COMBINED ORAL CONTRACEPTIVES (COCs) FOR SOUTH AFRICAN WOMEN – NEW CHOICES, BENEFITS AND RISKS

The recent launch of a new contraceptive (Zoely) in South Africa has highlighted factors to consider when prescribing COCs to women, particularly as early sexual debut and late menopause mean that women may require contraception for up to 30 years.

Although there is already a wide choice of contraceptives available to women, there are continuing research efforts to develop COCs with reduced side-effects so as to avoid early discontinuation and to fulfil the different needs of women. As the average woman no longer has more than two children, aside from the period of trying to conceive, women may well need contraception for 28-30 years of their lives.

The principal reasons given by women for discontinuing a particular contraceptive therapy are unwanted side-effects and concern about the risk of venous thromboembolism (VTE). This has resulted in a pharmaceutical focus on reduced estrogen content and the use of more ‘physiological’ forms of estrogen. Looking for new progestogens is an additional focus.

In a presentation to South African clinicians, Diana Mansour, Consultant in Community Gynaecology and Reproductive Healthcare, Newcastle upon Tyne, UK, highlighted the requirements of future COCs (Table 1).1

“Clearly high specificity for both the estrogen and progestogen receptors (ERs and PRs) determines effectiveness of the COCs and reduces the potential for other side-effects.”

The mechanisms of action of COC components are summarised in Figure 1.

Table 1. The COC of the future

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Progestogen</th>
<th>Combination</th>
</tr>
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<tbody>
<tr>
<td>High affinity for ER</td>
<td>High affinity for PR</td>
<td>Reliable and robust efficacy</td>
</tr>
<tr>
<td>High selectivity for ER</td>
<td>High selectivity for PR</td>
<td>Monophasic dosing</td>
</tr>
<tr>
<td>Metabolically neutral</td>
<td>Strong antigonadotropic activity</td>
<td>Cycle control and predictability</td>
</tr>
<tr>
<td>Minimal haemostatic impact</td>
<td>No estrogenic effects</td>
<td>Infrequent periods/short, light periods</td>
</tr>
<tr>
<td></td>
<td>No androgenic effects</td>
<td>Neutral to positive impact on non-reproductive systems</td>
</tr>
<tr>
<td></td>
<td>No glucocorticoid effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No mineralocorticoid effects</td>
<td></td>
</tr>
</tbody>
</table>

PR = progesterone receptor; ER = estrogen receptor

Notes: FSH - follicle stimulating hormone; LH as luteinising hormone

Figure 1. The mechanisms of action of COC components

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Modernising the estrogen component of COCs
The advent of a physiological estrogen, 17β-estradiol, which has been included in the new COC, Zoely, marks a move away from ethinyl estradiol, which was the mainstay of earlier COCs. 17β-estradiol is metabolised in the liver to estrone, providing levels that are contraceptively efficient and sufficient to protect bone mineral density. This form of estradiol is highly protein bound; 17β-estradiol contrasts with ethinyl estradiol which has a higher biological activity than natural estrogen. It is metabolised slowly and has a long-half life, with low protein binding and high bioavailability. This means that women on ethinyl estradiol have higher circulating levels of estrogen than women on 17β-estradiol, increasing the risk of unwanted side-effects such as a higher risk of thromboembolic events and cerebrovascular complications.

Modernising the progestogen component
Zoely contains a third-generation progestogen, nomegestrol acetate (NOMAC), which is a selective progestogen structurally similar to progesterone. It has modest anti-adrenergic activity and does not affect lipid or carbohydrate metabolism, bone mineral density or cardiovascular parameters.4

Clinical study experience with NOMAC/17β-estradiol
Two large randomised clinical trials are relevant to the evaluation of the efficacy, cycle control, tolerability and safety of this monophasic COC pill containing 1.5mg estradiol and 2.5mg NOMAC in a 24/4 day regimen, compared to the COC combination of drospirenone and ethinyl estradiol.

In a study conducted in the USA and several Latin American countries, 2281 healthy women aged 18-50 years were allocated NOMAC/17β-estradiol in a ratio of 3:1 in a 24/4 day regimen or drospirenone 3mg/estradiol 30mg in a 21/7 regimen for 13 consecutive cycles.4

The index of clinical efficacy in pregnancy prevention (number of pregnancies divided by the number of months) is referred to as the Pearl index. In this study, the Pearl indices for the younger subset of women (18-35 years of age) were 1.3 (95% CI: 0.66-2.2) and 1.9 (95% CI: 0.69-4.11) in the study drug and comparator

Figure 2. Nomegestrol Acetate introduction
Whenever physicians interact with women regarding their contraceptive needs, the cardiovascular risk must be assessed, as it is a major killer of women today” Professor Alan Alperstein, UCT, Kingsbury Hospital, Cape Town.

“Whenever physicians interact with women regarding their contraceptive needs, the cardiovascular risk must be assessed, as it is a major killer of women today” Professor Alan Alperstein, UCT, Kingsbury Hospital, Cape Town.

groups, respectively. The one-year cumulative pregnancy rates were 1.2 and 1.8 respectively. At the end of the year of observation, 32.9% of the women in the NOMAC/17β-estradiol group reported shorter, lighter bleeding. The most common side-effects with the new COC were acne (16.4%) weight gain (9.5%) and irregular withdrawal bleeding (9.1%).

A similar study was conducted in gynaecological and/or general practices in Europe, Asia and Australia. A total of 1591 women were randomised to the NOMAC/17β-estradiol COC and 535 to a drospirenone/ethinyl estradiol COC. Pearl indices were generally lower than in the previous study and were 0.38 and 0.81 in the NOMAC/17β-estradiol and comparator group, respectively, for women under 35 years and 0.31 and 0.66, respectively, for the total population of women treated (18-50 years of age).

Prevalence of acne compared to baseline decreased over time with both treatments (Figure 3). Weight change with Zoely over the one-year study period was a 1kg increase, which was comparable with that seen in women who do not use hormonal contraception.

Venous thromboembolism (VTE) and pulmonary embolism (PE) in women using COCs

VTE and PE are major concerns with the use of various different COCs and constitute well-established, serious adverse events, although they are more likely to occur in the first year of use. Nonetheless, no reports have yet been published on the prevalence of VTE with these new COCs. However, the controversy regarding VTE and the use of COCs containing ethinyl estradiol and a new progestogen remains. Many confounding factors such as obesity, a sedentary lifestyle and smoking, among others, need to be taken into account. The introduction of new progestogens and the use of low doses of estrogen and novel estrogens are strategies that may contribute to reducing the incidence of VTE.

References
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Questions

1. The physiological hormone, 17β-estradiol has fewer haemostatic effects than ethinyl estradiol.
   - [ ] A True
   - [ ] B False

2. New Combined Oral Contraceptives (COC) concentrate on providing estrogens and progesterones that are highly specific for the respective receptors in order to reduce side-effects.
   - [ ] A True
   - [ ] B False

3. The combination of 17β-estradiol and a third-generation progestogen, nomegestrol acetate (NOMAC) does not affect lipid or carbohydrate metabolism, bone mineral density or CV risk.
   - [ ] A True
   - [ ] B False

4. Women on ethinyl estradiol have lower circulating levels of estrogen than women on 17β-estradiol.
   - [ ] A True
   - [ ] B False

5. The PEARL Index is determined by the number of pregnancies divided by the number of months of treatment and with the combination of 17β-estradiol and NOMAC, this index was lower than with ethinyl estradiol/drospirenone COCs.
   - [ ] A True
   - [ ] B False

6. The PEARL index in a larger European, Asian and Australian Study for women younger than 35 years was even lower at:
   - [ ] A 0.8
   - [ ] B 0.6
   - [ ] C 0.3

7. The average weight gain on the new COC containing 17beta-estradiol and NOMAC was:
   - [ ] A 2.5kg
   - [ ] B 2kg
   - [ ] C 1kg

8. The most common side-effects of COC’s are:
   - [ ] A Acne
   - [ ] B Weight gain/loss
   - [ ] C Irregular withdrawal bleeding
   - [ ] D All of the above

9. The prevalence of acne tends to decrease over time with the use of COC’s.
   - [ ] A True
   - [ ] B False

10. Prior to prescribing COC’s, the cardiovascular risk of the individual patient must be assessed.
    - [ ] A True
    - [ ] B False