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 seems 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 I always try 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) produces reviews of the pill. In 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.’ This 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 difficulty for clinicians is that 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.’ 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 reviews is affiliated to the company that manufactures the pill. If this is an issue, then we must consider that none of those undertaking the desogestrel-only pill review have any relevant associations with manufacturers of other progestogen-only pills (POPs), who are unlikely to have different views about their own products.

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. We really are 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 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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Letters

CEU New Product Review of the desogestrel-only pill

Madam

The Clinical Effectiveness Unit (CEU)’s product review of the desogestrel-only pill and the recent article ‘Is Cerazette the minipill of choice?’ in the Drug and Therapeutics Bulletin (DTB)1 are both good reviews of the issue with most 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 citing 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 present. Pending more data, evidence-based medicine (EBM) must be subjected to informed clinical judgement, based on all available evidence (including the reported pharmacology of the product) and – dare I say it? – clinical common sense.

The statement of the DTB1 is not inaccurate when it states (in nearly the same words as the CEU?) ‘There is insufficient evidence on whether it [Cerazette] is a more effective contraceptive than other POPs in terms of efficacy’. The evidence on the first trimester pregnancy rates for the desogestrel-only pill could only be subject to detailed 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 report’s own words) is ‘its primary mode of action’. Since when was such data of any help to a 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 good non-compliance, the pregnancy rate found was only 0.17 (CI 0.004–0.928) per 100 woman-years. Such a low rate (with an upper bound of 1 per 100) would not be considered by any regulatory body as being materially different from non-pregnant women in this age group. And I see no special reason to use it in women with inflammatory bowel disease. And I see no special reason to use it in women with inflammatory bowel disease.

The DTB1 says (in nearly the same words as the CEU?) ‘In all aspects the desogestrel-only pill is currently not recommended for use in women with inflammatory bowel disease’. I would judge the chances of this product not being recommended by the CEU staff to be very, very, very small. So it would be equally valid for the two reviews to have concluded: ‘There is insufficient evidence on whether it [Cerazette] is 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 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 should not be subject to informed clinical judgement, based on all available evidence (including the reported pharmacology of the product) and – dare I say it? – clinical common sense.

The Clinical Effectiveness Committee soon after the Unit was established. This eight-point code of practice does not include an explicit statement of interests. One would judge the chances of this product not being recommended by the CEU staff to be very, very, very small. So it would be equally valid for the two reviews to have concluded: ‘There is insufficient evidence on whether it [Cerazette] is 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 any relevant associations with manufacturers of other progestogen-only pills.’

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