LETTERS

Evidence-based reproductive medicine

Madam
I look forward to the arrival of the Journal. It is always a good read, full of relevant and practical information – much more 'user-friendly' than most journals I receive these days. July's edition seemed particularly interesting with a number of interesting articles.

However, my interest was quickly replaced by irritation. There is a lot to be said for evidence-based medicine (EBM) and it is always helpful to have a review of the current evidence available in order to provide women with accurate information when discussing contraception. However, it is not sufficient just to provide the 'evidence'. EBM must consider that clinicians need practical guidance with decision making.

The Clinical Effectiveness Unit (CEU) product review of the desogestrel-only pill is just one example of EBM being unhelpful to our clinical practice. It states: 'an evidence-based recommendation cannot be made that the desogestrel-only pill is different from other POPs in terms of efficacy, nor that it is similar to combined oral contraception (COC) in this respect.'[1] The recommendation is based on insufficient evidence to support lower failure rates with the desogestrel pill. This is despite another study showing that the desogestrel-only pill was sufficient to inhibit ovulation in 97% of cycles and that this is its primary mode of action.

The suggestion that the data provided by the manufacturers may not be credible raises an additional concern. In the same edition an excellent article on evidence-based reproductive health by Robbie Foy quotes a Chinese proverb: 'Be careful what you wish for: it may come true'.[2] The author adds that pharmaceutical industry-funded trials tend to report more favourable findings than those funded by other means, noting that one of the trial authors for the desogestrel-only pill studies is affiliated to the company that manufactures the pill. If this is an issue, then we must equally be assured that none of those undertaking the desogestrel-only pill review have any relevant associations with the manufacturers of other progestogen-only pills (POPs), who are unlikely to welcome this new competitor.

I am not denying the need for more unbiased clinical trial evidence; I am just despairing at our sudden inability to put the information to practical rather than theoretical use. Are we really supposed to tell women that a POP that inhibits ovulation in 97% of cycles is no more effective than currently available POPs?

One final point refers to the FFPRHC Guidance on Contraceptive Choices for Women with Inflammatory Bowel Disease[3] which includes the repeated comment that WHO 3 implies cannot use, e.g. 'Women with primary sclerosing cholangitis should not use the POP (WHO Category 3 – risks outweigh the benefits)'. I am concerned that the CEU is perpetuating this misinterpretation of the WHO 3 category that does not absolutely contraindicate use, although other methods should be the first choice.

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1 FFPRHC Clinical Effectiveness Unit. New Product Review (April 2003). Desogestrel-only pill (Cerazette). *J Fam Plann Reprod Health Care* 2003; **29**(3): 162–164.
2 Foy R, Crilly M, Brechin S. Evidence-based reproductive health: testing times for treatments. *J Fam Plann Reprod Health Care* 2003; **29**(3): 165–168.
3 FFPRHC Clinical Effectiveness Unit. FFPRHC Guidance (July 2003). Contraceptive choices for women with inflammatory bowel disease. *J Fam Plann Reprod Health Care* 2003; **29**(3): 127–135.

CEU New Product Review of the desogestrel-only pill

Madam
The Clinical Effectiveness Unit (CEU)'s product review of the desogestrel-only pill[1] and the recent article 'Is Cerazette the minipill of choice?' in the *Drug and Therapeutics Bulletin* (DTB)[2] are both good reviews of all the relevant studies. But in my opinion they are marred by their surprisingly negative conclusions.

What do we do when the evidence from clinical trials and epidemiology is not as complete as we would all like, but we have clients sitting in front of us wanting our help in choosing from the available options? It is then not sufficient just to provide the 'evidence' from an ivory tower. A decision has to be made, at time present. Pending more data, evidence-based medicine (EBM) must be subjected to informed clinical judgement, based on all the available evidence (including the reported pharmacology of the product) and – dare I say it? – clinical common sense.

The statement of the DTB[1] is not inaccurate when it says (in nearly the same words as the CEU[2]) 'There is insufficient evidence on whether it [Cerazette] is a more effective contraceptive than other POPs in terms of efficacy'. The evidence being alluded to is apparently the single collaborative bleeding pattern and efficacy trial (discussed below). Yet another study showed that the desogestrel-only pill inhibits ovulation in 97% of cycles [compared with only 61–64% of cycles with the levonorgestrel progestogen-only pill (POP)], which (in the CEU review's own words) 'is its primary mode of action'. Since when was such data from a double-blind controlled trial in basic clinical pharmacology not 'evidence'?

The main collaborative European multicentre study was indubitably underpowered, as regards efficacy, in the levonorgestrel POP comparator arm. However, among more than 600 women in the other (desogestrel) arm, who were not breastfeeding and with known gross non-compliance excluded, the Pearl failure rate was only 0.17 (CI 0.004–0.928) per 100 woman-years. Such a low rate (with an upper bound of the CI being less than 1), in any clinical study of a POP over the past 40 years, is historically unprecedented. So it would have been equally valid for the two reviews to have concluded: 'There is insufficient evidence on whether it [Cerazette] is not a more effective contraceptive than other POPs in terms of efficacy'. Indeed, taken with the two studies showing inhibition of ovulation and – something overlooked by both reviews – the fact that Cerazette does not have that inbuilt contraceptive weakness of the combined pill (i.e. the pill-free interval[3]), I would judge the chances of this product not being ultimately found significantly more effective than other POPs to approach, very closely, to zero.

Therefore I consider this product a useful new addition to the range of contraceptives, particularly for a young, non-breastfeeding woman wanting a pill method but recommended, or wishing, to avoid the combined oral contraceptive (COC). It is highly likely (though again this is not yet fully established) to be more forgiving of late pill-taking than other POPs. But users will, as usual for all POPs, need forewarning about the occurrence of irregular bleeding. And I see no special reason to use it in those situations where the combination with a cheaper old-type POP is already virtually 100%, such as in lactation, or in older women, especially those aged over 45 years.

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References
1 FFPRHC Clinical Effectiveness Unit. New Product Review (April 2003). Desogestrel-only pill (Cerazette). *J Fam Plann Reprod Health Care* 2003; **29**(3): 162–164.
2 Anonymous. Is Cerazette the minipill of choice? *Drug Ther Bull* 2003; **41**: 68–69.
3 Korver T, Goorissen E, Guillebaud J. The combined oral contraceptive pill: what advice should we give when tablets are missed? *Br J Obstet Gynaecol* 1995; **102**: 601–607.

Reply

Madam
On behalf of the FFPRHC Clinical Effectiveness Unit (CEU), I thank you for the opportunity to respond to the letter from Anne MacGregor concerning two articles in the July 2003 issue of the Journal relating to the desogestrel-only pill. I am sorry that your correspondent found the New Product Review from our Unit irritating, rather than clinically useful.

We also welcome the opportunity to respond to the letter from John Guillebaud on the same theme.

In my view, our New Product Review[1] provides an utterly objective summary of currently available evidence concerning the desogestrel pill. I stand by our statements that 'on theoretical grounds, we would expect the desogestrel pill to be more effective than existing progestogen-only pills ... but we do not have trial evidence to support this'. The evidence-based reproductive health paper by Foy et al.[2] is commended by your first correspondent but reaches the same conclusion as our New Product Review: 'You cannot tell if the DSG pill is superior or inferior to other POPs'.

Dr MacGregor mentions 'the suggestion that the data provided by the manufacturers may not be credible'. Nowhere in our New Product Review is any comment or suggestion made relating to claims or data provided by the manufacturers. She goes on to seek assurance 'that none of those undertaking the desogestrel-only pill review have any relevant associations with manufacturers of other progestogen-only pills'.

The New Product Review from the CEU does not include an explicit statement of interests. However, CEU staff members are bound by a formal code of practice on 'Relationships with the Pharmaceutical Industry', which was drawn up in consultation with the FFPRHC Clinical Effectiveness Committee soon after the Unit was established. This eight-point code of practice includes the following statements: 'In all aspects of the work of the CEU, staff will be required to appraise the relative benefits of individual contraceptive products and groups of products. Such appraisals will always be conducted in an impartial manner, and be based on available research evidence.' and 'CEU staff should not accept any honoraria or consultancy payments from pharmaceutical companies – either for their personal accounts or for CEU funds'.

Dr MacGregor also comments on the FFPRHC Guidance on Contraceptive Choices for Women with Inflammatory Bowel Disease,[3] developed by our Unit and included in the same issue of the Journal. She feels that we have misrepresented 'Category 3' (risks outweigh benefits) as described in the WHO publication *Medical Eligibility Criteria for Contraceptive Use*,[4] giving the impression that 'Category 3' equates to absolute contraindication. This was certainly not our intention, and I fully agree with Dr MacGregor's interpretation that 'Category 3' indicates that a method should not be advised as a woman's first choice, but may be used after appropriate counselling. I can only apologise if, in the interests of brevity, this distinction was unclear in this particular FFPRHC Guidance.

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I trust that your readers can be reassured that the CEU is committed to providing objective summaries of available evidence as a service to Faculty members. Our documented code of practice precludes any relationships with pharmaceutical companies that might represent competing interests in our product reviews. In line with established principles of evidence-based medicine, we do not make clinical practice recommendations based on assumptions, personal beliefs or inappropriate extrapolations from research data. On this basis, we stand by our published conclusions and recommendations regarding the desogestrel pill.

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References
1 FFPRHC Clinical Effectiveness Unit. New Product Review (April 2003). Desogestrel-only pill (Cerazette). J *Fam Plann Reprod Health Care* 2003; **29**(3): 162–164.
2 Foy R, Crilly M, Brechin S. Evidence-based reproductive health: testing times for treatments. *J Fam Plann Reprod Health Care* 2003; **29**(3): 165–168.
3 FFPRHC Clinical Effectiveness Unit. FFPRHC Guidance (July 2003). Contraceptive choices for women with inflammatory bowel disease. *J Fam Plann Reprod Health Care* 2003; **29**(3): 127–135.
4 World Health Organization (WHO). *Medical Eligibility Criteria for Contraceptive Use*. Geneva, Switzerland: WHO, 2000.

New GyneFix® introducer

Madam
We wish to share our experience with using the new GyneFix® introducer.

The Abacus Centre in Liverpool was the first service to offer the frameless intrauterine device, GyneFix in the UK, when it was introduced in 1997. To date we have fitted 1750 of these devices. Our audit of the first 100 insertions showed we had 11 failed insertions (of the 1000). Since the introduction of the new GyneFix introducer in our service in early 2002, we had anecdotal reports of failed insertion by all doctors carrying out insertions in our service. Initially we considered this to be part of the learning curve with the introduction of any new technique. However, when the failed insertions continued, we undertook an audit of failed GyneFix insertions from January 2003 to August 2003. During this period there were 50 attempted GyneFix insertions of which 38 were successful and 12 failed to anchor the device. In 7/38 successful insertions, there was more than one attempt to implant the GyneFix. We wasted 18 devices during the 50 attempted insertions. There was no indication that doctors with greater experience in GyneFix fitting had fewer failed insertions compared to those who had fitted fewer devices. This has raised difficulties in our counselling of women for GyneFix insertions as well as in our ability to continue to offer it as part of our contraceptive menu. We have reported these failed insertions to the manufacturer. We have heard from them that they have decreased the thickness of the tail of the inserter, which may reduce this problem. However, this modification is only in the GyneFix 200, which only has four beads and for which there are few published long-term data.

We will be very interested to hear from other services as to whether they are experiencing similar problems with the new GyneFix introducer.

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Reference
1 Dennis J, Webb A, Kishen M. Expulsions following 1000 GyneFix insertions. *J Fam Plann Reprod Health Care* 2001; **27**(3): 135–138.

Dieting and breakthrough bleeding on COCs

Madam
When dealing with the Margaret Pyke postbag, I was interested to receive a couple of queries requesting advice on the development of breakthrough bleeding (BTB) on combined oral contraceptives (COCs) in women who had had a regular bleeding pattern until they went on diets and lost a lot of weight quite quickly. In one case, the Atkins diet (high protein, low carbohydrate) had been followed; in another, the woman was using Lighter Life® meal replacements. All other causes of BTB had been excluded.

I would be interested to know if other readers have come across this phenomenon and if I should add a question about dieting and weight loss to my list for women who present with BTB.

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NEWS ROUNDUP

A new IT solution for sexual health?

Information technology (IT) has been promoted as a panacea for all ills and sexual health is no exception. The technological boom is here to lend a helping hand to deal with the current sexual health crisis facing the country! The IBM partner, Appareo, aims to provide an effective, national, specialist, sexual health performance management system based around a data warehousing approach. The two critical elements are personal client data and clinical data and application.

The director assures us that the system will cater to the requirements of the national IT strategy and health care clinicians. Other benefits proposed are reduction in waiting times, improved patient access and an annual savings of £9 million.

The infrastructure needs to be clarified, in terms of the staff, resources and training. Should the responsibility for its smooth functioning rest with the already burdened clinicians or with new staff (with an added cost implication)? These issues warrant exhaustive thought before the adoption of such a system. For more details contact **beyondpr@blueyonder.co.uk.**

New national standards for HIV and AIDS care

Funded by the Department of Health, these standards were drawn up in line with the National Strategy for Sexual Health and HIV.[1] The Medical Foundation for AIDS and Sexual Health (MedFASH), a charity sponsored by the British Medical Association, is publishing the standards. They cover all aspects of HIV care from prevention and diagnosis to palliative care. Each of the 12 standards is accompanied by the evidence base and lists the key interventions. They include the implications for service planning, guidelines for administrative and clinical practice, as well as suggestions of how to audit what is provided. The main challenge will be how to implement these excellent standards. Primary care organisations may find the standards difficult to fund and implement because of competition with other areas, better funded, or more socially acceptable such as coronary heart disease. The standards can be downloaded from **www.medfash.org.uk.**

Reference
1 National Strategy for Sexual Health and HIV. http://www.doh.gov.uk/sexualhealthandhiv/index.htm

Changes to cervical cytology screening

Liquid-based cytology will now be the preferred method of examination. In this method of screening the sample is collected from the cervix in the same way, but using a special plastic broom-like device which is swept over the transitional zone five times to collect cellular material. The broom is rinsed or broken off in a vial of preservative. The vial is mixed in the laboratory and treated to remove unwanted material by an automated process. The remaining suspension of cells can be stained and the prepared slide looks much clearer for examination. The number of unsatisfactory (inadequate) slides is reduced and fewer women will be made anxious by being recalled.

The frequency of screening will also be changed to a more equitable system. All women, wherever they live, are to be screened every 3 years from the age of 25–49 years, and then every 5 years until the age of 64 years. Further information is available at **www.nice.org.uk.**

Male contraception

Health professionals may have been perplexed by reports in the media about 'The risk-free pill for men' (*Daily Mail*) or 'Male birth control pill successfully tested' (*The Daily Telegraph*). These newspapers had picked up on a report from Australia that showed no pregnancies in the partners by the end of 12 months. The men received an injection of 150 mg depot medroxyprogesterone acetate every 3 months, together with an implant of 800 mg testosterone every 4 months. No serious side effects such as weight gain or hypertension were recorded in the 55 men studied. All male methods requiring sperm suppression have a long lead-in period, of course. It will be interesting to see if larger studies are as free from problems, such as mood swings or loss of libido, which have limited previous studies of this combination of therapies. Further information on male contraception is available from **www.malecontraceptives.org.**

Four periods a year

Seasonale® has been approved by the Food and Drug Administration in the USA. It contains levonorgestrel and ethinyl oestradiol and is taken consecutively for 84 days, followed by seven pill-free days to produce a withdrawal bleed. Trials showed a similar effectiveness to conventional combined oral contraceptives. Some of the comment surrounding this alternative has suggested that it is healthier to avoid menstrual loss, a statement that cannot be backed up by evidence at present. Making Seasonale available will expand women's contraceptive options and increase convenience for some. This advance should not be undermined, however, by over-promising and over-promotion or by stigmatising menstruation. More information is available from **www.womenshealthnetwork.org.**

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