# Combined hormonal contraceptives
# CHC Session I

## Pharmacokinetics and Basic principles of steroid hormones used in contraception

Advanced slide kit complementing the
WHO training tool www.fptraining.org

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# Contents

To enable teachers to understand and explain:

- Clinical relevant metabolic effects of ethinylestradiol (EE)
- The variations in individual steroid plasma levels and potential clinical consequences
- The difference between the mostly used progestins in CHCs
- Typical properties of progestins
- Types and dosages of CHCs
- Clinical effects of a lower EE dosage
- Difference between pills with estradiol /estradiolvalerate and EE

# Combined hormonal contraceptives (CHC) contain 2 compounds

1. Estrogen (synthetic or natural)

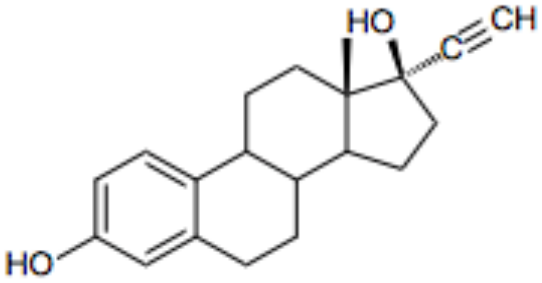
+

2. Progestin (synthetic)

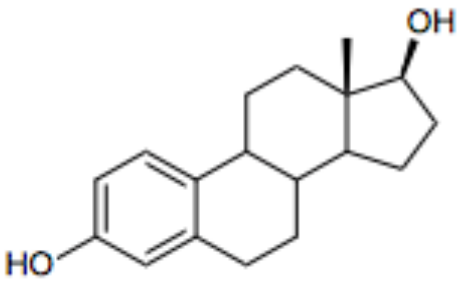
# The estrogen component in CHC

- In modern preparations estrogen is not needed for inhibition of ovulation; ovulation is inhibited by the progestin component
- The estrogenic effect on the endometrium reduces breakthrough bleedings during CHC use
- Estrogens are the main reason why women develop vascular complications such as venous thromboembolism

# Ethinylestradiol (EE)



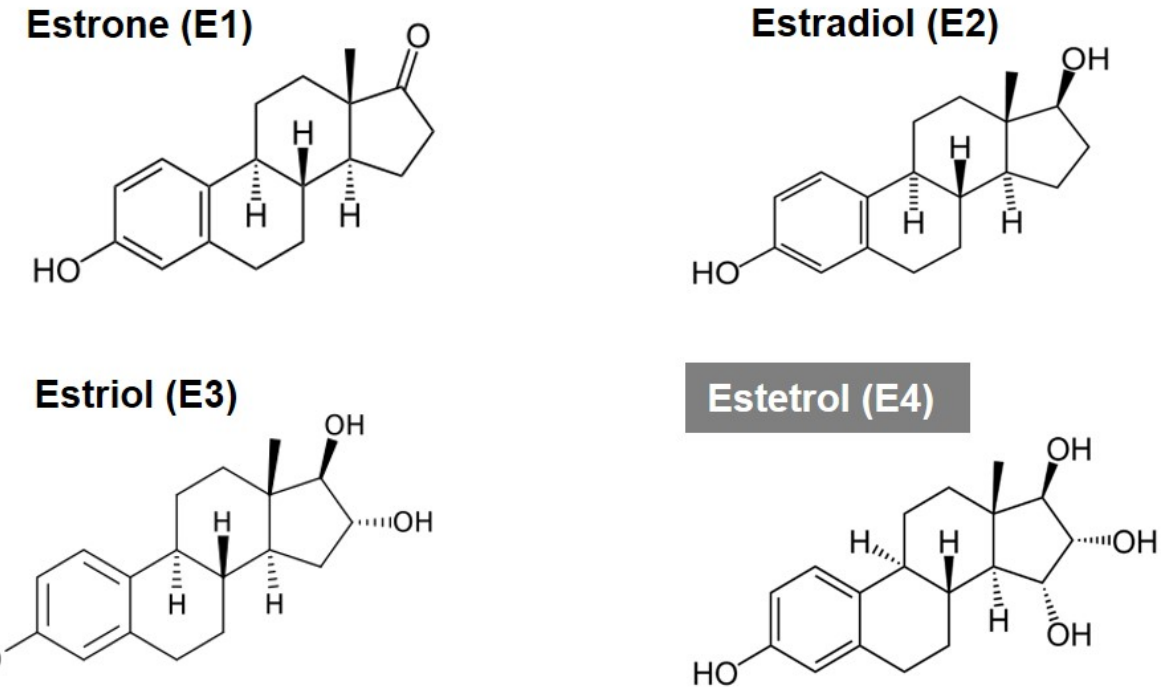

Ethinylestradiol




Estradiol

- Ethinylestradiol is the most widely used estrogen in combined pills
- It was developed because quick metabolism of estradiol in the endometrium results in an unstable bleeding pattern in CHC users
- Adding an ethinylgroup to estradiol resulted in delayed metabolism in the liver and in the endometrium and a stable bleeding pattern

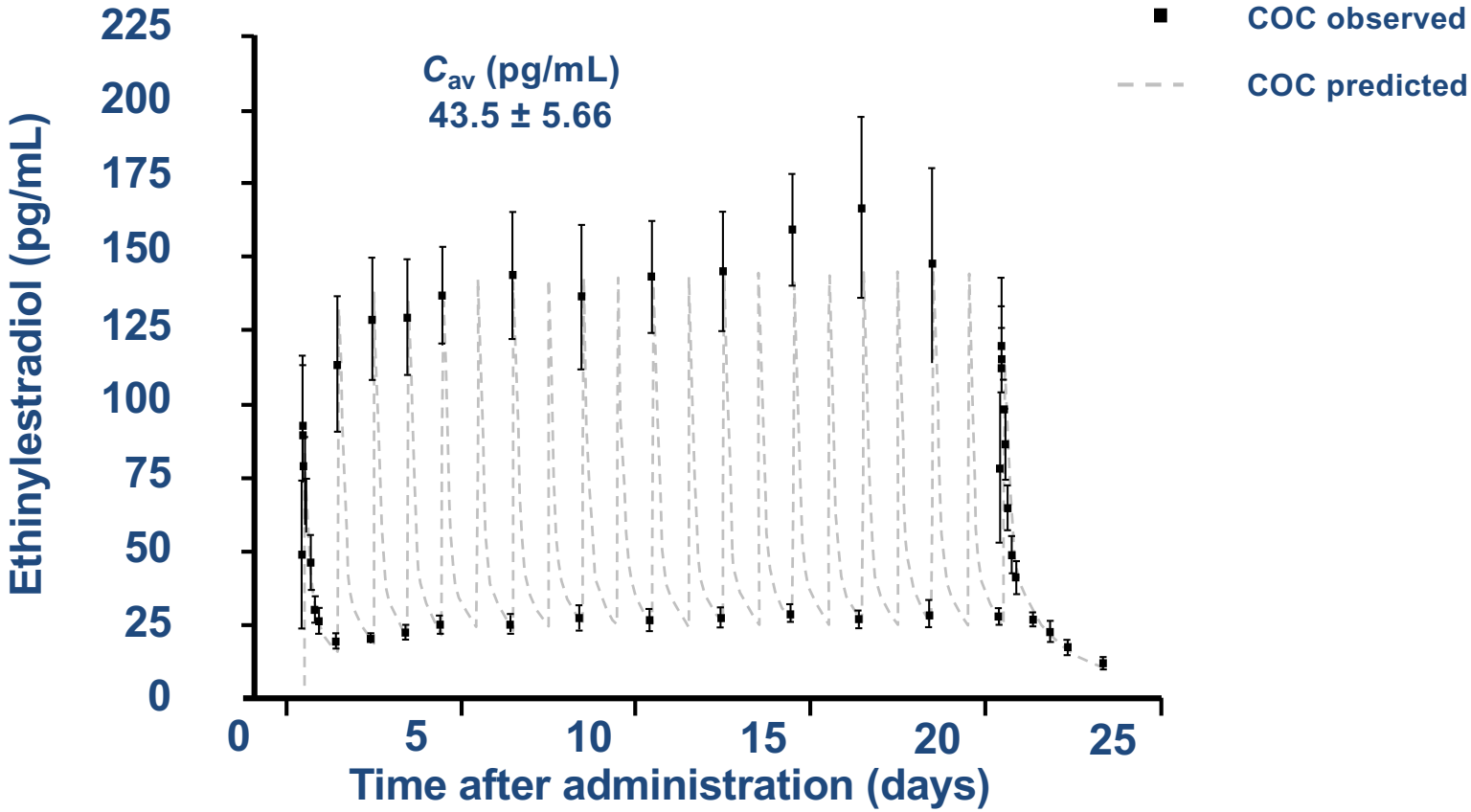
# Estetrol (E4)




- E4 is a weak estrogen, which is produced from the fetal liver and detectable in humans only during pregnancy
- In contrast to estradiol the oral bioavailability is high (80 % vs. 1%)

Ref 1

# Interindividual variability in plasma levels of ethinylestradiol in COC




Mean EE concentration–time curves for women treated with a COC (*n*=8), including 95% confidence intervals for mean values.
Adapted from Ref 1

Ref 1,2

# Ethinylestradiol – Metabolic effects

Effects on liver parameters play a crucial role!

- Increased production of clotting factors (risk of VTE)
- Increased production of sexual hormone binding globulin (SHBG) and other binding globulins (decrease of free testosterone, positive effect on the skin)

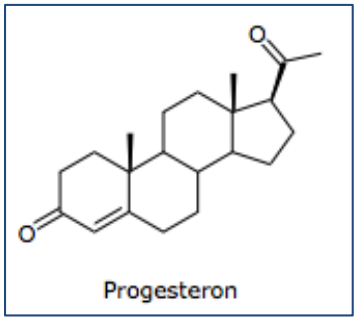
# Estetrol /Drospirenone Metabolic effects in comparison with EE 30µg/LNG150 mg

- In spite of the higher neutrality of E4 there is a significant impact of the E4/DRSP on haemostatic parameters comparable to those with low-dosed EE30/LNG150
- Endocrine effects are also comparable with EE/LNG, however there is less increase in binding proteins like SHBG and CBG*
- Levels of free testosterone do not differ
- There is no negative impact on carbohydrate metabolism or plasma lipids

Ref 1

# Progestins in CHC

- Progestins are steroid hormones and therefore interact with other steroid receptors as agonists or antagonists
- Inhibit ovulation
- Suppress proliferation of the endometrium
- Modify the liver metabolism of the estrogen compound and thus have an influence on the risk for VTE
- Modern progestins were developed main to reduce the androgenic side effects of older progestins and remove unfavourable receptor interactions
- Natural progesterone is not used in CHC



Progesteron

# Progestins in CHC
# Generations of progestins

- **Second Generation**
  - Levonorgestrel
- **Third generation**
  - Desogestrel
  - Gestoden
- **Fourth generation**
  - Drospirenone

- **Progesterone derivatives**:
  - Cyproteronacetate
  - Chlormadinonacetate
  - Medroxyprogesterone acetate
- **Others**
  - Dienogest

# Progestins in CHC
# Generation and some properties

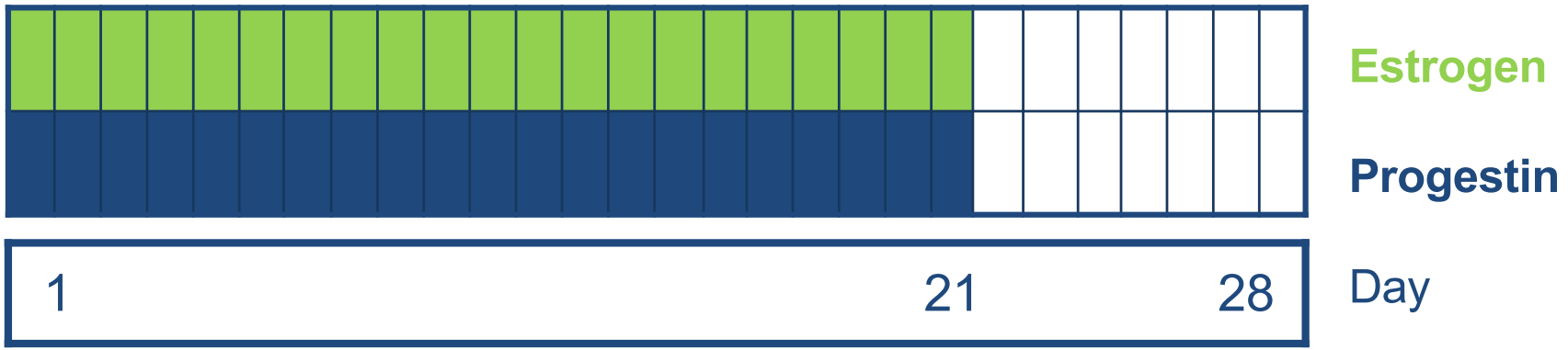
| Progestin | Generation | Anti-androgenic | Andro-genic | Anti-Mineralo-corticoid |
|---|---|---|---|---|
| Progesterone | | (+) | | (+) |
| Norethisterone | 2 | | (+) | |
| Levonorgestel | 2 | | (+) | |
| Gestodene | 3 | | (+) | |
| Desogestrel | 3 | | (+) | |
| Drospirenone | 4 | + | | + |
| Dienogest | n.a. | + | | |
| Cyproterone Acetate | n.a. | + | | |
| Chlormadinon Acetate | n.a. | + | | |
| Nomegestrol Acetate | n.a. | (+) | | |

Ref 1

# Types and dosages of CHC

- Today only low-dose CHC should be used
- Low-dose CHC contain 15-35 µg EE* and a progestin

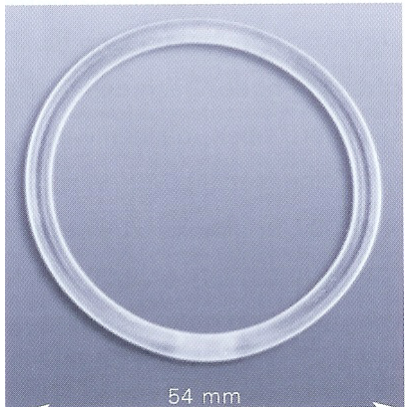
  or estradiol / estradiolvalerate / estetrol and a progestin
- CHC are used in regimen of 21-26 days (with a 7 or 2-4 days break)



# Types and dosages of CHC

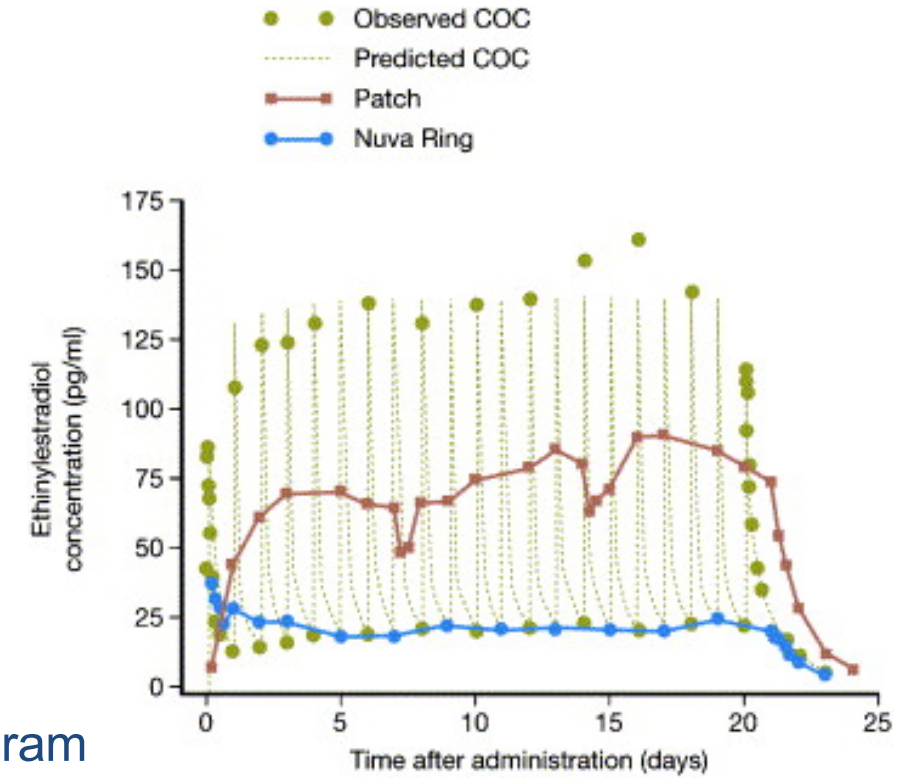
CHC are available as pill, patch or vaginal ring





# Types and dosages of CHC

## Hormone release of different applications

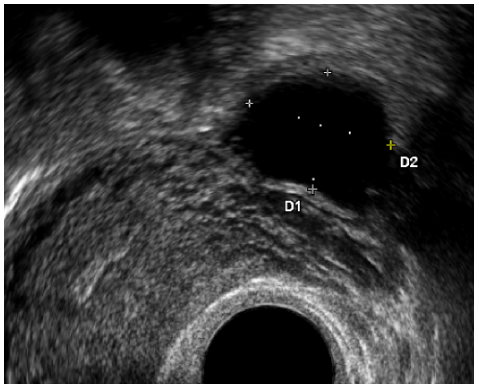



Ref 1 Source of diagram

Ref 1

# Lowering the EE dose

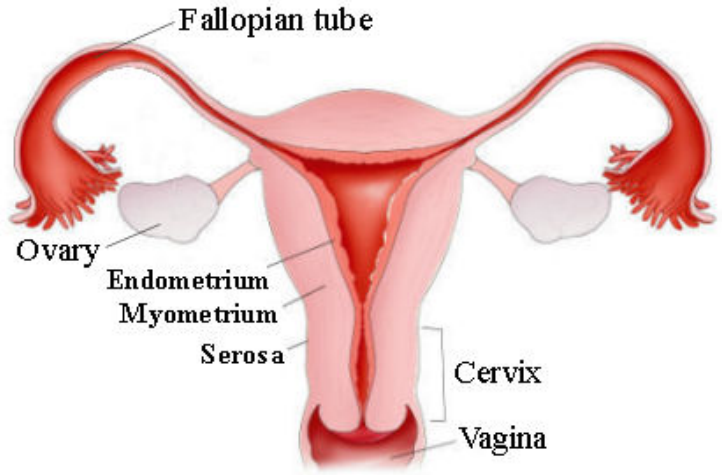
Estrogenic side effects as a result of non-ruptured follicles




- CHC suppress follicular activity in the ovary
- When using CHCs with an EE content of 20µg or 15µg follicular activity is less suppressed
- Small follicular cysts may develop causing estrogenic side effects like breast tenderness
- If this occurs, dose should be increased to 30µg EE

# Lowering the EE dose in CHCs

## Breakthrough bleeding

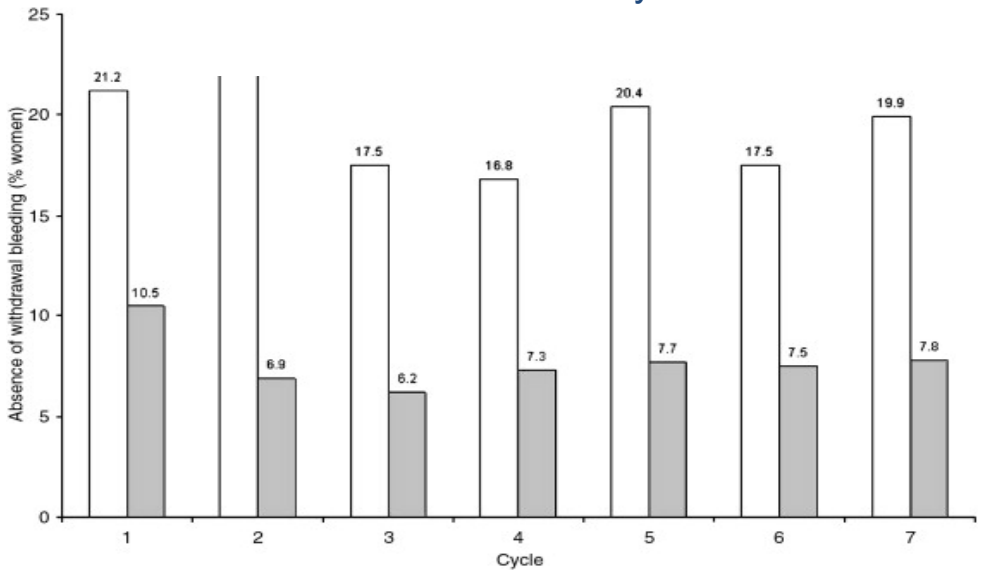



- Pills containing 20 µg or 15 µg EE may make the endometrium less stable and increase the likelihood of harmless breakthrough bleeding
- If this bothers the patient, change the dose to 30 µg EE

# Substitution of EE with estradiol/estradiol valerate

Cycles with amenorrhoea (%)

White bars E2V/DNG  Grey bars EE/LNG




- Pills containing estradiol/estradiol valerate cause a less stable endometrium and more breakthrough bleeding/amenorrhoea
- The four-phase pill containing estradiol valerate and dienogest is associated with more amenorrhoea during the pill break

Ref 1

# E4/DRSP bleeding pattern

- Pills containing E4 also cause a less stable endometrium and more breakthrough bleeding (→ CHC session 3)
- The amenorrhoea-rate is around 10% / cycle
- The frequency of absence of scheduled bleeding ranges from 13-17%

# Substitution of EE by estadiol/estradiol valerate

## Typical bleeding pattern

- Changes in bleeding pattern have to be addressed during counselling
- If changes in bleeding pattern bother the patient, pills containing EE might be a better option
- Do not forget that irregular bleeding could also derive from gynaecological condition or interactions with medication

# Contraceptive failure rates

| Method | % of women experiencing an unintended pregnancy within first year of use | |
|---|---|---|
| | Typical use | Perfect use |
| No method | 85 | 85 |
| Spermicides | 28 | 18 |
| Condom male | 18 | 2 |
| Diaphragm | 12 | 6 |
| Combined pill | 9 | 0.3 |
| Evra Patch | 9 | 0.3 |
| NuvaRing | 9 | 0.3 |
| Progestin –only pill | 9 | 0.3 |
| Depo-Provera | 6 | 0.2 |
| Implanon | 0.05 | 0.05 |
| IUD Copper T380Ag* | 0.3 | 0.3 |
| IUD Mirena (LNG)* | 0.2 | 0.2 |
| Female sterilisation | 0.5 | 0.5 |
| Male sterilisation | 0.15 | 0.1 |

*Source I.Sivin, Contraception 1990,; Vol.42 NO 4.; adapted from Trussel Contraception 2011

Ref 1

# Efficacy

CHC are highly efficient if they are used correctly

If a pill (or pills) is forgotten, the procedures outlined below apply. If pills are frequently forgotten, other contraceptive options should be discussed with the patient