Combination oral contraceptives – a practice-guided overview of everyday problems and their solutions

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Introduction

Combination oral contraceptives (COCs) are some of the most commonly prescribed drugs for women between the ages of 15–45¹ and while they are accepted to be safe and highly effective, their use is often associated with a number of minor side-effects. Considering the limited nature of this review, a detailed overview of the complete clinical profile of COCs falls beyond the current scope. Rather, we will focus on the most frequently reported side-effects of COCs *that do not necessitate treatment withdrawal*. Adverse effects that require immediate withdrawal of therapy are usually related to deep vein thrombosis (DVT) and other cardiovascular events, malignancies or hepatic pathology² and would require a more in-depth review.

Against this background, the following general principles and points of departure should be kept in mind:

- While COCs have initially been marketed only for the purposes of female contraception, they are also prescribed for a number of unrelated conditions, e.g. *inter alia* menstrual cycle irregularity, endometriosis, dysmenorrhoea, mood instability and acne.^{3,4}
- For most of these conditions, COCs provide symptomatic relief; they are not curative. In other words, it is likely that the pre-existing condition will resurface following treatment withdrawal.
- Long-term COC use is not associated with an increased risk for infertility. In fact, in cases where patients find it difficult to conceive, it can often be related to a condition that predated the use of COCs.⁴
- Most side-effects of COCs manifest within the initial one to three cycles of treatment. Hence, prescribers are advised that after careful selection of the appropriate formula, changes to prescriptions should preferably not be made until at least three cycles have been used, except in instances which require the immediate withdrawal of therapy.
- The two components of COCs, i.e. oestrogen and progesterone, are steroid hormones. In other words, they are highly lipid soluble and extensively bound to plasma proteins. Therefore, practitioners should be cognisant of the fact that body composition can have marked influence on the efficacy,

therapeutic outcomes and side-effect profiles associated with the use of COCs.

- While oestrogen is responsible for endometrial proliferation, progestin, irrespective of the molecule, inhibits endometrial growth and maintains the integrity of the endometrial lining. As such, where the balance in terms of physiological response is tipped in favour of the oestrogenic component, excessive endometrial proliferation and its associated side-effects can be expected and *vice versa*.
- Lower- vs. higher-dose formulations are categorised based on the oestrogen component. Considering the availability of modern formulas, lower-dose formulations are those containing 20 µg or less ethinyl oestradiol (EE), while higher-dose formulations are those that contain 30 µg or more.
- Most progestin components included in currently available COCs, e.g. gestodene and levonorgestrel, have little to no androgenic effect. Indeed, some, e.g. drospirenone, are moderate antagonists of the androgen and aldosterone receptors, the latter resulting in sodium and water excretion. That said, these molecules are also weaker agonists of the progesterone receptor and are often associated with higher incidences of breakthrough bleeding and other symptoms of inadequate cycle control.
- There is no clinical evidence to indicate the new generation, so-called 'natural' oestrogenic molecules to be of more benefit than EE.
- The placebo component included in COCs has no functional purpose other than inducing a regular menstrual cycle for the duration of treatment. In most cases, this in turn has no therapeutic value.⁵
- On the question of using mono- vs. multiphasic preparations, it suffices to argue that monophasic preparations should be the prescriber's first choice. This is because the greatest degree of therapeutic benefit can be reached with constant, and not changing, oestrogen levels.⁶ However, certain conditions, e.g. oestrogen-withdrawal-induced migraine, may benefit from multiphasic preparations and will require special consideration.
- In terms of prescribing COCs, high risk individuals include smokers older than 35 years and patients with a history of

any one of the following: complicated migraine, i.e. migraine that presents with an aura; DVT or being immobilised; existing or recent breast or hepatic carcinoma and other hepatic pathology; diabetes associated with underlying vascular pathology; and established or suspected pregnancy. Such individuals will require careful evaluation and monitoring and should be initiated on COCs only after careful consideration by a gynaecologist.

Common side-effects of COCs

Breast tenderness

Breast tenderness is a relatively common side-effect of the COCs,⁷ especially during the initial stages of treatment. Although the incidence is higher in women using the oestrogen/norelgestromin patches (Evra®)⁸ and the vaginal ring (Nuvaring®) breast tenderness can result from both oestrogenic (most commonly) and progestin stimulation as well as from water retention caused by some progestin constituents.^{7,9-11} Further, it can either manifest as a result of a sudden increase in systemic hormone concentrations, i.e. during the first week of administering the active (hormone-containing) tablets or present without cyclic variation. While breast tenderness can last up to several months in some women, sufficient interventions can be made if the condition does not resolve within the first three months of treatment.

Intervention(s):

- i. If possible, reduce the EE dose by 5–10 µg. Follow up the patient for at least two cycles and monitor for cycle irregularity. If no clinical response is seen after two cycles,
- ii. change the progestin component altogether. If an anti-aldosterone or other third generation progestin, e.g. dienogest, has been used prior to the intervention,¹² switch to a gonane, e.g. gestodene. Do the opposite if a gonane has been prescribed before.

Headaches

Attention will only be afforded here to headaches that cannot be regarded as migraine. Migraine in women treated with COCs necessitates in-depth evaluation and often requires immediate withdrawal of hormone therapy.^{13,14} However, mild to moderate headaches that are responsive to nonsteroidal anti-inflammatory and analgesic drugs (NSAIDs), e.g. aspirin and paracetamol, are one of the most frequently reported side-effects of COCs and a major driver of treatment discontinuation.¹⁵ Often, a transient change in headache frequency is observed in women following initiation of COCs due to the vasoactive properties of oestrogen, but also as a result of an altered water and electrolyte balance. In this instance, it is likely that either aldosterone-neutral or anti-aldosterone progestin components can contribute to the manifestation of headache. That said, symptoms should be alleviated by the third cycle of treatment.¹⁶

Intervention(s):

- i. Monitor for complicated migraine. If excluded, manage any change in headache activity during the first three cycles with NSAIDs.
- ii. If a multiphasic formulation has been used prior to the intervention, switch to a monophasic preparation to exclude any potential effect of changing oestrogen concentrations on the vasculature.
- iii. If changes to the headache activity persist after three cycles, change the progestin component, switching between aldosterone and anti-aldosterone formulations.
- iv. Use COCs with a shortened placebo phase¹⁷ or omit the placebo phase altogether, i.e. use active tablets every day without a hormone-free interval. In this instance, only use the placebo component every three to four cycles to lower the risk for breakthrough bleeding.

Spotting and breakthrough bleeding

Irregular bleeding is probably one of the most prominent side-effects associated with the use of most COCs. Although relatively uncomplicated, such symptoms are inconvenient and result in higher rates of treatment non-adherence. Importantly, clear distinction should be made between spotting and breakthrough bleeding as they are managed differently. Whereas spotting refers to light, intermittent bleeding after initiating patients on COC,¹⁸ breakthrough bleeding refers to more sustained periods of bleeding that occur after a few months of COC use, and which are not associated with a placebo-induced reduction in hormone concentration as is normally the case. Rather, breakthrough bleeding occurs during the active, i.e. hormone-containing phase of the cycle. Further, while spotting is normal and quite common due to the slow adaptation of the endometrial lining to an initial change in hormonal stimulation, breakthrough bleeding occurs after a prolonged time of endometrial build-up and inadequate endometrial breakdown.

Importantly and contrary to what is commonly believed, both mono- and multiphasic preparations are associated with spotting and breakthrough bleeding.^{19,20} That said, formulas containing newer generation progestins of the gonane class, e.g. gestodene and levonorgestrel, are associated with better outcomes in terms of breakthrough bleeding.²¹ It should also be noted that while some newer generation progestins, e.g. dienogest and drospirenone, present with some useful therapeutic benefit with respect to their diuretic and anti-androgenic effects, they are more often than not associated with higher incidences of breakthrough bleeding due to their weaker progestin action.²² This may especially be true in some individuals that use low-dose, extended formulas.

Intervention(s):

- i. Spotting should reduce within the first three cycles of therapy. If it persists, introduce an incremental increase in the EE concentration, e.g. switch to 20 µg from 15 µg. However, keep the strength of the progestin component the same as far as it may be possible.

- ii. In the case of breakthrough bleeding, stop treatment altogether until the bleeding stops. In the event that the bleeding does not stop within 10 days after its onset and after discontinuation of treatment, treat with oral medroxyprogesterone (10 mg per day for one week). Allow for progesterone withdrawal bleeding to occur.
- iii. In the absence of significant changes in physical activity and/or body composition since the previous initiation of COC, reinstate on either the same formula or a formula containing 5–10 µg less EE. Re-evaluate after three cycles.
- iv. Important: irregular and persistent menstrual bleeding may be indicative of an underlying uterine pathology unrelated to the use of COCs.² If symptoms persist after these interventions, further clinical investigation will be necessary.

Dysmenorrhoea

In the absence of secondary pathology, e.g. endometriosis, uterine fibroids or anatomical abnormality, dysmenorrhoea, or painful menstruation, usually arises as a function of the interaction between two main factors, i.e. the degree of endometrial proliferation and tissue necrosis prior to menstruation, and the extent to which inflammatory mediators are secreted prior to and during endometrial detachment. Endometrial necrosis normally coincides with a reduction in the oestrogen and progesterone concentration between days 25 and 28 of the menstrual cycle. This causes a reduction in endometrial nitric oxide production resulting in local vasoconstriction and ischaemia. Moreover, the reduction in progesterone facilitates a pro-inflammatory response associated with the secretion of local hormones e.g. prostaglandin E (PGE) and substance P as well as cytokines that may to a varying extent modulate and influence nociceptive pathways.²³ Further, while mediators acting on myometrial smooth muscle, e.g. PGE, are partly responsible for uterine contractions and eventual menses, a linear relationship will often also exist between the degree of necrosis, and the extent to which inflammatory mediators are secreted and pain facilitated.

With respect to the use of COCs, patients often experience symptom alleviation after two to three cycles of COC use, mainly due to the fact that most formulas contain both oestrogen and a progestin for the full duration of the active tablet phase. Hence, endometrial proliferation is kept to a minimum. However, some patients will continue to experience dysmenorrhoea even after three cycles. In this case, two useful strategies can be followed.

Intervention(s):

- i. Reduce the EE dose by 5–10 µg or increase the progestin concentration or introduce a combined approach.
- ii. Initiate NSAID therapy in divided doses according to half-life for four doses prior to the expected onset of menses. For example, if naproxen is to be used, administer a single 500–550 mg tablet every 12 hours beginning 48 hours prior to menses. In the case of mefenamic acid, use 500 mg every six hours from 24 hours prior to menses. Such approaches are often effective as they blunt and reduce the excessive secretion of inflammatory mediators which subsequently results in less pronounced uterine contractions and a lower degree of nociceptive pathway stimulation.

Conclusion

While most women will experience at least some of the side-effects and symptoms related to the use of COCs discussed in this brief review, most of these are transient in nature and can be avoided or alleviated by subtle adjustment of the therapeutic regimen.

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