ E<sub>2</sub>V

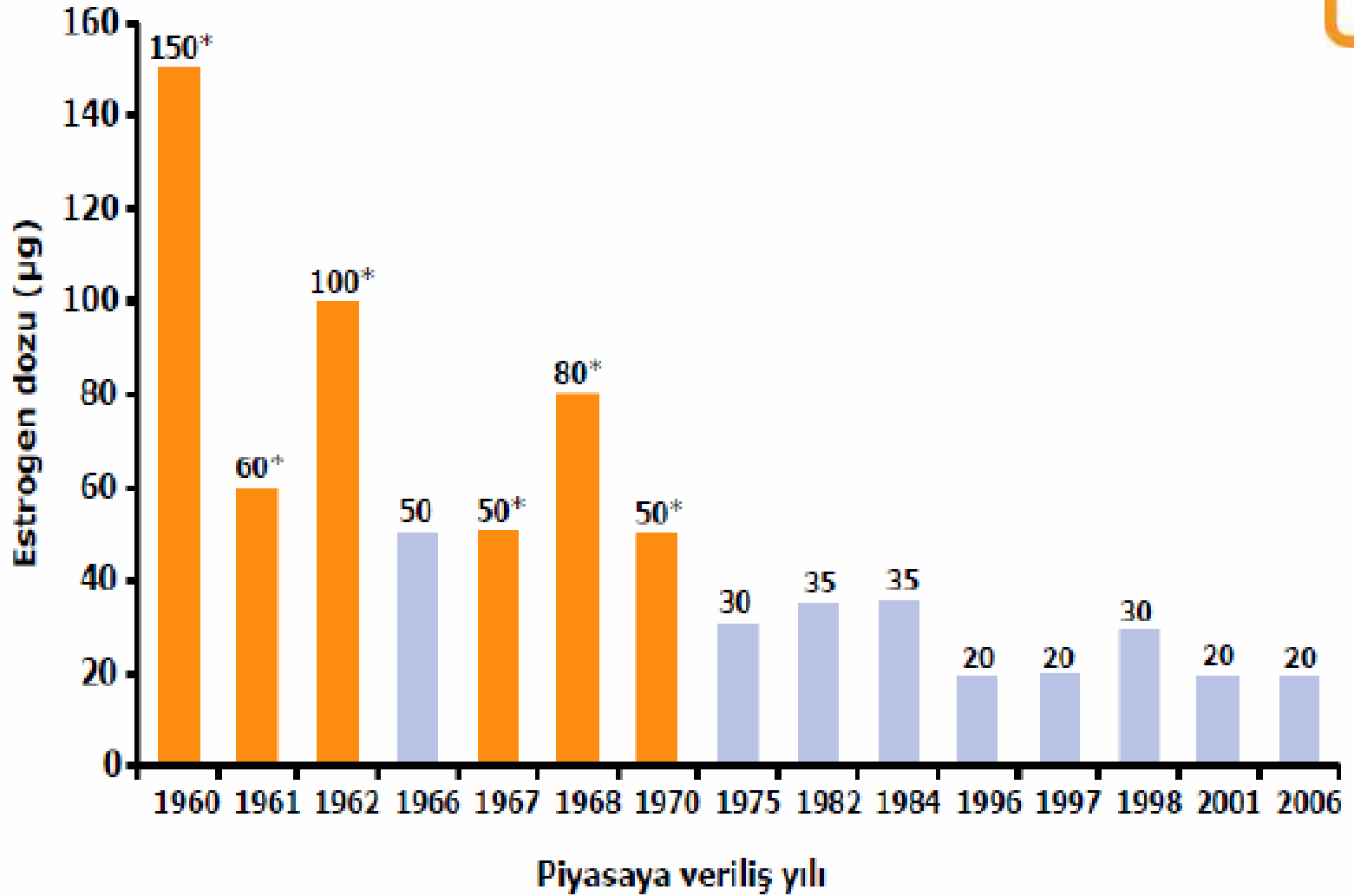
- **Projestin (P)**

- ✓ Doz
- ✓ Yeniler
- ✓ Sadece P

- **Interval**

- ✓ 7 ⇌ 4 ⇌ 2 gün
- ✓ Kesintisiz rejim





\*Mestranol içeren oral kontraseptifler

Ethinyl estradiol içeren oral kontraseptifler



## EE Dozu 15-20 $\mu$ g vs > 20 $\mu$ g

- **Kullanım emniyeti** (Ca, CVD, TE, MI)
- **Etkinlik** [ovulasyon supresyonu (farklı bireysel ve günlük deęişkenlik, ilaç etkileşimleri)]
- **Kanama profili** (E dozu, P tipi, sigara, düzensiz kanama öyküsü)
- **Kullanım süresi** (siklus kontrolü, yan etkiler)
- **Yan etkiler** (E doz azaltılması)
- **Non-kontraseptif yararlar** (over kanseri, endometrial kanser, fonksiyonel over kistleri, akne)



# Estrojen Dozu 15-20 $\mu$ g vs > 20 $\mu$ g EE<sup>1</sup>

- **Kontraseptif etkinlik** – benzer
- **Kullanım süresi** – metroraji nedeniyle **daha kısa**
- ✓ EE 20  $\mu$ g / NETA 1 mg
- ✓ EE 20  $\mu$ g / DGL 150  $\mu$ g
  
- **Düzensiz kanama**, uzun mens, metroraji **daha sık**
- ✓ EE 15  $\mu$ g vs EE 20  $\mu$ g<sup>2</sup>
- ✓ EE 20  $\mu$ g / DGL 150  $\mu$ g
- ✓ EE 20  $\mu$ g / DPN 3 mg
- ✓ EE 20  $\mu$ g / NETA 1 mg
  
- **Yan etkiler** – baş ağrısı, davranış durum bozukluğu, kilo alma daha çok, meme hassasiyeti, baş dönmesi daha az
- EE 20  $\mu$ g / DGL 150  $\mu$ g
- EE 20  $\mu$ g / LNG 100  $\mu$ g

<sup>1</sup>Gallo MF et al. 20  $\mu$ g versus >20  $\mu$ g estrogen combined oral contraceptives for contraception. Cochrane Database of Systematic Reviews 2013, Issue 8.

<sup>2</sup> Gestodene Study Group 322. The safety and contraceptive efficacy of a 24-day low-dose oral contraceptive regimen containing gestodene 60 microg and ethinylestradiol 15 microg. Eur J Contracept Reprod Health Care 1999;4(Suppl2):9–15.



- **E<sub>2</sub>V (1,5-2,0 mg) /CP**
- ✓ Kimyasal olarak 17β-ε
- ✓ Valerat ile hızlı emilim
- ✓ FSH supresyon gücü
- ✓ EE'e göre hepatik pro
- ✓ Hemostaz belirteçleri
- ✓ 4 fazlı (-bi / -trifazik ba

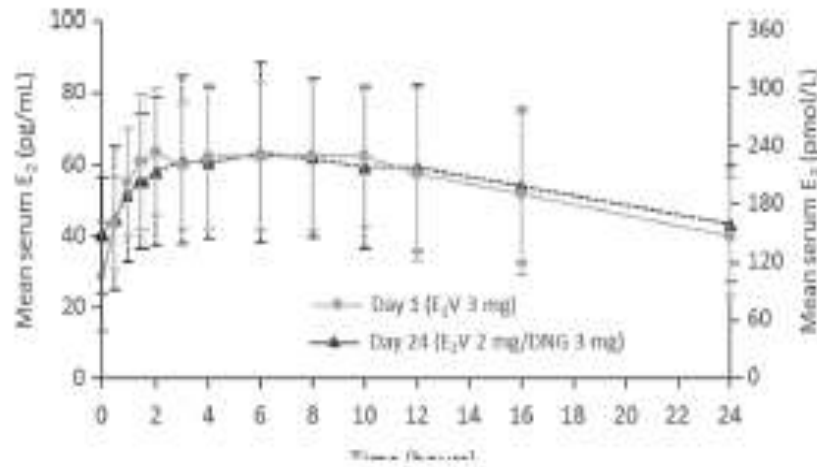


Figure 1. Mean serum estradiol (E<sub>2</sub>) concentration over 24 h following oral administration of estradiol valerate (E<sub>2</sub>V)/dienogest (DNG) [17]. Zeun S, et al., Eur J Contracept Reprod Health Care, 2009;14(3):221-32, copyright© 2009, Informa Healthcare. Reproduced with permission of Informa Healthcare.

ya yarı ömür

daha zayıf

- **EE (15-30 µg)**
- ✓ Sentetik
- ✓ Yüksek oral biyoyarar
- ✓ SHBG bağlanmaz
- ✓ 17 β hidroksilaz'a rezi
- ✓ Reseptör afinitesi yük
- **E<sub>2</sub>V & DNG vs EE &**
- ✓ Çekilme kanaması da
- ✓ Sentetik değil, DNG a

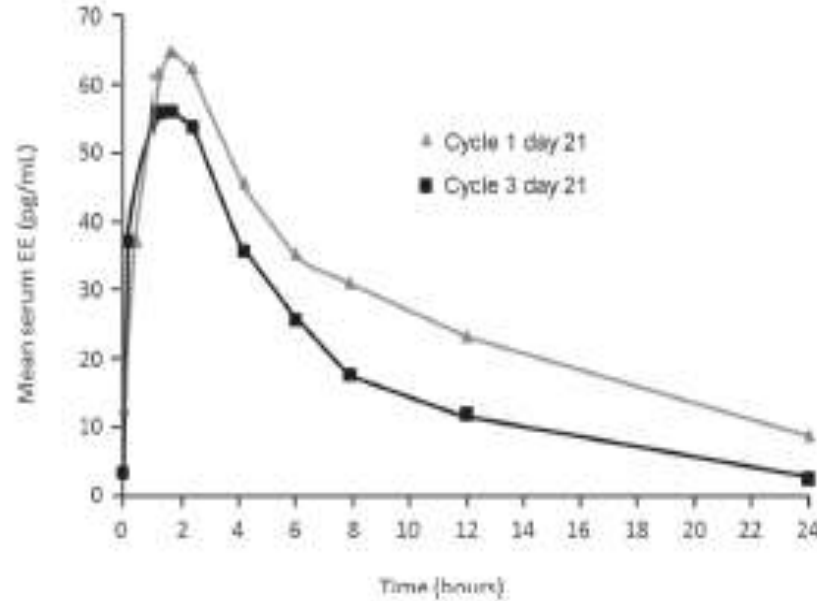


Figure 2. Mean ethinyl estradiol (EE) concentration over 24 hours following oral administration of EE 20 µg/levonorgestrel (LNG) 100 µg [18]. Endrikat J, et al., Eur J Contracept Reprod Health Care, 2002;7(2):79-90, copyright© 2002,

lat)

kanama benzer

Brynhildsen J. Combined horm  
Saf 2014;5(5):201-213

versus risks. Ther Adv Drug



## Etinyl Estradiol vs Estradiol Valerat

- Hedef organa göre (HPO aks, over, endometrium) reseptör üzerindeki etkinlik değişken
- EE, FSH supresyonunda doğal estrogenlerden çok daha potent
- ✓ 1 mg E<sub>2</sub>V = 0.76 mg E<sub>2</sub>
- ✓ 2 mg E<sub>2</sub>V = 4-20 µg EE (FSH supresyon / endometrial stimülasyon)
- ✓ = 20 µg EE (vajinal hücre maturasyonu)
- ✓ = <20 µg EE (KC'de SHBG, angiotensinogen ve hemostasis parametreleri)

[Endrikat J, et al.](#) Ovulation inhibition with four variations of a four-phasic estradiol valerate/dienogest combined oral contraceptive: results of two prospective, randomized, open-label studies. [Contraception](#). 2008;78(3):218-25

[Wiegratz I, et al.](#) Effect of four oral contraceptives on hemostatic parameters. [Contraception](#). 2004 ;70(2):97-106

[Lindberg UB, et al.](#) A comparison between effects of estradiol valerate and low dose ethinyl estradiol on haemostasis parameters.

[Thromb Haemost.](#) 1989 ;61(1):65-9

[Helgason S.](#) Estrogen replacement therapy after the menopause. Estrogenicity and metabolic effects.

[Acta Obstet Gynecol Scand Suppl.](#) 1982;107:1-29

[Mashchak CA, et al.](#) Comparison of pharmacodynamic properties of various estrogen formulations. [Am J Obstet Gynecol.](#) 1982;144(5):

511-8



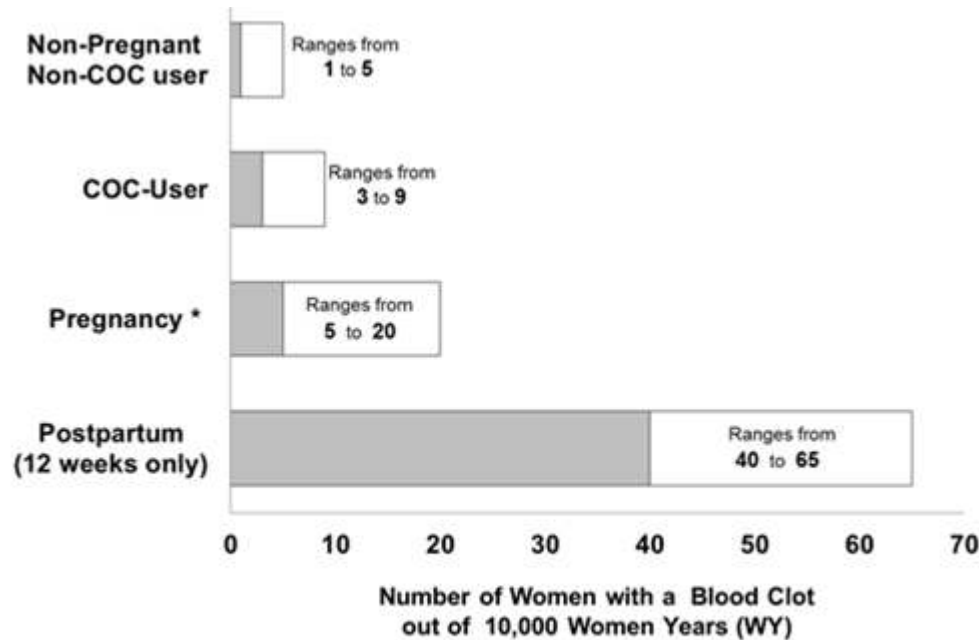
# Türkiye Hap Pazarı

- **DIENILLE** [DNG 2 mg & EE 0.03 mg]
- **QLAIRISTA** [DNG 2 mg (3-7 gün), DNG 3 mg (8-24 gün) & E<sub>2</sub>V 3 mg (1-2 gün), 2 mg (3-24 gün), 1 mg (25-26 gün) & PL (27-28 gün)]
  
- **DROSPERA** [DPN 3 mg & EE 0.02 mg] 24 & 4 Pl.
- **DROSETIL** [DPN 3 mg & EE 0.03 mg]
- **MINAYA** [DPN 3 mg & EE 0.02 mg] 24 & 4 Pl.
- **YASMIN** [DPN 3 mg & EE 0.03 mg]
- **YAZZ** [DPN 3 mg & EE 0.02 mg] 24 & 4 Pl.
  
- **REGINON** 21, 63 dr. [GDN 0.075 mg & EE 0.02 mg]
- **GINERA** [GDN 0.15 mg & EE 0.03 mg]
  
- **MYRALON** [DGL 0.15 mg & EE 0.02 mg]
- **DESOLETT** [DGL 0.15 mg & EE 0.03 mg]
  
- **BELARA** [CMA 2 mg & EE 0.03 mg]
  
- **JERBERA** [LNG 0.15 mg & EE 0.03 mg]
- **MICROGYNON** [LNG 0.15 mg & EE 0.03 mg]
- **MIRANOVA** [LNG 0.1 mg & EE 0.02 mg]
- **TRIQUILAR** [LNG 0.05 mg (1-6 gün), 0.075 mg (7-11 gün), 0.125 mg (12-21 gün) & EE 0.03 mg (1-6 gün), 0.04 mg (7-11 gün), 0.03 mg (12-21 gün)]



# Tromboemboli

- **Venöz – E doz / süre**



\* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

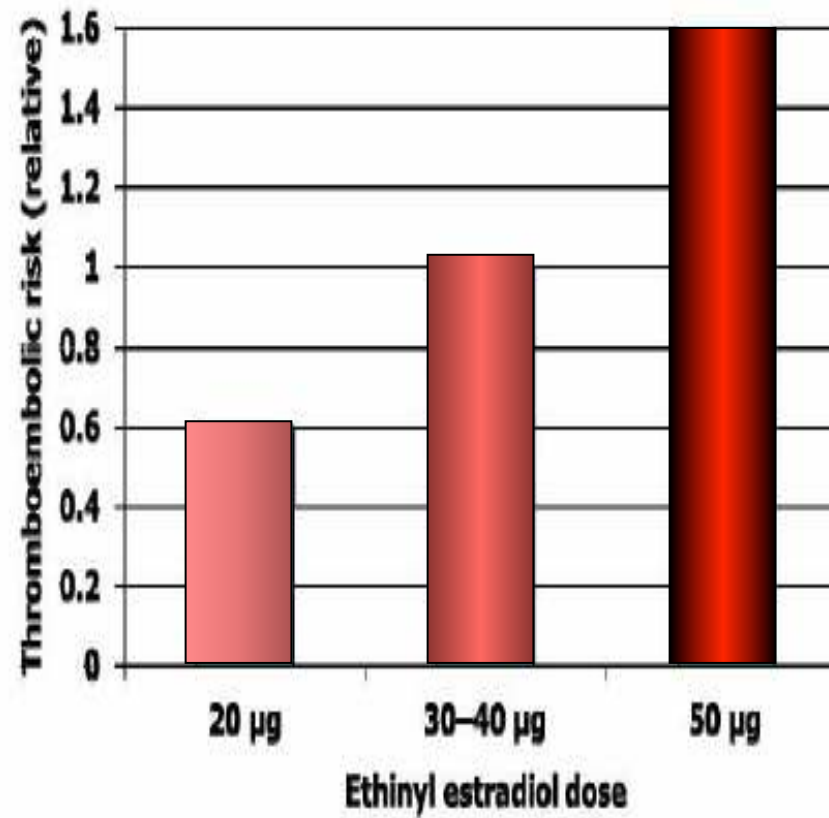
Shapiro S, Dinger J. Risk of venous thromboembolism among users of oral contraceptives: a review of two recently published studies. J Fam Plann Reprod Health Care. 2010;36(1):33-38

Pomp ER et al. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. J Thromb Haemost. 2008;6:632-637

Reid RL et al. Oral contraceptives and venous thromboembolism consensus opinion from an international workshop held in Berlin, Germany in December 2009. J Fam Plann Reprod Health Care. 2010;36(3):117-122.



## EE dozu - VTE





# Tromboemboli

- **Venöz** – P tipine bakılmaksızın tüm kombine oral kontraseptif haplar benzer risk taşıır<sup>1</sup>
- **RR<sup>2</sup> : 20-30 µg EE & LNG vs**
- Gestodene 1.3–1.5
- Desogestrel 1.8–1.9
- Drospirenone 1.6–1.7
- Cyproterone 1.6–1.8
- **Dikkat<sup>3</sup>** - Obesite, sigara, >35 yaş, PCOS (1,5- 2X), immobilite, herediter trombofili
- **Arteriyel** – P önemsiz
- ✓ **Dikkat<sup>4</sup>** - Sigara, >35 yaş, HT, PCOS, DM, lipidemi
- ✓ **RR<sup>4</sup> :30-40 vs 20 µg EE :** 1,3-2,3 vs 0,9-1,7X (mutlak risk 1-2/10,000 kadın/yıl)
- <sup>1</sup>Reid RL et al. Oral contraceptives and venous thromboembolism consensus opinion from an international workshop held in Berlin, Germany in December 2009. J Fam Plann Reprod Health Care. 2010;36(3):117-122
- <sup>2</sup>de Bastos M et al. Combined oral contraceptives: venous thrombosis. Cochrane Database Syst Rev. 2014;3:CD010813
- <sup>3</sup>ESHRE Capri Workshop Group. Venous thromboembolism in women: a specific reproductive health risk. Hum Reprod Update. 2013;19:471–482
- <sup>4</sup>Lidegaard Ø et al. Thrombotic stroke and myocardial infarction with hormonal contraception. NEJM.2012;366:2257–2266



# VTE

**Table 3.** Risk of developing venous thromboembolism in a year according to the European Medicines Agency [European Medicines Agency, 2013].

|  |                                |
|--|--------------------------------|
| Women <b>not using</b> a combined hormonal pill/patch/ring and are not pregnant                                      | About 2 out of 10,000 women    |
| Women using a combined hormonal contraceptive (CHC) containing <b>levonorgestrel, norethisterone or norgestimate</b> | About 5–7 out of 10,000 women  |
| Women using a CHC containing <b>etonogestrel or norelgestromin</b>   | About 6–12 out of 10,000 women |
| Women using a CHC containing <b>drospirenone, gestodene or desogestrel</b>   | About 9–12 out of 10,000 women |
| Women using a CHC containing <b>chlormadinone, dienogest or nomegestrol</b>  | Not yet known <sup>1</sup>     |

<sup>1</sup>Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products.

Bir VTE olgusunu önlemek için yılda 2000 kadının desogestrel, gestoden, drospirenon içeren hapını levonorgestrel içeren hapa değiştirmesi gerekir

Lidegaard Ø et al. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-2009. *BMJ*. 2011 Oct 25;343:d6423



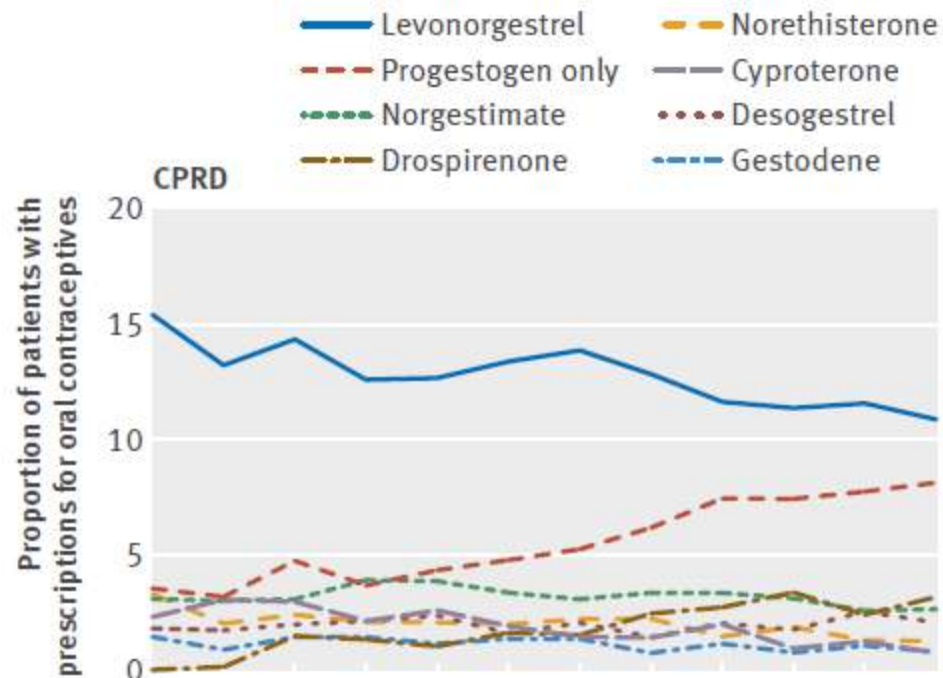
# Projestin

- E metabolik etki (KC proteinleri ve koagülasyon faktörleri) = P
- ✓ Potent androjenik P = Potent E baskısı
- ✓ Antiandrojenik P = Zayıf E baskısı
- En potent antiandrojen CPA
- DNG / DPN 30-40% potent

Sitruk-Ware R, Nath A. Characteristics and metabolic effects of estrogen and progestins contained in oral contraceptive pills. Best Pract Res Clin Endocrinol Metab. 2013;27:13–24

- P ≠
- ✓ 5  $\alpha$  redüktaz
- ✓ Androjen reseptörü
- ✓ Adrenal androjen yapımı

Fauser BC et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012;97:28–38.e25



Vinogradova Y et al. Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ* 2015;350:h2135

“Bir kadının

doğurmak için de

doğurmamak için de

yapamayacağı şey yoktur”

