



POST GRADUATE COURSE IN REPRODUCTIVE MEDICINE AND REPRODUCTIVE BIOLOGY

COMBINED ORAL CONTRACEPTIVES

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COMBINED ORAL CONTRACEPTIVES

- Number of Google hits 1 April 2003: over 147 000
- Publications in Medline (from 01/01/83 to 31/03/03):

Antibiotics	236 437
Antihypertensive drugs	110 258
Oral contraceptives	78 793
Cancer drugs	36 784



COMBINED ORAL CONTRACEPTIVES

- General issues
- Mechanism of action
- Common side effects
- Advantages of low-dose COCs
- Non-contraceptive benefits
- Disadvantages of low-dose COCs
- Cancer and COCs
- Cardiovascular disease and COCs



COMBINED ORAL CONTRACEPTIVES

The widespread adoption of contraception fundamentally changed the approach to reproductive health, the use of family planning, the timing of planned births and the concept of gender equity

(Diczfalusy, 1997)



COMBINED ORAL CONTRACEPTIVES

- Development of COCs
 - 1960- ENOVID marketed in the USA
 - 1970- 1980 Reduction of estrogen dose to less than 35 µg; use of mestranol disappeared
 - 1980 -1990 Introduction of new progestins
 - Currently: search for new estrogens better than EE



COMBINED ORAL CONTRACEPTIVES

1960: FDA approves the first OC, ENOVID

This pill contained 9.85 mg of norethynodrel
150 μg of mestranol

These amounts represent 10 times the progestin and 4 times the estrogen contained in pills used today



COMBINED ORAL CONTRACEPTIVES

- Composition of COCs

- Estrogen (dose of 35 μg or less)

Compound most widely used: ethynil estradiol

- Progestin (dose may vary from 30 to 400 μg depending on compound used:

Second generation: levonorgestrel and norethindrone

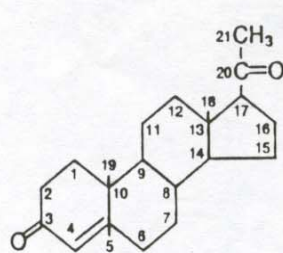
Third generation: gestodene, desogestrel and norgestimate

Estranes: those compounds that metabolize to norethindrone

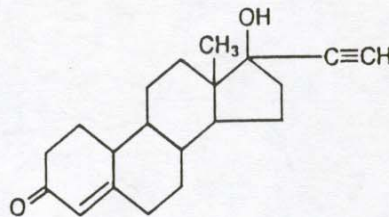
Gonanes: those compounds that metabolize to levonorgestrel



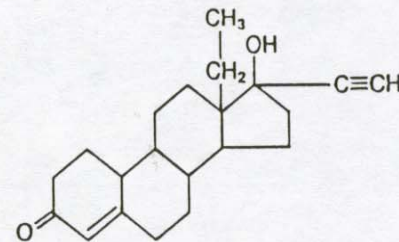
Structural formulas of progesterone and contraceptive progestins



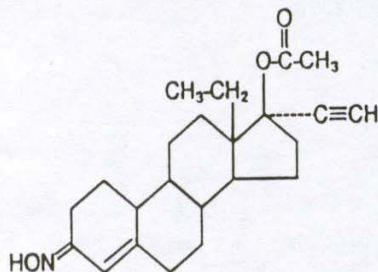
Progesterone



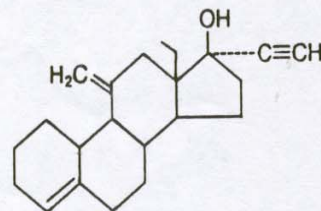
Norethindrone



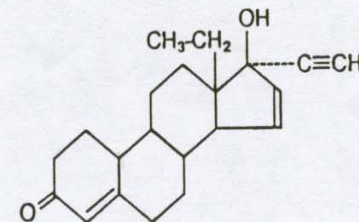
Levonorgestrel



Norgestimate



Desogestrel



Gestodene

Fig. 1. Structural formulas of progesterone and contraceptive progestins.



COMBINED ORAL CONTRACEPTIVES

- Mechanisms of action
 - Confirmed
 - Suppression of ovulation via hypothalamic and pituitary effects
 - Progestin-mediated alterations in the consistency and properties of cervical mucus
 - Unconfirmed
 - Alterations in the endometrial lining
 - Alterations of tubal transport mechanisms



COMBINED ORAL CONTRACEPTIVES

- Common side effects
 - Breakthrough and other bleeding irregularities
 - Nausea
 - Weight gain
 - Headaches
 - Mood changes
 - Breast tenderness



COMBINED ORAL CONTRACEPTIVES

- Advantages of low-dose COCs
 - Very effective with correct use
 - Safety is well established
 - Independent of coitus
 - Client controlled
 - Reversible
 - Non-contraceptive health benefits
 - Non-clinical distribution possible



COMBINED ORAL CONTRACEPTIVES

- Advantages of low-dose COCs

- Non-contraceptive benefits

COC use results in decreased incidence of:

endometrial cancer

ovarian cancer

ectopic pregnancy

acute pelvic inflammatory disease

anemia

benign breast disease

endometriosis symptoms

dysmenorrhea



COMBINED ORAL CONTRACEPTIVES

- Disadvantages of low-dose COCs
 - only moderately effective with “typical use”
 - require daily correct use
 - require regular supply
 - common bothersome effects
 - extremely rare serious complications for some women
 - misconceptions of safety
 - delivery often “overmedicalized”
 - least appropriate method when breastfeeding
 - do not prevent STDs/HIV



COMBINED ORAL CONTRACEPTIVES

- Cancer and COCs

Results of WHO Study (1992)

Type of Cancer	Relative risk	95% Conf. Limits
Breast	1.2	(1.02 - 1.29)
Cervical	1.2	(0.99 - 1.44)
Endometrial	0.6	(0.26 - 1.17)
Ovarian	0.8	(0.56 - 1.01)
Liver	0.7	(0.40 - 1.20)



COMBINED ORAL CONTRACEPTIVES

- Cancer and COCs

Meta-analysis (Lancet, 347, 1996)

- no long term increase in breast risk
- small increase in current users and for several years thereafter
- tumors detected earlier clinically and less likely to have spread
- protection against ovarian and endometrial cancer
- no variation by country, ethnicity, family history of breast cancer or reproductive history



COMBINED ORAL CONTRACEPTIVES

- Cancer and COCs

OCs and cervical cancer in women with HPV infection
(Lancet, 359, 2002)

	Odds-ratio	95% CI
Never use	1.0	
Use less 5 years	0.73	(0.52 - 1.03)
Use 5 to 9 years	2.82	(1.46 - 5.42)
Use 10 years or longer	4.03	(2.09 - 8.02)

Long term use of OCs could be a cofactor that increases the risk of cervical carcinoma up to four-fold in women positive for HPV DNA



COMBINED ORAL CONTRACEPTIVES

- Cancer and COCs

OCs and breast cancer (Women 35-64 yrs. old)
(NEJM, 346, 2002)

- Relative risk was 1.0 for women currently using (CI: 0.8-1.3)
- Relative risk was 0.9 for those who had previously used them (CI: 0.8-1.0)
- Relative risk did not increase consistently with longer periods of use or with higher doses of estrogen
- Results were similar among white and black women
- Use of OC by women with family history of breast cancer not associated with increased risk



COMBINED ORAL CONTRACEPTIVES

- Cancer and COCs

OCs and breast cancer (Br.J. Cancer, 2003)

- Women who recently used OC with more than 35 µg of estrogen at higher risk of breast cancer than users of low dose preparations (RR: 1.99 and 1.27, respectively, P trend < 0.01)
- Relationship more marked in women less than 35 years in whom RR: 3.62 and 1.91, P trend < 0.01
- Significant trend of increasing breast cancer risk for pills with higher estrogen and progestin potencies, most pronounced for women less than 35 yrs.



COMBINED ORAL CONTRACEPTIVES

- Cardiovascular disease and COCs

First case reports of association of adverse cardiovascular effects of combined Ocs

Jordan WM. Pulmonary embolism. Lancet 1961;ii: 1146-47

Lorentz IT. Parietal lesion and Enavid. Brit Med J 1962; ii: 1191

Boyce J, Fawcett JW, Noall EWP. Coronary thrombosis and Conovid. Lancet 1963; i: 111



Around 1980, the general consensus was that combined oral contraceptives were associated with:

- about a 4 to 6-fold increased risk of venous thromboembolic disease
- about a 5-fold overall increased risk of stroke (haemorrhagic and ischaemic combined)
- about a 3 to 4-fold overall increased risk of acute myocardial infarction



**Around 1980, the general
consensus was that:**

OC-associated risks of stroke and acute myocardial infarction were augmented by smoking, history of preclampic toxemia and hypertension, diabetes mellitus, and certain forms of hyperlipidemia



Around 1980, although data were sparse and fragmentary, it was believed that:

- the risk of cardiovascular disease among current OC users was directly related to both the estrogen and progestogen content;
- the low-dose estrogen pills carried less risk of adverse cardiovascular events.



Around 1990, several large-scale studies were initiated to further evaluate the cardiovascular safety of low estrogen dose combined oral contraceptives, and to obtain such data from developing countries. These studies are:

- World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception; VTE, stroke, myocardial infarction (funded by WHO/HRP)
- Transnational Research Group on Oral Contraceptives and the Health of Young Women; VTE, ischaemic stroke, myocardial infarction (funded by Schering AG)
- The Kayser Permanente Medical Care Programme; strokes, myocardial infarction (funded by NICHD, NIH)



How did these studies on OC cardiovascular safety differ from previous studies?

- Better diagnostic instruments allowing more exact case definition;
- Better *a priori* knowledge about confounders;
- Higher prevalence of use of <50ug EE pills, and new progestogens have been introduced;
- Inclusion of developing country settings.



WHO CVD Study

- Hospital-based case-control study
- 17 countries (12 developing, 5 in Europe)
- Feb 1989 - Jan 1993
- First time cases of stroke, AMI or VTE in women aged 20-44 years
- 3 controls per case, matched on age, hospital and time period



Use of combined oral contraceptives and risk of ischaemic stroke

Overall adjusted relative risk estimates of recent studies

WHO, Europe	2.99 (1.65-5.40)
WHO developing countries	2.93 (2.15-4.00)
Kaiser Permanente, California	1.18 (0.54-2.59)



Cardiovascular disease and combined oral contraceptives (OCs)

Conclusions: ischaemic stroke

- In healthy, non-smoking women, current use of OCs is associated with a small increase in risk of ischaemic stroke. The increase in risk is in the order of a relative risk of not more than 1.5.
- Smoking and hypertension adversely modify the OC-associated risk.
- Risk of ischaemic stroke associated with smoking and hypertension are adversely modified by current use of OCs.



Acute myocardial infarction and current use of combined oral contraceptives

Overall adjusted relative risk estimates, recent studies

WHO, Europe	5.01 (2.54-9.90)
WHO, developing countries	4.78 (2.52-9.07)
Kaiser Permanente, California	1.67 (0.48-5.85)



Acute myocardial infarction and current use of combined oral contraceptives

Adjusted OC-associated relative risks by smoking, and history of hypertension, in developing countries, WHO Collaborative Study

OC, non-smokers	4.5	(1.89-10.7)
OC, smokers (<10 cigarettes)	10.7	(2.49-45.9)
OC, smokers (>10 cigarettes)	22.6	(7.60-67.2)
OC, no hypertension history	3.7	(1.81-7.39)
OC, history of hypertension	15.3	(3.27-71.6)



Acute myocardial infarction and current use of combined oral contraceptives, WHO Study

Estimated incidence and attributable risk per 1 million woman-years by use of OCs, smoking, and age, (Oxford, UK)

	Non-users Ocs	Users OCs	Attributable risk
Women <35 years			
Non-smoker	0.8	3.6	2.7
Smoker	7.8	42.7	34.9
Women >35 years			
Non-smoker	9.5	40.4	31.0
Smoker	88.4	484.6	396.2



Venous Thromboembolism

	Europe	Developing
Cases / controls	433 / 1044	710 / 1954
OC use (case/cntl)	61% / 34%	29% / 12%
Risk <i>cf</i> non-users	4.1 (3.1, 5.6)	3.3 (2.6, 4.1)

Adjusted odds ratio (95% CI)



VTE and Low Estrogen OCs

Europe

	Cases	Controls	Odds ratio (95% CI)
Non-user	168	687	1.0 (ref)
Norethindrone	10	18	3.4 (1.4, 7.9)
Levonorgestrel	102	163	3.6 (2.5, 5.1)
Third generation	53	51	7.4 (4.2,12.9)

Adjusted odds ratios



Current use of low-dose combined oral contraceptives and risk of venous thromboembolic disease (VTE)

Overall adjusted relative risk estimates

WHO Collaborative, Europe	3.9 (2.96-5.28)
WHO Collaborative, developing countries	3.2 (2.59-4.08)
Transnational Research Group	4.0 (3.1-5.3)



Adjusted relative risk (RR) estimates of VTE for current use of low-dose combined oral contraceptives containing 2nd and 3rd generation progestogens vs. non-users, and 3rd vs. 2nd generation

Study	RR 2nd gen.	RR 3rd gen.	RR 3rd vs 2nd gen.
WHO, all	3.4 (2.5-4.6)	8.6 (5.3-14.2)	2.7 (1.6-4.6)
WHO, Oxford, UK	3.1 (1.7-5.5)	6.8 (3.5-13.4)	2.2 (1.1-4.2)
Jick, et al.			2.2 (1.0-4.1)
Leiden group	4.2 (1.8-9.7)	9.2 (3.9-21.4)	
Transnational	3.2 (2.3-4.3)	4.8 (3.4-6.7)	1.5 (1.1-2.1)



Current use of low-dose combined oral contraceptives and risk of venous thromboembolic disease

Estimated incidence per 100,000 woman-years of venous thromboembolic disease by type of progestogen

	WHO Oxford Centre	Jick, et al.
No use/past use	3.9	3.8
Levonorgestrel	10.3	16.1
3rd generation	21.3	28.8



Cardiovascular disease and combined oral contraceptives (OCs)

Conclusions: venous thromboembolic disease (VTE)

- Overall, current use of OCs increases risk of VTE 4-fold; current data strongly suggest that 3rd generation OCs increase this risk 8-fold.
- Incidence of VTE varies by prevalence of inherited APC resistance; incidence of VTE is probably 25% lower in non-Caucasian than in Caucasian populations.
- Apart from personal and family history, there is no practical clinical marker to predict risk of VTE.



Oral contraceptives and myocardial infarction (NEJM: 345, 2001 and 346, 2002)

- Odds ratio for MI among any women who used any type of COCs versus non-users was 2.0 (95% CI: 1.5-2.8).
- Adjusted odds ratio for those who used second generation was 2.5 (95% CI: 1.5-4.1) and 1.3 (95% CI: 0.7 -2.5) among those who used third-generation OCs.
- Risk of MI similar among women who used OCs whether or not they had a prothrombotic mutation.



COMBINED ORAL CONTRACEPTIVES

Useful web addresses

www.who.int/reproductive-health

www.reproline.jhu.edu

www.engenderhealth.org/wh/fp

www.rho.org/html/cont-ocs.htm

www.fhi.org/en/fp/nfp.html

www.ippfwhr.org/publications