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**REVIEW**

*This review is intended as an educational exercise and reports the personal views of the authors*

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## Hormonal contraception and migraine

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### How to use a FACT

A FACT is an up-to-date review of a subject relevant to the speciality, intended to help you fulfil your CPD requirements in your home or place of work. Whilst FACTs are edited and reviewed at various levels within the Faculty, the actual contents and views expressed are those of the authors and not the Faculty. More specifically, these reviews are not guidelines. The CEC is producing clinical guidelines separately.

FACTs have three sections: a review, a true/false test, and discussion points. To use a FACT to earn CPD credits you should do the following:

1. **Working alone:** Read the review and do the test on page 52. The answers are provided on page 59 so you can mark yourself. If there are points you are unsure about, disagree with, or need further clarification on, make a note of these for use at a later date. This should take you no more than 1 hour. Keep a record of having done this in your CPD diary and, unless indicated otherwise on the FACT, this will earn you 1 hour (DFFP), 1 credit (MFFP).
2. **Working as a group:** arrange a meeting of at least 1 hour with colleagues to discuss the discussion points given in the FACT (page 52) and any issues the participants have come up with as a result of reading the FACT. Keep a record of having done this in your CPD diary and, unless indicated otherwise on the FACT, this will earn you 1 hour (DFFP), 1 credit (MFFP).

### Introduction

For most women, combined oral contraceptives (COCs) are a safe and highly effective method of contraception with added non-contraceptive health benefits. However, current recommendations from the Faculty of Family Planning identify subgroups of women, including those with migraine with aura, who should not be prescribed COCs in view of additional stroke risk.<sup>1</sup> This is because, although the incidence of ischaemic stroke is very low in women of reproductive age, it is increased in women with migraine, particularly if they also take COCs.

### Migraine

Migraine is an episodic headache disorder. It affects 25% of women at some time in their lives, compared with only 8% of men.<sup>2</sup> Despite this high prevalence, migraine remains under-diagnosed and under-treated. The two main types of migraine are migraine without aura (known previously as simple or common migraine) accounting for approximately 70% of attacks and migraine with aura (previously focal or

classic migraine) accounting for approximately 30% of attacks.<sup>3</sup> Migraine headache is typically severe, mostly unilateral and pulsating in quality. Headache lasts 4-72 hours and may be accompanied by nausea, vomiting, photophobia and/or phonophobia. Migraine with aura is preceded by neurological symptoms such as visual or sensory disturbance. Some patients experience both types of migraine.

### Diagnosis of migraine aura

The aura comprises focal neurological symptoms, which usually precede and resolve before onset of migraine headache and associated symptoms.<sup>3</sup> Aura should not be confused with prodromal symptoms such as hyper- or hypo-activity, depression, food cravings or repetitive yawning, which may occur in the day or two preceding any type of migraine attack.

Accurate diagnosis of migraine aura is essential for the safe prescribing of COCs. Visual aura is the most common symptom, occurring in 99% of auras.<sup>4</sup> Aura can be identified by asking "Have you ever had visual disturbances

lasting 5-60 minutes followed by headache?"<sup>5</sup> However, not all visual disturbances reported by migraine sufferers are aura. A migrainous scotoma is typically a bright spot, which may gradually increase in size to the shape of a letter 'C', developing scintillating edges that appear as 'zigzags' (fortification spectra). The aura usually starts at or near the centre of fixation, gradually spreading laterally, increasing in size over a period of 5-60 minutes. Generalised 'spots before the eyes', 'flashing lights', blurring of vision, or photophobia of variable duration before or with headache often occur during migraine and are not suggestive of focal ischaemia.

Sensory symptoms are less common and nearly always occur in association with visual aura. They have a unilateral distribution, affecting one arm and spreading over several minutes to affect the mouth and tongue. This 'cheiro-oral' distribution is characteristic of migraine.<sup>6</sup>

Migraine aura should also be distinguished from transient ischaemic attacks. The most important features from the history are the character, progression, distribution and duration of symptoms (Table 1).

### COCs and ischaemic stroke

Combined oral contraceptives are a risk factor for ischaemic stroke, the risk related to the dose of oestrogen. There is no difference in the ischaemic stroke risk between low-dose COCs (< 50 µg ethinylloestradiol) that contain second generation progestogens and those that contain third generation progestogens.<sup>7,8</sup>

The association between use of oral contraceptives and risk of ischaemic stroke was established in studies from Europe and the USA during the 1960s and 1970s. Since then the dose of oestrogen and progestogen in COCs has progressively decreased, associated with reduction in the risk of ischaemic stroke.

The 1975 Collaborative Group Study demonstrated a four-fold increase in the risk of stroke in COC users of pills containing 350 µg ethinylloestradiol compared to non-users, which was independent of other risk factors.<sup>9</sup>

Lidegaard studied all 794 Danish women aged 15-44 who had suffered a cerebral thromboembolic attack during 1985-89 and 1588 age matched controls.<sup>10</sup> Odds ratios for risk of ischaemic stroke were 2.9 (95% CI 1.6 to 5.4), 1.8 (95% CI 1.1 to 2.9) and 0.9 (95% CI 0.4 to 2.4) for 50 µg, 30-40 µg and progestogen-only preparations, respectively. It was concluded that COCs were still associated with increased risk of ischaemic stroke although the risk decreased with lower dose COCs and was not demonstrable with progestogen-only pills. Interestingly, the relatively

high numbers of 'never users' of COCs may suggest that a more carefully selected population was using COCs in Denmark in the late 1980s.

The WHO Collaborative Study of 1996 was an international multicentre case-control study of stroke in women aged 20-44 years.<sup>11</sup> A three-fold increase in risk of ischaemic stroke was demonstrated in COC users overall (OR 2.93 [95% CI 2.15 to 4.00]). However, odds ratios were less raised in younger women, non-smokers and those women who had had their blood pressure checked. COC users with a history of hypertension increased their risk of ischaemic stroke by at least 10-fold (OR 10.7 [95% CI 2.04 to 56.6]).

### Migraine and risk of ischaemic stroke

Migraine has been identified as an independent risk factor for ischaemic stroke. Lidegaard found an odds ratio of 2.8 (95% CI not reported) for risk of cerebral thromboembolic events in women with migraine compared to a control population of women without migraine and not using COCs.<sup>12</sup>

Several different mechanisms might cause ischaemic stroke in migraine sufferers. Migraine aura is associated with a regional reduction in cerebral blood flow, which may fall below the ischaemic threshold.<sup>3</sup> Platelet activation occurs during acute migraine attacks and may predispose to vascular occlusion.<sup>13</sup> Dehydration from nausea and vomiting could predispose to cerebral vascular thrombosis.<sup>13</sup> The International Headache Society (IHS) classification recognises that the pathophysiology of the migraine itself may lead to ischaemic stroke - so called 'migrainous infarction'.<sup>3</sup>

Sub-analysis from two different case-control studies of stroke in men and women have shown that the association between migraine and risk of ischaemic stroke is limited to young women under age 45, the risk being greater for migraine with aura than migraine without aura.<sup>14,15</sup>

From a case-control study Tzourio et al reported significant ORs of 3.0 (95% CI 1.5 to 5.8) in migraine without aura, 6.2 (95% CI 2.1 to 18.0) for migraine with aura.<sup>16</sup> Carolei et al reported ORs of 1.0 (95% CI 0.5 to 2.0) in migraine without aura and 8.6 (95% CI 1 to 75) in migraine with aura.<sup>15</sup>

More recently, Chang et al published a case-control study of self-reported headache in 291 women aged 20 to 44.<sup>17</sup> OR for ischaemic stroke was 2.97 (95% CI 0.66 to 13.5) in women with migraine without aura and 3.81 (95% CI 1.26 to 11.5) in migraine with aura.

Although all three studies show an increased risk in migraine with aura, there is debate about the extent and significance levels of this, which may in part be due to differences in study design.

**Table 1** Distinguishing migraine aura from transient ischaemic attacks (TIA)

	TIA	Migraine aura
History	No previous episodes	May have had similar attacks in the past
Onset and progression of symptoms	Sudden (seconds) and unilateral	Slow evolution over several minutes
Duration	> 1 hour	< 1 hour (typically 20-30 mins)
Timing	Occurs with or without headache, with no temporal relationship	Usually precedes and resolves before onset of typical migraine headache
Visual symptoms	negative (dark) scotoma (amaurosis fugax)	Homonymous positive (bright) scotoma affecting both eyes (but often perceived as unilateral) developing into fortification spectra
Sensory/motor symptoms	May occur without visual symptoms May include leg Negative (limb feels 'dead')	One-third auras - usually in association with visual symptoms Rarely affects leg Positive ('pins and needles')
Headache	25% may have headache but symptoms continue with headache	Migraine headache and associated symptoms typically follow resolution of aura. Aura may occur without headache, but confirm past history of migraine with or without aura

The studies by Tzourio et al and Chang et al also identified smoking as an independent risk factor for ischaemic stroke in women with migraine (ORs 10.2 [95% CI 3.4 to 29.2] and 7.39 [95% CI 2.1 to 25.5], respectively).<sup>16,17</sup>

### Ischaemic stroke in women with migraine taking COCs

The Collaborative Group Study was the first to identify a higher risk of ischaemic stroke in COC users who also had migraine (RR 5.9 [95% CI 2.9 to 12.2]).<sup>9</sup> The study is open to criticism since accepted diagnostic criteria for migraine were not published until 1988.<sup>3</sup> Lidegaard reported an OR of 5.0 (95% CI not reported) for women with migraine taking COCs compared to population controls without either risk factor.<sup>12</sup> Tzourio et al reported an OR of 13.9 (95% CI 5.5 to 35.1) for women with migraine who took COCs compared to hospital controls.<sup>16</sup> Chang et al reported an OR for ischaemic stroke of 16.9 (95% CI 2.72 to 106) for women with migraine using all COCs compared to hospital controls, although the OR was lower in women using COCs containing < 50 µg ethinylloestradiol (OR 6.59 [95% CI 0.79 to 54.8]).<sup>17</sup> This study also highlighted the synergistic effects of multiple risk factors with an OR of 34.4 (95% CI 3.27 to 361) for ischaemic stroke in migraineurs who smoke and use COCs. It is worth noting that the wide range and large values given for confidence intervals reflects the small number of incidents of ischaemic stroke.

To date, no study has been able to assess the separate risks associated with migraine with aura and migraine without aura in COC users, because the low absolute risk of ischaemic stroke in this population results in numbers too small for sub-group analysis.

Despite the strong association, migraine may only be a risk factor for ischaemic stroke in women whose migraine is a symptom of an unidentified predisposing condition for stroke. For example, many of the cases in the Tzourio study had underlying pathology, and controls did not undergo the same investigations.<sup>17</sup>

### Implications of these findings

Because ischaemic stroke is rare in women of reproductive age, the odds ratios should be interpreted in the context of absolute risk. In Europe annual incidence rates range from one to three per 100 000 for all women younger than 35, rising to 10 per 100 000 in all women over 35.<sup>11</sup> However, given that the expected incidence of ischaemic stroke in women with migraine with aura taking a low dose COC may be around 10 times higher than that of a woman of the same age without migraine and not using COCs, increasing age is significant when considering risk in relation to this minority group of women (Table 2).<sup>18</sup>

A headache history should be included in the standard assessment prior to commencing COCs. Accurate diagnosis of migraine and aura is essential. Healthcare professionals should be aware of the significance of migraine at initial COC prescription, and should ask about headache at every follow-up. Women with migraine should receive clear advice about the symptoms that should be reported promptly. A wide range of effective alternatives is available for women for whom ethinylloestradiol is contraindicated. Assessment of risk factors such as smoking or hypertension is mandatory for all women taking COCs, but is especially important for those with migraine.

### What are the absolute contraindications to COC use in women with migraine?

Contraindications for the use of COCs in women with migraine are based on the above limited evidence and on

**Table 2** Expected incidence of ischaemic stroke (strokes per 100 000 women per year)

Age	Women without migraine		Women with migraine with aura		
	Overall	No COC use	COC use	No COC use	COC use
15-19	0.6	0.4	0.8	2	5
20-24	1.8	1.4	3	8	16
25-29	2.7	1.9	4	11	23
30-34	3.3	2.4	5	14	29
35-39	4.8	3.4	7	20	41
40-44	16.2	11.6	23	70	139

From reference 18

expert opinion. These recommendations are intended to enable the majority of women with migraine to use COCs safely with minimal risk of ischaemic stroke, while protecting the minority at increased risk. These contraindications apply whether the conditions are present before starting COCs, or arise during COC use.

1. Migraine with aura in which there are focal neurological symptoms preceding the headache onset.<sup>1</sup>
2. Migraine without aura in a woman who has a history of more than one additional risk factors for stroke<sup>1</sup> (Table 3). Presence of multiple risk factors reflects the need for more caution.<sup>19</sup> In clinical practice, this often contraindicates COC use. For instance a 35-year-old woman should not be prescribed COCs if she smokes. A 35-year-old woman with migraine without aura might only be prescribed COCs if the history excludes other additional risk factors.
3. Severe migraine/‘status migrainosus’: attacks of migraine, which are unusually severe, lasting longer than 72 hours despite treatment.<sup>1</sup>
4. Migraine treated with ergot derivatives.<sup>1</sup>

**Table 3** Risk factors for ischaemic stroke<sup>1</sup>

Age 35 and over
Diabetes mellitus
Close family history of arterial disease under 45 years
Combined oral contraceptives
Hyperlipidaemia
Hypertension
Migraine
Obesity (BMI > 30)
Smoking

### In what situations should the COC be used with caution in women with migraine?

COCs may be used with caution in a woman with migraine without aura who has a history of one additional risk factor for stroke, which does not in itself contraindicate COC use. Particular caution is advised for women with migraine who smoke, due to evidence of the increased risk of ischaemic stroke.<sup>16,17</sup> Such women might better be advised to switch to a progestogen-only or non-hormonal method.

### What are the alternatives when COCs are contraindicated?

The good news is that all progestogen-only contraceptives (progestogen-only pill [POP]; Depo-Provera; implants; and intra-uterine system [IUS]); can be used by all women with any type of migraine as they are not associated with an increased risk of ischaemic stroke.<sup>10,20,21</sup> Women can be changed from the COC to progestogen-only methods immediately, even during a migraine attack. However, younger women (< 35) should be counselled about the small

reduction in contraceptive efficacy in switching to the POP. If appropriate, non-hormonal methods could be considered.

### Emergency contraception (postcoital contraception)

The progestogen-only method is now recommended as the first choice for emergency contraception in all women, since a trial comparing levonorgestrel with the combined hormonal emergency contraception method showed that the former is more effective in preventing conception and is better tolerated.<sup>22</sup> Unlike combined hormonal emergency contraception, the progestogen-only method is not contraindicated for women presenting during an attack of migraine with aura.

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### Discussion points

- What tools could be developed in order to help diagnose migraine quickly and correctly during a family planning consultation?
- What do you do when you are not sure whether the patient has migraine with aura or not?
- Should women with migraine without aura and a single risk factor for ischaemic stroke be withheld COCs?
- What do you do when a patient in whom you have identified migraine with aura is adamant that she does not want to stop COCs?
- Should women with migraine always be referred to a doctor for prescription of COCs?

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QUESTION SHEET

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## Hormonal contraception and migraine

Indicate your answer by ticking the appropriate box for each question

	True	False
1. The risk of ischaemic stroke is reduced with low dose COCs (< 350 µg ethinylloestradiol) compared to high dose COCs (> 350 µg ethinylloestradiol)	<input type="checkbox"/>	<input type="checkbox"/>
2. Low-dose COCs may be prescribed safely to smokers over the age of 35.	<input type="checkbox"/>	<input type="checkbox"/>
3. The expected incidence of ischaemic stroke in women with migraine with aura taking a low dose COC is more than 10 times higher than the expected incidence of ischaemic stroke in women of the same age without migraine and not using COCs.	<input type="checkbox"/>	<input type="checkbox"/>
4. Smoking is not a significant risk factor for ischaemic stroke in women with migraine.	<input type="checkbox"/>	<input type="checkbox"/>
5. All young women with migraine are at high risk of ischaemic stroke.	<input type="checkbox"/>	<input type="checkbox"/>
6. COCs may be used with caution in a woman with migraine with aura if she has no more than one additional risk factor for stroke.	<input type="checkbox"/>	<input type="checkbox"/>
7. Depo-Provera should not be used by a woman who suffers from migraine with aura.	<input type="checkbox"/>	<input type="checkbox"/>
8. COCs containing third generation progestogens are associated with a lower risk of ischaemic stroke compared to COCs containing second generation progestogens.	<input type="checkbox"/>	<input type="checkbox"/>
9. Depression and food cravings are typical symptoms of migraine aura.	<input type="checkbox"/>	<input type="checkbox"/>
10. The evolution of migraine aura is slow, taking several minutes to spread to maximum distribution.	<input type="checkbox"/>	<input type="checkbox"/>

Turn to page 59 for answers