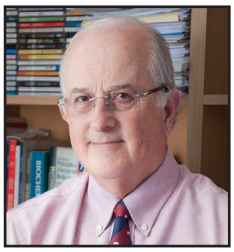
COMBINED ORAL CONTRACEPTIVES (COCS) FOR SOUTH AFRICAN WOMEN – NEW CHOICES, BENEFITS AND RISKS



Dr Diana Mansour
Consultant in Community Gynaecology and Reproductive Healthcare
Newcastle upon Tyne
United Kingdom



Professor Alan Alperstein
Department of Obstetrics and Gynaecology
University of Cape Town
Kingsbury Hospital

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.

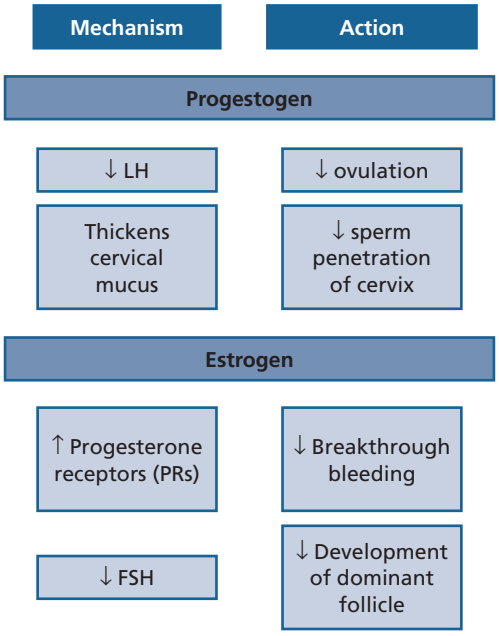
Although there is already a wide choice of contraceptives available to women, there are continuing research efforts to develop COCs with reduced side-effects so as to avoid early discontinuation and to fulfil the different needs of women.[1] As the average woman no longer has more than two children, 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[2] 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.



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

Figure 1. The mechanisms of action of COC components

Table 1. The COC of the future

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

PR = progesterone receptor; ER = estrogen receptor

This article was made possible by an unrestricted educational sponsorship from MSD, which had no control over content.

MSD Be well

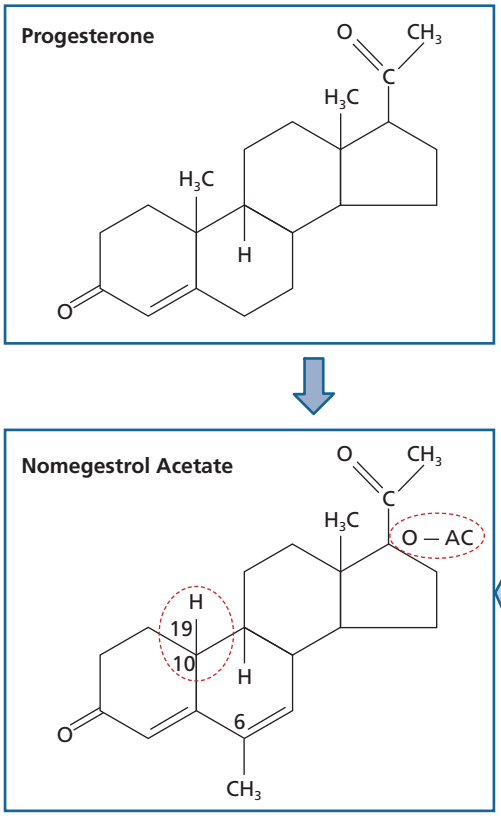
"The formulation of Zoely, which contains 17β-estradiol and NOMAC, is vascularly and metabolically neutral with no androgenic or estrogenic effects and is highly suitable for contraceptive purposes" Professor Alan Alperstein, SASOG Congress 2014, Cape Town

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.[3] (Figure 2)



- Activity similar to progesterone
- Highly selective:
  - Strong antigonadotropic activity
  - No glucocorticoid, mineralocorticoid, estrogenic or androgenic activity
- 46 hour half-life (nomegestrol acetate)

Figure 2. Nomegestrol Acetate introduction
Schindler A. *Maturitas* 2008; **61**: 171-180.

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

Earn 3 CPD points at
www.denovomedica.com
Click on 'Accredited CPD modules'.

"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.[5] 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).

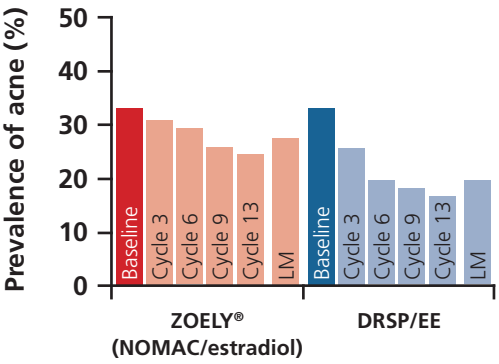
Prevalence of acne compared to baseline decreased over time with both treatments (Figure 3).[5]

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.[6, 7] 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.[1]

Prevalence of acne compared to baseline decreased over time with both treatments.



DRSP = drospirenone; EE = ethinyl estradiol; LM = last measurement.

Figure 3. SAMBA: Acne[5]

References

1. Bahamondes L, Bahamondes MV. New and emerging contraceptives: a state-of-the art review. *Int J Women's Health* 2011; **6**: 221-234.
2. Burkman R, Bell C, Sarfaty D. The evolution of combined oral contraception: improving the risk-to-benefit ratio. *Contraception 2011*; **84**: 19-34.
3. Van Dieper HA. Preclinical pharmacological profile of nomegestrol acetate: a synthetic 19-norprogesterone derivative. *Reprod Biol Endocrinol* 2012; Oct 8. 10.85 doi: 10:1186/14 77-78 27-10-85.
4. Westhoff C, Kaunitz AM, Korver T, *et al*. Efficacy, safety, and tolerability of a monophasic oral contraceptive containing nomegestrol acetate and 17β-estradiol: a randomized controlled trial. *Obstet Gynecol* 2012; **119**(5): 989-999.
5. Mansour D, Verhoeven C, Sommer W, *et al*. Efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17β-estradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen. *Eur J Contracept Reprod Health Care*. 2011; **16**(6): 430-443.
6. Lidegaard O, Nielsen LH, Skovlund CW, Lokkegaard E. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-2010. *BMJ* 2012; **344**: E2990.
7. Bitzer J, Amy JJ, Beerthuizen R, *et al*. Statement on combined hormonal contraceptives containing third- or fourth-generation progestogens or cyproterone acetate, and the associated risk of thromboembolism. *Eur J Contracept Reprod Health Care* 2013; **18**(3): 143-147.

Earn CPD points online

Visit www.denovomedica.com

Click on 'Accredited CPD modules'.

Log in or register and start earning CPD points today.

Certificates will be emailed to you.

current care.za

Disclaimer

The views and opinions expressed in the article are those of the presenters and do not necessarily reflect those of the publisher or its sponsor. In all clinical instances, medical practitioners are referred to the product insert documentation as approved by relevant control authorities.

Published by

deNovo Medica

70 Arlington Street, Everglen, Cape Town, 7550

Tel: (021) 976 0485 | info@denovomedica.com

current care.za

COMBINED ORAL CONTRACEPTIVES CPD QUESTIONNAIRE

EARN 3 CPD POINTS ONLINE

Complete and email to **info@denovomedica.com** or fax to **0866103395**. Alternatively you can complete this questionnaire online at **www.denovomedica.com**. Fill in your details on this questionnaire using **clear block letters** and mark the answers with a tick (✓)

Your CPD-accredited certificate will be forwarded to you via email.

First Name		**Surname**	
City		**Telephone**	
HPCN No.		**Profession**	
E-mail			

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, nomegesterol 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