EDITORIAL

How to read articles

I was once told how to read journal articles. It was as follows:

Read the title and if you can't understand the purpose of the publication – forget it.
If you can understand the title and it interests you – read the abstract (well, the conclusions at least).
If the outcome is NOT what you expect – read the article.

This facile view does contain some truths. None of us has time to read journal articles outside our immediate spheres of interest, so skimming through the specialist journals is all we can manage. The most significant O&G information is published in the 'big four' general journals, these being the *British Medical Journal*, *The Lancet*, the *New England Journal of Medicine* and the *Journal of the American Medical Association*. They have the largest circulations, the highest citation indices, the highest impact factors and the most prestige. But even these august publications are having to adapt to the challenge of on-line journals and the lower costs of receiving medical information electronically. The *BMJ* has been the most progressive in its make-over, and if you have not seen a copy for the past few years you will be surprised to find it more like the *Financial Times* or *Newsweek* than the traditional journal of old.

But educationally we build on knowledge. It is the only way we learn. We gain experience through play as children or through the building blocks given at school, but everything depends on what you – the learner – brings to the situation. So if your time is limited, find out what is counterintuitive and focus on that.

Much in the journals these days seems to be stating the obvious, simply because modern statistical gathering has become sophisticated enough for data to be produced demonstrating that what we always suspected is now evidence-based. Cochrane Reviews have allowed us to replace intuition with facts. Non-inferiority trials often show one method of management to be no better or worse than another, which sometimes threatens our jealously preserved prejudices about 'our' way of doing things.

In the recent past, however, there have been articles published that could sway practice but need to be read with circumspection before we are persuaded to adopt new stances and clinical practice. Examples are as follows.

Think again – the WHI trial revisited

The Women's Health Initiative trial compared a combination of conjugated equine estrogens (CCE) 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg with placebo in 16 000 women. The women were recruited in the 1990s and were supposed to participate in the study for 8 years, but the trial was stopped after 5 years because the risks outweighed the benefits.

Although mortality was not affected during the trial, adverse effects of the active medication occurred with an increase in the risk of cardiovascular effects, breast cancer and stroke which were not balanced by the beneficial effects of a lowered risk of fracture and colorectal cancer. After the trial was stopped the women were still followed up, and Heiss *et al.*[1] showed that 3 years later the cardiovascular consequences had all but disappeared but there were more malignancies – including breast – in those who had taken the hormones compared with placebo, which resulted in a somewhat higher all-cause mortality. Their global index of risk versus benefit remained unchanged with a hazard ratio of 1.12, indicating the lack of positive outcomes in prescribing this particular combination of hormonal therapy under the circumstances of the trial.

The WHI trial continues to generate bad news. The negative effects of oestrogens on clotting on older women were not unexpected, but at least they appear to wear off after 3 years, while the carcinogenic effects appear to take longer to subside, which may be a function of the rate of progression of the neoplasia. The women will continue to be followed up.

Comment

Critique of the WHI trial has been considerable and justifiable. To start with, the hormones chosen were inappropriate. Although the CEE/MPA combination was the most popular prescription in the USA at the time the trial began, very few clinicians in other countries would have supported such a choice of oestrogen – nor would the dose or mode of delivery have been endorsed.

Secondly, the age of the population being studied did not match those usually starting HRT. The recruits were aged between 50 and 80 years with a mean age of 63 years. To give hormones designed to treat menopausal symptoms to women well past the climacteric in the

hope of preventing chronic disorders seems optimistic. To measure the quality of life outcomes was misguided, especially since the vast majority were asymptomatic.

Thirdly, the women in the cohort were not risk-free to start with; 70% were overweight or obese and 38% were hypertensive, hardly a group for which clinicians would normally prescribe medication with potentially thrombophilic properties.

Finally, the interpretation of the WHI results was far-reaching. There was an over-reaction against all oestrogen prescribing because of the trial's results, with a blanket condemnation of all replacement therapy and understandable reluctance to research the long-term effects of more appropriate hormones initiated at more logical times. In retrospect, the wrong hormones were given to the wrong group of women, at the wrong age, by the wrong route, in the wrong dose. Unsurprisingly, the researchers came up with the wrong result.

Beware human papillomavirus (HPV) testing as a screening tool

There is strong evidence of cause and effect between recurrent high-risk HPV infection and cervical neoplasia. It is tempting to use the new technology of HPV DNA testing to screen women to determine their vulnerability to potential malignancy, but caution needs to be exercised.

Finding evidence of oncogenic HPV types on routine screening is difficult to interpret and, especially in young women, can lead to over-investigation, particularly unwarranted colposcopy. This conclusion is supported by a prospective study of dual cytology and HPV testing on 10 000 women in the US by Datta *et al*.[2]

For example, in women over 30 years of age with a normal Pap smear finding, 10% had positive high-risk HPV tests and would be candidates for repeat testing or further investigation.

An editorial by Sawaya[3] warns about 'shoot first and ask questions later' approaches to new screening technologies and reiterates the need for informed consent before testing and being prepared to discuss the implications of positive results with patients. He does not see the wisdom of introducing dual Pap and HPV screening at this stage of our knowledge.

The technology is available to test for and type HPV from vaginal swabs using the polymerase chain reaction, which indicates recent infection to a very high degree of accuracy – as little as the equivalent to 1 pg of HPV DNA per millilitre. Research indicates that the molecular screening may well be a more sensitive means of screening than cytology, and it could be incorporated into programmes or used in triage algorithms in resource-rich situations.[4,5] Whether it should be introduced to precede, or in tandem with, cytology or for clarification of equivocal results is not clear from the scientific point of view.

What have not been aired are the moral and ethical points of view. Pragmatically, we have to consider how such testing could wreck a relationship.

As clinicians we need to prepare ourselves for a scenario such as the following:

A young woman comes to you for a check-up as she is sexually active. She has had one previous sexual relationship, some time ago. You do a Pap smear and a HPV test. The cytology is normal but the PCR is positive for an oncogenic HPV type, so you ask her to come in and have the results explained to her.

Are you prepared to answer the following questions?

Have I been infected by my present partner?

Could I have been infected by my previous partner?

How long ago could the infection have occurred?

How do I know if I got it from my previous or my present partner?

Should I tell my previous partner?

How long will I stay at risk of developing cancer?

If I have been infected by my present partner – should he tell his previous partner/s?

If not infected by my present partner – have I passed it on to him?

Can you test him?

Will he harbour the virus and re-infect me?

Should we use condoms from now on?

How long will he stay infected?

Will he infect others if he moves on from our relationship?

Will he need to tell his next partner?

Can't you treat us with antiviral medication?

Are you or am I morally or legally obliged to notify my partner?

Should you not have asked for informed consent before testing me?

The possibility of relationship fallout is considerable.

We need more than scientific evidence of 'increased sensitivity' before embarking on routine HPV DNA testing. The potential misery it could generate needs to be carefully weighed against any real gain. Remember: First do no harm.

There is a wealth of wisdom in modern journals – but do read them critically.

Athol Kent
Editor

1. Heiss G, Wallace R, Anderson GL, *et al*. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA* 2008; 299:1036-1045.
2. Datta SD, Koutsky LA, Ratelle S, *et al*. Human papillomavirus infection and cervical cytology in women screened for cervical cancer in the United States, 2003 - 2005. *Ann Intern Med* 2008; 148: 493-500.
3. Sawaya GF. Adding human papillomavirus testing to cytology for primary cervical cancer screening: shooting first and asking questions later. *Ann Intern Med* 2008; 148: 557-559.
4. Mayrand M-H, Duarte-Franco E, Rodrigues I, *et al*. Human papillomavirus DNA versus papanicolaou screening tests for cervical cancer. *N Engl J Med* 2007; 357: 1579-1588.
5. Naucler P. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. *N Engl J Med* 2007; 357: 1589-1597.