Combined Oral Contraceptives: Where we’ve been and where we’re going

21 May 2010, 10:30-12:00
The World Forum Center, World Forum Theater
Den Haag, The Netherlands
Evolution of the pill

Dr Diana Mansour

Clinical Director, Sexual Health Services,
Newcastle and North Tyneside, UK
Deanery Advisor,
Faculty of Sexual and Reproductive Healthcare, UK
Evolution of COCs: key aspects

- Pill story
- Reduction in estrogen dose
- New progestogens
- Changes in dosing schedule
  - Regimens
  - Phasic nature
- What’s in the pipeline?

COCs=combined oral contraceptives
Evolution of combined oral contraceptives

1. Pill story
Pill story

John Rock  Katherine McCormick  Margaret Sanger  Gregory Pincus

Mexican yam
Pill development for use in treating infertility

- In 1952, John Rock gave increasing oral doses of estrogen (diethylstilbestrol 5–30 mg/day) and progesterone (50–300 mg/day) to 80 infertile women\textsuperscript{1}
  - 16\% became pregnant within 4 months of discontinuation

- In 1953, at Pincus' suggestion, Rock used a cyclical progesterone-only regimen for 20 days each month\textsuperscript{2}
  - 15.4\% pregnancy rate after discontinuation of medication
  - No amenorrhea but 20\% had BTB (breakthrough bleeding), and ovulation suppressed in only 85\% of the women

- A more orally active progestogen was needed

First oral contraceptive

- Norethynodrel and norethindrone synthesized\(^1\)
  - Contaminated with mestranol
  - BTB occurred when mestranol reduced to less than 1%

- 0.15–0.23 mg mestranol combined with 10 mg norethynodrel ENOVID\(^2\)
  - First contraceptive trial in Puerto Rico started in 1956\(^3\)

- June 10, 1957, FDA approved ENOVID for gynecological disorders\(^4\)

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First oral contraceptive

- June 23, 1960 – FDA approves ENOVID 10 mg for contraception\textsuperscript{1,2}
  - FDA insisted lower dosage forms withdrawn from application
  - Available for 3 years in USA
  - At least half a million women had taken it for “menstrual disorders”

Evolution of combined oral contraceptives

2. Reduction in estrogen dose
Reduction in estrogen dose

1960

FDA approval of ENOVID®
Norethynodrel 10 mg + mestranol 150 mcg

1961

German approval of Anovlar®
Norethisterone 4 mg + ethinylestradiol 50 mcg

2000

EMEA approval of Minesse®
Gestodene 0.06 mg + ethinylestradiol 15 mcg
Reduction in dose, 1964 to 1988

Retail oral contraceptive prescriptions by estrogen dose, United States – marked reduction in COC estrogen dose

### Estrogen dose and venous thromboembolism

<table>
<thead>
<tr>
<th>Estrogen (ethinyl estradiol) dose</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–40 mcg</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>50 mcg</td>
<td>1.6 (0.9–2.8)</td>
</tr>
<tr>
<td>20 mcg</td>
<td>0.6 (0.4–0.9)*</td>
</tr>
</tbody>
</table>

*P=0.02
Cerebral thromboembolic risk with oral contraceptives according to estrogen content

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>OC non-users</th>
<th>Progestogen only</th>
<th>30–40 mcg estrogen</th>
<th>50 mcg estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Lidegaard Ø et al. BMJ 1993;3:06956–963
Other side effects of estrogen at higher dose

Ratio of COC-related symptoms with 35 mcg EE pill compared with 20 mcg EE pill

Relative risk ratio

- Bloating
- Breast tenderness
- Nausea

*P<0.01 35 vs 20 µg EE

Evolution of combined oral contraceptives

3. New progestogens
Use of alternative progestogens: rationale

- Discovery of new progestogens

- Potent progestational and anti-gonadotropin actions may
  - Improve bleeding patterns/cycle control
  - Further suppress gonadotrophins thereby increasing contraceptive action

- Improvement in target tissue selectivity could
  - Reduce side effects
  - Improve acceptability/continuance
## Evolution of progestogens in available COCs

<table>
<thead>
<tr>
<th>Classification by structure</th>
<th>‘First’</th>
<th>‘Second’</th>
<th>‘Third’</th>
<th>‘New’ progestogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estranes</td>
<td>• Norethindrone</td>
<td></td>
<td></td>
<td>• Dienogest</td>
</tr>
<tr>
<td></td>
<td>• Norethynodrel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnanes</td>
<td>• Chlormadinone acetate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cyproterone acetate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Medroxyprogesterone acetate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonanes</td>
<td></td>
<td>• Levonorgestrel</td>
<td>• Desogestrel</td>
<td>• Drospirenone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Norelgestromin</td>
<td>• Etonogestrel</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Norgestimate</td>
<td>• Gestodene</td>
<td></td>
</tr>
<tr>
<td>Spironolactone-derived</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-nor-pregnanes</td>
<td></td>
<td></td>
<td></td>
<td>• Nomegestrol acetate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Nestorone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Trimegestone</td>
</tr>
</tbody>
</table>

Adapted from: Sitruk-Ware R. *Drugs Aging* 2004;21:865–883
### In vitro progestogen binding with steroid receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>NETA</th>
<th>MPA</th>
<th>LNG</th>
<th>GES</th>
<th>DRSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>--</td>
</tr>
<tr>
<td>Androgen</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>--</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>--</td>
<td>+/-</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Mineralocorticoid</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Estrogen</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Red=first generation; pink=second generation, purple=third generation; blue='new' generation

*Relative to reference hormones set at 100% (estradiol, testosterone, aldosterone, cortisol and progesterone).

'+' = >100%; '++' = >200%; '++++' = >400%; '+++++' = >800%; ‘+/−’ = <100%;

‘−’ =<50%; ‘−−’ =<20%; ‘−−−’ =<10%; ‘−−−’ =<0.1%

NETA=norethindrone acetate; MPA=medroxyprogesterone acetate; LNG=levonorgestrel; GES=gestodene; DRSP=drospirenone

Sitruk-Ware R. *Hum Reprod Update* 2006;12:169–178
Evolution of combined oral contraceptives

4. Changes in dosing schedule
Reducing the Hormone Free Interval (HFI): rationale

- COCs originally designed to mimic 28-day menstrual cycle\(^1\)
  - 21 days active treatment, 7 days HFI
- COCs associated with hormone withdrawal symptoms during HFI
  - Shortening HFI may improve symptoms\(^1\)

- Flexible dosing regimens, such as including a short hormone free interval during extended regimens improves bleeding profile\(^2\)

Active pill days and symptom days

<table>
<thead>
<tr>
<th></th>
<th>21 active pill days</th>
<th>7 day HFI</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic pain</td>
<td>21%</td>
<td>70%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Headaches</td>
<td>53%</td>
<td>70%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>19%</td>
<td>58%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bloating/swelling</td>
<td>16%</td>
<td>38%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of medication for pain</td>
<td>43%</td>
<td>69%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Reducing the Hormone Free Interval (HFI): rationale

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  - 21 days active treatment, 7 days HFI
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Ovarian suppression and reduced HFI

- Randomized, double-blind, parallel-group study
  - Compared 24/4 vs 21/7 dosing of DRSP 3 mg/EE 20 mcg
  - 128 women
  - In third cycle, first three pills replaced with placebo to simulate dosing error

- 24/4 dosing gave greater ovarian suppression with or without intentional dosing error

Rationale for extended 84/7 dosing

• Cyclic bleeding not medically essential

• Surveys report considerable interest among women to reduce frequency of menstruation
  • 37–46% wish to avoid menstruation completely\(^1\)

• Extended dosing reduces number of bleeding episodes per year\(^2\)

• Comparable contraceptive efficacy\(^3\)

• No increase in endometrial abnormalities\(^4\)

• Improvement of mood, headaches and pelvic pain\(^5\)

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Multiphasic COC dosing: rationale

- Provides lower overall steroid dose by increasing doses to maximal levels at key point in menstrual cycle

- Triphasic COCs favored over biphasic due to lower incidence of breakthrough bleeding\(^1\)

- Appears complex
  - Skipping withdrawal bleed difficult
  - Missed pill guidance confusing

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Triphasic versus monophasic dosing

- No evidence of any differences in contraceptive efficacy with triphasic versus monophasic regimens
- Reports of improved bleeding patterns with triphasic versus monophasic dosing
- No significant difference in discontinuations due to cycle disturbances or intramenstrual bleeding

Summary of COC evolution to date

- Modern COCs aim to provide effective contraception with reduced risk of side effects and additional non-contraceptive benefits
- Last 50 years have seen significant evolution of the pill, but there is still room for improvement
What is in the pipeline?

- **Estrogen**
  - $17\beta$-estradiol
  - Selective estrogen-receptor modulators

- **Progestogens**
  - With high progesterone-receptor selectivity
  - Selective progesterone-receptor modulators
Combined Oral Contraceptives: Where we’ve been and where we’re going

21 May 2010, 10:30-12:00
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Estradiol – A new option for combined oral contraception

Frank Z. Stanczyk, PhD

Professor of Obstetrics and Gynecology, and Preventive Medicine
Director, Reproductive Endocrine Research Laboratory
University of Southern California, Keck School of Medicine
Los Angeles, California, USA
Outline of presentation

- Rationale for replacing ethinyl estradiol (EE) in combined oral contraceptives (COCs)
- Physiology and pharmacokinetics of endogenous estradiol (E₂)
- Pharmacology of orally administered estradiol
  - Pharmacokinetics
  - Pharmacodynamics
Health concerns and side effects associated with COCs

**Concerns**
- Cancer
- Blood clots
- Heart attacks
- Stroke
- Weight gain
- Reduction in libido

**Side effects**
- Breakthrough bleeding
- Breast tenderness
- Weight gain
- Nausea
- Headache
- Mood changes
Approaches to improve tolerability and acceptability of COCs

- Lowering the EE dose from >50 µg to 15–20 µg per day

- Use of EE in combination with progestins without residual androgenic activity, and with additional anti-androgenic and anti-mineralocorticoid activities

- Replacement of EE, a synthetic estrogen, with the natural estrogen, \( E_2 \)
Chemical structures of EE and $E_2$

ETHINYL ESTRADIOL  
(SYNTHETIC ESTROGEN)

ESTRADIOL  
(NATURAL ESTROGEN)
Rationale for replacing EE in COCs

- EE is suspected of being responsible for most adverse events of COCs:
  - Influence on hepatic proteins, particularly coagulation factors
  - Potential increase of venous thromboembolism
  - High potency
Potency of EE

- In vitro and in vivo studies demonstrate high potency of EE compared to natural estrogens, eg, E\textsubscript{2}

- EE has an inherent high potency resulting from the addition of the ethinyl group on E\textsubscript{2} molecule (at C-17)

- Lack of affinity of EE to a plasma binding protein, eg, SHBG, allows the potent EE molecules to be readily available for action in estrogen-responsive target cells of different organs
Attempts to develop a COC based on natural estrogen

- **Different estrogens**
  - Primarily $E_2$ and the synthetic estrogen, $E_2$ valerate ($E_2V$), which is converted to $E_2$

- **Different progestins**
  - Norethindrone, desogestrel, cyproterone acetate (CPA)

- **Different doses and regimens**
  - Mainly monophasic regimens
Conclusions on early attempts to develop COCs containing $E_2$ or $E_2V$

**Contraceptive efficacy**
- Achievable

**Cycle control**
- Unsatisfactory high incidence of intracyclic bleeding
- Higher incidence of amenorrhea
- Monophasic, biphasic or triphasic regimens could not overcome poor cycle control
Femilar® – E$_2$V/cyproterone acetate (CPA)

- Marketed since 1993 in Finland: 7% of the Finnish market
- Biphasic 21-day regimen
  - 10 days E$_2$V 1 mg plus CPA 1 mg
  - 11 days E$_2$V 2 mg plus CPA 2 mg
- Good efficacy: 95% ovulation inhibition rate$^1$
- Indicated for contraception in women aged $\geq$40 years or with contraindication for EE
- Insufficient cycle control: intermenstrual bleeding/spotting incidence 20%–40%$^{1,2}$

Rationale for bleeding problems using E\textsubscript{2} or E\textsubscript{2}V in COCs

- Due to the activity of endometrial 17\beta-hydroxysteroid dehydrogenase, which is stimulated by progestins, E\textsubscript{2} is rapidly converted to estrone (E\textsubscript{1})

- In addition, progestins reduce nuclear E\textsubscript{2} receptor concentrations and thereby decrease nuclear estrogen bioavailability resulting in an antimitotic effect

- Decrease of endometrial proliferation depends on the antiestrogenic effect of the progestin component
Qlaira®: E₂V/dienogest (DNG)

- **26 active tablets**
- **22 E₂V/DNG days per cycle (Days 3–24)**
- **4 E₂V only days (Days 1–2 and 25–26)**
- **2 hormone-free tablets per cycle (placebo, Days 27–28)**
In development: $E_2$/nomegestrol acetate (NOMAC)

- 28 active tablets

- Monophasic 28-day regimen
  - 24 days $E_2$ 1.5 mg plus NOMAC 2.5 mg
  - 4 days hormone free
Physiology of estradiol
Principal physiological estrogens

17β-ESTRADIOL
(ESTRADIOL, E₂)

ESTRONE (E₁)

ESTRIOL (E₃)
Physiological aspects of endogenous $E_2$

- Produced predominantly ($\approx 95\%$) by the ovaries; remainder comes from peripheral sources
- Serum levels vary widely during the menstrual cycle; rate of secretion is dependent on the cycle phase
- In circulation, $\approx 37\%$ is bound to sex hormone-binding globulin (SHBG) with high affinity
- Undergoes extensive metabolism and enterohepatic recirculation
Estrone: important metabolite of $E_2$

 Estradiol $\xrightarrow{17\beta\text{HSD2}}$ Estrone

$\rho E_2 E_1 = 17\%$
$17\beta\text{HSD1}$
$\rho E_1 E_2 = 4\%$

Longcope C. Estrogens and Progestogens in Clinical Practice, 1998, p. 89
Estrone sulfate: Major metabolite of $E_2$ and $E_1$

 Estradiol $\xrightarrow{42\%} -$ Estrone $\xrightarrow{3\%} -$ Estrone Sulfate ($E_1S$) $\xrightarrow{40\%} -$ Estradiol

 Estradiol $\xleftarrow{15\%} -$ Estrone Sulfate ($E_1S$) $\xleftarrow{15\%} -$ Estradiol

Longcope C. Estrogens and Progestogens in Clinical Practice, 1998, p. 89
Serum levels of $E_1S$, $E_2$, and $E_1$ during the menstrual cycle

Hawkins RA, Oakey RE. *J Endocrinol*. 1974;60:3–17
Pharmacokinetics of endogenous $E_2$

- Based on its volume of distribution, $E_2$ is widely distributed in organs and tissues.
- $E_2$ is cleared rapidly from the circulation ($MCR = 1100-1200$ L/day).
- The half-life of $E_2$ is $\approx 1.7$ hrs, which is about 4 times less than that of $E_1$ and $E_1S$. 

Normal physiology modulates activity of E₂

- Production rates and circulating levels of E₂ and E₁ vary during the cycle
- Metabolic oxidation of E₂ results in substantial formation of less active E₁
- Inactive E₁S serves as a reservoir for both active estrogens
- A substantial amount of E₂ is bound to SHBG
Pharmacology of estradiol
Serum levels of E$_2$ and E$_1$ following oral administration of micronized E$_2$ (2 mg)

Pharmacokinetics of oral E2

- **Bioavailability:** ≈5%
- **Half-life:** 13–20 hours

Kuhnz W et al. Estrogens and Antiestrogens II. Springer-Verlag; 1999;261–322
Biologic actions of $E_2$ in various tissues
Study Design

- 23 healthy postmenopausal women
- Treatment:
  - Estrogens and doses studied
    - **Micronized estradiol**: 1, 2 and 10 mg
    - Piperazine estrone sulfate: 0.3, 0.625, 1.25, 2.5 and 5.0 mg
    - Conjugated estrogens: 0.3, 0.625, 1.25 and 2.5 mg
    - Diethylstilbestrol (DES): 0.1 and 0.5 mg
    - Ethinyl estradiol: 0.01 and 0.02 mg
  - Each dose given orally QD am for 2 weeks to three subjects, with a 30-day washout period between doses
- Evaluations:
  - Serum samples obtained pretreatment and after 11\textsuperscript{th} and 14\textsuperscript{th} doses
  - FSH, LH, CBG, SHBG and angiotensinogen were measured
Effect of estrogens on FSH and hepatic proteins

Results

<table>
<thead>
<tr>
<th>Estrogen preparation*</th>
<th>FSH</th>
<th>CBG</th>
<th>SHBG</th>
<th>Angiotensinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperazine estrone sulfate</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Micronized estradiol</td>
<td>1.3</td>
<td>1.9</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Conjugated estrogens</td>
<td>1.4</td>
<td>2.5</td>
<td>3.2</td>
<td>3.5</td>
</tr>
<tr>
<td>DES</td>
<td>3.8</td>
<td>70</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>(80–200)†</td>
<td>(1000)†</td>
<td>614</td>
<td>232</td>
</tr>
</tbody>
</table>

*Potency determined relative to reference curve of piperazine estrone sulfate; † Estimate in the absence of parallelism

- On a weight basis, micronized estradiol and piperazine estrone sulfate were essentially equipotent for all responses
- The potency of ethinyl estradiol was dramatically higher
Effect of E2 on blood pressure

A and B = normotensive groups; C and D = hypertensive groups

# Effect of E$_2$ on lipids, carbohydrates and coagulation factors

| Effects after treatment of postmenopausal women with 1 mg micronized E$_2$ in comparison to placebo |
|---|---|---|
| **Lipids** | **Carbohydrates** | **Coagulation factors** |
| • Decreases total cholesterol slightly | • Reduces insulin and C-peptide levels | • Blunts or reverses increases in fibrinogen and PAI-1 levels, which are considered to reduce thrombogenicity |
| • Decreases LDL-cholesterol significantly | • These responses suggest improved insulin sensitivity with oral E$_2$ treatment | • Suppresses antithrombin III activity, but remains within the normal range and is not a major factor responsible for increased risk of thromboembolic events associated with estrogen therapy |
| • Increases HDL-cholesterol | | |
| • Increases triglycerides significantly | | |
| • Does not alter Lp(a) and ApoB concentrations | | |
| • Increases Apo A-1 concentration significantly | | |
| • Favorable changes by oral E$_2$ on HDL- and LDL-cholesterol and Apo A-1 may offset the unfavorable change in triglycerides and even produce a beneficial effect in the lipid profile | | |

Effect of oral 1mg E$_2$ on carotid intima-media thickness

EPAT primary trial results

EPAT=Estrogen in the Prevention of Atherosclerosis Trial; CIMT=change in intima-media thickness

Effect of oral 0.25mg E$_2$ on bone

E$_2$ has profound actions throughout the CNS

- Brain regions and neurochemical systems affected by E$_2$: hippocampus, spinal cord, glial cells, cerebral vasculature and the basal forebrain cholinergic, midbrain serotonergic, midbrain and hypothalamic dopamine, and brainstem catecholaminergic systems

- Estrogen actions include effects on:
  - Mood
  - Cognitive function
  - Dementia
  - Motor coordination and movement disorders
  - Excitability and epilepsy
  - Pain

**Pharmacokinetics of orally administered E₂**

- Due to hepatic first pass metabolism, only a small fraction of E₂ becomes bioavailable; its principal metabolites, E₁ and E₁S enter the circulation in much larger amounts.
- E₂ has a relatively long terminal half-life.
Pharmacodynamic studies show that oral E₂ has the following effects:

- Approximately 300–600 times less potent than EE on estrogen-sensitive hepatic proteins
- Lowers blood pressure in both normotensive and hypertensive women
- Has beneficial effects on cardiovascular risk markers
- Increases bone density and reduces bone turnover
- Plays important role in modulation of brain function
Conclusions

- $E_2$ is an attractive choice as a new option for the estrogenic component of COCs
- It is the same estrogen that is made in the body (natural), is metabolized extensively to less potent and inactive estrogens, and binds substantially to SHBG, thereby decreasing its estrogenic potency
  - Compared to EE, the potency of $E_2$ is up to several hundred times lower
- $E_2$ has favorable effects on cardiovascular markers, bone and brain
Combined Oral Contraceptives: Where we’ve been and where we’re going

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Nomegestrol acetate
– a new and different progestin

Alfred O. Mueck, MD, PharmD, PhD
Professor of Experimental Endocrinology and Clinical Pharmacology
University Women’s Hospital of Tuebingen, Germany
Dept. of Endocrinology and Menopause, Head

Centre of Women's Health of Baden-Württemberg
(District South Germany), Head
Nomegestrol acetate – pharmacology with importance for use in contraception

• Chemical structure

• Preclinical pharmacology
  • Affinity and activity to steroid receptors
  • Cardiovascular effects
  • Metabolic effects: lipids, carbohydrates, clotting factors, etc.
  • Preclinical pharmacology – summary

• Clinical pharmacology (premenopausal)
  • Pharmacokinetics
  • Ovulation inhibition
  • Cervical mucus
  • Metabolic and hepatic effects

• Pharmacology – summary
Nomegestrol acetate – pharmacology with importance for use in contraception

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- Pharmacology – summary
Classification of progestins

Derived from progesterone

- Dydrogesterone
- Medrogestone

**17-OH Progesterone (Pregnanes)**
- Medroxyprogesterone Ac
- Cyproterone Ac
- Chlormadinone Ac
- Megestrol Ac

**19-Norprogesterone**
- Nestorone
- NOMAC
- Trimegestone

Derived from testosterone

**Estranes**
- Norethisterone
- Dienogest (non-ethyl)

**13-Ethyl gonanes**
- Levonorgestrel
- Desogestrel (etonogestrel)
- Gestodene
- Norgestimate (norelgestromin)

Spironolactone
- Drospirenone
NOMAC chemical structure

- Principal human progestogen
- More potent than progesterone
- Limited oral activity

Progesterone

19-Norprogesterone

Nomegestrol acetate (NOMAC)
- Highly selective progestogen
- Orally active
- Derivative of 19-norprogesterone
Nomegestrol acetate – pharmacology with importance for use in contraception

• Chemical structure

• **Preclinical pharmacology**
  • Affinity and activity to steroid receptors
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• Pharmacology – summary
NOMAC: high selectivity for progesterone receptor binding

<table>
<thead>
<tr>
<th>Relative binding affinity</th>
<th>Endogenous hormone</th>
<th>Second generation</th>
<th>‘New’ progestagens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone receptor</td>
<td>50</td>
<td>150</td>
<td>250</td>
</tr>
<tr>
<td>Androgen receptor</td>
<td>0</td>
<td>45</td>
<td>19</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>0</td>
<td>0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Glucocorticoid receptor</td>
<td>10</td>
<td>1</td>
<td>3–11</td>
</tr>
<tr>
<td>Mineralocorticoid receptor</td>
<td>100</td>
<td>75</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

Binding affinity relative to: androgen receptor, metribolone=100%; estrogen receptor, estradiol 17=100%; glucocorticoid receptor, dexamethasone=100%; mineralocorticoid receptor, aldosterone=100%

- NOMAC shows a high degree of selectivity and specificity for the progesterone receptor
Nomegestrol acetate – receptor binding affinities from animal models

- Progesterone receptor: very specific binding
- Estrogen receptor: no binding (rat)
- Antiandrogenic: moderate
- Glucocorticoid receptor: weak to no binding (3% of dexamethasone)
- Mineralocorticoid receptor: no affinity (rats)
In vivo bioassays for progestin evaluation

<table>
<thead>
<tr>
<th>Test</th>
<th>Model</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiestrogenic</strong></td>
<td>McPhail</td>
<td>Rabbit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrium</td>
</tr>
<tr>
<td><strong>Antiovulatory</strong></td>
<td>Ovulation inhibition</td>
<td>Rat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N ovum</td>
</tr>
<tr>
<td><strong>Antiandrogenic</strong></td>
<td>Hershberger</td>
<td>Immature male rat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate growth</td>
</tr>
<tr>
<td><strong>Antiestrogenic</strong></td>
<td>Uterine/vaginal corn</td>
<td>Ovx female rats</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterine growth</td>
</tr>
<tr>
<td><strong>Glucocorticoid</strong></td>
<td>Thymus/liver glycogen</td>
<td>Adx rats</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thymus growth</td>
</tr>
<tr>
<td><strong>Mineralocorticoid</strong></td>
<td>NA/K retention</td>
<td>Adx rats</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Na elimination</td>
</tr>
</tbody>
</table>

N=number; Corn=cornification; Ovx=ovariectomized; Adx=adrenalectomized
Androgenic (sex organ weights) activity – results

In vivo effect of NOMAC on ventral prostate and seminal vesicles of castrated male rats

<table>
<thead>
<tr>
<th>Treatments (dose in mg/animal/day)</th>
<th>Ventral prostate, mg</th>
<th>Seminal vesicles, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact controls</td>
<td>68.1±5.1*</td>
<td>31.3 ± 2.2*</td>
</tr>
<tr>
<td>Castrated controls</td>
<td>11.8±0.5</td>
<td>10.8 ± 0.4</td>
</tr>
<tr>
<td>Norethindrone acetate (2.5)</td>
<td>25.3 ± 2.5*</td>
<td>25.1 ± 1.6*</td>
</tr>
<tr>
<td>Norethindrone acetate (5)</td>
<td>34.3 ± 2.2*</td>
<td>27.3 ± 0.6*</td>
</tr>
<tr>
<td>Norethindrone acetate (10)</td>
<td>42.3 ± 3.2*</td>
<td>33.1 ± 1.8*</td>
</tr>
<tr>
<td>NOMAC (10)</td>
<td>12.1 ± 0.6</td>
<td>12.8 ± 0.7</td>
</tr>
</tbody>
</table>

Mean±SEM (n=8); *p<0.001 as compared to castrated.

- At 10 mg for 10 days, NOMAC was unable to stimulate the growth of the involuting ventral prostate and seminal vesicles
### Hormonal activities of progestogens

<table>
<thead>
<tr>
<th>Progestogen</th>
<th>AE</th>
<th>EST</th>
<th>AND</th>
<th>AA</th>
<th>GLU</th>
<th>AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>(+)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>+</td>
<td>-</td>
<td>(+)</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Medrogestone</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>(+)</td>
<td>-</td>
</tr>
<tr>
<td>Dienogest</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Nestorone</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>NOMAC</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>(+)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Trimegestone</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>(+)</td>
<td>-</td>
<td>(+)</td>
</tr>
<tr>
<td>Tibolone metabolites</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

++ highly effective; + effective; (+) weakly effective; - not effective

AE=antiestrogenic; EST=estrogenic; AND=androgenic; AA=antiandrogenic; GLU=glucocorticoid; AM=antimineralocorticoid
Nomegestrol acetate – pharmacology with importance for use in contraception

• Chemical structure

• **Preclinical pharmacology**
  • Affinity and activity to steroid receptors
    – **Cardiovascular effects**
  • Metabolic effects: lipids, carbohydrates, clotting factors, etc.
  • Preclinical pharmacology – summary

• Clinical pharmacology (premenopausal)
  • Pharmacokinetics
  • Ovulation inhibition
  • Cervical mucus
  • Metabolic and hepatic effects

• Pharmacology – summary
In vitro cardiovascular effects – eNOS/NO results

**In vitro** effect of NOMAC on NO synthesis and eNOS activity in HUVECs treated for 48 hours

- NOMAC administration (48 h) increased NO synthesis and eNOS activity in a concentration-dependent manner

![Graph showing the effect of NOMAC on NO synthesis and eNOS activity](image)

* *p<0.05 for all

**eNOS**=endothelial nitric oxide synthase; **NO**=nitric oxide; **HUVECs**=human umbilical vein endothelial cells
**In vitro** cardiovascular effects – eNos/NO results

- NOMAC and P had comparable increases in NO synthesis and eNOS activity
- MPA had no effect on NO synthesis and eNOS activity

---

**In vitro** effect of progestins on NO synthesis and eNOS activity in HUVECs treated for 48 hours

* eNOS=endothelial nitric oxide synthase; NO=nitric oxide; HUVECs=human umbilical vein endothelial cells; NOMAC=nomegestrol acetate; P=progesterone; MPA=medroxyprogesterone acetate; RU=RU-486

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Simoncini T. Obstet Gynecol. 2006;108:69–78
In vitro cardiovascular effects – eNOS/NO results

In vitro effect of progestins in the presence of E2 on NO synthesis and eNOS activity in huvecs treated for 48 hours

- E2 produced strong increases in NO synthesis and eNOS activity
- NOMAC and P did not lead to significant changes in E2 induced effects
- MPA significantly interfered with E2 effects

eNOS=endothelial nitric oxide synthase; NO=nitric oxide; E2=estradiol; HUVECs=human umbilical vein endothelial cells; NOM AC=nomgestrol acetate; P=progesterone

Simoncini T. Obstet Gynecol. 2006;108:69–78
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In vivo cardiovascular blood chemistry effects – study design

**TREATMENTS:**

Control: no hormonal treatment

E2: 0.1 mg E2 in diet/kg/d

E2 + NA: 0.1 mg E2 + 0.25 mg NA in diet/kg/d

TPC = total plasma cholesterol; HDL-C = high density lipoprotein-C

Wagner J. J Clin Endocrinol Metab. 1998;83:896–901
**In vivo cardiovascular blood chemistry effects – plasma markers**

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 12)</th>
<th>Estradiol (n = 10)</th>
<th>Estradiol + NA (n = 12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.64 ± 0.08</td>
<td>2.98 ± 0.14</td>
<td>2.68 ± 0.14</td>
<td>0.05</td>
</tr>
<tr>
<td>Treatment</td>
<td>2.94 ± 0.06</td>
<td>2.75 ± 0.07</td>
<td>2.84 ± 0.06</td>
<td>NS</td>
</tr>
<tr>
<td>TPC (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>404 ± 38</td>
<td>434 ± 63</td>
<td>423 ± 29</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment</td>
<td>417 ± 38</td>
<td>445 ± 71</td>
<td>420 ± 47</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>34 ± 5</td>
<td>35 ± 5</td>
<td>35 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment</td>
<td>43 ± 5</td>
<td>39 ± 6</td>
<td>35 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>LDL size (nm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>349 ± 9</td>
<td>324 ± 13</td>
<td>316 ± 8</td>
<td>0.06</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>65 ± 3</td>
<td>74 ± 4</td>
<td>71 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment</td>
<td>52 ± 3</td>
<td>65 ± 3</td>
<td>57 ± 3</td>
<td>0.02</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21 ± 4</td>
<td>21 ± 5</td>
<td>20 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment</td>
<td>29 ± 6</td>
<td>35 ± 6</td>
<td>36 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin:glucose ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.32 ± 0.05</td>
<td>0.31 ± 0.08</td>
<td>0.28 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.56 ± 0.10</td>
<td>0.49 ± 0.12</td>
<td>0.64 ± 0.10</td>
<td>NS</td>
</tr>
</tbody>
</table>

BW=body weight; NS=nonsignificant; TPC=total plasma cholesterol; HDL=high density lipoprotein; LDL=low density lipoprotein

- The addition of NOMAC to E2 did not adversely affect cardiovascular risk markers (ie, vs. controls)
**In vivo** cardiovascular (blood flow) effects – responses in coronary arteries

**In vivo** effect of NOMAC on dilator responses of coronary arteries of monkeys to acetylcholine and nitroglycerin

- NOMAC did not diminish the beneficial effects of E2 on coronary dilator responses

OVX=ovariectomy; E2=estradiol; E2 + NMA=estradiol plus NOMAC; ACH\(^{-8}\)=acetylcholine at 10\(^{-8}\) mol/L; ACH\(^{-7}\)=acetylcholine at 10\(^{-7}\) mol/L; ACH\(^{-6}\)=acetylcholine at 10\(^{-6}\) mol/L; NTG=nitroglycerin; mol/L=moles per liter

*Williams JK. Am J Obstet Gynecol 1998;179:1288–94*
Summary of preclinical pharmacology

• High antigonadotropic action
• No androgenic effect
• Low antiandrogenic effect
• No estrogenic effect
• No glucocorticoid action
• No mineralocorticoid action
• Neutral in vascular and metabolic effects

→ highly suitable for contraceptive use!
Nomegestrol acetate – pharmacology with importance for use in contraception

• Chemical structure

• Preclinical pharmacology
  • Affinity and activity to steroid receptors
  • Cardiovascular effects
  • Metabolic effects: lipids, carbohydrates, clotting factors, etc.
  • Preclinical pharmacology – summary

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  • Ovulation inhibition
  • Cervical mucus
  • Metabolic and hepatic effects

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  - Ovulation inhibition
  - Cervical mucus
  - Metabolic and hepatic effects

- Pharmacology – summary
Pharmacokinetic parameters of various progestins

<table>
<thead>
<tr>
<th>Progestin</th>
<th>Bioavailability (%)</th>
<th>Elimination ½ life (β) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOMAC*</td>
<td>~63</td>
<td>35–51</td>
</tr>
<tr>
<td>NET</td>
<td>64¹</td>
<td>8²</td>
</tr>
<tr>
<td>NETA</td>
<td>60³</td>
<td>6⁴</td>
</tr>
<tr>
<td>LNG¹</td>
<td>89–99¹</td>
<td>9.9–13.2¹</td>
</tr>
<tr>
<td>DSG¹</td>
<td>62–76¹</td>
<td>11.9–23.8¹</td>
</tr>
<tr>
<td>GSD¹</td>
<td>87–99¹</td>
<td>12–14¹</td>
</tr>
<tr>
<td>CYPA</td>
<td>100⁴</td>
<td>54.0–78.6¹</td>
</tr>
<tr>
<td>PROG</td>
<td>9</td>
<td>16.2–18.3¹</td>
</tr>
</tbody>
</table>

NOMAC=nomegestrol acetate; NET=norethisterone; NETA=norethisterone acetate; LNG=levonorgestrel; DSG=desogestrel; GSD=gestodene; CYPA=ciproterone acetate; PROG=progesterone; h=hours, l/Kg=liters per kilogram

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- **Clinical pharmacology (premenopausal)**
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  - **Ovulation inhibition**
  - Cervical mucus
  - Metabolic and hepatic effects

- Pharmacology – summary
Ovulation inhibition – study design

• 13 healthy volunteer women
  • Mean age 34 (range 25–42)
  • Mean weight 55.2 kg (range 48–65)

• Treatment:
  • 2 control and 1 treatment cycle
  • Cycle 1: daily basal temperature (BBT), occurrence and duration of menses
  • Cycle 2: daily BBT; FSH, LH & E (days 5–25); P (days 12–25)
  • Cycle 3: NOMAC days 5–15 at:
    • 1.25 mg/d (n=3)
    • 2.5 mg/d (n=5)
    • 5.0 mg/d (n=5)

• Evaluations:
  • Daily BBT, FSH, LH, E and P per Cycle 2

Bazin B. Br J Obstet Gynaecol. 1987;94:1199–1204
Dose-ranging effects of NOMAC on ovulation – luteinizing hormone levels

Before treatment

During treatment

LH=luteinizing hormone; NOMAC=nomegestrol acetate; IU/L=international units per liter; mg/day=milligrams per day

Bazin B. Br J Obstet Gynecol. 1987;94:1199–1204
Dose-ranging effects of NOMAC on follicular growth – estradiol levels

Before treatment

Days

During treatment

Days

LH=luteinizing hormone; NOMAC=nomegestrol acetate; pg/mL=picograms per milliliter; mg/day=milligrams per day
Dose-ranging effects of NOMAC on follicular growth – progesterone levels

NOMAC=nomegestrol acetate; ng/mL=nanograms per milliliter; mg/day=milligrams per day

Bazin B. Br J Obstet Gynecol. 1987;94:1199–1204
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  • **Cervical mucus**
  • Metabolic and hepatic effects

• Pharmacology – summary
Effects of nomegestrol acetate on the spinability of human cervical mucus

- NOMAC 5.0 mg daily:
  - No dendrite or arborization was visible at midcycle
  - Mucus framework was substantially tightened
Nomegestrol acetate – pharmacology with importance for use in contraception

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  • Cardiovascular effects
  • Metabolic effects: lipids, carbohydrates, clotting factors, etc.
  • Preclinical pharmacology – summary

• **Clinical pharmacology (premenopausal)**
  • Pharmacokinetics
  • Ovulation inhibition
  • Cervical mucus
  • **Metabolic and hepatic effects**

• Pharmacology - Summary
Nomegestrol acetate and hepatic effects – study design

• 36 regularly menstruating women
  • Mean age: 38.8 (18–49) yrs
  • Mean BMI: 22.4 (19.1–29.8)

• Treatment:
  • Control (pre-treatment cycle)
  • Treatment (6 consecutive menstrual cycles): oral NOMAC 5 mg/d on days 6–25

• Evaluations:
  • Pre-treatment cycle, and between Days 18 and 25 of Cycle 3 and Cycle 6
  • Body weight, blood pressure
  • Fasting blood samples: nomegestrol acetate, estradiol, progesterone, sex hormone binding globulin, corticosteroid binding globulin, renin substrate, lipids, apolipoproteins, blood glucose, insulin, coagulation factors

## Hepatic effects – SHBG, CBG and renin

Plasma levels of hormones, SHBG, CBG, renin substrate before and during treatment with NOMAC 5 mg/d for 20 d/cycle

<table>
<thead>
<tr>
<th></th>
<th>Normal ranges</th>
<th>Basal</th>
<th>3rd cycle</th>
<th>6th cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (pmol/l)</td>
<td>250–800</td>
<td>418 ± 51</td>
<td>146 ± 35*</td>
<td>98 ± 13*</td>
</tr>
<tr>
<td>Progesterone (nmol/l)</td>
<td>10 –75</td>
<td>14.6 ± 2.5</td>
<td>0.6 ± 0.03*</td>
<td>0.6 ± 0.03*</td>
</tr>
<tr>
<td>SHBG (ug/ml)</td>
<td>3–6</td>
<td>3.4 ± 0.3</td>
<td>2.9 ± 0.2</td>
<td>2.6 ± 0.2</td>
</tr>
<tr>
<td>CBG (ug/ml)</td>
<td>33–49</td>
<td>37.7 ± 1.0</td>
<td>39.3 ± 0.9</td>
<td>37.5 ± 1.1</td>
</tr>
<tr>
<td>Renin substrate (ng/ml)</td>
<td>600–1500</td>
<td>1116.7 ± 52.8</td>
<td>1125.8 ± 47.4</td>
<td>1162.3 ± 40.6</td>
</tr>
</tbody>
</table>

*p<0.001 as compared with basal values; estradiol: 1 pmol/l=0.27 pg/ml; progesterone: 1 nomol/l=0.031 ng/ml

- **Average NOMAC blood levels**: 10.4 ± 6.5 ng/mL (Cycle 3)
  8.8 ± 7.2 ng/mL (Cycle 6)
**Metabolic effects – results**

**Metabolic parameters before and during treatment with NOMAC 5 mg/d for 20 d/cycle**

<table>
<thead>
<tr>
<th></th>
<th>Normal ranges</th>
<th>Basal</th>
<th>3rd cycle</th>
<th>6th cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td>59.3 ± 1.5</td>
<td>57.2 ± 2.3</td>
<td>59.9 ± 1.7</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>3.60–6.10</td>
<td>5.00 ± 0.14</td>
<td>4.93 ± 0.13</td>
<td>4.99 ± 0.15</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.40–2.10</td>
<td>0.89 ± 0.08</td>
<td>0.75 ± 0.06</td>
<td>0.83 ± 0.05</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>0.80–2.10</td>
<td>1.13 ± 0.03</td>
<td>1.15 ± 0.04</td>
<td>1.12 ± 0.04</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>1.60–4.90</td>
<td>3.67 ± 0.43</td>
<td>3.62 ± 0.12</td>
<td>3.70 ± 0.15</td>
</tr>
<tr>
<td>Apolipoprotein A1 (g/l)</td>
<td>1.00–2.00</td>
<td>1.56 ± 0.04</td>
<td>1.41 ± 0.04**</td>
<td>1.45 ± 0.04**</td>
</tr>
<tr>
<td>Apolipoprotein B (g/l)</td>
<td>0.80–1.60</td>
<td>0.99 ± 0.04</td>
<td>0.99 ± 0.04</td>
<td>0.99 ± 0.04</td>
</tr>
<tr>
<td>Apo A1/Apo B</td>
<td>&gt;1.40</td>
<td>1.68 ± 0.07</td>
<td>1.55 ± 0.11</td>
<td>1.54 ± 0.07</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>3.80–6.10</td>
<td>4.82 ± 0.08</td>
<td>4.92 ± 0.07</td>
<td>4.77 ± 0.08</td>
</tr>
<tr>
<td>Insulin (mUI/l)</td>
<td>10–15</td>
<td>11.5 ± 0.8</td>
<td>11.4 ± 0.6</td>
<td>11.8 ± 0.6</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.01 as compared with basal values; cholesterol: 1 mmol/l; triglycerides: 1 mmol/l=0.81 g/l; glucose: 1 mmol/l=0.18 g/l
Metabolic effects – results

Hemostatic parameters before and during treatment with NOMAC 5 mg/d for 20 d/cycle

<table>
<thead>
<tr>
<th></th>
<th>Normal ranges</th>
<th>Basal</th>
<th>3rd cycle</th>
<th>6th cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin III (%)</td>
<td>80–120</td>
<td>99 ± 1</td>
<td>106 ± 1**</td>
<td>105 ± 2**</td>
</tr>
<tr>
<td>(immunodiffusion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombin III (%)</td>
<td>80–120</td>
<td>99 ± 1</td>
<td>106 ± 1</td>
<td>104 ± 2*</td>
</tr>
<tr>
<td>(amidolytic method)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasminogen (%)</td>
<td>70–130</td>
<td>106 ± 3</td>
<td>107 ± 2</td>
<td>104 ± 2</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2–4</td>
<td>3.2 ± 0.1</td>
<td>3.4 ± 0.1</td>
<td>3.2 ± 0.1</td>
</tr>
</tbody>
</table>

*p<0.01; **p<0.001 as compared with basal values
Nomegestrol acetate – pharmacology with importance for use in contraception

- Chemical structure
- Preclinical pharmacology
  - Affinity and activity to steroid receptors
  - Cardiovascular effects
  - Metabolic effects: lipids, carbohydrates, clotting factors, etc.
  - Preclinical pharmacology – summary

- Clinical pharmacology (premenopausal)
  - Pharmacokinetics
  - Ovulation inhibition
  - Cervical mucus
  - Metabolic and hepatic effects

- Pharmacology – summary
Preclinical pharmacology summary

- High antigonadotropic action
- No androgenic effect
- Low antiandrogenic effect
- No estrogenic effect
- No glucocorticoid action
- Neutral in vascular and metabolic effects

➤ highly suitable for contraceptive use!
## Clinical pharmacology summary

### Outcome

- NOMAC is readily bioavailable and has a long elimination half-life (35-51 h)

- **Contraceptive effects**
  - potent antigonadotropic (ovulation inhibition) effect at hypothalamic and pituitary level
  - potent ovulation inhibition (LH surge, FSH surge, progesterone levels)
  - a potent effect on the spinability of cervical mucus

- **Cardiovascular and metabolic effects**
  - no significant change in body weight
  - no deleterious effects on fasting blood glucose and insulin
  - induced only minor changes in lipoprotein metabolism
  - no deleterious effects on coagulation parameters

» **highly suitable for contraceptive use!**
Nomegestrol acetate – a new and different progestin

Thank you for your attention!

Alfred O. Mueck, MD, PharmD, PhD
Combined Oral Contraceptives: Where we’ve been and where we’re going

21 May 2010, 10:30–12:00
The World Forum Center, World Forum Theater
Den Haag, The Netherlands
NOMAC/E2
(nomegestrol acetate/17β-estradiol)

Dr. Tjeerd Korver

Global Head Contraception Research
Global Clinical Development – Women's Health
Merck Research Laboratories
The continued evolution of combined contraception

Clinical pharmacology of the NOMAC/E2 combination
NOMAC/E2 combined oral contraceptive

- New combined oral contraceptive
- $17\beta$-estradiol (E2)
  - The natural estrogen produced in the body
- Nomegestrol acetate (NOMAC)
  - Progesterone-derived progestin
  - Mildly antiandrogenic
  - Devoid of estrogenic, androgenic, glucocorticoid and mineralocorticoid activity

![Chemical structures of NOMAC and E2]
NOMAC/E2
Dose finding
NOMAC alone
Effects on HPO axis

NOMAC/E2 combination Effects on HPO axis

**FSH**

![Graph showing FSH levels](image)

**LH**

![Graph showing LH levels](image)

**E2**

![Graph showing E2 levels](image)

**P**

![Graph showing P levels](image)

Source: Chabbert-Buffet et al. 8th Congress of the European Society of Gynecology; Sep 10-13; 2009; Rome, Italy; 2009.
NOMAC/E2 combination
Effects on vaginal bleeding pattern

Incidence of inter-menstrual bleeding/spotting over time in women treated with E2 1.5 mg and NOMAC 0.625, 1.25 or 2.5 mg

Source: MSD data on file
Summary

- NOMAC provides maximum inhibition of follicular growth and ovulation inhibition at 2.5 mg/d
- Oral E2 1.5 mg/d:
  - Compensates for reduced endogenous E2 synthesis
  - Reinforces the antigonadotropin activity of NOMAC
- NOMAC 2.5/E2 1.5 mg daily provides the best vaginal bleeding pattern
- The combination of NOMAC 2.5 mg and E2 1.5 mg was selected for further development
NOMAC 2.5/E2 1.5 mg
Regimen finding: 24/4 vs 21/7 regimen
Comparison 24/4 and 21/7 regimen

- Comparison of NOMAC 2.5/E2 1.5 mg 21/7 versus 24/4 regimen with respect to:
  - Ovarian activity
  - Vaginal bleeding patterns
- Three treatment cycles, pre- and post-treatment cycle
- N=40 per group

Source: Serfaty et al. 19th World Congress of Gynecology and Obstetrics, Oct 4-9; Cape Town, South Africa 2009.
24/4 vs 21/7: FSH concentrations and Follicular diameter

Source: Serfaty et al. 19th World Congress of Gynecology and Obstetrics, Oct 4-9; Cape Town, South Africa 2009.
24/4 vs 21/7: ovulation

- No individual progesterone value >0.3 ng/mL at any time
- No ultrasound evidence of follicular rupture
- No ovulation observed in 75 subjects / 222 cycles
  - 21/7 regimen: 36 subjects/107 cycles
  - 24/4 regimen: 39 subjects/115 cycles

Source: Serfaty et al. 19th World Congress of Gynecology and Obstetrics, Oct 4-9; Cape Town, South Africa 2009.
24/4 vs 21/7: vaginal bleeding

- The 24/4 regimen displays in comparison to the 21/7 regimen:
  - Lower total number of bleeding days
    - 4.2 vs 5.3 days per cycle
  - Shorter mean duration of withdrawal bleeding
    - 3.7 vs 4.9 days per cycle
  - Shorter mean duration of breakthrough bleeding
    - 2.3 vs 5.7 days per cycle

Source: Serfaty et al. 19th World Congress of Gynecology and Obstetrics, Oct 4-9; Cape Town, South Africa 2009.
Summary: 24/4 vs 21/7 regimen

- Compared to the 21/7 regimen, the 24/4 regimen demonstrates:
  - Increased contraceptive robustness
  - Better cycle control

- The combination of NOMAC 2.5 mg and E2 1.5 mg in the 24/4 regimen was selected for further clinical development

Source: Serfaty et al. 19th World Congress of Gynecology and Obstetrics, Oct 4-9; Cape Town, South Africa 2009.
NOMAC 2.5/E2 1.5 mg
24/4 regimen

Pharmacokinetics
and
Pharmacodynamics
Steady state pharmacokinetic parameters of NOMAC, E2 and E1 during treatment with the NOMAC 2.5/E2 1.5 mg combination

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NOMAC</th>
<th>E2</th>
<th>E1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>$T_{\text{max}}$*</td>
<td>1.5 (1.0-2.0) h</td>
<td>6.0 (0.5-144) h</td>
<td>3.0 (1.5-6.0) h</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>12.3 ± 3.50 ng/mL</td>
<td>86.0 ± 51.3 pg/mL</td>
<td>440 ± 339 pg/mL</td>
</tr>
<tr>
<td>AUCss (0–24)</td>
<td>106 ± 33.1 ng.h/mL</td>
<td>1208 ± 616 pg.h/mL</td>
<td>6366 ± 4321 pg.h/mL</td>
</tr>
<tr>
<td>$T_{\frac{1}{2}}$ el</td>
<td>45.9 ± 15.3 h</td>
<td>n.c.</td>
<td>n.c.</td>
</tr>
<tr>
<td>$C_{\text{ss,av}}$</td>
<td>4.44 ± 1.38 ng/mL</td>
<td>50.3 ± 25.7 pg/mL</td>
<td>265 ± 180 pg/mL</td>
</tr>
<tr>
<td>$C_{\text{ss, min}}$</td>
<td>3.08 ± 1.07 ng/mL</td>
<td>n.c.</td>
<td>n.c.</td>
</tr>
</tbody>
</table>

*For $T_{\text{max}}$, median (minimum-maximum) is presented

Source: MSD data on file
Mechanism of action study

- Open-label, randomized, comparative trial
- 1 screening cycle, 6 treatment cycles, 1 post-treatment cycle
- NOMAC 2.5/E2 1.5 mg vs DRSP 3.0/EE 0.03 mg
- 32 vs 16 subjects, 18–35 years of age, confirmed ovulatory
- Assess
  - Ovarian function (follicular growth, FSH, LH, E2, P)
  - Endometrial thickness (ultrasound)
  - Cervical mucus (Insler score)
  - Return of ovulation (ibidem)
  - Sex hormone binding globulin (SHBG) and androgens

Source: Duijkers et al. (Abst 423). 14th World Congress of Gynecological Endocrinology; Florence, Italy; 2010
Duijkers et al. (Abst 426). 14th World Congress of Gynecological Endocrinology; Florence, Italy; 2010
Duijkers et al. Eur J Contracept Reprod Health Care Submitted for Publication. 2010
Mechanism of action study

Study design

<table>
<thead>
<tr>
<th>Screening</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 0</td>
<td>Cycle 1</td>
<td>Cycle 2</td>
<td>Cycle 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cycle 4</td>
<td>Cycle 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cycle 6</td>
<td>Cycle 7</td>
</tr>
</tbody>
</table>

M1: Menstruation
Ov: Ovulation

Pre-treatment
Treatment
Post-treatment

Periods of intensive TVUS and endocrine sampling:
every 3rd day, or every 2nd day in case of ovulation

Source: Duijkers et al. (Abst 423). 14th World Congress of Gynecological Endocrinology; Florence, Italy; 2010
Duijkers et al. (Abst 426). 14th World Congress of Gynecological Endocrinology; Florence, Italy; 2010
Duijkers et al. Eur J Contracept Reprod Health Care Submitted for Publication. 2010
Follicular development

Source: Duijkers et al. (Abst 423). 14th World Congress of Gynecological Endocrinology; Florence, Italy; 2010
Duijkers et al. *Eur J Contracept Reprod Health Care* Submitted for Publication. 2010
Ovulation inhibition

Source: Duijkers et al. (Abst 423). 14th World Congress of Gynecological Endocrinology; Florence, Italy; 2010

Duijkers et al. Eur J Contracept Reprod Health Care Submitted for Publication. 2010
Endometrium thickness

Source: Duijkers et al. (Abst 426). 14th World Congress of Gynecological Endocrinology; Florence, Italy; 2010
Duijkers et al. Eur J Contracept Reprod Health Care Submitted for Publication. 2010
Cervical mucus receptivity (Insler score)

Insler score incorporates amount of mucus, spinnbarkeit, ferning and cervical opening to assess quantity and quality of mucus secreted by the cervix.

Source: Duijkers et al. (Abst 423). 14th World Congress of Gynecological Endocrinology; Florence, Italy; 2010
Duijkers et al. *Eur J Contracept Reprod Health Care* Submitted for Publication. 2010
## Return of ovulation

### Post-treatment day (after last *active* tablet)

<table>
<thead>
<tr>
<th>Statistic</th>
<th>NOMAC/E2 (n=32)</th>
<th>DRSP/EE (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>20.8 ± 4.57</td>
<td>20.5 ± 3.12</td>
</tr>
<tr>
<td>Median (range)</td>
<td>20 (16–31)</td>
<td>20 (16–28)</td>
</tr>
</tbody>
</table>

Post-treatment return of ovulation in both groups: ~3 weeks after the last *active* tablet intake

Source: Duijkers et al. (Abst 423). 14th World Congress of Gynecological Endocrinology; Florence, Italy; 2010
Duijkers et al. *Eur J Contracept Reprod Health Care* Submitted for Publication. 2010
SHBG and androgens

Median change from baseline at Cycle 6

- **NOMAC/E2**
- **DRSP/EE**

* P<0.05; DHT=dihydrotestosterone; DHEAS=dehydroepiandrosterone

Source: Agren et al 14th World Congress of Gynecological Endocrinology; Florence, Italy; 2010.
Summary

- NOMAC/E2 provides consistent and robust inhibition of ovulation
- The suppressive effects of NOMAC/E2 on the ovaries are at least as strong as those of DRSP/EE
- Ovulation returned in ~3 weeks after last active tablet intake of NOMAC/E2 and DRSP/EE
- NOMAC/E2 induced an approximate 50% to 60% increase in SHBG from baseline, a change that was much smaller than that induced by DRSP/EE (>300%)
- Decreases in androgen concentrations were smaller in women who used NOMAC/E2 compared with those who used DRSP/EE
NOMAC 2.5/E2 1.5 mg [24/4]

Hemostasis study
Hemostasis

Study design

• To compare the effect of NOMAC 2.5/E2 1.5 mg and LNG 100/EE 20 µg* with respect to parameters of coagulation and fibrinolysis
• Double-blind, randomized, parallel group
• Treatment duration 3 cycles
• N=45 per group

*COCs containing 30 µg EE recommended as the standard comparator for this type of study.

Source: Gaussem et al. (Abst 550) 14th World Congress of Gynecological Endocrinology Florence, Italy; 2010.
Effects on markers of hemostasis

**Prothrombin fragment 1+2**

- **LNG/EE**
  - Mean + SEM change from baseline (nmol/L)
  - Mean: 0.10
  - SEM: 0.05
  - P-value: 0.007

- **NOMAC/E2**
  - Mean: 0.00
  - SEM: 0.05
  - P-value: NA

**D-Dimer**

- **LNG/EE**
  - Mean + SEM change from baseline (ng/mL)
  - Mean: 75
  - SEM: 25
  - P-value: <0.001

- **NOMAC/E2**
  - Mean: 50
  - SEM: 25
  - P-value: NA

**Activated Protein C resistance - normalized ratio**

- **LNG/EE**
  - Mean + SEM change from baseline (Rosing)
  - Mean: 0.60
  - SEM: 0.20
  - P-value: 0.004

- **NOMAC/E2**
  - Mean: 0.40
  - SEM: 0.20
  - P-value: NA

**Antithrombin**

- **LNG/EE**
  - Mean + SEM change from baseline (%)
  - Mean: 2
  - SEM: 4
  - P-value: 0.0007

- **NOMAC/E2**
  - Mean: -4
  - SEM: 6
  - P-value: NA

Gaussem et al. (Abst 550) 14th World Congress of Gynecological Endocrinology Florence, Italy; 2010.
Summary

- Compared with the 21-day LNG/EE pill regimen, the 24-day monophasic NOMAC/E2 pill regimen appears to have fewer effects on blood coagulation and fibrinolysis
Conclusions

- NOMAC 2.5/E2 1.5 mg [24/4]:
  - Effectively inhibits ovulation
  - Provides cycle control similar to low dose EE COCs
  - Has less hemostatic impact than low dose EE COCs
Combined Oral Contraceptives: Where we've been and where we're going

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