Hypercoagulation and pregnancy

In the developed world, venous thrombo-embolism (VTE) and pulmonary embolism (PE) are the leading causes of maternal mortality. The prevention, diagnosis and management of PE are crucial to reducing mortality rates (Bourjeily *et al*., *Lancet* 2010; 375: 500-512).

- The incidence of VTE is 10/10 000 pregnancies.
- This is 10 times the incidence in matched non-pregnant controls.
- Deep-vein thrombosis is three times more common than PE.
- Pregnancy-related DVTs are 85% left-sided.
- The incidence of VTE in the first 6 weeks postpartum is 5/10 000 deliveries.
- The authors cite caesarean section as a possible risk factor.

Postoperative DVT

Both men and women are at increased risk of VTE postoperatively. This is well known, and preventive measures should be used in all women undergoing major gynaecological surgery. Evidence is accumulating that the risk lasts longer than 2 weeks after surgery – and may extend to day-care surgery.

Sweetland *et al*. (*BMJ* 2009; 339: b4583) report on data derived from the UK Million Women Study and show that the risk of VTE reaches its peak 3 weeks after surgery and remains elevated for 12 weeks.

A middle-aged woman having an operation is 70 times more likely to be admitted to hospital with a VTE than someone not operated on during the first 6 weeks after inpatient surgery, and the risk is still present for another 6 weeks thereafter. These facts are 'a wake-up call to all surgeons', says Cohen (*BMJ* 2009; 339: b4477), because most prophylaxis is confined to hospital stays or the week thereafter, missing the period of highest risk. Even the latest figures are probably an under-estimate, as most VTEs are undiagnosed, untreated and managed outside hospitals.

The UK National Institute for Health and Clinical Excellence (NICE) has published recommendations for all patients in hospital, and estimates that only half of those who should receive prophylaxis actually get it. The summary by Hill *et al*. (*BMJ* 2010; 340: C95) enumerates the following risk factors: cancer patients, age over 60 years, admission to critical care, dehydration, thrombophilia, obesity, common co-morbid medical conditions such as heart disease, metabolic, endocrine or respiratory pathology, infections or inflammatory diseases, a personal or close family history of VTE, hormone use, and smoking.

Preventative strategies include practical measures of mobility and hydration, mechanical devices to aid circulation, and drugs such as fondaparinux sodium and low-molecular-weight heparin (or unfractionated heparin). These drugs should be continued until 'the patient is no longer at increased risk of VTE'. Given the most recent data, this is clearly longer than was previously thought. It is essential that every woman leaving hospital after surgery should receive active discharge management.

Skin prep

The prevention of operative infections involves a combination of surgical technique, patient healing ability and antimicrobial prophylaxis. Pre-operative antibiotics have found favour in many procedures, including caesarean sections, but skin preparation formulas have received less attention. A trial has now been published to redress this lack of evidence in a broad series of patients undergoing major surgery, including gynaecological cases (Darouiche *et al*., *NEJM* 2010; 362: 18-26).

In the USA the most popular skin preparation is 10% aqueous povidone-iodine, and in their trial the authors test it against 2% chlorhexidine gluconate and 70% alcohol. The chlorhexidine solution proved much better than the iodine at reducing superficial and deep wound sepsis immediately and over the first 30 postoperative days. Few side-effects were noted, so it remains to be seen if these results will change policies, for example at caesarean section.

HPV vaccination and testing

Human papillomavirus (HPV) vaccinations hold a commanding position in the prevention of cervical cancer. There is accumulating evidence that the protection offered by the vaccines is enduring, which is encouraging if extensive programmes are rolled out in developing countries where booster doses would increase the complexity of delivery.

The latest data show that Cervarix is effective in preventing recurrent HPV infections in HPV-naïve young women who were vaccinated 6 years previously. In a trial by the GlaxoSmithKline Vaccine HPV-007 Study Group (*Lancet* 2009; 374: 1975-1985) the vaccine prevented any cervical neoplasia associated with types 16 and 18, as well as most other lesions independent of HPV DNA type.

Possibly more significantly, levels of neutralising antibodies were sustained in the study population. Naturally occurring infections are superficial and do not provoke strong antibody responses, unlike the injected vaccines, which result in high levels of circulating antibodies. The vaccine antibodies peak at 7 months then taper off, but it appears as if they are maintained – at least from 3 to 6 years – suggesting long-term immunity with models of 20 years being quoted.

These encouraging data should galvanise international efforts such as the GAVI Alliance to provide vaccines for the poorest countries. Eighty per cent of cervical cancers occur in developing countries, and if the vaccine price could be reduced to US$10, cost-effective worldwide protection is possible (Clifford, *Lancet* 2009; 374: 1948-1949).

The situation in developed countries is eloquently drawn together in an article by Crosbie and Brabin (*BJOG* 2010; 117: 137-412), which opens the question of future screening by cytology and HPV DNA testing.

The present consensus is that cytology screening before the age of 21 years is not recommended. Sawaya (*NEJM* 2009; 361: 2503-2505) describes the evidence in favour of this age restriction as 'compelling' and suggests that earlier testing simply leads to unnecessary and harmful interference. The updated American guidelines from the American College of Obstetrics and Gynecology (*Obstet Gynecol* 2009; 114: 1409-1420) are summarised as follows:

- Age less than 21 years — Avoid screening
- 21 - 29 years — Screen every 2 years
- 30 - 65 years — May screen every 3 years
- 65 - 70 years — May stop screening

The 'may' refers to low-risk women with three consecutive negative smears.

These pronouncements are sure to put question marks against the traditional American annual 'pelvic exam', but the motivation is as it should be – to balance benefits and harms to the individual and not financial or political considerations.

The situation in terms of HPV DNA testing is far more complicated. Because HPV infections are common and self-limiting in young women, HPV testing is contraindicated. Our state of knowledge is evolving for 35+-year-olds, and it may be that HPV testing followed by cytological triaging will prove the most cost-effective strategy.

It is too early to change policies for HPV testing, and cytology itself will change as vaccinated women may only be required to start screening later than age 21 years as the 'non-16 and 18-type' neoplasms occur at a later age. Cytology may improve as well because molecular markers or cell-cycle detection may make the prediction of progression likelihood more accurate.

Screening is rightly being reviewed as the evidence accumulates. The sad thing is that those most at risk – the poor, the disadvantaged and women in developing countries – are least likely to be vaccinated and least likely to present for screening. The screening net needs to be widened as well as refined.

Cervical screening for lesbians

Should lesbian and bisexual women go for the cervical cancer screening? Yes they should, according to www.cancerscreening.nhs.uk/cervical/publications/screening-lesbians-bisexual-women.pdf. The human papillomavirus is transmitted by skin-to-skin contact and has been found to be present in 3 - 30% of lesbians and bisexual women in recent surveys. HPV can be acquired by oral transmission and sexual play, so these women need to make informed choices about joining screening programmes.

Smoking in pregnancy

Apart from being associated with growth restriction, sudden infant death syndrome and childhood asthma, smoking in pregnancy now appears to be a risk factor for behavioural problems. Looking at children in school in Germany, Ruckinger *et al*. (*Environ Health Perspect* 2010; 118: 150-154) noted that those exposed to tobacco smoke *in utero* were twice as likely as those not exposed to have behavioural, emotional and relationship problems as well as hyperactivity. The differences persisted after adjusting for parental education, age and social status. It seems that exposure *in utero* is a more potent cause of childhood difficulties than postnatal exposure.

The long list of harmful effects of smoking on the fetus includes miscarriage, growth restriction, premature rupture of the membranes and placenta praevia. Now a new study adds prematurity due to iatrogenic delivery (Lu *et al*., *Am Coll Prev Med* AGM 2010, Abstract 212669). Pregnancies in women who smoke are correctly considered high risk, should have high surveillance, and require early delivery more frequently than pregnancies in non-smokers.

Emerging literature links smoking in pregnancy to childhood asthma and obesity – and so the list grows.

Irrespective of pregnancy, it is always a positive move to quit smoking. Even lung cancer sufferers stand to gain from stopping compared with those who continue (Treasure and Treasure, *BMJ* 2010; 340: b5630). Asking about smoking in all our patients and encouraging quitting should be on our list of 'essential questions'.

HPV vaccines and pregnancy

The initial reports on the quadrivalent human papillomavirus vaccines and pregnancy look promising. Clearly administering the HPV vaccine to young women needs to be checked out for safety in relation to pregnancy, and two reports have now been published.

Dana *et al*. (*Obstet Gynecol* 2009; 114: 1170-1178) have access to the Pregnancy Registry for Gardasil (Merck), which monitors miscarriages, stillbirths, live births and fetal anomalies in women exposed to the HPV vaccine. Over 500 pregnancies have been recorded, and the rates of adverse outcomes are not statistically different from those anticipated from a non-exposed control group.

Garland *et al*. (*Obstet Gynecol* 2009; 114: 1179-1189) looked at the outcomes of pregnancies of women participating in the initial vaccine trials in which they could have received the vaccine or placebo. The 4 000 pregnancies were roughly evenly distributed between those who had received and those who had not received the active vaccine, and the numbers of congenital abnormalities were not statistically significantly different. All comments are guarded because of the preliminary nature of the research, but so far there is no cause for pessimism.

Designer vagina

Vaginal rejuvenation, G-spot amplification, revirgination and designer vaginoplasty are all being marketed to 'enhance' normal vaginal anatomy. In addition, labial surgery is offered for those dissatisfied with their vulval morphology. These procedures are presented as risk-free solutions to women's concerns about their genital structure and function.

It is a source of amazement to the vast majority of gynaecologists that these operations are promoted by their colleagues. Most feel these are greedy doctors exploiting gullible patients – but journals are loath to put matters that bluntly. What they are saying is that there is no scientific background to support such surgery. Liao *et al*. (*BJOG* 2010; 117: 20-25) confirm that no meaningful studies endorse cosmetic genital surgery in treating sexual dysfunction.

No evidence exists in favour of this type of surgery and the possibility of harm is real, so it is irresponsible and unethical to operate where no pathology exists. Or is this just plastic surgery in another guise?

HRT and endometrial cancer

Eighty per cent of endometrial cancers are type 1 tumours. These are mostly low-grade adenocarcinomas with a good prognosis and well-described risk factors such as nulliparity, obesity, hyperoestrogenism, other cancers, tamoxifen use and inadequate progestin cover when taking oestrogens.

In contrast, type 2 tumours such as serous papillary carcinomas, clear-cell adenocarcinomas and squamous carcinomas are not derived from hyperplastic endometrial lesions and carry a poorer prognosis. They do not have clearly associated risk factors.

It is the type 1 lesions that can be protected against by the addition of progestins in HRT, and data are accumulating about the safest means of administering the progestins. Jaakkola *et al*. from Finland (*Obstet Gynecol* 2009; 114: 1197-1204) compared continuous with sequential progestin additions to oestrogen therapy in women over the age of 50 years. Those using progestins continuously had far greater risk reduction than those taking progestins sequentially. The type of progestin did not make a difference, and nor did the route of administration.

The absolute numbers are interesting. Using the sequential therapy, 1 000 women would develop 8 extra cases of endometrial cancer over a 10-year period, whereas the same number of women over the same number of years using continuous therapy would be likely to develop 4 cases.

Drugs and breast cancer

Conventional treatment of breast cancer includes surgery, radiation, chemotherapy and hormonal therapy. It now seems that women who in addition take aspirin may be protecting themselves from recurrence or metastases. Holmes *et al*. (*J Clin Oncol* doi:10.1200/JCO2009.22.7918) accessed data from the Nurses Health Study and found that breast cancer survivors had a better prognosis if they took aspirin regularly. Although this was an observational study, the results appeared robust and did not differ according to stage, menopausal status, body mass index or oestrogen receptor status. Promising.

Equally, there are some drugs that breast cancer survivors should avoid. Drugs of note are the selective serotonin re-uptake inhibitor (SSRI) antidepressants paroxetine and fluoxetine in women who are taking tamoxifen. Tamoxifen has a major protective effect against cancer recurrence and requires a particular liver enzyme to convert it to its active metabolite. This enzyme is inhibited by paroxetine or fluoxetine, which reduce tamoxifen's effectiveness.

Given the prevalence of mood depression in breast cancer sufferers, it is not surprising that nearly a third of them resort to SSRI treatment, but the researchers (Kelly *et al*., *BMJ* 2010; 340: C693) suggest alternative medication to derive the full benefit of hormonal adjuvant therapy.

Oxytocin abuse again

Obstetricians tend to use too much oxytocin. Used to initiate or augment labour, it is the commonest cause of asphyxial damage to infants from hyperstimulation leading to indefensible medico-legal cases. It is also dangerous for the mother.

In large doses it is antidiuretic, and even at therapeutic doses it is responsible for major shifts in blood distribution. It causes subcutaneous vessel vasodilatation and splanchnic bed plus coronary vessel vasoconstriction, with a resultant drop in mean arterial pressure (MAP), while stimulating myocardial conductivity and heart rate (Ajmal, *BJOG* 2010; 117: 118-119). These effects are especially noticeable when it is given as a rapid intravenous bolus at caesarean section to contract the uterus after delivery.

Jonsson *et al*. from Sweden (*BJOG* 2010; 117: 76-83) highlight the cardiac and blood pressure effects of 5 IU and 10 IU of oxytocin given at caesarean section, which cause a significant drop in MAP, being 9 mmHg for 5 units and double that for 10 units, as well as ST depression on ECG. They question the need for the higher dose and the speed of infusion, with the UK National Institute for Excellence recommending 5 IU of oxytocin given slowly as an intravenous bolus. Maybe a diluted solution over a longer period would be less risky but equally effective. 'More is better' certainly does not apply, and increases the risks of serious side-effects.

Menopause transition data

The Study of Women's Health Across the Nation (SWAN) is an American initiative that documents women through their menopause transition. Over 1 000 women are being monitored from about the age of 47 years for the next 10 years of their lives.

Sutton-Tyrell *et al*. (*J Am Coll Cardiol* 2009; 54: 2366-2375) report that deleterious lipid changes coincide with the cessation of menstruation. More precisely, in the year before and after her final menstrual period a woman is likely to experience substantial increases in total cholesterol levels. Also raised are low-density lipoproteins and apolipoprotein B, which are associated with raised cardiovascular risk. The changes are independent of age and ethnicity. Quite how these changes can be influenced by exogenous hormones or lifestyle remains to be seen.

Postmenopausal cervical ripening

Cervical ripening is usually thought of in the context of pregnancy. Enhancing cervical dilatation prior to uterine evacuation or the induction of labour is well documented, but little is known about 'ripening' in postmenopausal women.

When access is required to the uterus to investigate pathology via a hysteroscope, cervical dilatation is desirable to allow the atraumatic passage of a 10 mm diameter operating instrument. Damage from a grasping volsellum or tenaculum to the anterior lip or forcible expansion with Hegar dilators to the cervical canal can be reduced by pre-operative preparation. Oppergaard *et al*. from Denmark (*BJOG* 2010; 117: 53-61) studied the use of misoprostol prior to hysteroscopic evaluation in postmenopausal women. All the patients were undergoing endometrial investigation and had received 2 weeks of treatment with 25 µg of vaginally delivered oestradiol. They were then allocated to 1 000 µg misoprostol or placebo. The operators were blind to the immediate pre-treatment, which was self-administered by the patients the evening before.

The misoprostol was effective in that it allowed less force to be used in dilating the cervix. The method was acceptable to the patients, it is cheap, and there were minimal side-effects.

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