Combined oral contraceptive: **Issues for current users**

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Approximately 147,000 women in New Zealand take oral contraceptives. About 80% of these women take combined oral contraceptives (COC) containing oestrogen and a progestogen.[1]

This article offers guidance for managing situations when women who are currently using COCs:

- Develop conditions which affect their suitability for COC use.
- Require other medicines that interact with COCs.
- Experience adverse effects.

A follow up visit is appropriate to measure blood pressure and assess any problems, three months after a first prescription of an oral contraceptive, and then at least yearly thereafter. Women should also be advised to return if any problems arise.[2]

Medical conditions that affect the suitability of COC use

The use of COCs must be carefully considered in certain medical conditions. The UK Medical Eligibility Criteria (UKMEC) for combined oral contraceptive use provides guidance on suitability of COCs in particular conditions (pages 28–29).[2]

Conditions that may require review of COC use

Women whose clinical condition changes while using hormonal contraception require assessment on an individual basis. It may be appropriate to discuss risks and benefits and offer alternative contraceptive methods that pose less risk.

COCs are contraindicated in migraine with aura

Combined oral contraceptives increase the risk of stroke in women who suffer from migraines with aura. COC's should therefore not be started by women of any age who suffer from migraine with aura. They should also be discontinued in women who develop migraine with aura whilst already on COC.[3] Progestogen only or non hormonal methods can be considered for these women.[3]

COCs are best discontinued if migraine without aura develops

It is usually recommended that women who develop migraine without aura following initiation of COC should discontinue use, especially women over 35 years. Progestogen only or non hormonal methods can also be considered for these women.[3]

Pre-existing migraine without aura in women less than 35 years old is not a contraindication to COC initiation.

COCs increase the risk of venous thromboembolism

Combined oral contraceptive users have a higher risk of venous thromboembolism (VTE) than non-users (see side bar).

COCs are contraindicated for women with a current or past history of VTE and best avoided for those at high risk. Risk factors include obesity, smoking, or a family history of VTE in a first degree relative younger than 45 years old.[3] Progestogen only or non hormonal methods can be used.

COC use in heavy smokers substantially increases cardiovascular risk.[3]

COCs can generally be used in women younger than 35 years who smoke, however their use is not advised in women over 35 years who smoke. Progestogen only or non hormonal methods can be used in women who smoke.

Progestogen Only Pills (POPs)

POPs available in New Zealand contain; levonorgestrel, norethisterone or desogestrel. POPs mainly work by their action on the cervical mucous, however Cerazette is different in that the mode of action is ovulation inhibition. They have less contraindications to use compared with COCs however they require much more rigid compliance and have to be taken at the same time every day (within three hours, or within 12 hours for Cerazette). Breakthrough bleeding or spotting is more common with POP use than with COCs. Androgenic side effects, such as acne, may be a problem for some women.[5]

Components of progestogen-only pills

Progestogen (micrograms)	**Brand names**
Desogestrel 75	Cerazette
Levonorgestrel 30	Microlut
Norethisterone 350	Noriday 28 Day*

*Fully funded

Risk of venous thromboembolism (VTE)[3, 4]

Circumstance	Risk of VTE per 100,000 women	Relative risk
Healthy non-pregnant women (not taking any oral contraceptive)	About five cases per year	Baseline
COC containing norethisterone (1st generation) or levonorgestrel (2nd generation)	About 15 cases per year of use	three-fold increase
COC containing gestodene or desogestrel (3rd generation)	About 25 cases per year of use	five-fold increase
Pregnancy	About 60 cases per year	12-fold increase

COCs may increase the risk of MI or stroke in the presence of multiple cardiovascular risk factors

There is weak evidence that COCs increase the risk of myocardial infarction and ischaemic stroke, however the absolute risk is still low.[3]

In women with multiple cardiovascular risk factors (e.g. older age, smoking, diabetes, hypertension, obesity or a family history of cardiovascular disease before age 50) the risk may be increased further.

COCs are best avoided in these women, however progestogen only or non hormonal methods can be used.[8]

Important drug interactions

Ethinyloestradiol and progestogens are metabolised by liver enzymes. Induction of these enzymes by certain drugs may affect the plasma concentration of contraceptive hormones. Some anti-epileptics and antibiotics are examples of drugs that may reduce the concentration of hormonal contraceptives and decrease their efficacy. Table 1 provides a list of drugs that interact with oral contraceptives. The list is not comprehensive.

Practice points for oral contraceptive interactions

Liver enzyme inducing drugs:

COCs and POPs are both affected; alternative methods of contraception may be a better choice for women using enzyme inducers long-term.

For short-term use of enzyme inducers, women taking COCs should use a 50 microgram daily dose of ethinyloestradiol and use additional precautions for the duration of treatment and for four weeks afterwards.

Antibiotics:

The antibiotics listed in the table as liver enzyme inducers should be dealt with as above. Although other antibiotics are not liver enzyme inducers, they may temporarily decrease colonic bacteria and therefore inhibit the enterohepatic circulation of ethinyloestradiol.[7] Progestogen is not affected.

Generally the evidence for this interaction is weak and often based on anecdotal reports, however because the consequences of an unwanted pregnancy can be serious the following advice is provided for all antibiotics:

Table 1: Interactions with oral contraceptives[6, 7]

Drug class	Examples	Effect	Examples that do not affect OCs
Anti-epileptics	Carbamazepine Oxcarbazepine Phenytoin Phenobarbital Primidone Topiramate	Induce liver enzymes resulting in a reduction in ethinyloestradiol and progestogen concentrations	Ethosuximide Gabapentin Lamotrigine Levetiracetam Valproate Vigabatrin
Antibiotics	Rifampicin Rifabutin	Induce liver enzymes resulting in a reduction in ethinyloestradiol and progestogen concentrations, breakthrough bleeding	No alternatives
	All other antibiotics narrow- and broad-spectrum	Potential reduction in ethinyloestradiol concentration due to effect on gut flora	

Table 2: Components of combined oral contraceptives (COC)[3, 5, 11]

Oestrogen level **Ethinyloestradiol (micrograms)**	**Progestogen** **(micrograms)**	**Brand names**
20 micrograms	Levonorgestrel 100	Loette Microgynon 20 ED
	Desogestrel 150	Mercilon 21 Mercilon 28
30 micrograms	Gestodene 75	Femodene 28 Minulet 28
	Levonorgestrel 150	Levlen ED* Microgynon 30 Microgynon 30 ED Monofeme* Nordette
	Desogestrel 150	Marvelon 21 Marvelon 28
	Drospirenone 3000	Yasmin
35 micrograms	Cyproterone 2000	Estelle 35 ED* Diane-35 ED
	Norethisterone 500	Norimin*
	Norethisterone 1000	Brevinor 1/21* Brevinor 1/28*
50 micrograms	Levonorgestrel 125	Microgynon 50 ED*
Phasic 30/40/30	Levonorgestrel 50/75 /125	Trifeme 28* Triphasil 28 Triquilar ED
Mestranol† 50 micrograms	Norethisterone 1000	Norinyl 1/28

* Fully funded

† Mestranol is converted in the liver to ethinyloestradiol; 50 micrograms of mestranol is pharmacologically equivalent to 35 micrograms of ethinyloestradiol.[8]

Women on short courses (less than three weeks) of antibiotics should be advised to use additional precautions during the course and until seven consecutive active pills have been taken after antibiotics have been discontinued. This may require missing the inactive pills or the pill-free week.

It is thought that gut flora develop resistance to non-enzyme inducing antibacterials after three weeks of treatment and for this reason additional precautions are not required after this time.[6]

Minor adverse effects

Most COCs contain the same oestrogen (ethinyloestradiol) and for that reason the properties of individual products are based on the amount of ethinyloestradiol in the tablet along with the varying properties of the progestogen (Table 2).

The activity of various progestogens is largely based on animal experiments and how this applies to humans is largely unknown. The dose is often adjusted to make different progestogens approximately equivalent in terms of their activity and for these reasons there is some debate about whether different progestogens are better or worse in terms of side effects or clinical responses.[9]

There is limited clinical evidence to guide pill changes when women experience adverse effects on a particular pill; however there are some principles that may guide choice (Table 3). Often a change in COC type can help to improve some adverse effects as long as it does not increase the risk of more serious medical conditions. Many side effects are commonly experienced in the first three months and may subside after this time therefore it is best to try a particular pill for at least three cycles before switching.[5, 9]

Level of oestrogen affects side effect profile

COCs contain 20–50 micrograms of ethinyloestradiol; 20 micrograms being considered low-strength, 30–40 micrograms standard-strength and 50 micrograms high-strength.

Generally, advice at present is to start with a standard dose pill and a first or second generation progestogen (lower VTE risk) e.g. Levlen, Monofeme or Norimin. These pills are fully funded and cost $3 for six months supply.

GPs may favour using the lowest effective dose of ethinyloestradiol as it would theoretically carry a lower risk of adverse effects associated with oral contraceptive use such as thrombosis or myocardial infarction.

Authors of a Cochrane review compared lower- versus higher-dose oestrogen for contraception. While they could not detect differences in rare adverse effects or contraceptive effectiveness they found lower-dose oestrogen COCs resulted in higher rates of bleeding pattern disruptions and early trial discontinuation.[10]

High-strength preparations containing 50 micrograms of ethinyloestradiol are generally used only in situations

Note on Yasmin

Yasmin contains ethinyloestradiol and the relatively new progestogen, drospirenone. Drospirenone is an analogue of spironolactone therefore caution is required in women with renal impairment or those taking potassium-sparing drugs because there is potential for hyperkalaemia.[3] There is also limited data on VTE risk, however some evidence suggests that the risk of VTE is comparable to that of other COCs (e.g. levonorgestrel)

Yasmin is claimed to have beneficial effects on acne, treating premenstrual syndrome, and less weight change however there is limited evidence of clinically significant advantages over other standard strength COCs.[4, 9] In New Zealand, Yasmin is not funded and would cost a patient approximately $20/month.

Table 3: Combined oral contraceptive adverse effects and potential solutions[3, 5, 10]

Adverse effect	Action needed	Pill Suggestions
Acne	Increase oestrogen Reduce progestogen or change to less androgenic progestogen	Marvelon Femodene Yasmin Estelle 35 ED* Mercilon
Amenorrhoea	Increase oestrogen Decrease progestogen	Norimin* Brevinor-1*
Breakthrough bleeding • Early to mid cycle	Increase oestrogen	Levlen*, Monofeme*, Microgynon 30 Marvelon
• Late cycle	Increase progestogen or change type	Femodene Trifeme*, Triphasil, Triquilar
Breast soreness	Decrease oestrogen Decrease progestogen	Loette, Microgynon 20 Mercilon
Depression, moodiness or irritability	Decrease progestogen	Norimin* Loette, Microgynon 20 Trifeme*, Triphasil, Triquilar
Headache in pill-free week	Tri-cycle pills (skip two pill-free weeks in every three months)	
Menstrual cramps	Increase progestogen or tri-cycle pills	
Nausea	Decrease oestrogen	Loette, Microgynon 20 Mercilon
Weight gain	Decrease oestrogen Decrease progestogen	Loette, Microgynon 20 Mercilon

* Fully funded

where the bioavailability of ethinyloestradiol will be reduced, for example in women who are concomitantly taking enzyme-inducing drugs.[2]

Type of progestogen may affect side effect profile

A Cochrane review that compared various progestogens in COCs found that second and third generation progestogens were preferred to norethisterone (first generation) across all acceptability indices they measured including; effectiveness (pregnancy rates), discontinuation rates, reasons for discontinuation, cycle control, and side effects. It also found that gestodene has comparable contraceptive effectiveness to levonorgestrel and desogestrel and that drospirenone is similar to desogestrel.[12]

The newer progestogens, gestodene and desogestrel are associated with a slightly increased absolute risk of VTE compared with levonorgestrel or norethisterone. Cyproterone acetate has a higher risk and is not generally recommended unless the woman has androgenic features such as acne and hirsutism or polycystic ovary syndrome (see page 12).

Switching COCs

When switching COCs containing different progestogens, the new COC should be started the day after the last active pill has been taken from the previous COC. For 28 day packs, this will mean missing out the seven inactive pills. If a seven-day break is taken before starting the new brand then additional precautions will be required until seven active pills have been taken.

Summary

COCs are generally safe, however their use may need review in some situations.

Medical conditions may arise where a COC is no longer suitable and is best discontinued or the experience of adverse effects may require a trial of a different COC. Drug interactions may affect COC efficacy and additional precautions may be required.

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UK Medical Eligibility Criteria (UKMEC) for combined oral contraceptive use[2]

UKMEC Category 1 – Unrestricted Use

Age – menarche to <40 years

Parity – nulliparous and parous

Breastfeeding – >6 months postpartum

Postpartum – >21 days if not breastfeeding

Post-abortion – immediately first and second trimester, and post-septic

Past ectopic pregnancy

History of pelvic surgery

Minor surgery without immobilisation

Varicose veins

Non-migrainous headaches – mild or severe

Epilepsy – and not using liver enzyme-inducers

Depressive disorders

Vaginal bleeding – unsuspicious irregular, heavy or prolonged

Endometriosis

Benign ovarian tumour

Severe dysmenorrhoea

Gestational trophoblastic neoplasia – when hCG is normal

Cervical ectropion

Breast disease – benign breast disease or a family history of breast cancer

Endometrial or ovarian cancer

Uterine fibroids – with or without distortion of the uterine cavity

PID – current; or past history of, with or without subsequent pregnancy

STI – current, vaginitis or increased risk of STI

HIV/AIDS – risk of HIV/AIDS, current HIV not using antiretroviral therapy

Schistosomiasis, pelvic and non-pelvic tuberculosis, malaria

Diabetes – history of gestational disease

Thyroid disorders

Viral hepatitis – carrier

Anaemias – thalassaemia, iron deficiency

Raynaud's disease – primary without lupus anticoagulant

UKMEC Category 2 – Benefits generally outweigh risks

Age – ≥40 years[a]

Breastfeeding – between 6 weeks and 6 months postpartum and partially breastfeeding (medium to low)

Smoking – aged <35 years, or aged ≥35 years and stopped smoking ≥1 year ago

Obesity – BMI ≥30–34 kg/m2

History of high blood pressure during pregnancy

Family history of VTE in a first-degree relative aged ≥45 years

Major surgery without prolonged immobilisation

Superficial thrombophlebitis

Known hyperlipidaemias – e.g. common hypercholesterolaemia or familial combined hyperlipidaemia

Valvular and congenital heart disease – uncomplicated

Migraine headaches – without aura in women aged <35 years

Vaginal bleeding – suspicious for serious condition before evaluation

CIN and cervical cancer

HIV/AIDS – current HIV using antiretroviral therapy, or current AIDS and using HAART

Diabetes – NIDDM and IDDM, non-vascular disease

Gallbladder disease – asymptomatic or treated with a cholecystectomy

History of cholestasis – pregnancy-related

Inflammatory bowel disease

Sickle cell disease

Raynaud's disease – secondary without lupus anticoagulant

Non-liver enzyme-inducing antibiotics

Highly active antiretroviral therapy (HAART)

UKMEC Category 3 – Risks generally outweigh benefits[b]

Breastfeeding – between 6 weeks and 6 months postpartum and fully or almost fully breastfeeding

Postpartum – <21 days postpartum

Smoking – aged ≥35 years and smoking <15 cigarettes per day, or stopped smoking <1 year ago

Obesity – BMI 35–39 kg/m2

Cardiovascular disease – multiple risk factors for arterial cardiovascular disease

Hypertension – elevated blood pressure >140 to 159 mmHg systolic or >90 to 94mmHg diastolic

Family history of VTE in a first-degree relative aged <45 years

Immobility (unrelated to surgery) – e.g. wheelchair use, debilitating illness

Known hyperlipidaemias – e.g. familial hypercholesterolaemia

Migraine headaches – without aura in women aged ≥35 years; or a past history of migraine with aura at any age

Breast disease – past history of breast cancer and no evidence of recurrence for 5 years; carriers of known gene mutations associated with breast cancer (e.g. BRCA1); undiagnosed mass

Diabetes – with nephropathy/retinopathy/neuropathy; or other vascular disease or diabetes of >20 years' duration (category given will depend on disease severity)

Gallbladder disease – symptomatic medically treated or current

History of cholestasis – past COC-related

Cirrhosis – mild compensated disease

Drugs which induce liver enzymes – e.g. rifampicin, rifabutin, St John's Wort, griseofulvin and certain anticonvulsants (i.e. phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)

UKMEC Category 4 – Unacceptable health risk and should not be used

Breastfeeding – <6 weeks postpartum

Smoking – aged ≥35 years and smoking ≥15 cigarettes per day

Obesity – BMI ≥40 kg/m2

Cardiovascular disease – multiple risk factors for arterial cardiovascular disease

Hypertension – blood pressure ≥160 mmHg systolic and/ or ≥95 mmHg diastolic; or vascular disease

VTE – current (on anticoagulants) or past history

Major surgery with prolonged immobilisation

Known thrombogenic mutations

Current and history of ischaemic heart disease

Stroke

Valvular and congenital heart disease – complicated by pulmonary hypertension, atrial fibrillation, history of subacute bacterial endocarditis

Migraine headaches – with aura at any age

Gestational trophoblastic neoplasia – when hCG is abnormal

Breast disease – current breast cancer

Diabetes – with nephropathy, retinopathy, neuropathy or other vascular disease, or diabetes of >20 years' duration (category given will depend on disease severity)

Viral hepatitis – active disease

Cirrhosis – severe decompensated disease

Liver tumours – benign and malignant

Raynaud's disease – secondary with lupus anticoagulant and thus a tendency to thrombosis

a Age ≥40 years: women may use COC until age 50 years if there are no medical contraindications.

b Definition of UKMEC 3 – the risks generally outweigh the benefits but the method can be considered for use with clinical judgement and/ or specialist referral if other methods are unacceptable.

AIDS, acquired immune deficiency syndrome; **BMI**, body mass index; **CIN**, cervical intraepithelial neoplasia; **HAART**, highly active antiretroviral therapy; **hCG**, human chorionic gonadotrophin; **HIV**, human immunodeficiency virus; **IDDM**, insulin-dependent diabetes; **NIDDM**, non-insulin-dependent diabetes; **PID**, pelvic inflammatory disease; **STI**, sexually transmitted infection; **TB**, tuberculosis; **VTE**, venous thromboembolism.