

Letters to the Editor

Use of contraception outside the terms of the product licence

That it should take our experts 17 pages to explain the problem of prescribing outside the licences of contraceptives surely exposes a credibility gap between regulation and prescribing. It seems we are now expected to know the detail of every licence of every drug we use and to tell the patient when we are outside the licence.

This is not practical advice. For example, how many of us when prescribing the progestogen-only pill from up to 5 days after Day 1 without an additional method will then explain that this is outside the licence? I suggest the answer is none! To follow the advice of the Clinical Effectiveness Unit (CEU) would be time consuming and may confuse the patient. Furthermore, what about the great majority of prescribers, within and without family planning, who do not read our Journal? How are they expected to follow the advice given? The licence system is clearly discredited, and in my opinion can safely be ignored providing one follows the best expert prescribing advice available. That surely is what we actually do and will continue to do.

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Reply

Thank you for the opportunity to respond to the comments from Dr Michael Cox regarding our CEU Guidance on 'The use of contraception outside the terms of the product licence'.¹ Dr Cox considers that it is unnecessary and impractical to inform patients when drugs are prescribed in circumstances outside the terms of manufacturers' product licences. He suggests that providing this information would cause confusion for patients.

The General Medical Council (GMC) website includes frequently asked questions on prescribing and indicates: "some medicines are routinely used outside the scope of their licence ... where current practice supports the use of a medicine in this way it may not be necessary to draw attention to the licence when seeking consent". Thus, the GMC supports doctors who make a judgment that certain examples of 'off-label' prescribing are so well established that explicitly informing patients is superfluous.

Nevertheless, in the context of contraceptive prescribing, patients will receive their medicine in the manufacturer's packaging along with the manufacturer's patient information leaflet. This leaflet will describe use of the medicine in accordance with the product licence. The CEU considers that a patient should always be informed about any aspects of her regimen that differ from this source of information, in order to minimise confusion and concern.

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Reference

- 1 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (July 2005). The use of contraception outside the terms of the product licence. *J Fam Plann Reprod Health Care* 2005; 31: 225-242.

Confusion surrounding liver enzyme-inducing drugs

In the CEU Guidance on 'Drug interactions with hormonal contraception' it states in Box 9 that "No evidence was identified that supports omitting or reducing the pill-free interval to reduce the risk of

ovulation in women using liver enzyme-inducers (Good Practice Point)".¹ In contrast, in the CEU Guidance on 'The use of contraception outside the terms of the product licence' it states in Box 23 that "Women may be given advice regarding 'tricycling' combined hormonal contraception ... if using liver enzyme-inducing drugs (Good Practice Point)".² Please clarify.

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References

- 1 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (April 2005). Drug interactions with hormonal contraception. *J Fam Plann Reprod Health Care* 2005; 31: 144.
- 2 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit FFPRHC Guidance (July 2005). The use of contraception outside the terms of the product licence. *J Fam Plann Reprod Health Care* 2005; 31: 235.

Reply

Thank you for your letter allowing us to clarify a discrepancy between two of the most recent evidence-based guidance documents from the CEU.^{1,2}

In developing evidence-based guidance documents the CEU undertake a systematic literature review using standard search strategies. In addition to this process our Expert Group may identify publications that we have missed during our systematic review. During the development of guidance on 'Drug interactions with hormonal contraception'¹ we did not identify any published evidence to support improved efficacy of combined oral contraception by avoiding a pill-free interval for women using liver enzyme-inducing drugs. Nevertheless, during a further systematic review for subsequent guidance on 'The use of contraception outside the terms of the product licence'² we identified one publication³ that provided some evidence to support a reduction in the pill-free interval. This evidence was taken into account in the most recent Guidance document.²

The CEU are unable to sustain 'living guidance', which would be actively updated as new information became available. All CEU Guidance documents are developed with the intention of being updated every 3 years. We are grateful to all journal readers and Faculty members who identify errors or inconsistencies, which we will ensure are addressed and rectified where necessary during the process of updating CEU Guidance.

Two CEU Guidance documents – those on 'Emergency contraception'⁴ and 'First prescription of combined oral contraceptive pill'⁵ – are due to be updated in 2006. We have requested feedback from Faculty members on these Guidance documents.

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References

- 1 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (April 2005). Drug interactions with hormonal contraception. *J Fam Plann Reprod Health Care* 2005; 31: 139-150.
- 2 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (July 2005). The use of contraception outside the terms of the product licence. *J Fam Plann Reprod Health Care* 2005; 31: 225-242.
- 3 Spona J, Elstein M, Feichtinger W, Sullivan H, Ludicke F, Muller U, et al. Shorter pill-free interval in combined oral contraceptives decreases follicular development. *Contraception* 1996; 54: 71-77.
- 4 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (April 2003). Emergency contraception. *J Fam Plann Reprod Health Care* 2003; 29(2): 9-16.
- 5 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFPRHC Guidance (October 2003). First prescription of combined oral contraception. *J Fam Plann Reprod Health Care* 2003; 29(4): 209-222.

Drug interactions with hormonal contraception

As the authors of the CEU Guidance document on 'Drug interactions with hormonal contraception'¹ make clear, the evidence base in this area remains poor. But when the very-best evidence runs out, as clinicians we still have a woman in front of us who needs help: based on the next-best evidence ...

I argue here that, of three appropriate contraceptive interventions for long-term users of enzyme-inducing drugs (EIDs) using the combined oral contraceptive (COC), available data suggest that eliminating as many pill-free intervals (PFIs) as cycle control allows, plus shortening those that are taken to 4 days, will make a substantial contribution to effectiveness: at least as great as increasing the COC dose or added condom use.

Yet in Box 9 and on page 145 we read: "No evidence was identified that supports omitting or reducing the pill-free interval to reduce the risk of ovulation in women using liver enzyme-inducers (Good Practice Point)".

First, the obvious: 'absence of evidence' is not the same as 'evidence of absence', that an effect is real. In this case, where is the evidence that such shortening or elimination of PFIs would *not* reduce the risk of ovulation?

Second, there is evidence: the research work reviewed by the world Health Organization (WHO) and the CEU² itself, establishing beyond reasonable doubt that the PFI is when ovarian follicular activity may return, more in some women than others; and that the longer the PFI the greater the ovulation risk. The reverse is also true, as in the very title of one of the reviewed papers, namely 'Shorter pill-free interval in combined oral contraceptives decreases follicular development'.³ The limit of shortening is elimination; and oddly enough the CEU recognises this in Table 3¹ when advising on the lower-risk drug interaction with *non-liver* enzyme-inducing antibiotics: "If fewer than seven pills are left in the packet after antibiotics have stopped the pill-free interval should be omitted....".

Whenever there is reduced ovarian inhibition due to enzyme induction, how could standard 'tricycling' as recommended⁴ and practised for more than 20 years in the UK – by the elimination of usually three PFIs and the shortening of the fourth (since 1999, to the 4 days evaluated by Sullivan *et al.*⁵) – not be advantageous? Pending a definitive randomised controlled trial comparing ovulation rates in EID users on 50 µg COCs with and without tricycling, the biological plausibility that tricycling increases COC efficacy is overwhelming.

As regards long-term users of liver EIDs, the CEU Guidance rightly states that: "Information should be given on the use of alternative methods".

By classifying use of these drugs in Category WHO 3 for the COC,⁶ WHO intends that the COC method "should not usually be recommended". Hence the preferability of an alternative unaffected method, ideally a long-acting method, is not in dispute – and it has been my recommendation for many years.

But what if the woman, after good counselling, comprehensively rejects or has contraindications to the available effective alternatives to the COC? This Guidance makes no distinction between short- and long-term users. It seems that, even in monogamous relationships, a long-term EID user should use an added method such as condoms together with (an increased dose of) the COC, indefinitely. Given how badly condoms are often used, especially I submit by men who perceive that their partner is already protected, the woman's conception risk will remain high.

Worryingly, it is not entirely reassuring that at least she will be using stronger COCs than usual. The problem of breakthrough pregnancies with

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EID use and normal 7-day PFIs first emerged in the 50–100 µg pill era! Indeed, in the Mayo Clinic-based collected series,⁷ 16/25 women who, despite allegedly good pill-taking, conceived on enzyme-inducers were taking 50 µg pills; and the remaining nine were taking 100 µg pills (with mestrano!)

Please, may we have our tricycle back?

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References

- 1 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFRHC Guidance (April 2005). Drug interactions with hormonal contraception. *J Fam Plann Reprod Health Care* 2005; **31**: 139–150.
- 2 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Faculty Statement from the CEU on a New Publication: WHO Selected Practice Recommendations for Contraceptive Use Update. Missed pills: new recommendations. *J Fam Plann Reprod Health Care* 2005; **31**: 153–155.
- 3 Spona J, Elstein M, Feichtinger W, Sullivan H, Ludicke F, Muller U, et al. Shorter pill-free interval in combined oral contraceptives decreases follicular development. *Contraception* 1996; **54**: 71–77.
- 4 Guillebaud J. *Contraception: Your Questions Answered*. Edinburgh, UK: Churchill Livingstone, 1985; 142.
- 5 Sullivan H, Furniss H, Spona J, Elstein M. Effect of 21-day and 24-day oral contraceptive regimens containing gestodene (60 microg) and ethinylestradiol (15 microg) on ovarian activity. *Fertil Steril* 1999; **72**: 115–120.
- 6 World Health Organization (WHO). *Medical Eligibility Criteria for Contraceptive Use* (3rd edn). Geneva, Switzerland: WHO, 2004. <http://www.who.int/reproductive-health/publications/mec/index.htm>.
- 7 Coulam CB, Annegers JF. Do anticonvulsants reduce the effectiveness of oral contraceptives? *Epilepsia* 1979; **20**: 519–525.

Reply

We welcome the opportunity to respond to these comments on our FFRHC Guidance on 'Drug interactions with hormonal contraception' published in the April issue of the Journal.¹ Your correspondent draws attention to a paper by Spona *et al.* which provides some evidence to support a reduction in the pill-free interval in women taking concurrent liver enzyme-inducers.² As explained in our response to your correspondent, Graham Davies, we failed to identify this paper during our systematic review for the 'Drug interactions' Guidance; but did identify it during development of our subsequent Guidance on 'The use of contraception outside the terms of the product licence'.³

Within the limits of our resources, the CEU always endeavours to undertake a fully comprehensive and systematic literature search in the preparation of Guidance. Nevertheless, relevant papers occasionally are missed by the search strategies used. We are always grateful to Faculty members for alerting us to evidence that we may have overlooked. Such evidence will be taken into account when Guidance is updated.

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- 1 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFRHC Guidance (April 2005). Drug interactions with hormonal contraception. *J Fam Plann Reprod Health Care* 2005; **31**: 139–150.
- 2 Spona J, Elstein M, Feichtinger W, Sullivan H, Ludicke F, Muller U, et al. Shorter pill-free interval in combined oral contraceptives decreases follicular development. *Contraception* 1996; **54**: 71–77.
- 3 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFRHC Guidance (July 2005). The use of contraception outside the terms of the product licence. *J Fam Plann Reprod Health Care* 2005; **31**: 225–242.

Missed pill guidelines

We manage a family planning contraception service for the under-25s in South West Essex, and we are writing to express our service's concerns about the new missed pill guidelines. Our young service users often lead chaotic lifestyles with

subsequent chaotic pill taking. By promoting the new advice we feel that we would be giving them further leeway to miss pills, which could result in an increase in unwanted pregnancies. Some of our service users have poor literacy skills and would have difficulty following the new advice in the fpa leaflet. They have to rely on a clear explanation of pill taking from staff, and the old advice is a lot easier to explain verbally. At present the fpa leaflet advice contradicts that given in the patient information leaflets provided by the pill manufacturers. We understand that the manufacturers advice is unlikely to change since this would involve new product licences being sought. Our concerns were discussed at Thurrock PCT's Medicine Management Committee last month and it was decided that at present all contraception providers working for the PCT should continue to adhere to the former missed pill advice. This recommendation is to be taken to the South West Essex Medicine Management Committee.

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Ivy Whitwell, Qualifications?

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Reply

We welcome the opportunity to respond to these comments on the 'new missed pill rules' published by the WHO¹ and endorsed in our Faculty Statement published in the April 2005 issue of the Journal.² Your correspondents' main points are: that young people often have chaotic lifestyles and chaotic pill-taking routines (and that the 'new rules' appear to promote greater leeway and laxity); and that the 'new rules' are at odds with information in the patient information leaflets provided by manufacturers.

We acknowledge the lifestyle factors that influence contraceptive choices for young people. The new 'missed pill rules' do not negate or contradict the responsibility of clinicians caring for young people to promote the fundamental importance of regular, disciplined, pill-taking routines. Pragmatic measures, such as use of the alarm call facility on a mobile phone, can assist young people in maintaining the necessary routine. We do not believe that evidence-based missed pill rules, which minimise unnecessary interventions for the maximum number of women, condone or reinforce poor pill-taking routines. If a young woman has a lifestyle that is incompatible with regular pill taking, then she needs a user-independent method of contraception, not 'stricter' missed pill rules.

We also acknowledge that the new WHO recommendations differ from the advice given in manufacturers' leaflets. However, the problem of conflicting information from different sources is not new. Advice given in different manufacturers' leaflets varies in some details, as does advice in the *British National Formulary*. Achievement of uniformity and consistency was one of the reasons given by the WHO for publishing the new advice.

We disagree that the new advice is more difficult than the old to explain verbally to an individual patient. Each woman need only be given the 'rules' that apply to her own pill formulation (20 µg or ≥30 µg ethinylestradiol); there are fewer circumstances in which she must adopt any special measures (only if she has missed 'two for twenty' or 'three for thirty' pills); and there are fewer circumstances in which emergency contraception must be considered (only if pills have been missed in Week 1 of the pill-taking cycle).

Thus, the CEU stands by their endorsement of the WHO's 'missed pill rules'. Nevertheless, an individual clinician managing an individual patient may choose to give different advice tailored to individual circumstances, or based on his/her own interpretation of available evidence.

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References

- 1 World Health Organization (WHO). *Selected Practice Recommendations for Contraceptive Use* (2nd edn). Geneva, Switzerland: WHO, 2005. http://www.who.int/reproductive-health/publications/spr_2/index.html [Accessed 19 August 2005].
- 2 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Faculty Statement from the CEU on a New Publication: WHO Selected Practice Recommendations for Contraceptive Use Update. Missed pills: new recommendations. *J Fam Plann Reprod Health Care* 2005; **31**: 153–155.

Preoperative counselling for female sterilisation

I read with great interest the article by Philip Owen and colleagues on 'Documentation of preoperative counselling for female sterilisation'.¹ A similar audit was conducted recently in the Department of Obstetrics and Gynaecology, Nobles Hospital, Isle of Man and included 81 cases which were admitted for sterilisation between October 2002 and September 2004. The auditable standards were obtained from the Clinical Guidelines No. 4 of the Royal College of Obstetricians and Gynaecologists (RCOG), (published in January 2004) and the RCOG Consent Advice 3 (published in October 2004). Data were collected retrospectively from the case notes.

The results of the audit were as follows:

- Discussion regarding vasectomy was recorded in 60% of the case notes.
- Discussion regarding Implanon® was recorded in 60% of the case notes.
- Discussion regarding Mirena® was recorded in 84% of the case notes.
- Discussion regarding Depo-Provera® was recorded in 54% of the case notes.
- Discussion regarding the failure rate was recorded in 95% of the case notes.
- Discussion regarding risks specific to laparoscopy and risk of minilaparotomy were recorded in 89% of the case notes.
- Discussion regarding the risk of ectopic pregnancy in cases of failure was recorded in 85% of the case notes.
- Discussion regarding irreversibility was recorded in 94% of the case notes. However, discussion regarding the reversal procedure and its success rates were only recorded in 1% of the case notes.
- Advice regarding use of effective contraception until the next periods was recorded in 19% of the case notes.

It was concluded that documentation of preoperative counselling for female sterilisation needs to be improved. It was recommended that a 'tick box' proforma should be used, and to do a re-audit in 12 months' time to check whether the introduction of the proforma has resulted in an improvement of documentation.

The female sterilisation procedure is very commonly performed and has the potential to attract complaints and litigation. I have a few comments to make regarding the sample proforma that was included in the article.

The Consent Advice 3 of the RCOG recommends that the procedure should be called a laparoscopic tubal occlusion. Moreover, the risk of death (which is 1 in 12 000 procedures performed) should be mentioned. During the preprocedure discussion it is difficult to emphasise the irreversibility of the procedure whilst at the same time talking about the reversal procedures and their success rates.