

# Migraine and use of combined hormonal contraceptives: a clinical review

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## Overview

Headache is a common condition affecting the majority of women at some time in their lives. Epidemiological studies of migraine also confirm that up to one-third of women will experience migraine, particularly during their fertile years. Studies suggesting that migraine in young women is associated with an increased risk ischaemic stroke have led to particular concerns regarding the additional effect of other risk factors such as use of combined oral contraceptives (COCs).

This paper reviews the effect that COCs have on headache and migraine and considers the data on the risk of ischaemic stroke in COC users with migraine. This evidence will be used to support practical guidance on the management of women with migraine wishing to use COCs.

Whilst the evidence presented is based on studies of COCs, there is no evidence to suggest that the effects of other combined hormonal contraceptives (CHCs) are any different. Until further data are available on the different routes of delivery, the following recommendations apply to all CHCs.

## Search strategy

A MEDLINE search from 1950 to April 2007 using the search terms 'headache', 'migraine', 'contraception', 'ethinyl(o)estradiol', 'progesterone', 'progesterone', '(o)estrogen', '(o)estradiol' and 'isch(a)emic stroke' identified 272 publications, which were scrutinised for relevancy to this review.

In addition, references from the author's own files, a hand-search of the journals *Cephalalgia* and *Headache*, and peer-reviewed presentations at international congresses were considered.

## Effect of COCs on headache

Headache is a common condition in the absence of COC use. In order to assess its true relationship to COCs, baseline assessment and placebo-controlled trials are necessary.

Studies reviewing headache over time suggest that initial exacerbation in the early cycles of use is followed by resolution with continued use.<sup>1-3</sup> If headache occurs, it is most likely to be during the hormone-free interval.<sup>4-6</sup>

Of 3679 women starting COCs for the first time, using 20 µg ethinylestradiol (EE) and 150 µg desogestrel, 36% reported headache at baseline.<sup>2</sup> After three cycles, 14% reported that headache had worsened, 57% reported improvement and 28% reported no change. New onset of headache affected only 0.5%.

In a study of 3267 women starting a COC containing 30 µg EE and 75 µg gestodene, 46% were first-time COC

users and 54% were switching from another brand.<sup>3</sup> Of the 16% of women with headache at baseline, 63% reported improvement over the 18-cycle study. New onset of headache was reported by 8.8% of women in cycles 1 to 3, 3.9% in cycles 4 to 6, 3.9% in cycles 10 to 12, and 2% in cycles 16 to 18. There was no analysis of new users versus switchers.

In addition, frequency of headache may depend on the type of progestogen and the dose of oestrogen used. Studies of COCs containing 30 µg EE and levonorgestrel (a second-generation progestogen) note headache in approximately 10% of all cycles.<sup>7</sup> It might appear that use of COCs containing third-generation progestogens is associated with less headache, as a review of studies using COCs containing 30 µg EE and 150 µg desogestrel found headache affected only 5% of women during the sixth cycle.<sup>8</sup> However, this could be accounted for by differences in study design as other studies have not found any differential effect between progestogens in COCs.<sup>9-11</sup>

Dose of EE may be relevant as fewer than 2% of women using 20 µg EE and 150 µg desogestrel reported headaches by the sixth cycle.<sup>12</sup>

## Effect of COCs on migraine

Few studies have specifically assessed migraine in COC users. The majority of publications assess high-dose COCs containing at least 50 µg EE and predate the International Headache Society (IHS) diagnostic criteria. Migraine improves in a significant proportion of women and many report no change in migraine frequency or severity.<sup>13-20</sup>

As with headache, migraine – typically without aura – occurs during the hormone-free interval.<sup>18-22</sup> In a retrospective study of patients on COCs with unwanted withdrawal symptoms (35% reporting headache as a symptom), almost all side effects of COCs were found to be significantly worse during the 7-day hormone-free interval compared to the 21 days of pill-taking.<sup>23</sup> Changing the pattern to longer continuous periods with hormones reduced symptoms overall but they still occurred in the hormone-free period. Such symptoms result from withdrawal of EE, similar to the oestrogen 'withdrawal' mechanism for menstrual migraine.<sup>24</sup>

The prevalence of headache and migraine among women using COCs was examined in a large, cross-sectional population-based study in Norway of 13 944 women.<sup>25</sup> There was a significant association between use of COCs and migraine [30 µg EE, odds ratio (OR) 1.4, 95% CI 1.2-1.8,  $p < 0.001$ ] and for non-migrainous headache (30 µg EE, OR 1.2, 95% CI 1.0-1.4,  $p = 0.025$ ). In contrast, there was no significant association between progestogen-only pills and migraine (OR 1.3, 95% CI 0.9-1.8,  $p = 0.156$ ) or non-migrainous headache (OR 1.0, 95% CI 0.8-1.3,  $p = 0.1$ ).

A clinic-based case-control study reviewed 39 women with migraine with aura and 83 women with migraine without aura who had used COCs.<sup>26</sup> Migraine with aura was reported as worsening in 56.4% of cases compared to 25.3% of women with migraine without aura (OR 3.8, 95% CI 1.6-9.3). There was no change in 38.5% of women with migraine with aura compared to 67.5% of women with migraine without aura (OR 0.3, 95% CI 0.1-0.7). Improvement was reported by 5.1% of women with

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**Table 1** Effect of migraine on risk of ischaemic stroke

Study	Study design	Sample size on which OR based	All migraine [OR (95% CI)]
Tzourio <i>et al.</i> (1993) <sup>27</sup>	Case-control	20 cases, 20 controls age <45 years	4.3 (2.1–16.3)
Tzourio <i>et al.</i> (1995) <sup>28</sup>	Case-control	72 cases, 173 controls age <45 years	3.5 (1.8–6.4)
Carolei <i>et al.</i> (1996) <sup>35</sup>	Case-control	39 cases, 43 controls age <45 years	1.9 (1.1–3.1) 3.7 (1.5–9.0) age <35 years
Chang <i>et al.</i> (1999) <sup>40</sup>	Case-control	71 cases, 88 controls age <45 years	3.54 (1.30–9.61)
Lidegaard and Kreiner (2002) <sup>32</sup>	Case-control	107 cases, 258 controls age <45 years	3.2 (2.5–4.2)
Nightingale and Farmer (2004) <sup>31</sup>	Case-control	16 cases, 44 controls age <50 years	2.33 (1.04–5.21)
Kurth <i>et al.</i> (2005) <sup>36</sup>	Cohort	7329 women age ≥45 years reporting any history of migraine at baseline (5173 with migraine in the previous year)	1.30 (0.93–1.81) (hazard ratio)
Schwaag <i>et al.</i> (2003) <sup>30</sup>	Case-control	75 cases, 75 controls age ≤45 years	2.68 (1.25–5.75)

OR, odds ratio.

migraine with aura compared to 7.2% of women with migraine without aura (OR 0.7, 95% CI 0.1–4.1).

A review of 36 women with migraine with aura and 86 women with migraine without aura using COCs attending a headache clinic noted 50% of women with migraine with aura reported worsening of migraine with COC use compared to 34.8% of women with migraine without aura.<sup>13</sup> There was no change in 27.7% of women with migraine with aura compared to 44.1% of women with migraine without aura. Improvement was reported by 0% of women with migraine with aura compared to 4.6% of women with migraine without aura. New onset of migraine was reported by 22.2% of women with migraine with aura and 16.2% of women with migraine without aura. In both groups, worsening during COC intake was more likely than improvement ( $p < 0.0001$ ). Worsening was reported as an increase in both frequency and intensity of headache attacks. Eight of the patients who reported a worsening in headache patterns during the first cycle of COC use developed aura symptoms for the first time, associated with a worsening in headache intensity.

### Risk of ischaemic stroke

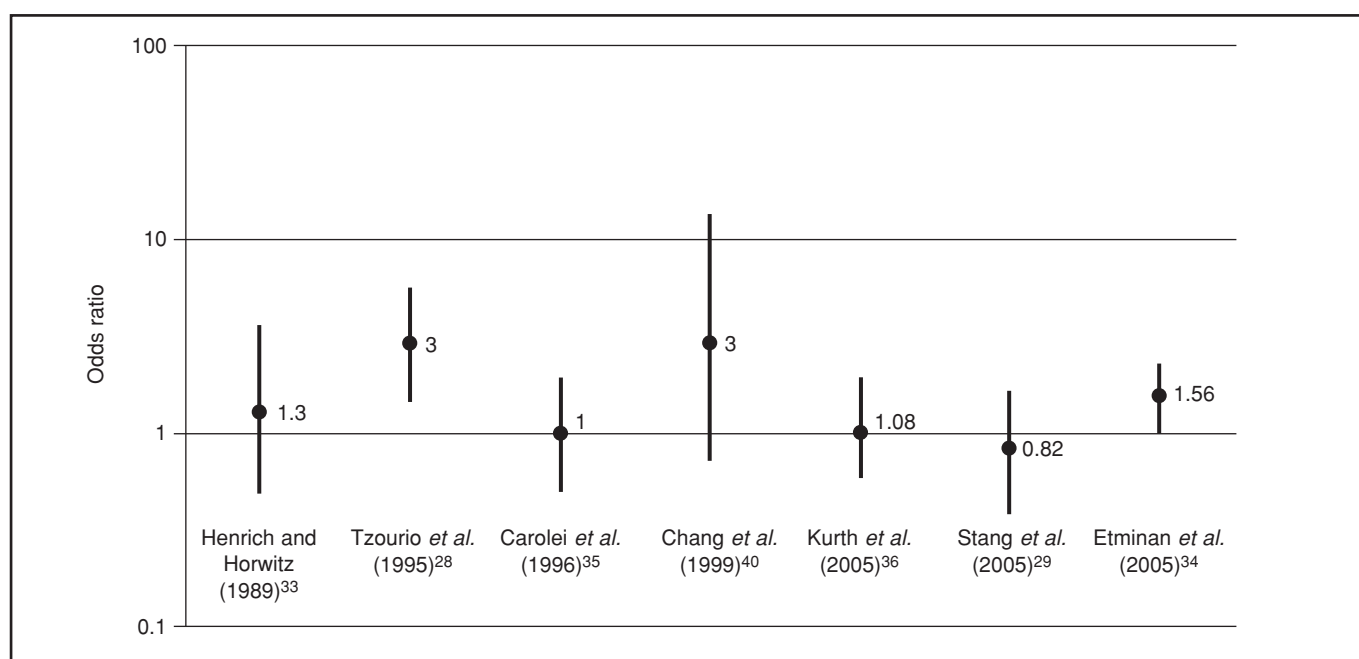
#### Risks of ischaemic stroke in women with migraine

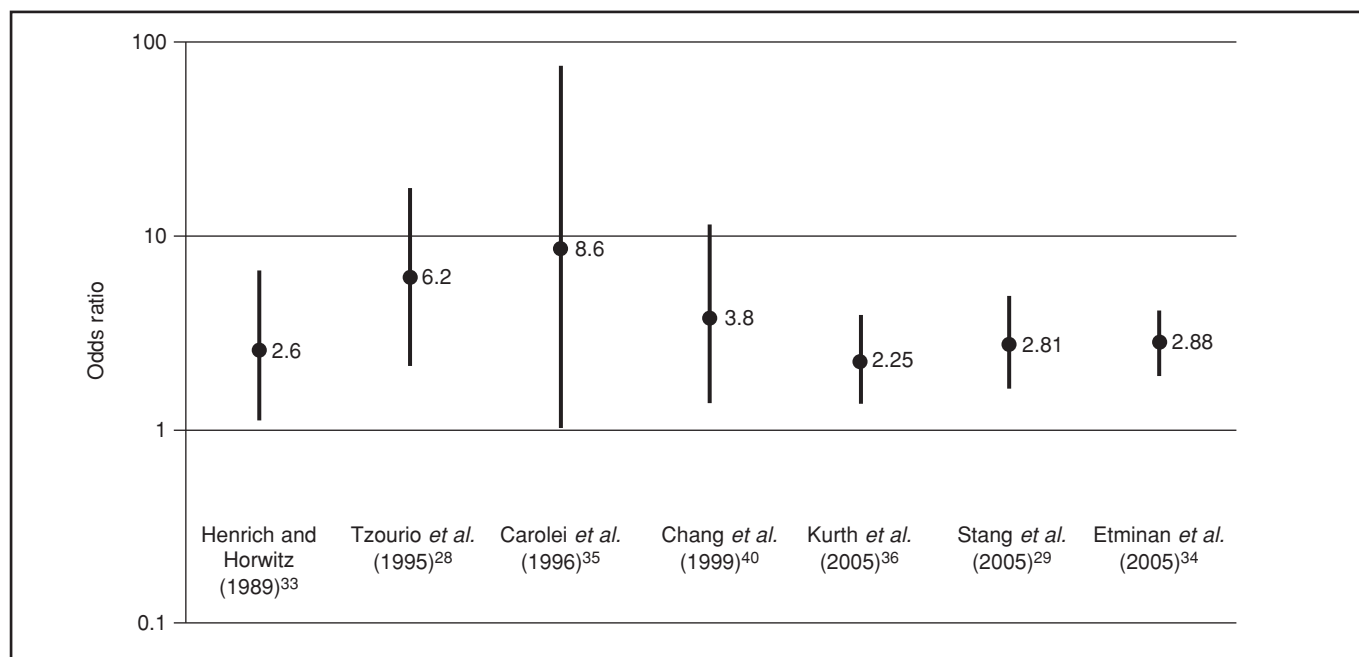
Case-control and cohort studies and a meta-analysis

confirm that migraine is an independent risk factor for ischaemic stroke (Table 1).<sup>27–36</sup> The majority of these studies suggest that migraine with aura, not migraine without aura, is associated with increased risk (Figures 1 and 2). Particularly in studies where aura was self-reported, women with premonitory symptoms could have been included in the 'aura' group, thus diluting the true risk of aura (see section on 'Aids to diagnosing migraine aura' for description of premonitory symptoms).

This risk appears to affect young women and is not evident in women aged over 50 years.<sup>37,38</sup>

A study of brain magnetic resonance imaging assessed infarcts in 161 patients with migraine with aura, 134 patients with migraine without aura and compared the findings with 140 controls with no history of migraine.<sup>39</sup> No participants reported a history of stroke or transient ischaemic attack or had relevant abnormalities at standard neurological examination. They found no significant difference between patients with migraine and controls in overall infarct prevalence (8.1% vs 5.0%). However, in the cerebellar region of the posterior circulation territory, patients with migraine had a higher prevalence of infarct than controls (5.4% vs 0.7%,  $p = 0.02$ , adjusted OR 7.1, 95% CI 0.9–55). This risk was mostly attributed to migraine with aura and the adjusted OR was 13.7 (95% CI

**Figure 1** Risk of ischaemic stroke in women with migraine without aura



**Figure 2** Risk of ischaemic stroke in women with migraine with aura

1.7–112) for patients with migraine with aura compared with controls.

#### Recency and frequency

Assessing 74 cases with migraine and 96 controls, Chang *et al.* showed increased risk of ischaemic stroke in women who had ever had even just a single attack with aura.<sup>40</sup>

The study by Donaghy *et al.* comprising 86 migraine cases and 214 controls also showed increased risk of ischaemic stroke if initial attacks were migraine with aura (OR 8.38, 95% CI 2.33–30.1).<sup>41</sup> These findings suggest that even a distant past history is associated with increased risk. In contrast, the large Women's Health Study reported that only active migraine with aura at

**Table 2** Effect of ethinylestradiol dose on risk of ischaemic stroke

Study	Study design	Sample size in study	Setting	EE ( $\mu$ g)	COC use [OR (95% CI)]
CGSS (1975) <sup>94</sup>	Case-control	430 cases, 151 controls	91 hospitals in 12 USA cities	$\geq 50$	4.9 (2.9–8.3)
Lidegaard (1993, 1995) <sup>95,96</sup>	Case-control	320 cases, 1197 controls	Denmark	50 30–40	2.9 (1.6–5.4) 1.8 (1.1–2.9)
Lidegaard and Kreiner (2002) <sup>32</sup>	Case-control	626 cases, 4054 controls	Denmark	50 30–40 20	4.5 (2.6–7.7) 1.6 (1.3–2.0) 1.7 (1.0–3.1)
Tzourio <i>et al.</i> (1995) <sup>28</sup>	Case-control	72 cases, 173 controls	France	All doses 50 30–40 20	3.1 (1.2–8.2) 4.8 (95% CI NR) 2.7 (95% CI NR) 1.7 (95% CI NR)
Carolei <i>et al.</i> (1996) <sup>35</sup>	Case-control	308 cases, 591 controls	Italy	All doses	1.3 (0.6–2.6)
Petitti <i>et al.</i> (1996) <sup>44</sup>	Case-control	295 cases, 774 controls	USA	<50	1.18 (0.54–2.59)
WHO Collaborative Study (1996) <sup>45</sup>	Case-control	697 cases, 1962 controls	International	All doses (Europe) $\geq 50$ <50	2.99 (1.65–5.40) 5.3 (2.56–11.00) 1.53 (0.71–3.31)
Schwarz <i>et al.</i> (1998) <sup>47</sup>	Case-control Analysis of two studies	175 cases, 191 controls	USA	<50	0.66 (0.29–1.47)
Chang <i>et al.</i> (1999) <sup>40</sup>	Case-control	291 cases, 736 controls	5 European centres	All doses $\geq 50$ <50	2.76 (1.01–7.55) 7.95 (1.94–32.60) 1.19 (0.33–4.29)
Kemmeren <i>et al.</i> (2002) <sup>97</sup>	Case-control	203 cases, 925 controls	9 Dutch centres, population-based	All types	2.3 (1.6–3.3)
Siritho <i>et al.</i> (2003) <sup>46</sup>	Case-control	234 cases, 234 controls	4 Australian hospitals	$\leq 50$	1.76 (0.86–3.61)
Nightingale and Farmer (2004) <sup>31</sup>	Case-control	190 cases, 1129 controls	UK General Practice Research Database	<50	2.30 (1.15–4.59)

COCs, combined oral contraceptives; EE, ethinylestradiol; NR, not reported; OR, odds ratio.

**Table 3** Effect of type of progestogen on risk of ischaemic stroke

Study	Study design	Sample size in study	Setting	COC type <sup>a</sup>	OR (95% CI)
WHO Collaborative Study (1996) <sup>45</sup>	Case-control	697 cases, 1962 controls	21 centres in Africa, Asia, Europe and Latin America	First	5.96 (1.42–24.90)
				Second	1.53 (0.69–3.39)
				Third	1.76 (0.33–9.36)
Heinemann <i>et al.</i> (1997) <sup>75</sup>	Case-control	220 cases, 775 controls	16 centres in UK, Germany, France, Switzerland and Austria	First	4.4 (2.0–9.9)
				Second	3.4 (2.1–5.5)
				Third	3.9 (2.3–6.6)
				Third vs second	1.2 (0.7–2.0)
Poulter <i>et al.</i> (1999) <sup>98</sup>	Case-control	122 cases, 191 controls	21 centres in Africa, Asia, Europe and Latin America	Second	2.7 (1.77–4.14)
Kemmeren <i>et al.</i> (2002) <sup>97</sup>	Case-control	203 cases, 925 controls	9 Dutch centres	Third	1.75 (0.59–5.16)
				First	1.7 (0.7–4.4)
				Second	2.4 (1.6–3.7)
				Third vs second	2.0 (1.2–3.5)
Lidegaard and Kreiner (2002) <sup>32</sup>	Case-control	626 cases, 4054 controls 212 cases, 1208 controls were current COC users	Denmark	Third vs second	1.0 (0.6–1.8)
				First	4.5 (2.6–7.7)
				Second	2.2 (1.6–3.0)
				Third	1.4 (1.0–1.9)
				Third vs second	0.6 (0.4–0.9)

<sup>a</sup>First-generation,  $\geq 50$   $\mu\text{g}$  EE; second-generation,  $< 50$   $\mu\text{g}$  EE containing progestogens other than desogestrel or gestodene; third-generation,  $< 50$   $\mu\text{g}$  EE containing desogestrel or gestodene. COC, combined oral contraceptives; EE, ethinylestradiol; OR, odds ratio.

baseline was associated with increased risk of ischaemic stroke (OR 1.91, 95% CI 1.17–3.1) and neither active migraine without aura (OR 1.27, 95% CI 0.77–2.09) or prior migraine, more than one year ago (OR 0.77, 95% CI 0.43–1.38), were associated with increased risk of any ischaemic event at follow-up.<sup>37</sup>

Frequency of migraine attacks may also be important. Donaghy *et al.* showed that ischaemic stroke is significantly associated with migraine with aura occurring more than 12 times a year (OR 10.4, 95% CI 2.18–49.4).<sup>41</sup> Posterior circulation silent infarcts have also been shown to be more prevalent in people with migraine with aura, the highest risk being in people with one or more attacks per month (OR 15.8, 95% CI 1.8–140).<sup>39</sup>

### Risk of ischaemic stroke in women using COCs

#### Effect of ethinylestradiol

COC use is an independent risk factor for ischaemic stroke with risk related to the dose of EE (Table 2). A meta-analysis of 36 studies reported a relative risk (RR) of 2.74 (95% CI 2.24–3.35) for ischaemic stroke in women using low-oestrogen preparations.<sup>42</sup> A separate meta-analysis of 16 studies reported an overall summary risk estimate for ischaemic stroke among current COC users of 2.75 (95% CI 2.24–3.38).<sup>43</sup> For low-dose COCs containing less than 50  $\mu\text{g}$  EE the RR was 2.08 (95% CI 1.55–2.80). Risk remained elevated for low-oestrogen preparations in population-based studies controlling for smoking and hypertension (RR 1.93, 95% CI 1.35–2.74). This would lead to an estimated additional 4.1 ischaemic strokes per 100 000 healthy, non-smoking, non-hypertensive women using COCs. Hence a woman's annual stroke risk would increase from 4.4 to 8.5 per 100 000 based on background incidence rates.<sup>44</sup>

#### Effect of type of progestogens

The risk of ischaemic stroke associated with different generations of progestogens in COCs is shown in Table 3. The conclusion is that any effect noted relates to the dose of EE with little difference in risk associated with low-dose COCs containing second-generation progestogens such as levonorgestrel or norethisterone, compared with third-generation progestogens such as gestodene or desogestrel.

### Risk of ischaemic stroke in women with migraine using COCs

Use of COCs is, in itself, an established risk factor for ischaemic stroke although the absolute risk is very small since the incidence of ischaemic stroke is very low in healthy young women with no vascular risk factors.<sup>45</sup>

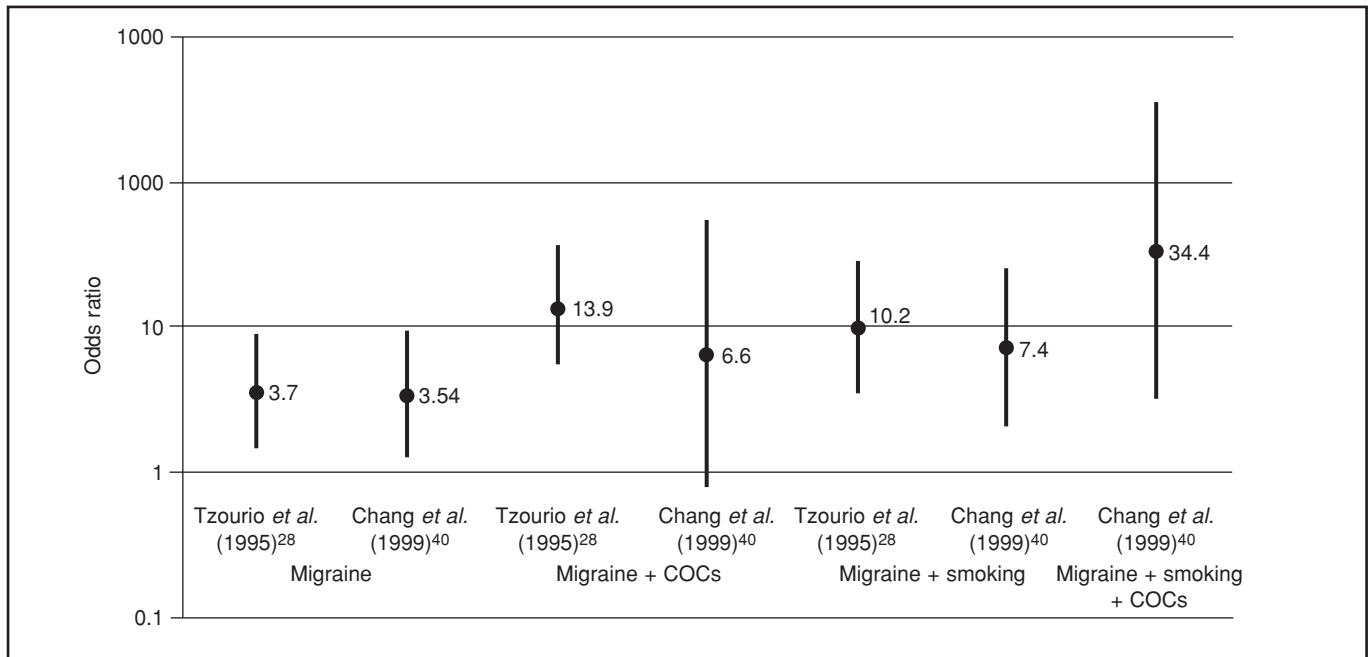
Several case-control studies and a meta-analysis have reported synergism between migraine and use of COCs on the risk of ischaemic stroke (Figure 3). Chang *et al.* highlighted the synergistic effects of multiple risk factors with an OR of 34.4 (95% CI 3.3–361) for ischaemic stroke in migraineurs who smoke and use COCs.<sup>40</sup>

### How robust is the evidence?

Although the body of evidence confirms that EE and migraine, particularly with aura, are independent risk factors for ischaemic stroke, there are a number of concerns with the studies to date. Case-control studies are vulnerable to recall bias; control for confounding risk factors such as family history, smoking, diabetes, hypertension and common treatments may not have been uniform; high-risk patients with migrainous symptoms due to other conditions were excluded in some but not all studies; uncertainty existed in some studies about the diagnosis of migraine and even of stroke (transient ischaemic attacks were sometimes included); no distinction is made between users of oral contraceptive pills containing high doses of EE ( $\geq 50$   $\mu\text{g}$ ) and those containing low doses ( $< 50$   $\mu\text{g}$ ). Notably, the risk associated with low-dose COCs is small.<sup>35,40,43–47</sup>

### Does stroke occur during migraine?

Cerebral blood flow reduces during migraine aura, varying from a 7% to a 53% decrease.<sup>48,49</sup> Combined with the prothrombotic effects of EE, it would be expected that if migraine were a direct cause of ischaemic stroke, stroke would occur in direct temporal relationship to a migraine attack. However, such migrainous infarction is rare and most ischaemic strokes are unrelated to migraine attacks.<sup>28</sup> Rather than migraine being causal it is more likely that women who suffer migraine with aura have additional factors that contribute to an increased risk of ischaemic stroke.



**Figure 3** Effect of multiple risk factors on risk of ischaemic stroke. COCs, combined oral contraceptives

Several studies have reported on strong associations between migraine with aura and increased risk of cardiovascular disease.<sup>37,50</sup>

Evidence suggests that migraineurs have a higher prevalence of other risk factors for ischaemic stroke such as hypertension, elevated cholesterol, abnormalities of haemostasis and patent foramen ovale.<sup>37,51–54</sup> The risk associated with migraine is independent of these factors as it remains increased even when the analyses control for other major stroke risk factors.<sup>37,51</sup>

Limited evidence from studies of high-dose COCs suggests that the development of aura in women using COCs correlates with increased platelet activation associated with starting COC. Reduction in platelet aggregation following cessation of COCs is associated with loss of aura. However, the degree of platelet hyperaggregation is extremely variable due to the marked variation in plasma levels of EE in individual women.<sup>55–57</sup> In particular, Hanington *et al.* showed that platelets from patients with severe migraine with aura exhibited increased aggregation to 5-hydroxytryptamine (5HT).<sup>58</sup> More importantly, women developed migraine after the onset of COC use in association with increased platelet aggregation to 5HT. Cessation of COCs led to a gradual reduction in frequency of attacks associated with significant reduction in extent and rate of platelet aggregation with 5HT. Mazal reported on a case of a woman who developed typical migraine with aura after starting COCs associated with increased platelet aggregability. Improvement after stopping COCs was related to a gradual return to normal platelet activity.<sup>59</sup>

### Alternatives to CHCs

#### Effect of progestogen-only methods on headache and migraine

Few studies differentiate between headache and migraine in progestogen-only users, most citing incidence of headache only. Consequently, any adverse events reporting will include headache and migraine. Since there are no studies comparing active with placebo, the true effect of progestogen-only methods is not clear. In women not using hormonal contraception, a recognised trigger of 'menstrual' migraine is oestrogen withdrawal in the late luteal phase of the menstrual cycle.<sup>24</sup> Somerville and Carey

also noted a close relationship between migraine and uterine bleeding in women taking progestogens, even when ovulation was suppressed.<sup>60</sup> Although these authors suggested that this may be due to fluctuations in oestrogen levels, prostaglandins have also been implicated, levels of which increase three-fold in the uterine endometrium during the luteal phase with a further increase during menstruation.<sup>61,62</sup> Since most progestogen-only methods – with the exception of injectable progestogens – do not entirely abolish the ovarian cycle but often disrupt it, hormonal triggers of migraine remain. Even when ovulation is suppressed, fluctuations in oestrogen levels can still occur.<sup>63,64</sup>

#### Progestogen-only pill

A MEDLINE search did not reveal any published studies specifically assessing headache associated with use of the progestogen-only pill. However, headache is listed as a side effect in the Summary of Product Characteristics for most progestogen-only pills. Anecdotally, headache and migraine are more likely to improve in women who achieve amenorrhoea.<sup>60,65</sup>

#### Subdermal implants

Headache is a common complaint in implant users and may lead to discontinuation of the method.<sup>66</sup>

Studies comparing Norplant<sup>®</sup> with COCs and other methods report no significant differences in headache between Norplant and COCs (39% vs 37% during 1 year) but a significant difference between these hormonal methods and condoms or no method (10%).<sup>67</sup>

Studies with Implanon<sup>®</sup> report headache to be the most common drug-related adverse event, affecting 7% of women.<sup>68</sup> A retrospective study reported that headache affected 18% of women using Implanon at follow-up (mean, 16 months) with 3% of women reporting worsening of headache.<sup>69</sup>

#### Depot progestogens

Two studies have shown increase in headache reported over time with both depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN). A World Health Organization study reported more frequent

**Table 4** Progestogen-only methods and stroke

Study	Study design	Method	OR (95% CI)
Tzourio <i>et al.</i> (1995) <sup>28</sup>	Case-control	Progestogen-only pill	1.0 (95% CI NR)
WHO Collaborative Study (1998) <sup>99</sup>	Case-control	Progestogen-only pill Injectable progestogens	1.01 (0.60–1.69) 0.89 (0.53–1.49)
Heinemann <i>et al.</i> (1999) <sup>75</sup>	Case-control	Progestogen-only pill	1.60 (0.24–10.72)
Poulter <i>et al.</i> (1999) <sup>74</sup>	Case-control	Therapeutic doses	1.13 (0.18–7.13)
Lidegaard and Kreiner (2002) <sup>32</sup>	Case-control	Progestogen-only pill	1.0 (0.3–3.0)

NR, not reported; OR, odds ratio.

headache in DMPA users (10.7%) than with NET-EN subjects (6.9%), a difference that was statistically significant.<sup>70</sup> Furthermore, there was a consistent increase in the proportion of DMPA subjects complaining of headache from 8.5% during the first visit to 15.7% during the fourth visit ( $p < 0.01$ ). No comparable increase was observed in NET-EN users.

Similar results for DMPA were reported in a later study.<sup>71</sup> Among DMPA users, headache was reported in 11.6% of users at 3 months and 15% at 12 months. An increase over time was also seen among NET-EN users, with headache reported in 3.2% of users at 3 months and 19.4% at 12 months.

Anecdotally, improvement is more likely in women achieving amenorrhoea.

#### Levonorgestrel-releasing intrauterine system

Headache is a common complaint in the early months of use but settles with continued use. Andersson *et al.* reported a 2.8% incidence of headache in levonorgestrel-releasing intrauterine system (LNG-IUS) users 3 months after insertion compared to 0.8% in women using a copper intrauterine device (IUD).<sup>72</sup> By 60 months of use, headache in LNG-IUS users had fallen to 1.6% compared with 1% in copper IUD users. A European multicentre randomised controlled trial comparing the LNG-IUS with a copper IUD noted significant differences in removal rates due to headache (1.9% LNG-IUS vs 0.25% Cu Nova-T<sup>®</sup>200) at 5 years.<sup>72</sup> A multinational randomised controlled trial of the LNG-IUS and a copper IUD reported a statistically significant difference in headache (8.3% LNG-IUS vs 4.3% TCu 380A<sup>®</sup>) at 7 years.<sup>73</sup>

#### Effect of progestogens on risk of ischaemic stroke

There is no evidence that use of progestogen-only contraception is associated with an increased risk of ischaemic stroke (Table 4).<sup>28,32,44,74,75</sup>

#### Diagnosing migraine aura (formerly known as 'focal' or 'classical' migraine)

The 1-year prevalence rates for migraine in women are 11% for migraine without aura and 5% for migraine with aura, respectively. Less common is migraine aura without headache. Many patients who have frequent attacks with aura also have attacks without aura.<sup>76</sup>

In contrast to migraine without aura, which is most prevalent during a woman's reproductive years and improves in later life, the prevalence of migraine with aura increases with age. A prevalence study which assessed aura accompanying migraine reported that aura accompanied 13.2% of attacks in the age group 18–29 years, increasing to 20.1% in the age group 40–49 years (OR 1.7, 95% CI 1.5–1.8), and up to 41% of attacks in people with migraine aged 70 years or older (OR 4.6, 95% CI 3.1–6.8).<sup>77</sup>

The aura is the complex of neurological symptoms that

occurs just before or at the onset of migraine headache. Before or simultaneously with the onset of aura symptoms, regional cerebral blood flow is decreased in the cortex corresponding to the clinically affected area and often including an even wider area. Blood flow is usually above the ischaemic threshold.

The IHS describes migraine with aura as a "recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5–20 minutes and last for less than 60 minutes. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent".

Symptoms of aura usually resolve completely before the onset of headache (Table 5). Headache follows within an hour of resolution of aura.<sup>76,78</sup>

#### Visual symptoms

Visual symptoms are most common, and experienced in 99% of auras.<sup>79</sup> Aura without visual symptoms is rare.<sup>78</sup> Visual symptoms are usually symmetrical, affecting one hemifield of both eyes, although subjectively they may appear to affect only one eye. The typical 'fortification spectra' begins with a bright migrainous scotoma starting as a small spot and gradually increasing in size to assume a C-shape (Figure 4).<sup>80</sup> It often develops scintillating edges that appear as zigzags or fortifications – a term coined in the late eighteenth century because the visual disturbances resembled a fortified town surrounded by bastions. Visual symptoms can begin either in the centre or in the periphery of the visual field, gradually spreading across the field of vision and increasing in size over a period of 5 to 30 minutes.

**Table 5** Characteristics of migraine aura

Characteristic	Comments
History	Similar attacks in the past (typically migraine onset in childhood/early adulthood)
Onset/progression of symptoms	Slow evolution (over several minutes)
Duration	<1 hour (typically 20–30 minutes)
Timing	Precedes and resolves before onset of typical migraine headache
Visual symptoms (in 99% of auras)	Homonymous, positive (bright) scotoma, gradually enlarging across the visual field into a C-shape with scintillating, zigzag edges
Sensory/motor symptoms (in 33% of auras)	Usually in association with visual symptoms, rarely affects leg, and positive ('pins and needles')
Headache	Migraine headache and associated symptoms typically follow resolution of aura. Aura may occur without headache, but a history of migraine must be confirmed



Figure 4 Illustration of visual migraine aura<sup>80</sup>

**Sensory symptoms**

Sensory disturbance is less common (31%), and is usually associated with visual symptoms.<sup>78,79</sup> They are typically positive (i.e. a tingling sensation of ‘pins and needles’). Migraine symptoms have a characteristic unilateral distribution affecting one arm, often spreading over several minutes proximally from the hand to affect the mouth and tongue (i.e. cheirooral distribution). The leg is rarely affected in migraine. Motor weakness is not a feature of typical migraine with aura.

**Other symptoms**

Speech disturbance and motor symptoms can also be present (18% and 6%, respectively) but only in association with visual and/or sensory symptoms. Symptoms usually follow one another in succession (i.e. visual symptoms, sensory symptoms and then dysphasia).

**Aids to diagnosing migraine aura**

The diagnosis is usually evident after a careful history alone, although there are rare secondary mimics including carotid dissection, arteriovenous malformation and seizure.

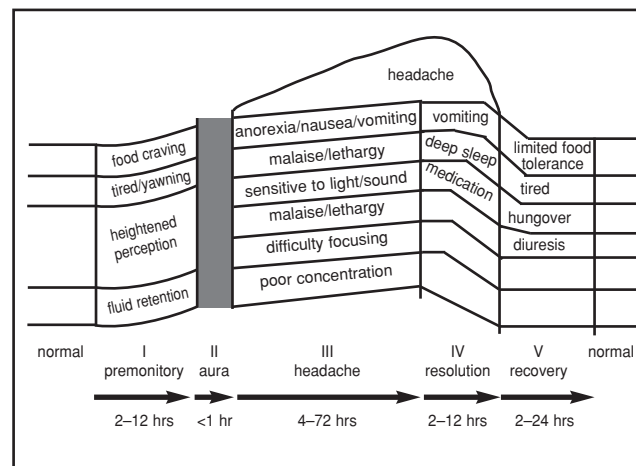


Figure 5 The five stages of a migraine attack (adapted from Blau<sup>81</sup>)

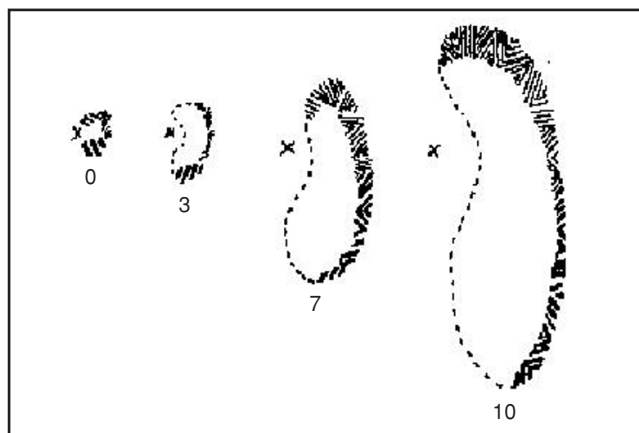
Migraine auras usually follow a similar pattern for each attack, although the duration of aura may vary. Therefore, a long history of similar attacks, particularly if onset is in childhood or early adult life, is reassuring. If aura symptoms suddenly change, further investigation may be warranted.

It can be difficult to distinguish between non-significant premonitory symptoms and migraine aura (Figure 5, Table 6).<sup>81</sup> It is necessary to take a careful history as specific features of the migraine aura can help to differentiate between aura and generalised premonitory symptoms. Premonitory symptoms occur hours to a day or two before a migraine attack (with or without aura). These include various combinations of fatigue, difficulty in concentrating, neck stiffness, sensitivity to light or sound, nausea, yawning and pallor. Generalised visual disturbances, which can include ‘flashing’ or flickering lights’ are normal prodromal symptoms of migraine. These occur up to 24 hours before the onset of headache and can last throughout the attack.<sup>82</sup>

A migrainous scotoma is typically a bright spot, which may gradually increase in size to the shape of a letter ‘C’,

Table 6 Differences between premonitory symptoms and migraine aura

Characteristic	Premonitory symptoms	Migraine aura
History	Identified in up to 70% of attacks once symptoms highlighted	Present in 10–30% of attacks
Onset/progression of symptoms	Slow evolution over several hours	Slow evolution over several minutes
Duration	Up to 24 hours (occasionally longer)	<1 hour (typically 20–30 minutes)
Timing	Precedes onset of typical migraine aura (if present) and headache	Precedes and <i>resolves before</i> onset of typical migraine headache
Symptoms	Vague and generalised: Feeling ‘high’ or ‘low’ Extreme lethargy, yawning Hunger, sweet craving, nausea Pale appearance Muscular aches and pains Photo- and phono-phobia, <i>generalised</i> ‘spots in front of the eyes’	Specific: <u>Visual in 99% auras:</u> Homonymous positive (bright) scotoma gradually enlarging across visual field into C-shape with scintillating zigzag edges <u>Sensory in 33% auras:</u> asymmetrical, usually in association with visual symptoms; positive (‘pins and needles’); usually spreads up arm into face; leg rarely affected
Headache	Follows gradual build up of premonitory symptoms	Headache follows resolution of aura  Aura may or may not be preceded by premonitory symptoms  Aura may occur without headache



**Figure 6** Four subsequent migraine scotomata drawn by Lashley (1941).<sup>83</sup> The crosses indicate the centre of gaze, and the numbers state the time in minutes that passed for each fortification pattern since its first appearance close to the centre of gaze

developing scintillating edges that appear as ‘zig-zags’ (fortification spectra). The aura usually starts at or near the centre of fixation, gradually spreading laterally and gradually increasing in size (Figure 6).<sup>83</sup> In my experience, when asked to describe the symptoms, patients will draw a zig-zag line in the air, representing the scintillations. In contrast to these specific symptoms of aura, 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 cerebral ischaemia. Transient monocular blindness, atypical or permanent symptoms warrant further investigation.

Other important points when diagnosing aura are the duration and relationship of the symptoms to the headache. Aura symptoms start before the onset of headache, last up to an hour (usually around 20–30 minutes) and resolve before the onset of headache (Boxes 1 and 2).<sup>84,85</sup> Aura can occur without subsequent headache but the nature and duration of the aura is unchanged.

Common mistakes that patients make when describing aura include reports of sudden onset when it is gradual, of

**Box 1: International Headache Society (IHS) diagnostic criteria for typical aura with migraine headache<sup>84</sup>**

Typical aura consisting of visual and/or sensory and/or speech symptoms. Gradual development, duration no longer than 1 hour, a mix of positive and negative features and complete reversibility characterise the aura, which is associated with a headache fulfilling the criteria for ‘1.1 Migraine without aura’.

**1.2 Migraine with aura**

*Diagnostic criteria:*

- A. At least two attacks fulfilling criteria B–D
- B. Aura consisting of at least one of the following, but no motor weakness:
  1. Fully reversible visual symptoms including positive features (e.g. flickering lights, spots or lines) and/or negative features (i.e. loss of vision)
  2. Fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
  3. Fully reversible dysphasic speech disturbance
- C. At least two of the following:
  1. Homonymous visual symptoms<sup>1</sup> and/or unilateral sensory symptoms
  2. At least one aura symptom develops gradually over  $\geq 5$  minutes and/or different aura symptoms occur in succession over  $\geq 5$  minutes
  3. Each symptom lasts  $\geq 5$  and  $< 60$  minutes
- D. Headache fulfilling criteria B–D for ‘1.1 Migraine without aura’ begins during the aura or follows aura within 60 minutes
- E. Not attributed to another disorder

monocular disturbances that are homonymous, describing sensory loss as weakness, and incorrect duration.<sup>84</sup> If there is any uncertainty, patients should be encouraged to record their symptoms contemporaneously in a headache diary.

**Practical recommendations**

**Women with current migraine with aura**

There is good evidence that migraine with aura is associated with an increased risk of ischaemic stroke, which appears to be stronger among the young but may persist in the elderly. Pre-existing migraine with aura is an absolute contraindication to use of CHCs (WHO 4, UKMEC 4). If a woman develops her first attack of migraine with aura when using CHCs, she should stop the pill immediately, even during an attack, and further CHC use may be contraindicated (WHO 4, UKMEC 4). Case reports suggest less risk if CHCs are stopped promptly.<sup>86</sup>

Contra-indicating CHCs for women with aura is justifiable since contraceptive efficacy need not be compromised, as several progestogen-only and non-hormonal methods are equally, if not more, effective. Women can be reassured that irrespective of the type, frequency and severity of headache or migraine, there is no evidence that use of progestogen-only methods increases risk of ischaemic stroke. On this basis, there is no restriction on initiation and continuation of progestogen-only methods for women with migraine with aura (i.e. they should be WHO 2 or UKMEC 2).

**Women with a past, but not current, history of migraine with aura**

A brief history of such attacks occurring, for example, more than 5 years before commencing CHC use, or a history of migraine with aura only during pregnancy, may be regarded as relative contraindications. CHCs may be given a trial, with counselling and regular supervision. Women should be given a specific warning that onset of migraine aura or other focal neurological symptoms after starting CHCs means that they should stop the pill immediately, use alternative contraception, and seek medical advice as soon as possible.

**Women with current migraine without aura**

Prospective data do not support an association between migraine without aura in women of any age and ischaemic stroke, therefore there is no indication to restrict use of CHCs in women with migraine without aura (WHO 2, UKMEC 2). There is some evidence that headache reported with COC is greater in older COC users compared to younger users.<sup>7</sup> This is most likely a reflection of the background prevalence of migraine in the different age groups.<sup>87</sup>

It is generally considered that an increase in frequency or severity with CHCs should lead to CHC discontinuation. However, although attacks may increase when CHCs are initiated, there is usually improvement with continued use. Women can be advised that if headache or migraine increases in the first cycle of CHC use, there is only a one in three chance of experiencing headache in the second cycle and a one in ten chance of experiencing headache in the third cycle.<sup>88</sup> If headaches persist, it may be worth changing to a progestogen-only or non-hormonal method

**Box 2: A simple screen for migraine with aura<sup>85</sup>**

- Do you have visual disturbances:
- Starting before the headache?
  - Lasting up to 1 hour?
  - Resolving before the headache?
- If the answer to all three questions is ‘Yes’ then it is likely that the symptoms are aura.



to assess if they are related to CHCs or if non-hormonal causes are more relevant. There appears to be a latent period of at least 4 weeks before any benefit from stopping COCs is seen.<sup>16</sup> Although studies report less headache in women taking COCs containing 20 µg EE compared to COCs containing 30 µg EE, no studies have assessed if changing from a COC containing 30–35 µg EE to 20 µg, or switching to a different progestogen, will benefit headache. On empirical grounds, it may be worth trying.

The treatment of migraine in women using CHCs does not differ from standard recommendations.<sup>89</sup> There has been concern regarding the combined effects of ergots and EE, and although no studies have been undertaken in women taking low dose CHCs the availability of effective alternative treatments means that use of ergots is contraindicated (WHO 4, UKMEC 4).<sup>90</sup> In contrast, there is no association between triptan prescription and stroke in women not otherwise at risk (hazard ratio 1.13, 95% CI 0.78–1.65).<sup>50</sup>

### Women with headache or migraine without aura in the hormone-free interval

Given the association between migraine without aura and withdrawal of EE, treatment strategies have focused on preventing the oestrogen fall. A study in women with migraine during the pill-free interval of COCs also suggested that 50 µg patches are a suboptimal dose to prevent oestrogen 'withdrawal' attacks associated with contraception.<sup>21</sup>

The 'tricycle' regime (i.e. taking three packets without a break), using the lowest acceptable fixed-dose formulation, has been used empirically and means that the woman has only five such migraines a year instead of 13.<sup>91</sup> Randomised trials of extended regimens using oral and transdermal CHCs show evidence of reduced headache compared to standard 21/7 regimens.<sup>5,6</sup> There is also increasing clinical experience of the benefits of continuous, rather than just extended, CHCs. A Cochrane Review reported that a continuous-dosing group had greater improvement of menstrual-associated symptoms (headaches, genital irritation, tiredness, bloating and menstrual pain) compared to the cyclical regimen.<sup>92</sup>

### Assessing women with headaches

A headache history should be included in the standard assessment prior to commencing CHCs. Accurate diagnosis of migraine and aura is essential. A positive response to recent headaches being associated with nausea, photophobia and disability in an otherwise well person suggests migraine.<sup>93</sup> Diary cards are an invaluable aid to diagnosis and can also help establish an association between headaches and use of hormones. Diary cards can be downloaded from the City of London Migraine Clinic website ([www.migraineclinic.org.uk](http://www.migraineclinic.org.uk)). Health care professionals should be aware of the significance of migraine at initial CHC prescription and should ask about headache at every follow-up. Women with migraine should receive clear advice about aura symptoms that should be reported promptly. Assessment of risk factors such as smoking or hypertension is mandatory for all women taking CHCs but especially important for those with migraine.

In line with standard recommendations for prescription of CHCs, migraineurs who smoke more than 20 cigarettes per day, or who have multiple thrombotic risk factors such as hypertension, diabetes, hyperlipidemia or obesity, should be advised not to take the pill.<sup>28,44</sup>

Any unusual headache, with a sudden onset, a long duration, or associated with focal neurological symptoms,

particularly if different from typical migraine aura, should lead to immediate discontinuation of CHCs and prompt appropriate neurological investigations in order to rule out a cerebrovascular complication. Further use of CHCs should be reviewed depending on the outcome.

### Conclusions

The absolute risk of ischaemic stroke in young women is low. Use of CHCs is associated with a 1.5–2-fold increased risk of ischaemic stroke in all users. There are no studies to assess the separate risk associated with migraine with aura and migraine without aura in women using CHC. However, the body of evidence available to date suggests that there is no reason to restrict use of CHC by healthy non-smoking women with migraine without aura. In contrast, women with migraine with aura are predisposed to increased risk of ischaemic stroke and additional risk factors, including CHCs, have a synergistic effect on risk. Since alternatives to CHC are available without loss of contraceptive efficacy, current migraine with aura is an absolute contraindication to use of CHCs. A past history of migraine with aura can be considered a relative contraindication and a woman can be given a trial of CHCs provided that she is clear that if she develops aura, CHCs should be stopped immediately.

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### References

- Sluglett J, Lawson JP. Side-effects of oral contraceptives. *Lancet* 1967; **2**: 612.
- Ernst U, Baumgartner L, Bauer U, Janssen G. Improvement of quality of life in women using a low-dose desogestrel-containing contraceptive: results of an observational clinical evaluation. *Eur J Contracept Reprod Health Care* 2002; **7**: 238–243.
- Brill K, Schnitker J, Albring M. Long-term experience with a low-dose oral contraceptive. *Gynecol Endocrinol* 1990; **4**: 277–286.
- Sulak P, Scow R, Preece C, Riggs M, Kuehl T. Hormone withdrawal symptoms in oral contraceptive users. *Obstet Gynecol* 2000; **95**: 261–266.
- Sulak P, Willis S, Kuehl T, Coffee A, Clark J. Headaches and oral contraceptives: impact of eliminating the standard 7-day placebo interval. *Headache* 2007; **47**: 27–37.
- LaGuardia KD, Fisher AC, Bainbridge JD, LoCoco JM, Friedman AJ. Suppression of estrogen-withdrawal headache with extended transdermal contraception. *Fertil Steril* 2005; **83**: 1875–1877.
- Guillebaud J. The 150/30 formulation. Experience in the United Kingdom. *J Reprod Med* 1983; **28**(1 Suppl.): 66–70.
- Fotherby K. Twelve years of clinical experience with an oral contraceptive containing 30 micrograms ethinylestradiol and 150 micrograms desogestrel. *Contraception* 1995; **51**: 3–12.
- Koetsawang S, Charoenvisal C, Banharnsupawat L, Singhakovin S, Kaewsuk O, Punnahitanont S. Multicenter trial of two monophasic oral contraceptives containing 30 mcg ethinylestradiol and either desogestrel or gestodene in Thai women. *Contraception* 1995; **51**: 225–229.
- Dunson TR, McLaurin VL, Israngkura B, Leelapattana B, Mukherjee R, Perez-Palacios G, *et al*. A comparative study of two low-dose combined oral contraceptives: results from a multicenter trial. *Contraception* 1993; **48**: 109–119.
- Cullberg J. Mood changes and menstrual symptoms with different gestagen/estrogen combinations. A double blind comparison with a placebo. *Acta Psychiatr Scand Suppl* 1972; **236**: 1–86.
- Fotherby K. Clinical experience and pharmacological effects of an oral contraceptive containing 20 micrograms oestrogen. *Contraception* 1992; **46**: 477–488.
- Cupini LM, Matteis M, Troisi E, Calabresi P, Bernardi G, Silvestrini M. Sex-hormone-related events in migrainous females. A clinical comparative study between migraine with aura and migraine without aura. *Cephalalgia* 1995; **15**: 140–144.
- Dalton K. Migraine and oral contraceptives. *Headache* 1976; **15**: 247–251.
- Granella F, Sances G, Zanferrari C, Costa A, Martignoni E, Manzoni GC. Migraine without aura and reproductive life

- events: a clinical epidemiological study in 1300 women. *Headache* 1993; **33**: 385–389.
- 16 Kudrow L. The relationship of headache frequency to hormone use in migraine. *Headache* 1975; **15**: 36–40.
  - 17 Larsson-Cohn U, Lundberg PO. Headache and treatment with oral contraceptives. *Acta Neurol Scand* 1970; **46**: 267–278.
  - 18 Phillips BM. Oral contraceptive drugs and migraine. *BMJ* 1968; **2**: 99.
  - 19 Ryan RE. A controlled study of the effect of oral contraceptives on migraine. *Headache* 1978; **17**: 250–252.
  - 20 Whitty CW, Hockaday JM, Whitty MM. The effect of oral contraceptives on migraine. *Lancet* 1966; **1**: 856–859.
  - 21 MacGregor EA, Hackshaw A. Prevention of migraine in the pill-free interval of combined oral contraceptives: a double-blind, placebo-controlled pilot study using natural oestrogen supplements. *J Fam Plann Reprod Health Care* 2002; **28**: 27–31.
  - 22 Horowski R, Runge I. Possible role of gonadal hormones as triggering factors in migraine. *Funct Neurol* 1986; **1**: 405–414.
  - 23 Sulak PJ, Kuehl TJ, Ortiz M, Shull BL. Acceptance of altering the standard 21-day/7-day oral contraceptive regimen to delay menses and reduce hormone withdrawal symptoms. *Am J Obstet Gynecol* 2002; **186**: 1142–1149.
  - 24 MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. *Neurology* 2006; **67**: 2154–2158.
  - 25 Aegidius K, Zwart JA, Hagen K, Schei B, Stovner LJ. Oral contraceptives and increased headache prevalence: the Head-HUNT Study. *Neurology* 2006; **66**: 349–353.
  - 26 Granella F, Sances G, Pucci E, Nappi RE, Ghiotto N, Napp G. Migraine with aura and reproductive life events: a case control study. *Cephalalgia* 2000; **20**: 701–707.
  - 27 Tzourio C, Iglesias S, Hubert JB, Visy JM, Alperovitch A, Tehindranarivelo A, et al. Migraine and risk of ischaemic stroke: a case-control study. *BMJ* 1993; **307**: 289–292.
  - 28 Tzourio C, Tehindranarivelo A, Iglesias S, Alperovitch A, Chedru F, d'Anglejan-Chatillon J, et al. Case-control study of migraine and risk of ischaemic stroke in young women. *BMJ* 1995; **310**: 830–833.
  - 29 Stang PE, Carson AP, Rose KM, Mo J, Ephross SA, Shahar E, et al. Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. *Neurology* 2005; **64**: 1573–1577.
  - 30 Schwaag S, Nabavi DG, Frese A, Husstedt IW, Evers S. The association between migraine and juvenile stroke: a case-control study. *Headache* 2003; **43**: 90–95.
  - 31 Nightingale AL, Farmer RD. Ischemic stroke in young women: a nested case-control study using the UK General Practice Research Database. *Stroke* 2004; **35**: 1574–1578.
  - 32 Lidegaard O, Kreiner S. Contraceptives and cerebral thrombosis: a five-year national case-control study. *Contraception* 2002; **65**: 197–205.
  - 33 Henrich JB, Horwitz LA. A controlled study of ischemic stroke risk in migraine patients. *J Clin Epidemiol* 1989; **42**: 773–780.
  - 34 Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ* 2005; **330**: 63–65.
  - 35 Carolei A, Marini C, De Matteis G. History of migraine and risk of cerebral ischaemia in young adults. The Italian National Research Council Study Group on Stroke in the Young. *Lancet* 1996; **347**: 1503–1506.
  - 36 Kurth T, Slomke MA, Kase CS, Cook NR, Lee IM, Gaziano JM, et al. Migraine, headache, and the risk of stroke in women: a prospective study. *Neurology* 2005; **64**: 1020–1026.
  - 37 Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener H-C, Buring JE. Migraine and risk of cardiovascular disease in women. *JAMA* 2006; **296**: 283–291.
  - 38 Mosek A, Marom R, Korczyn AD, Bornstein N. A history of migraine is not a risk factor to develop an ischemic stroke in the elderly. *Headache* 2001; **41**: 399–401.
  - 39 Kruit MC, van Buchem MA, Hofman PAM, Bakkers JT, Terwindt GM, Ferrari MD, et al. Migraine as a risk factor for subclinical brain lesions. *JAMA* 2004; **291**: 427–434.
  - 40 Chang C, Donaghy M, Poulter N, and World Health Organisation Collaboration Study of Cardiovascular Disease and Steroid Hormone Contraception. Migraine and stroke in young women: case-control study. *BMJ* 1999; **318**: 13–18.
  - 41 Donaghy M, Chang CL, Poulter N, on behalf of the European Collaborators of the World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Duration, frequency, recency, and type of migraine and risk of ischaemic stroke in women of childbearing age. *J Neurol Neurosurg Psychiatr* 2002; **73**: 747–750.
  - 42 Chan WS, Ray J, Wai EK, Ginsburg S, Hannah ME, Corey PN, et al. Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. *Arch Intern Med* 2004; **164**: 741–747.
  - 43 Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. *JAMA* 2000; **284**: 72–78.
  - 44 Petitti DB, Sidney S, Bernstein A, Wolf S, Quesenberry C, Ziel HK. Stroke in users of low-dose oral contraceptives. *N Engl J Med* 1996; **335**: 8–15.
  - 45 World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives; results of an international, multicentre, case-control study. *Lancet* 1996; **348**: 498–505.
  - 46 Siritho S, Thrift AG, McNeil JJ, You RX, Davis SM, Donnan GA. Risk of ischemic stroke among users of the oral contraceptive pill: the Melbourne Risk Factor Study (MERFS) Group. *Stroke* 2003; **34**: 1575–1580.
  - 47 Schwartz SM, Petitti DB, Siscovick DS, Longstreth WT Jr, Sidney S, Raghunathan TE, et al. Stroke and use of low-dose oral contraceptives in young women. A pooled analysis of two studies. *Stroke* 1998; **29**: 2277–2284.
  - 48 Sanchez del Rio M, Bakker D, Wu O, Agosti R, Mitsikostas DD, Ostergaard L, et al. Perfusion weighted imaging during migraine: spontaneous visual aura and headache. *Cephalalgia* 1999; **19**: 701–707.
  - 49 Cutrer FM, Sorensen AG, Weisskoff RM, Ostergaard L, Sanchez del Rio M, Lee EJ, et al. Perfusion-weighted imaging defects during spontaneous migrainous aura. *Ann Neurol* 1998; **43**: 25–31.
  - 50 Hall GC, Brown MM, Mo J, MacRae KD. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; **62**: 563–568.
  - 51 Scher AI, Terwindt GM, Picavet HS, Verschuren WM, Ferrari MD, Launer LJ. Cardiovascular risk factors and migraine: the GEM population-based study. *Neurology* 2005; **64**: 614–620.
  - 52 Crassard I, Conard J, Bousser MG. Migraine and haemostasis. *Cephalalgia* 2001; **21**: 630–636.
  - 53 Schwertzmann M, Nedeltchev K, Lagger F, Mattle HP, Windecker S, Meier B, et al. Prevalence and size of directly detected patent foramen ovale in migraine with aura. *Neurology* 2005; **65**: 1415–1418.
  - 54 Anzola GP, Magoni M, Guindani M, Rozzini L, Dalla Volta G. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. *Neurology* 1999; **52**: 1622–1625.
  - 55 Kalendovsky Z, Austin J, Steele P. Increased platelet aggregability in young patients with stroke. Diagnosis and therapy. *Arch Neurol* 1975; **32**: 13–20.
  - 56 Gawel MJ, Rose FC. Platelet function in migraineurs. *Adv Neurol* 1982; **33**: 237–242.
  - 57 Couch JR, Hassanein RS. Platelet aggregability in migraine. *Neurology* 1977; **27**: 843–848.
  - 58 Hanington E, Jones RJ, Amess JAL. Platelet aggregation in response to 5HT in migraine patients taking oral contraceptives. *Lancet* 1982; **1**: 967–968.
  - 59 Mazal S. Migraine attacks and increased platelet aggregability induced by oral contraceptives. *Aust N Z J Med* 1978; **8**: 646–648.
  - 60 Somerville B, Carey M. The use of continuous progestogen contraception in the treatment of migraine. *Med J Aust* 1970; **1**: 1043–1045.
  - 61 Horrobin D. Prostaglandins and migraine. *Headache* 1977; **16**: 113–116.
  - 62 Speroff L, Fritz MA. *Clinical Gynecologic Endocrinology and Infertility* (7th edn). Baltimore, MD: Lippincott Williams & Wilkins, 2004.
  - 63 Shearman RP. Ovarian function during and after long-term treatment with ovulation inhibitors. *Lancet* 1964; **14**: 557–558.
  - 64 Croxatto HB, Makarainen L. The pharmacodynamics and efficacy of Implanon. An overview of the data. *Contraception* 1998; **58**(6 Suppl.): 91S–97S.
  - 65 Davies P, Fursdon-Davies C, Rees MC. Progestogens for menstrual migraine. *J Br Menopause Soc* 2003; **9**: 134.
  - 66 Glasier A. Implantable contraceptives for women: effectiveness, discontinuation rates, return of fertility, and outcome of pregnancies. *Contraception* 2002; **65**: 29–37.
  - 67 Dinerman LM, Wilson MD, Duggan AK, Joffe A. Outcomes of adolescents using levonorgestrel implants vs oral contraceptives or other contraceptive methods. *Arch Pediatr Adolesc Med* 1995; **149**: 967–972.
  - 68 Kiriwat O, Patanayindee A, Koetsawang S, Korver T, Bennink HJ. A 4-year pilot study on the efficacy and safety of Implanon, a single-rod hormonal contraceptive implant, in healthy women in Thailand. *Eur J Contracept Reprod Health Care* 1998; **3**: 85–91.
  - 69 Sergent F, Clamageran C, Bastard AM, Verspyck E, Marpeau L. Acceptability of the etonogestrel-containing contraceptive

- implant (Implanon) [in French]. *J Gynecol Obstet Biol Reprod* (Paris) 2004; **33**: 407–415.
- 70 World Health Organization. Multinational comparative clinical evaluation of two long-acting injectable contraceptive steroids: norethisterone oenanthate and medroxyprogesterone acetate. 2. Bleeding patterns and side effects. *Contraception* 1978; **17**: 395–406.
- 71 Salem HT, Salah M, Aly MY, Thabet AI, Shaaban MM, Fathalla MF. Acceptability of injectable contraceptives in Assiut, Egypt. *Contraception* 1988; **38**: 697–710.
- 72 Andersson K, Odland V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. *Contraception* 1994; **49**: 56–72.
- 73 Sivin I, Stern J. Health during prolonged use of levonorgestrel 20 micrograms/d and the copper TCu 380Ag intrauterine contraceptive devices: a multicenter study. International Committee for Contraception Research (ICCR). *Fertil Steril* 1994; **61**: 70–77.
- 74 Poulter NR, Chang CL, Farley TM, Meirik O. Risk of cardiovascular diseases associated with oral progestagen preparations with therapeutic indications. *Lancet* 1999; **354**: 1610.
- 75 Heinemann LA, Assmann A, DoMinh T, Garbe E. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. *Eur J Contracept Reprod Health Care* 1999; **4**: 67–73.
- 76 Kelman L. The aura: a tertiary care study of 952 migraine patients. *Cephalalgia* 2004; **24**: 728–734.
- 77 Bigal ME, Liberman JN, Lipton RB. Age-dependent prevalence and clinical features of migraine. *Neurology* 2006; **67**: 246–251.
- 78 Eriksen MK, Thomsen LL, Andersen I, Nazim F, Olesen J. Clinical characteristics of 362 patients with familial migraine with aura. *Cephalalgia* 2004; **24**: 564–575.
- 79 Russell MB, Olesen J. A nosographic analysis of the migraine aura in a general population. *Brain* 1996; **119**(Pt 2): 355–361.
- 80 Airy H. On a distinct form of transient hemiopia. *Phil Trans Roy Soc* 1870; **160**: 247–264.
- 81 Blau JN. Migraine: theories of pathogenesis. *Lancet* 1992; **339**: 1202–1207.
- 82 Giffin NJ, Ruggiero L, Lipton RB, Silberstein SD, Tvedskov JF, Olesen J, *et al.* Premonitory symptoms in migraine: an electronic diary study. *Neurology* 2003; **60**: 935–940.
- 83 Lashley KS. Patterns of cerebral integration indicated by scotomas of migraine. *Arch Neurol Psych* 1941; **46**: 333.
- 84 Headache Classification Subcommittee of the International Headache Society (IHS). *The International Classification of Headache Disorders* (2nd edn). *Cephalalgia* 2004; **24**(Suppl. 1): 1–160.
- 85 Gervil M, Ulrich V, Olesen J, Russell M. Screening for migraine in the general population: validation of a simple questionnaire. *Cephalalgia* 1998; **18**: 342–348.
- 86 Bickerstaff ER. *Neurological Complications of Oral Contraceptives*. Oxford, UK: Oxford University Press, 1975.
- 87 Steiner TJ, Scher AI, Stewart WF, Kolodner K, Liberman J, Lipton RB. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. *Cephalalgia* 2003; **23**: 519–527.
- 88 Loder EW, Buse DC, Golub JR. Headache as a side effect of combination estrogen-progestin oral contraceptives: a systematic review. *Am J Obstet Gynecol* 2005; **193**(Pt 1): 636–649.
- 89 Steiner TJ, MacGregor EA, Davies PTG. *Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache* (3rd edn). 2007. <http://www.bash.org.uk> [Accessed 25 April 2007].
- 90 Brohult J, Forsberg O, Hellstrom R. A case of multiple arterial thromboses after oral contraceptives and ergotamine. *Acta Med Scand* 1967; **181**: 453–456.
- 91 MacGregor EA, Guillebaud J. Combined oral contraceptives, migraine and ischaemic stroke. Clinical and Scientific Committee of the Faculty of Family Planning and Reproductive Health Care and the Family Planning Association. *Br J Fam Plann* 1998; **24**: 55–60.
- 92 Edelman A, Gallo MF, Nichols MD, Jensen JT, Schulz KF, Grimes DA. Continuous versus cyclic use of combined oral contraceptives for contraception: systematic Cochrane review of randomized controlled trials. *Hum Reprod* 2006; **21**: 573–578.
- 93 Lipton RB, Dodick D, Sadovsky R, Kolodner K, Endicott J, Hettiarachchi J, *et al.*; ID Migraine validation study. A self-administered screener for migraine in primary care: the ID Migraine (TM) validation study. *Neurology* 2003; **61**: 375–382.
- 94 Collaborative Group for the Study of Stroke in Young Women. Oral contraceptives and stroke in young women. Associated risk factors. *JAMA* 1975; **231**: 718–722.
- 95 Lidegaard O. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. *BMJ* 1993; **306**: 956–963.
- 96 Lidegaard O. Oral contraceptives, pregnancy and the risk of cerebral thromboembolism: the influence of diabetes, hypertension, migraine and previous thrombotic disease. *Br J Obstet Gynecol* 1995; **102**: 153–159.
- 97 Kemmeren JM, Tanis BC, van den Bosch MA, Bollen EL, Helmerhorst FM, van der Graaf Y, *et al.* Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. *Stroke* 2002; **33**: 1202–1208.
- 98 Poulter NR, Chang CL, Farley TM, Marmot MG, Meirik O. Effect on stroke of different progestagens in low oestrogen dose oral contraceptives. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet* 1999; **354**: 301–302.
- 99 World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case-control study. *Contraception* 1998; **57**: 315–324.

## BOOK REVIEW

**Integrated Contraceptive and Sexual Health Care: A Practical Guide.** S Bekaert, A White. Oxford, UK: Radcliffe Publishing, 2006. ISBN: 1-85775-723-8. Price: £21.95. Pages: 226 (paperback)

This book has been written for nurses with the express purpose of serving the needs of integrated sexual health services and is divided into two sections: sexual health and contraception. It contains a comprehensive, if superficial, coverage of clinical guidelines for symptom management, examinations and treatment protocols and contraceptive methods. It is a book of lists, with much information laid out in bullet point format. It suffers from a dearth of background detail, and the reference list at the end of each chapter seems sparse in

some places for a book of this nature.

The book is inconsistent in its presentation of information. While it explains in clear language the rationale behind questions asked in both contraceptive and sexual health history taking, instructions for taking combined oral contraceptives are written out in sentence format with unnecessary reference to previous, now unused, pill guidelines. At times it reads like a nursing text from the 1960s with instructions on how to carry out a vulval toilet.

The book does not serve fully the needs of specialists or learners in either branch of sexual or contraceptive health. The chapter on 'Further Supporting Information' covers reproductive anatomy, the menstrual cycle and international pill equivalents, which is illustrative of the inconsistency of detail contained in the book

and makes it hard to judge who it is aimed at: the student nurse on placement, the post-registration student or the experienced practitioner.

The book has a task-oriented, procedural focus, making it potentially useful as a clinic handbook, and contains useful contraceptive information for nurses who come from a background of genitourinary medicine (GUM) and similar pointers for family planning nurses inexperienced in GUM. However, I would not recommend this book for nurses studying either family planning or GUM modules.

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