## Preterm birth intervention

Fully three-quarters of preterm births occur spontaneously. In situations where some predisposing factors can be identified, there are primary, secondary and neonatal interventions available to reduce mortality and morbidity. Individualised maternal care, the use of steroids antenatally, surfactant postnatally – together with improved neonatal care – make a difference. The secondary manoeuvres of tocolysis and prolongation of gestation are less well evidence based but appear better researched than primary prevention.

On this score, there is new evidence about repeat courses of antenatal steroids. It has been established that their use does reduce mortality rates, respiratory distress and intraventricular haemorrhage but that weekly courses are associated with reduced birth weight and increased numbers of small-for- gestational-age infants. These side-effects together with developmental concerns have contraindicated serial administration of these agents. However, less clear is the use of a 'rescue' course under specific circumstances. Garite *et al*. (*AJOG* 2009; 200: 248-250) looked at the outcomes of infants whose mothers received steroids but who did not deliver within 2 weeks of this initial management. Where the pregnancy was <30 weeks gestation, membranes were intact and, in the obstetrician's opinion, delivery was imminent – a second rescue course or placebo was administered.

They found the rescue course to be beneficial in terms of neonatal outcomes without detrimental effects of low birth weight, growth restriction or reduced head circumferences.

One of the few primary preventive measures with potential is the use of progesterone in high-risk situations (Tita and Rouse, *AJOG* 2009; 200: 219-224). There are two types of progesterone in clinical practice:

**Natural progesterone.** Doses ranging from 90 mg to 400 mg of natural progesterone per day are administered as a vaginal gel from mid-pregnancy. The vaginal route excludes the hepatic first-pass effects, and it appears that the anatomical proximity to the uterus also has dose-related benefit. There are very few side-effects of sleepiness, fatigue or headache which can occur with oral use.

**17-alpha-hydroxyprogesterone.** This is a synthetic progesterone given in doses from 25 mg to 1 000 mg by intramuscular injection in schedules from weekly to thrice weekly. Side-effects, although common, are mild and are restricted to the injection sites. There are no reports of genital anomalies or gender-role alterations in children up to 4 years of age.

The indications for the use of progesterone are:

- **History of preterm birth.** Women with a history of spontaneous preterm birth have been incorporated in progesterone/placebo trials and the results have been promising. Positive outcomes of longer gestation, higher birth weight with lower mortality and morbidity rates in up to 50% of cases are reported with singleton pregnancies.
- **Short cervix.** Clinical trials have been published on the use of progesterone in women found to have a short cervix on routine screening. Those with a cervix <15 mm in length and who received progesterone had superior outcomes to those in the placebo arms in terms of delay in delivery and neonatal outcomes.
- **Arrested preterm labour.** Studies using progesterone after the inhibition of preterm labour are not robust. Some encouraging outcomes are reported but more convincing studies are required before routine clinical practice can be advised.
- **Multiple pregnancy.** Previous trials have found no advantages in the use of progesterone in multiple pregnancies. It therefore comes as no surprise that the latest study confirms these findings. The Study of Progesterone for the Prevention of Preterm Birth in Twins (STOPPIT) research in the UK was a placebo-controlled trial using 90 mg of progesterone daily per vaginam from 24 weeks (Norman *et al*. *Lancet* 2009; 373: 2034-2040). These pregnancies constituted 1.5% of all their deliveries but had stillbirth rates of 15 per 1 000 and neonatal mortality rates of 20 per 1 000, so improvements through the prolongation of gestation would be welcome. There were no improved outcomes in terms of fetal or neonatal wellbeing, so progesterone cannot be advised for use in uncomplicated twin pregnancies.

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## Eating in labour

What women are allowed to eat during labour varies considerably. There is little evidence to support nil per mouth, water only, fluids only or a light diet, but this does not prevent the holding of strong views.

If there are major obstetric complications with the likelihood of a general anaesthetic being necessary, different rules may apply but most women would like the choice of something comforting and nutritious to eat. A study by O'Sullivan *et al*. from London (*BMJ* 2009; 338: 880) suggests little harm can come from a low-fat, low-residue diet in uncomplicated labours. Allocating women to eating or water only did not affect spontaneous delivery rates or any other outcomes, so maybe there is an argument in favour of a relaxed policy towards oral intake in labour.

## The polypill

The principle of the polypill is simple – put 5 drugs known to reduce cardiovascular risk into a single pill and give it to middle-aged people to prevent cardiovascular disease. It is a great idea, proposed more than 5 years ago by Wald and Law (*BMJ* 2003; 326: 1419-1424) but somehow it has never caught on – or maybe it was not a proposition commercially.

The concept is back in favour with an Indian generic manufacturer making the running (The Indian Polycap Study, *Lancet* 2009; 373: 1341-1352). The capsule being tested contained 3 blood pressure reducing agents, a statin to lower cholesterol, and a low dose of aspirin to attenuate coagulation. The actual ingredients are an angiotensin-converting enzyme inhibitor (ramipril 5 mg), a beta-blocker (atenolol 50 mg), a diuretic (hydrochlorothiazide 12.5 mg), the statin simvastatin 20 mg, and aspirin 100 mg.

In their clinical trial, they report that this combination lowered blood pressure between 5 mmHg and 8 mmHg, reduced LDL cholesterol by 0.7 mmol/l, slowed heart rates by 7 beats per minute and decreased urinary thromboxane $B_2$ (a marker of prostinoid activity). The polypill or, in this case, the polycap, was well tolerated and the drug combinations were not antagonistic.

The overall reduction in cardiovascular risk was estimated to be between 50% and 75% for largely healthy people. Imagine the combination of the polypill and hormone replacement therapy. Will this be the next big controversy in preventive medication?

## Anti-epileptic drugs in pregnancy

It has long been believed that some anti-epileptic drugs constitute a danger to the fetus. Generally, women who suffer from epilepsy should stay on their medication during pregnancy because of the negative effects of seizures on mother and fetus. Certain agents are teratogenic but more subtle effects at lower doses may occur although they are less readily detectable. A new study by Meador *et al*. (*N Engl J Med* 2009; 360: 1597-605) is of considerable value in guiding prescribing.

The authors followed up the offspring of women taking single anti-epileptic drugs (carbamazepine, lamotrigine, phenytoin or valproate) at the age of 3 years and measured their neuro-developmental scores. Using IQ as the cognitive marker and after adjusting for maternal IQ, they found that the children exposed to valproate had scores 6 points lower than for carbamazepine, 7 points lower than for phenytoin and 9 points lower than for lamotrigine. The association between valproate and IQ was dose dependent. This impairment of cognitive function should persuade women of childbearing age with epilepsy not to use valproate as their first-choice drug.

## Endometrial polyp investigation

Transvaginal ultrasound examination of the uterus in postmenopausal women is commonly carried out. Where polyps are found in asymptomatic women, these are routinely removed hysteroscopically. However, there is little evidence that removal and histological examination are necessary practice.

Ferrazzi *et al*. from Italy looked retrospectively at >1 000 cases of women without symptoms who were found to have polypi and an atrophic endometrium (*AJOG* 2009; 200: 235-236). They also studied >700 women who had polypi and abnormal uterine bleeding. Those without bleeding had a 10 times lower prevalence (0.1%) of cancer than those with bleeding. The authors argue for a conservative approach in incidentally diagnosed asymptomatic polypi that are smooth, ovoid lesions and less than 18 mm in diameter. They say a 'see and treat' policy is questionable – so you decide.

## Ovulation induction and cancer

There are concerns that induction of ovulation increases the risks of ovarian cancer. Various hypotheses suggest that different types of ovarian stimulation can lead to a greater risk of later malignancy – a corollary of oral contraceptives' protective effect that is well documented.

The four types of ovulation agents are gonadotrophins, gonadotrophins-releasing hormone, human chorionic gonadotrophin and clomifene. All have been suspected of causing neoplasia but research results are mixed. Now, a definitive study from Denmark has been published, looking at >50 000 women undergoing infertility treatment and following them up for an average of 16 years (Jensen *et al*., *BMJ* 2009; 338: 580-583).

The researchers acknowledge that, as a group, women attending infertility clinics have an increased risk of ovarian cancers but this is not due to ovulation induction agents – neither the type of drug nor its duration of use. They looked at all the women who developed an ovarian malignancy and had sufficient numbers to conclude that ovulation stimulation made no difference to the risk. They concede that most of their patients have yet to reach the usual peak age for ovarian cancer but the results so far are reassuring.

## Ovarian cancer screening

Ovarian cancer is the most lethal of gynaecological cancers, presenting late and having a poor prognosis. This makes it an ideal candidate for screening in the anticipation of early detection and life-saving intervention. Hopes were high for positive results from the large trial using serum CA 125 and transvaginal ultrasound as the screening tools (Partridge *et al*. *Obstet Gynecol* 2009; 113: 775-783).

A sample of 35 000 women who were middle-aged and healthy were allocated to undergo the two screening modalities annually or 'usual care'. The number of women having both tests positive – an overall positive result – was less than 1 per 1 000 during any given year of the trial. These women had laparotomies but only 1 in 20 turned out to have ovarian cancer.

Even if one accepts this enormous screening effort plus the chances of a negative operation, there was still another vital question to be answered. Were the **early** cancers found amenable to successful intervention? Regrettably, fully 80% of those detected were already advanced lesions so the screening made no difference to the life expectancy of these women.

We remain unable to pick up – at an early enough stage – the 4 per 10 000 post-menopausal women who will develop ovarian cancer. The results of this study show that screening the general population for ovarian cancer cannot be justified, using the tools presently at our disposal.

Of the nearly 2 billion anticipated smokers world-wide by 2025, most will be in developing countries. It has been clearly shown that legislation against smoking reduces coronary events very rapidly, so there is much that politicians can do. Doctors have shown the way by quitting, but need to do more by actively encouraging quitting, supporting those giving up, and championing healthy life-styles (*Lancet* 2009; 373: 867).

The new facts about obesity put morbid obesity in the same category as smoking, which was only realised to be a major health hazard 50 years ago. Will the lag-time on combating being overweight take as long?

## Oophorectomy at hysterectomy

Oophorectomy is often performed at the time of hysterectomy for benign disease. It is estimated that half of women in their early forties and 80% of women ≥45 years of age will have their ovaries removed. The resultant loss of hormone production in premenopausal women is obvious but 'postmenopausal ovaries continue to produce significant amounts of testosterone and androstenedione, which are converted to estrogen peripherally'. This loss of oestrogen production translates into increased cardiovascular risk, so the prophylactic removal of the ovaries to prevent ovarian cancer has to be weighed against heart disease, stroke and deaths from cardiovascular events.

On balance, it is far better to preserve a woman's ovaries at hysterectomy – with all comparative studies reaching this conclusion – the latest being from Parker *et al*. (*Obstet Gynecol* 2009; 113: 1027-1037). The authors followed up nearly 30 000 women from the US Nurses Health Study who had undergone a hysterectomy and found that although oophorectomy decreased the risk of ovarian and breast cancer, it increased the risk of stroke, coronary heart disease and all-cause mortality.

Working on the assumption of a 35-year post-surgical life-span, one additional death could be anticipated for every nine oophorectomies performed. The message is clear; it is in a woman's interest to preserve her ovaries at hysterectomy, no matter her age.

## Obesity and death

Even 10 years ago, there were arguments about whether obesity shortened life expectancy – or did not. No more. A study published in *The Lancet* on 28 March 2009 by the Prospective Studies collaboration (pp. 1083 - 1096) leaves no room for doubt. Obesity increases mortality in a progressive correlation. The lowest death rates are in men and women with a body mass index (BMI) between 23 kg/m$^2$ and 25 kg/m$^2$.

The article delivers impressive data. There were 900 000 people followed up prospectively for 3 decades from middle age to death. Their survival was matched with their BMI and causes of death recorded. The statistical analysis takes into account variables such as age, smoking and sex, but the message remains the same: the greater the BMI, the greater the risk of death.

The greatest risks associated with rising BMI were cardiovascular disease; biochemical disorders such as diabetes, renal and hepatic dysfunction; malignancies and respiratory deaths. The researchers showed about a 30% rise in mortality rates for each 5-point rise in BMI, resulting in those with a BMI of 30 - 35 having their longevity reduced by 3 years on average, and those with a BMI of 40 - 45 a 9-year reduction on average. This latter figure is similar to the 10 years by which smoking reduces an individual's life expectancy.

The message jumps off the pages more forcefully than ever before. Individuals can affect their health positively by controlling their weight and not smoking.

The medical profession should promote health as actively as it treats disease. We are accused of not doing enough about smoking cessation and there is debate about whether people should be scared into stopping or helped to quit. Australian claims that scaring people out of smoking does work has statistical support (Chapman, *Lancet* 2009; 373: 701-703), whereas the UK approach of supporting those who wish to quit also has compelling arguments (Britton, pp. 703-705).

## Antioxidants and pre-eclampsia

Oxidative stress is thought to be an underlying mechanism in the cause of pre-eclampsia. At least its presence is associated with the condition, but whether it is causative or not is unclear. Nevertheless, it would seem logical to give antioxidants to women at high risk of developing pre-eclampsia in the hope of preventing the disease.

Those most likely to benefit from such an intervention would be women in developing countries of low socio-economic status who had risk factors, especially those who had pre-eclampsia in previous pregnancies.

To test this hypothesis, Villar *et al*. mounted a WHO international trial targeting just such a group and gave one half of the group 1 g of vitamin C plus 400 IU of vitamin E, and the other half placebo (*BJOG* 2009; 116: 780-788). The mean gestation was 18 weeks at the start of the trial, and medication was given throughout pregnancy. The investigators certainly picked an at-risk sample, with a quarter of their patients developing pre-eclampsia during the study. The disappointment was that the antioxidant vitamins had no benefit in reducing the prevalence of hypertensive disorders or any other outcomes.

Although the authors entertain the possibility that the medication used might have been 'too little, too late' and that negative effects were not observed, they counsel against the prescription of these vitamins because they have shown them to be ineffective.

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*Editor*