Oral contraceptives and BMI

In published trials, oral contraceptive efficacy rates are less than 1 pregnancy per 100 woman-years. In the real world, rates of up to 7 per 100 woman-years are reported, even in those who take their OCs consistently. It has been suggested that they work less well in overweight women.

To investigate the association between body mass index, overweight and OC failure, Holt *et al.* (*Obstet Gynecol* 2005; **105:** 46-52) studied confirmed pregnancies in consistent OC users and related incidence to BMI and weight. They found that compared with women of normal or low BMI, those with a BMI of 27 to 31 had more than double the risk of OC failure. The figure was even higher where the woman's BMI was greater than 32.

A cut-off of 75 kg was the upper limit beyond which risk rose significantly, and it doubled at 86 kg.

Starting hormonal contraception

When a woman begins using hormonal contraception, she is sometimes advised to start after her next period. This is conventional, but means a delay from the initial consultation to the time of starting which may be inconvenient or discourage compliance.

Westhoff *et al.* (*Obstet Gynecol* 2005; **105:** 89-96) decided to start women on oral or vaginal ring treatment on the day of their consultation at the clinic and assess their bleeding patterns. After routine history and examination, the women either took their first pill or personally fitted a contraceptive vaginal ring at the clinic, irrespective of where they were in their cycle. All the women were told to use condoms for the first week and to record their bleeding patterns on a daily basis.

This immediate or 'Quick Start' approach was well tolerated, whether going straight onto the low-dose triphasic OC or starting a vaginal ring releasing 15 mg ethinyl/oestradiol plus progesterone per day. The ring gave fewer spotting problems, but both methods resulted in the vast majority of women reporting favourable changes in their bleeding patterns. It seems the Quick Start is effective, acceptable and takes less counselling time, with advantageous bleeding patterns especially with the ring.

It is a myth that a woman has to start hormonal contraception 'after your next period'.

Contraceptive patches

Contraceptive patches applied weekly are pharmacologically similar to combined oral contraceptives in their hormonal delivery. Patches have the advantage of requiring 3 applications in every 4 weeks instead of daily pill taking, making perfect compliance more likely. The costs of any contraceptive method must be weighed against the cost of a pregnancy, so even small gains in effectiveness of any method are preferable when weighed against the financial implications of a pregnancy.

Sonnenberg *et al*. (*AJOG* 2005; **192:** 1-9) calculated these costs and showed that the patch is cost-effective as it outperforms COCs in preventing pregnancies and the annual purchase prices are similar. In the US the cost of a normal delivery runs at over $5 000, a CS doubles that, and special maternal or neonatal care readily trebles expenses. The cost advantages of the patches with their better compliance are especially noted in younger women, and particularly those under the age of 20 years.

Extended patch use

Women take oral contraceptives in 28-day cycles, or longer cycles if they wish. There are no physiological reasons to choose a 28-day cycle with 4-weekly withdrawal bleeds, and many women are changing to 12-week cycles with 4 withdrawal bleeds per year.

As the weekly oestrogen/progesterone patches compare favourably with the oral means of delivery, it is logical to explore extended active patch applications before having a patch-free week. Stewart *et al*. (*Obstet Gynecol* 2005; **105:** 1389-1396) compared two patch cycles – a 4-week cycle and a 12-week cycle. The first conventional group applied 3 active patches for a week each, followed by a 'week off'. The experimental group applied 12 active patches for a week each, before a 'week off'.

Unsurprisingly, the 12 consecutive patch regimen resulted in fewer bleeding episodes and less spotting. The authors conclude that women who prefer fewer withdrawal bleeds can safely change to using the norelgestromin/ethinyl/oestradiol weekly patches in 3-monthly cycles.

Recurrent miscarriage investigation

Because human reproduction is so inefficient, many pregnancies result in miscarriage. About a third of conceptions do not result in a live baby. Most early miscarriages are genetically non-viable and are not recognised as pregnancies. Others are clinically apparent but do not survive the first trimester and this group of women, which constitutes 10% of all pregnancies, suffer grief and feel bereaved.

Many couples who have two or three identifiable miscarriages seek help for their problem in the belief that a preventable cause will be found. Kavalier (*BMJ* 2005; **331:** 121-122) summarises the causes into genetic, anatomical, endocrine, immune, infective, thrombophilic and unexplained.

After three miscarriages, karyotyping of both the woman and her partner is considered mandatory, basically looking for balanced chromosomal translocations in which sections of chromosomes have changed their position on the chromosomal map, without any loss or gain of genetic material. The situation is found in 1 in 500 people, so around 5% of couples with recurrent miscarriages will have one partner who is a carrier.

There is an argument for taking a family history of recurrent miscarriages into account before peripheral blood karyotyping is offered, as this would increase the yield of positive genetic investigations. Franssen *et al*. (pp. 137-139) suggest chromosomal analysis after three miscarriages, a maternal age of less than 23 years with two miscarriages, or a strong family history, as this would delineate suitable criteria to decrease the number of genetic studies done annually and thus lower costs.

Congenital abnormalities of the uterus are a probable cause of recurrent miscarriage, but the contribution they make to overall numbers is uncertain.

Endocrine disorders occur in women having miscarriages with the same frequency as the general population, so endocrine screening is not worthwhile.

The antiphospholipid syndrome is worth investigating as treatment can significantly improve the chances of a live birth. By identifying anticardiolipin antibodies and lupus anticoagulant in a woman and treating her with aspirin or heparin, or both, there is a better likelihood of success in those having three or more miscarriages. Statistically, this group accounts for about 15% of recurrent miscarriages.

Testing for the classic TORCH screen that supposedly finds infections responsible for multiple miscarriages is pointless and should not be part of the work-up.

The thrombophilias are more debatable and since no clear guidelines are available, even for factor V Leiden deficiency, their use has to be individually assessed.

The bottom line, as the author states, is that three-quarters of these couples will have a successful pregnancy the next time around, even if no special management is applied, and reassurance and diligent care after appropriate investigation is the wisest course of action.

Misoprostol for early pregnancy failure

15% of pregnancies end in spontaneous miscarriage. One of every four women will experience an early pregnancy failure in her lifetime. It is the commonest reason why women seek emergency medical services. Management options range from expectant to immediate surgical evacuation. Expectant management is proven to be safe and does not compromise future fertility, but it is unpredictable and can take up to a month, so with the grief of pregnancy loss, waiting may be an unattractive option to many women.

The need for urgent surgical evacuation of retained products of conception has been increasingly questioned, and now two studies put the case for a middle course – the use of misoprostol.

The first by Blohm *et al*. from Sweden (*BJOG* 2005; **112:** 1090-1095) compares 400 µg of misoprostol vaginally with placebo, and their results are impressive. The women inserted the tablets themselves at home after routine clinic investigations, which included ultrasound confirming the pregnancy failure. Within a week, 80% of those allocated misoprostol and 50% of those receiving the placebo had a complete miscarriage requiring no further intervention and both figures rose by 10% after another fortnight.

As expected, those given the misoprostol had more pain and needed more analgesia, but overall patient acceptance rates were high and side-effects and consequences, including sick leave, were comparable between the two groups. The authors conclude that misoprostol is more effective than placebo and should become an option for early pregnancy failure where patient reliability and follow-up is high.

The second study by Zhang *et al*. from the US (*NEJM* 2005; **353:** 761-769) compared misoprostol use with surgical evacuation. Women with ultrasonically proven pregnancy failure were randomised to medical management with 800 µg of misoprostol placed vaginally by clinic staff, or manual vacuum aspiration of the uterus as an outpatient procedure.

The misoprostol group were asked to return 3 days later when a repeat dose of the medication was given if expulsion was not complete. If this repeat dose was not successful, evacuation was offered after 1 week. The results in the misoprostol group were 70% success after one dose and 85% after adding those requiring a second dose. The surgical evacuation success rate was 97%. The risks of haemorrhage and infection were low and the side-effects tolerable in both those treated medically with misoprostol and those treated surgically by evacuation. The medical management was also acceptable to most women, and proved to be a genuine alternative to expectant or surgical management.

There are many arguments in favour of offering misoprostol to women whose pregnancies miscarry incompletely or are anembryonic, or when a missed abortion is diagnosed. Evacuations are invasive procedures that require theatre availability and skilled personnel, and the costs are considerably greater. These negative factors have to be weighed up against misoprostol's 'off label' status, as it is not registered for gynaecological indications (Winikoff pp. 834-835).

HRT and breast cancer

The influence of hormone replacement therapy on breast cancer is difficult to quantify. It is even more difficult to explain to patients. Combined HRT is accepted as a risk factor, but quite how much it increases risk above the baseline requires understanding of the statistics. Women are living longer and the anticipated life expectancy in developed countries is now 80 years, so 3 decades of possible HRT need to be considered.

Coombs *et al.* (*BMJ* 2005; **331:** 347-349) from Sydney have produced a table which gives the added risk of HRT at different ages. It is assumed that the woman is not high-risk.

	% risk				
		Oestrogen only		Combined HRT	
Age (yrs)	No HRT	5 years	10 years	5 years	10 years
50	6.1	6.3	6.6	6.7	7.7
55	5.3	5.5	5.8	5.9	7.1
60	4.4	4.6	5.0	5.2	6.5
65	3.5	3.7	4.0	4.3	5.7
70	2.4	2.6	2.8	3.3	4.2

A 50-year-old woman has a 6.1% risk of developing breast cancer over the next 30 years with no HRT. If she chooses to take *oestrogen only* HRT for 5 years, her risk rises to 6.3 and if she takes it for 10 years, to 6.6. The oestrogen has added 0.2 and 0.5% to her chances.

If she chooses to take *combined* HRT, then her baseline risk of 6.1 rises to 6.7 after 5 years – and 7.7 after 10 years. The combined HRT has added an extra 0.6% and 1.6% to her chances.

If a 55-year-old woman starts HRT, her lifetime chances of developing breast cancer are as follows: no HRT 5.3%, *oestrogen only* for 5 years 5.5%, and for 10 years 5.8%. If she takes *combined* HRT, her percentages go up to 5.9 after 5 years and 7.1 after 10 years.

From the table it is possible to calculate a woman's risk of HRT increasing her chances of getting breast cancer at any age. It is also important to note the following points.

- A woman's chance of developing breast cancer decreases with age.
- The extra risk that hormones create is small.
- Death rates from breast cancer do not change with HRT.
- If a woman stops HRT, her risk reverts to the same as a 'never user'.

A logical approach for women who have not had a hysterectomy would be to fit a progestogen-releasing intrauterine device and use oestrogen-only HRT, probably transdermally or via a vaginal ring. Let us hope that such a trial is reported soon.

Oestrogens and incontinence

There are oestrogen receptors throughout the urogenital tract. Oestrogen therapy in postmenopausal women increases urethral closure pressure and blood flow while improving the cellular maturation of the vagina, urethra and bladder. It could, therefore, be anticipated that oestrogens given to hypo-oestrogenic women would improve their continence.

The results of randomised HRT trials are finding the opposite. The Nurses Health Study, the Women's Health Initiative and now the Heart Estrogen-progestin Replacement study all report an increased risk of stress and urge incontinence compared with placebo use.[1] Consistently, these trials show more women developing weekly incontinence, although in most women there was no change in function. According to the latest figures, treating 7 women will result in one additional woman reporting incontinence on a weekly basis. This applies to oral combined HRT but may not be generalisable to all forms of HRT or all routes of administration.

Oestrogen delivered in lower doses transdermally does not appear to have deleterious effects.[2] A report from a study mainly looking at bone density effects of ultra-low-dose oestrogen has shown that at 2 years of treatment there is no substantial change in incontinence risk for women aged 60 - 80 years. A patch was used to deliver oestrogen in about a quarter of the normal dosage, which is sufficient to resist bone resorption in women with an intact uterus.

Clearly there are complex physiological changes affected by the dose and mode of delivery of oestrogens and whether or not they are given in combination with progesterone. All those involved in the treatment of prolapse and incontinence are referred to the article by Moalli *et al.*,[3] which explains the biochemical evidence for tissue remodelling in the vaginal epithelium and surrounding connective tissue.

Severe stress incontinence can be diagnosed if a woman answers 'often' or 'all the time' to the question 'Does urine leak when you are physically active, cough or sneeze?'

In a French study 15% of recently menopausal women gave a positive response, and their parity plus mode of delivery was related to their incontinence. Women who had never been pregnant had about half the incontinence of parous women, but of those who had given birth, the method of delivery had little impact on their continence or not.[4]

1. Steinauer *et al. Obstet Gynecol* 2005; **106:** 940-945.
2. Woetjen *et al. Obstet Gynecol* 2005; **106:** 946-952.
3. Moalli *et al. Obstet Gynecol* 2005; **106:** 953-963.
4. Fritel *et al. BJOG* 2005; **112:** 1646-1651.

Ultra low-dose oestrogens

Ultra low-dose transdermal oestrogens may be the fashion of the future for post-menopausal women wanting skeletal protection. Whether this will be used in conjunction with progestogens delivered intra-uterinely is speculative.

An early report from Johnson *et al.* from the US (*Obstet Gynecol* 2005; **105:** 779-787) suggests that its effect on the uterus and vagina are minimal. In a patch versus placebo randomised trial over 2 years in women with a mean age of 67 years, there were no significant differences in the incidence of endometrial hyperplasia, vaginal bleeding or other adverse outcomes. There was a modest effect on vaginal epithelial cell maturation while the baseline median serum oestradial levels doubled, which may be sufficient to prevent bone loss and fractures. Watch this patch.

Oophorectomy at hysterectomy

Ninety per cent of hysterectomies are performed for benign indications. In these cases, the decision to remove the ovaries can be individualised and dogma – usually related to the woman's age – has been the surgeon's only guide. Now, with considerable survival data and mathematic modelling, Parker *et al*. have calculated the risks or benefits of bilateral oophorectomy at the time of hysterectomy (*Obstet Gynecol* 2005; **106:** 219-226).

The authors looked at the relative risks of ovarian cancer, coronary heart disease, hip fracture, breast cancer, and other factors in 5-year intervals from 40 to 80 years of age.

They found that conserving the ovaries offered protection from all-cause mortality – at all ages. The detrimental effects were more pronounced the earlier the oophorectomy was carried out but were still discernable up to the age of 75 years.

For example, a woman having a hysterectomy at the age of 55 years will lose 8% of her life expectancy if she has her ovaries removed at the same time.

Given these clear-cut calculations, it will be hard to justify oophorectomy in a woman without specific ovarian cancer risks. This study will have a profound effect on standard surgical practice as **there is no statistical argument in favour of prophylactic oophorectomy at any age** – with or without hormone replacement therapy thereafter.

Regional analgesia in labour

It is said that initiating an epidural in the latent phase of the first stage of labour, rather than in the active phase, leads to less desirable outcomes. The argument goes that early epidural analgesia is associated with higher caesarean section rates and more instrumental deliveries.

Although this association has never been proven, never mind cause and effect being related, the American College of Obstetricians and Gynecologists recommends that epidurals should be delayed until 4 cm dilatation and other analgesia (presumably opioids) be used till then. It could be that such delay is not in the mother or neonate's interests as the most effective form of analgesia is delayed and narcotics are administered which are potentially harmful to mother and fetus.

To resolve the issue, Wong *et al*. (*NEJM* 2005; **352:** 655-665) conducted a trial in which women were assigned to regional blockade or systemic opioids when they first requested analgesia in early labour. Those allocated to first-round systemic narcotics received an epidural later, so the effects of initial or delayed block could be compared. (The first analgesia was either 1 mg IV plus 1 mg IM of hydromorphine, or a regional block using 25 µg of intrathecal fentanyl. The epidural that followed for both groups was a bolus of combined bupivacaine plus fentanyl, with patient-controlled delivery thereafter.)

The outcomes in this cohort of primigravidas in spontaneous labour were CS rates of 18% and 20% respectively for those receiving regional blocks and systemic opioids. Instrumental delivery rates were 20% and 16%. These differences were not significant, leading the authors to conclude that starting with a regional block when analgesia is first required, in the form of spinal fentanyl followed immediately by a continuous blockade of local anaesthetic, was not detrimental to mother or fetus.

This research is important, and a delightful cameo editorial by Camann from Boston (pp. 718-720) recalls the historical controversy surrounding pain relief in labour. He also records that 60% of the 4 million women giving birth annually in the US today receive epidural analgesia. Why should these 2+ million women be given opiates on the invalid assumption that they are 'not yet ready' for regional pain relief? A slug of narcotics frequently causes maternal nausea and dissociation with a subdued rather than alert mother who is unlikely to enjoy this first, and usually inadequate, initial analgesia.

If there are no contraindications to regional block, an arbitrary degree of cervical dilatation should not be used to deprive women of the analgesia they require. Apart from providing superior pain relief and not causing a rise in CS rates, the early blockade reduced the duration of labour by an hour and a half with the second stage also shorter. The babies from the early epidural group had fewer low Apgar scores despite opioids being given hours earlier.

It seems the myth of regional blocks slowing labour, or causing more instrumental deliveries, or raising CS rates, has been quashed. It is clear the women in this study had a sophisticated sequence of neuraxial blockade with quality surveillance of their labour and their fetus. This raises the bar for the care of women in labour and similar standards will hopefully allow many more women to enjoy the experience of childbirth even more fully.

This is a landmark article.

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Editor