HPV vaccination in older women

The two vaccines currently available against the human papillomavirus (HPV) are highly effective in producing antibody responses. These responses are robust, are likely to be long-lasting and show every sign of protecting against cervical changes associated with cancer. Research has been conducted mainly in younger women, and vaccinations have been initiated in girls aged 11 - 13 years, with catch-up vaccinations variously implemented up to the age of 25 years.

Assuming a sexual debut between the ages of 15 and 25 years and knowing that women will have a peak incidence of HPV infection 5 - 10 years later, the interest shifts to a more mature group. Women are also marrying later and having more partners than they did 30 years ago. In the USA, 40% of women have married and divorced by the age of 55 years, so the window of sexual freedom and HPV exposure is widening. Clearly, women will want to know if the vaccine is indicated for them if they are over the age of 25. Is it efficacious and safe for their use? Neither of the commercially available vaccines claim to be therapeutic in that they do not hasten the regression of existing infection, but their place in prophylaxis in women older than 25 years in unclear.

A study by Munoz *et al*. now shows the quadrivalent vaccine to be effective and safe in the age group 25 - 45 years (*Lancet* 2009; 373: 1949-1957). They conducted a placebo-controlled trial among healthy women, some of whom were HPV DNA-negative while others were positive, and showed high levels of seroconversion following the vaccination course. Side-effects were rare, so it is up to each woman to decide whether to be vaccinated or not.

Prevention is better than cure

Prevention means just that. Preventing the condition – not detecting it early or in its treatable stages, but stopping it from occurring in the first place. This self-evident fact is confused with screening and normal ageing. As those in the forefront of family planning, we embrace preventive medicine, but the 'next big thing' will be the prevention of obesity with its looming threat of the metabolic syndrome.

The prevalence of type 2 diabetes is rising alarmingly, especially in Asian countries – for example from 1% to 6% in China over the last 20 years – so it seems that personal pollution is going hand in hand with environmental pollution (*JAMA* 2009; 301: 2129-2140).

In case you think this is for youngsters only, a large study in a group of men and women over 65 years old looked at exercise, healthy eating, smoking, alcohol and BMI. Those who had low risk factors were considerably less likely to develop type 2 diabetes, leading the authors to conclude that 'Overall 9 out of 10 new cases of diabetes appeared attributable to these 5 lifestyle factors' (Mozaffarian *et al*., *Arch Intern Med* 2009; 169: 798-807).

Check diet, exercise and other habits, but don't forget to laugh. Laughter decreases pulse wave velocity, which is an index of arterial stiffness (*Psychosomatic Med* 2009; 71: 446-453). So hold it lightly – or else!

Lifestyle and health

Articles keep appearing linking lifestyle to health. Two of the latest studies show how doctors and nurses live healthier, longer lives if they adhere to sensible lifestyles.

The first study tracked the health of 20 000 male doctors from their mid-50s to their mid-70s – all were in good health initially (Djousse *et al*., *JAMA* 2009; 302: 394-400). Their risk of heart failure during this time varied according to the following factors: hypertension, normal body weight, not smoking, regular exercise, moderate alcohol intake, and eating cereals, fruit and vegetables. Those with all the risk factors had a 20% risk of heart failure and those with none of the risk factors 10%.

In the second study – also from America – over 80 000 nurses were followed up for 15 years to see whether the onset of hypertension was associated with modifiable risk factors of lifestyle. The Nurses Study traced the women from adulthood to early middle age. The factors measured were BMI less than 25, daily vigorous exercise, healthy diet, modest alcohol intake (up to 10 g/day), conservative use of analgesics and supplemental folic acid intake.

Each of the 6 factors was shown to be effective in preventing hypertension in this group of women, prompting the unusual comment that adherence to all aspects was 'associated with dramatic reductions in the incidence of hypertension' – strong words from Forman *et al*. (*JAMA* 2009; 302: 401-411).

So eat, drink and be merry, but make it the right stuff in moderation together with other lifestyle factors for a long and healthy life.

Anti-emetics in early pregnancy

Metoclopramide is the anti-emetic of choice in early pregnancy in many European countries. In the USA it is used in severe cases, but it is not 'labelled' for treating gestational nausea and vomiting and there is surprisingly little evidence of its safety. To remedy the dearth of data concerning its use in the first trimester, Matok *et al*. from Israel looked into its track record in over 80 000 pregnancies (*NEJM* 2009; 360: 2528-2535).

About 5% of those whose records were scrutinised had used metoclopramide in the first 13 weeks of gestation, but the children exposed had the same rate of congenital abnormalities as those not exposed – around 5%. Rates for perinatal mortality, premature delivery and low birth weight were also comparable. Although the study was observational, it is likely that prescribed medications were fulfilled and taken, so it appears that metoclopramide is safe to use in early pregnancy.

Thalidomide caused a drug debacle, with many children being born with limb deformities after maternal ingestion during embryogenesis. Only now has the pathology it caused become unravelled. Therapontos *et al*. (*Proc Natl Acad Sci* 2009; 106: 8573-8578) have shown in experimental animals that thalidomide inhibits angiogenesis in early gestation and the loss of immature blood vessels that should supply limbs leads to stunted growth. This explanation, rather than inflammatory or metabolic mechanisms, clarifies the specificity of thalidomide embryopathy and has significant implications for its therapeutic application.

The risk of pre-eclampsia

The risk of a woman having pre-eclampsia in her first pregnancy is greater than in subsequent pregnancies. This is accepted information, but what are the modern data on subsequent pregnancies in woman who did – or did not – have pre-eclampsia the first time around?

Hernandez Diaz *et al*. from Sweden now provide the odds for their countrywomen in their first and in their next gestations (*BMJ* 2009; 338: b2255).

- Of 764 000 women, 4% had pre-eclampsia in their first pregnancy.
- Of these 4, 15% had pre-eclampsia again in their second pregnancy.
- Of the 96% who did not have pre-eclampsia, only 1% had pre-eclampsia in their second pregnancy.
- If a woman had pre-eclampsia in her second pregnancy only, then her risk is 15% for her third pregnancy.
- If a woman had pre-eclampsia in her first and second pregnancies, her risk rises to 30% for her third pregnancy.
- If a woman had no pre-eclampsia in her first or second pregnancies, her risk is 1% for her third pregnancy.

Recurrence rates were higher for women having pre-eclampsia associated with deliveries before 34 weeks' gestation than for those having pre-eclampsia with a longer gestation, suggesting two distinct conditions: 'a severe recurrent early-onset type affected by chronic factors, genetic or environmental, and a milder sporadic form affected by transient factors'.

Another study from Scandinavia, this time Denmark, links other pregnancy complications to their reappearance in a second pregnancy (Lykke *et al*., *Obstet Gynecol* 2009; 113: 1217-1224). Preterm delivery, growth restriction and pre-eclampsia all showed a pre-disposition to recurrence, and the data echoed a 'dose-response relationship' with early onset indicating a greater subsequent risk.

US sex education policy

JASS has been critical of the US Federal Government's stand on sex education for teenagers. Under the previous administration, the only funded programmes were abstinence-only instruction with purity covenants and virginity pledges as part of the package. Despite congressional commissions concluding that these policies did not work, $1.3 billion was squandered on them between 2001 and 2008 (Tanne, *BMJ* 2009; 338: 1232).

The Obama team budget has reversed the legislation and provided extra funds for evidence-based instruction promoting abstinence while providing medically accurate, age-appropriate information to young people who are sexually active.

Preaching abstinence before marriage clearly has not worked in the USA, which still has – by far – the highest teenage pregnancy rate of any developed country. In addition, the latest statistics show that 40% of women giving birth are unmarried, more than double the figure in 1980 (www.cdc.gov/nchs/olata/databriefs/db18.pdf).

Pelvic muscle training and birth outcomes

Pelvic floor muscle training in pregnancy is not commonly taught. There are stories of athletes having muscles that are too strong and inelastic as well as claims that regular training reduces perineal trauma, but little objective evidence exists.

Extensive data from Norway on nearly 20 000 women in their first pregnancy sheds some light on the subject (Bo *et al.*, *Obstet Gynecol* 2009; 113: 1279-1284). The fact that these were volunteers allowed high rates of follow-up with collection of accurate information. Their mean age was 28 years, and their mean BMI of 24 speaks volumes for their lifestyles.

Even in this high socio-economic group, regular pelvic floor training was carried out in less than one-third of women. Those who did regular training fared no better than those who did not. There was no difference between trainers and non-trainers in terms of episiotomy rates, tears, instrumental deliveries and caesarean section rates.

Antenatal testing

There is a fair amount of nucleic acid circulating in the maternal circulation during pregnancy. More than 90% of the DNA is maternal but the rest is fetal, originating from the placenta, and this is of great interest in terms of genetic diagnosis. This cell-free DNA consists of short fragments of nucleic acids rather than whole chromosomes and can be detected from 4 weeks' gestation. It has a short half-life of minutes and is undetectable 2 hours after delivery.

Although the technology for recovering the fetal cell-free DNA is complex, there are opportunities for both routine screening and specific diagnoses of rare inherited disorders (Wright and Chitty, *BMJ* 2009; 339: b2451). Its potential for non-invasive determination of sex and rhesus typing as well as for aneuploides is considerable, as the current methods involve both screening and invasive testing.

In the real world, there are many problems concerned with screening for chromosomal defects. A study of over 750 000 pregnancies in California, highlights some of these (Kazerouni *et al.*, *Obstet Gynecol* 2009; 114: 50-58). The authors found that the odds of a woman having a Down syndrome-affected fetus increased from 1:1 500 below the age of 20 years to 1:1 000 at 30 years to 1:100 at 40 years to 1:40 at 45 years.

Antenatal detection measures are by no means perfect.

- Rates vary with age, with less than two-thirds of affected infants picked up in women below the age of 35 years.
- About a third of women with pregnancies resulting in a Down syndrome delivery had a negative maternal serum triple test.
- Conversely, only half of those who tested positive opted for definitive chorion villus or amniocentesis testing.
- Of those undergoing amniocentesis and testing positive for Down syndrome, 60% had a termination and 26% a live birth of an affected neonate, the balance having an intra-uterine death or being lost to follow-up.

It seems that screening has to become more sophisticated, by additional biochemistry, adding ultrasound or developing cell-free DNA testing. Although the latter is attractive, it is not without its ethical pitfalls as it still will place the onus on the parents to opt for investigations that carry serious consequential steps.

Of all congenital abnormalities, chromosomal defects are not the most prevalent. Although the risk of Down syndrome and other aneuploides is known to be age-related, knowledge of non-chromosomal anomalies (NCAs) is lacking in terms of maternal age.

Eurocat is a population-based prevalence study that records congenital anomalies in one-third of European births and can therefore be used to calculate the incidence of non-chromosomal anomalies across age groups (Loane *et al.*, *BJOG* 2009; 16: 1111-1119). Since the mean age of pregnant women is rising annually in Europe, reassurance about NCAs is important.

The latest data include nearly 2 million births and show a shallow U-shaped curve relating NCAs to maternal age. The incidence varies from 24/1 000 to 26/1 000, which allows the authors to state that 'Reassurance can be given to older mothers that their age in itself does not confer extra risk for NCA.'

What concerns the authors is the fact that teenage and 40-plus pregnancies are related to poor socio-economic status and may well be linked to unsuitable diets and lifestyles that are known to be associated with infections in pregnancy and neural tube defects. Women and their fetuses at the extremes of childbearing age are at risk, but worries about NCAs are not the only significant factors.

Mammography screening

The mammography screening debate is alive and well in the UK. There is general dissatisfaction with the information leaflets sent to women encouraging them to attend the screening programme. The document in question, called 'Breast Screening: The Facts', suggests that there are mainly advantages in participating in the national programme and fails to present the downside.

The advantages are early diagnosis, which is always a good thing, and the reassurance of a negative result. Both these intuitive benefits bear closer examination. Early diagnosis and treatment should make a significant difference to survival, but as Heath from the UK (*BMJ* 2009; 338: 1534) points out, for every 2 000 women screened for 10 years, one death will be avoided. The percentage of women surviving a decade if not screened is 90.2%, compared with 90.25% if they are screened.

But what about the reassurance side of the story? There is a notion that screening appeals to our fear of the future. If we are smart, maybe we can predict what is to come and avoid it. Is screening a psychological trick to manage such a fear? To judge this concept, we at least need to know the chances of damaging false positives, as these can play havoc with our emotions. In fact, the chances of having a lesion discovered that turns out not to be cancer – a false positive – are considerable. This is called over-diagnosis. Over-diagnosis leads to over-treatment. Over-diagnosis and over-treatment have practical and psychological implications. When one considers that the odds are changed very little by screening – and there is the downside – there is plenty to ponder.

The extent of over-diagnosis and over-treatment is significant. For the same group of 2 000 women considered above, 6 extra women will have a lumpectomy, 4 extra women will have mastectomies and 200 will endure the anxiety of further invasive investigations that turn out to be negative. False negatives generate fear, while results are awaited with self-perceptions of being 'at high risk' emerging unnecessarily. Angst about susceptibility is created in partners, mothers, sisters and daughters who start to worry about a family history of breast cancer.

At least 1 in 6 breast cancers detected by screening will be over-diagnosed and over-treated (*BMJ* 2006; 332; 689-692, *BMJ* 2009; 339: b1425, *BMJ* 2009; 339: b2587).The chance of recall – i.e. some further investigation – in a woman aged 50 years who goes for mammography every 2 years till the age of 60 is about 50:50.

Screening mammography is not a 'no brainer'. It is a complex subject that is rightfully being scrutinised objectively. Before we pontificate on the topic, we could do well to guard against potential arrogance in the pursuit of preventive practice, which Sackett (*CMAJ* 2002; 167; 363-364) describes as having three elements:

- Aggressive assertiveness in prescribing what healthy people should do
- Confident presumptions that interventions will do more good than harm
- Overbearing assuredness and a lack of tolerance of those who challenge the principles.

Screening is not the same as preventive medicine, but the same rules apply. Our patients have the right to be told the drawbacks as well as the benefits of mammography and deserve our support when they have made up their minds one way or the other.

In the meantime deaths from breast cancer in the UK continue to decrease. Rates in the last 20 years have fallen from above 40 per 100 000 to below 30 per 100 000 women and seem set to fall further (*BMJ* 2009; 338; b1710). The reductions are across all age groups and are attributable to research leading to improved management and screening (www.info.cancerresearchuk.org/cancerstats/types/breast/mortality).

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