

Journal Article Summary Service

June 2005

Hormonal contraception news

Plan B is the oppositely named American levonorgestrel emergency contraceptive pill. It works up to 72 hours after unprotected sex by inhibiting ovulation, interfering with fertilisation and preventing uterine implantation. Its makers have requested that it be made available over-the-counter but this has met with controversy.

The Food and Drug Administration is under political pressure to resist its wider access from the conservative Bush administration so they have stalled its OTC status despite an overwhelmingly positive recommendation from their own expert committee. The concerns are that easy access will lead to moral decay, inappropriate contraceptive use and the spread of sexually transmitted infections. Although these fears are not supported by medical publications (Bissell & Anderson Lancet 2005;365:1668-70) the hesitation persists. Zwillich (pp 1677-8) suggests these political manoeuvrings may be exactly the press that emergency contraception needs as publicity on both sides of the Atlantic has helped to raise the profile of this form of contraception.

Advance provision in the UK does promote emergency contraception's more frequent use but the problem remains getting the product to those who need it most – young, socially deprived women. As suggested, it is time to de-stigmatise open discussion about sexual health as frankness and correct information can only improve the health of the nation.

While on the subject of political interference, The Lancet (p1826) reports that the US department of health has been lobbying the WHO not to approve the addition of mifepristone and misoprostol to their list of essential drugs. This is in the face of the Organisation's own report stating that there are 19 million unsafe abortions annually – the vast majority of which are in developing countries – resulting in 68 000 deaths.

Missed OCs

New evidence over missed pills is available. The Clinical Effectiveness Unit in the UK has said that missing three high-dose pills or two low-dose pills is a trigger for action. Action means mechanical protection or emergency contraception to be sure of not conceiving.

There are two problems with this advice. Firstly, is failing to start a new pack the same as missing active tablets mid-pack? It seems not, and failing to begin the next pack on schedule makes the woman more vulnerable than skipping pills later.

The second problem is that few women know what pill they are on in terms of the dosage. To simplify the advice, Mansour & Fraser suggest the two pill rule for all OC users. If you miss two – take other precautions. Possibly this information should be printed on each pack in plain language without divulging the contraceptive nature of the product.

Certainly there should be wider education about the importance of starting each new pack on time. (Lancet 2005;365:1670-1).

Physical activity after breast cancer

Physical activity lowers a woman's risk of developing breast cancer at any age. The mechanism is thought to be due to exercise lowering circulating ovarian hormone levels, but no data exist on the effect of activity on survival after diagnosis and treatment.

Holmes et al (JAMA 2005;293:2479-86) followed 3 000 nurses who were diagnosed with Stages One, Two and Three breast cancer in terms of their post-treatment activity, measured in metabolic equivalent task (MET) hours per week. Compared to those leading sedentary lives, a modest number of MET hours (3 – 9) reduced the women's relative risk to 0.8, and moderate to strenuous exercise reduced relative risk to 0.6.

Clearly brisk walking for half an hour per day for most days of the week improved breast cancer prognoses. The graph of survival shows impressive differences for 15 years after diagnosis so lifestyle changes or encouragement should be part of breast cancer care.

Medical therapy for breast cancer

A major overview of the treatment of breast cancer post-operatively has been published in The Lancet (2005;365:1687-717). This is the most comprehensive article ever published, and indeed the longest at 30 pages, on the value of chemotherapy and hormone therapy in women following surgery for breast cancer. The results are encouraging and the important facts are summarised as follows:

The latest anthracycline-based chemotherapy regimes given over six months for oestrogen-receptor positive cancers offer large reductions in mortality if followed by tamoxifen hormone therapy for five years. In women younger than 50 years, the reduction is 55% and for those between 50 and 70 years 45%.

This halving of mortality is accompanied by fewer recurrences and further improvements are anticipated as new drugs, such as taxanes and SERMs are used, when women on these regimens are followed up. The paper reports results over the last 15 years of randomised trials and concludes even more optimistic outcomes can be expected. These findings are from the Early Breast Cancer Trialists Collaboration Group and are followed by a seminar on breast cancer in the same issue (Veronesi et al pp 1727-41).

Fetal origins

Ten years ago David Barker put forward his ideas that intrauterine conditions may have an influence on future health. More accurately, he hypothesised that growth restriction could lead to heart disease in adulthood. There is now compelling evidence that impaired fetal growth is associated with coronary heart disease (Eriksson BMJ 2005;330:1096-7) and now further proof comes from the Nurses Health Study (Rich-Edwards pp 1115-8). Low birth weight was a risk factor for adult cardiovascular disease if these women became overweight later in life. Women who were born light but maintained a low/normal body mass index were not at risk.

It is worth questioning whether artificial means of altering the intra-uterine environment may also have long-term sequelae. Dalziel et al (Lancet 2005;365:1856-62) followed up people whose mothers had received betamethasone during their pregnancy as part of a controlled trial 30 years earlier. Despite finding carbohydrate intolerance differences between the groups, there were no cardiovascular problems, so the authors believe that single courses of steroids remain justified to protect against neonatal respiratory distress.

Episiotomy revisited

There are no benefits from routine episiotomy. This is the conclusion of Hartmann et al (JAMA 2005;293:2141-8) following a review of all the available literature.

Most trials compare routine versus restrictive use of episiotomies and outcomes are judged on perineal disruption, pain and healing in the short term, and incontinence and sexual function in the longer term. On all these counts there is no evidence of benefit and, indeed, the liberal use of episiotomies will result in surgical incisions where a lesser laceration would have occurred.

It appears that the decision to perform an episiotomy is arbitrary, depending on individual inclination and hospital policy, and not on evidence-based data. As the authors say, there are no data in favour of episiotomy and we as professionals should practice only what we can show to be helpful to our patients. They liken it to the previous generation's excess resort to tonsillectomy or knee surgery for arthritis, which fell into disfavour once the evidence had been produced.

On first principles, any procedure where the frequency of use varies from 10% to 85% must have a large amount of personal discrimination and idiosyncrasy, and it is unlikely to be underpinned by factual evidence.

The researchers' last words are that in the US about 1 million women are having unnecessary episiotomies every year, implying the profession is often not acting in the best interests of its clients.

To drain or not?

The number of obese women is increasing rapidly in developing countries. Obesity is linked to poor obstetric outcomes and the prevalence of caesarean delivery in this group of women is rising for reasons of gestational diabetes, hypertension, post-term situations and macrosomia. The CSs themselves are more risky because of anaesthetic complexity, technical surgical problems, post-operative infection (both chest and wound) and deep vein thromboses.

CS rates increase with body mass index and the higher the BMI, the greater the incidence of wound complications such as infection, seromas, dehiscence and haematomas. Techniques to reduce this morbidity include antibiotics, skin and/or vaginal disinfection, meticulous closure and drains.

Ramsey et al (Obstets Gynecol 2005;105:967-73) conducted a drain versus no drain trial in combination with subcutaneous tissue closure in women with greater than 3 cms of abdominal wall thickness. The "fat layer" closure was with a running, non-locking 3-0 Vicryl stitch after irrigation and haemostasis with cautery. A surgical drain was, or was not placed with a separate stab exit wound and stitched in place. The drain was removed on day 3 or earlier if the output was less than 30 ml/24 hours. All patients had a scheduled post-discharge follow-up for wound assessment.

On all criteria, including readmission, the women without the drain did better, allowing the authors to recommend careful technique, subcutaneous layer closure but no drainage in obese women undergoing caesarean section.

Adnexal masses

With routine ultrasound, more and more adnexal masses are being discovered in pregnancy. Most are functional cysts that resolve by 16 weeks gestation but those that persist may undergo torsion, rupture or turn out to be malignant (less than 10% of cases). The traditional management of laparotomy in mid-pregnancy is being questioned as high resolution imaging is increasingly able to distinguish benign from malignant disease.

Schmeler et al (Obstet Gynecol 2005;105:1098-1103) prospectively followed over a decade a practice where surgery was performed or withheld on the basis of ultrasonic findings where adnexal masses greater than 5 cms in diameter were present. They had 63 such cases in over 100 000 deliveries, an incidence of 0.05%. Less than one-third had a laparotomy because of suspicious ultrasound configurations or because symptoms developed. Of the 17 having antenatal operations for complex lesions or torsion, 12 had benign cysts – mostly dermoids – with 4 malignancies and 1 tumour of low malignant potential.

All the remaining women were observed and had adnexal surgery either post-partum or at caesarean section. None proved to be malignant. The authors state that their data support the observation with post-partum surgery for large persistent adnexal masses, provided their ultrasound characteristics are not suspicious of malignancy.

Antidepressants and neonatal effects

Depressive and anxiety disorders affect about 10% of women in their reproductive years and the primary treatment is serotonin re-uptake inhibitors. This implies that a fair number of infants will be exposed to these drugs in-utero and may suffer from withdrawal after delivery.

A withdrawal syndrome has been recognised and defined, with the main characteristics being signs of irritability, hypertonia, jitteriness and feeding troubles. Although these reactions are self-limiting and do not carry long-term sequelae, paediatricians should be notified if women are on selective serotonin or nor-epinephrine re-uptake inhibitors in the last trimester of their pregnancy. It has been suggested that tapering off the drugs two weeks prior to the expected delivery date can help. Infants with the syndrome are recommended to have quiet, low-light environments with frequent small feeds to match their increased calorie requirements.

Mother-infant skin contact is also advised but pharmacological treatment is rarely indicated (Moses-Kolko et al JAMA 2005;293:2372-83).

BMD and fracture risk

Osteoporosis increases the risk of fractures. The diagnosis of osteoporosis and the prediction of fracture risk depends heavily on bone mineral density measured by dual-energy Xray absorptiometry. The diagnosis of osteoporosis by BMD is two standard deviations below the score for healthy young adults, the T score, but it has been shown that having a BMD of one standard deviation below the norm increases a postmenopausal woman's chances of a fracture by 50%. Other features associated with fracture risk are age, female sex, slight body habitus and white race (Acheson JAMA 2005;293:2151-3).

Bischoff-Ferrari et al (pp 2257-64) show that a useful preventative measure is vitamin D in the form of oral cholecalciferol at a dose of 800 IU/day which reduces fracture risk but they also found that doses of 400 IU/day were ineffective. These authors conclude that their results are sufficiently compelling for all elderly people to be on such treatment but their research did not prove calcium supplementation was required, despite it being included in most recommendations.

An interesting aside is the protective effect of race. At all levels of BMD and age, black people have a substantially lower risk of fracture (Cauley et al pp 2102-8). This does not preclude absorptiometry as a diagnostic tool in this group, or the need for prophylaxis – nor is the defining of race always that easy.

The American College of Obstetricians and Gynecologists has recognised that osteoporosis is the epidemic of the future and has given clear guidelines as to the part the gynaecologists can play and believe it is our preventative and therapeutic remit. (Obstets Gynecol 2004;104:203)

As developed countries' populations age, there will be a dramatic change in social structures, medical requirements, costs and the need for health workers. Care for ageing people is much more likely to be in dedicated facilities rather than parents being cared for in their children's houses. This is due to shrinking family sizes with different-sized homes and the popularity of retirement villages.

Elderly people will live in homes, clinics and institutions where routine osteoporosis prevention regimes will be part of their lifestyle. Although this is seldom achieved today, with only 10% of such institutions providing adequate interventions, future public health planning will need to take skeletal health into account just as much as cardiovascular and mental health.

Prevention

A mixed diet containing fresh produce, dairy products, fish and nuts are all part of dietary prevention. Supplementation with vitamin D at 800 IU/day and probably calcium for all elderly people should be routine. Exercise is equally important, the minimum being half an hour of fast walking most days of the week.

Screening

On an epidemiological basis, age 70 +, white race and low body mass index are good indicators of the need for extra measures, but dual energy X-ray absorptiometry screening is the only really accurate predictor of fracture risk and is the best and definitive diagnosis of osteoporosis.

Irrespective of category, any person experiencing a low-trauma fracture should have prophylaxis. This seemingly sentinel event is too often not followed by active treatment.

Morbidity and mortality

Osteoporotic fractures are broadly divided into spinal and non-spinal fractures. Spinal fractures cause pain, decreased mobility and deformities. They are often associated with a spiralling down of activity, a sedentary lifestyle with its attendant risks. The statistics are frightening with estimates that one in two individuals over the age of 50 will experience an osteoporotic fracture as their life expectancy increases above 80 years.

One in six men and one in three women will have sustained a hip fracture by their ninth decade. Following a hip fracture, 50% of patients will be immobilised, 20% will be bed-ridden and 10% will die within the next year. This burden will still fall predominantly on women as they continue to outlive men.

Costs

Apart from the personal and social burden of hip fractures, the lack of mobility and health worker costs of this entity are enormous. In the US alone, the costs were \$7 billion fifteen years ago and will more than double in the next fifteen years. In that country there are two million people who suffer osteoporotic fractures annually and the figure expected to reach three million in the next generation. Clearly, preventative measures have major cost-saving incentives.

Anti-resorptive drugs

Oestrogens: The taking of oestrogens in the form of HRT for skeletal preservation undoubtedly works and has been shown to assist the maintenance of bone mass density which results in fewer fractures. The Women's Health Initiative Study showed this even though the women started their HRT well after the menopause (Rossouw et al JAMA 2002;288:321-33). Since then, more trials have yielded similar results for the reduction of hip fracture incidence on oestrogen only or oestrogen plus progesterone therapy. As primary prevention, it lowers hip fracture rates by about a third (RR 0.67) but these trials ended prematurely so continued compliance into old age when most fractures occur could not be properly evaluated.

This positive effect needs to be weighed individually against breast cancer, cardiovascular and thrombi-embolic risk by all women and their doctors embarking on HRT as a preventative measure (Beral et al BJOG 2005;112:692-5).

Selective oestrogen receptor modulators (SERMs) are being explored that will have a neutral effect on the uterus but will reduce bone reabsorption as well as reducing the risk of breast cancer. Raloxifene is the only one registered for osteoporosis prevention but there are others in clinical trial stages at the present time (Kuehn JAMA 2005;293:2458).

Bisphosphonates such as alendronate and risedronate taken daily or weekly are highly effective, but their precise ingestion requirements make compliance difficult, often increasing the medicinal load on older patients. Two advances offer relief – intravenous two-monthly injections or the latest advance: idrandonate for oral use monthly.

The caveats to treatment are also becoming clearer. Postmenopausal women with osteopenia, rather than osteoporosis, are not automatically candidates for bisphosphonate medication. Alendronate is expensive and it was not found to be cost effective in women with bone mass density T scores from -1.5 to -2.4, the osteopenic range (Ann Int Med 2005;142:734-441). These women should still be treated if they have indications such as previous fractures, advanced age or if they are taking steroids.

The anabolic agent teriparatide is a synthetic parathyroid hormone which helps build bone and can be given intravenously biannually or annually.

The latest approach is a monoclonal antibody that inhibits resorption and can also be given six-monthly with routine medical check-ups. Phase three trial results are awaited.

There is no lack of interest in the development of antiosteoporotic medications but it will be up to family doctors, physicians and gynaecologists to promote their use.

SNIPPETS

Screening for all

Screening, especially screening of doubtful value, is becoming the next medical battleground. The public are being exhorted to join screening programmes which offer little real benefit and sometimes are potentially dangerous. For example, celebrities are endorsing – presumably for substantial reward – campaigns backing full body computer tomography which exposes healthy people to unhealthy amounts of radiation.

In Australia, cricketing hero Alan Border and the “Prisoners” soapie star Val Lehman have very publicly backed the whole body scanning industry. The health authorities, concerned about the limited value and proven risks have countered by issuing a public health alert as to the dangers.

Closer to home for us, high profile women are promoting human papilloma virus testing for cervical cancer and this is likely to undermine trust in the profession as the case for HPV as a routine screening tool are far from proven, with its potential for anxiety and concern very high. The use of celebrities to encourage dubious screening projects is confusing and sets up the conflict between the profession and companies standing to gain from lucrative but equivocal programmes (Moynihan & Jakubowski BMJ 2005;330:1156).

Mammography screening

The benefits and harms of breast screening programmes are clear. In developed countries the outcomes of choosing screening or not screening are finely balanced, according to Taylor (BMJ 2005;330:915) and echoed by the new editor in her Editor’s choice column.

Adding data to the debate, Barratt et al (pp936-8) have created Markov models from which doctors can quote the facts to their clients. They assumed that the woman was of low risk and would stick with biennial mammography for each decade, or not be screened at all. Their table is summarised as follows;

Age starting	<u>40</u>		<u>50</u>		<u>60</u>		<u>70</u>	
	<u>Mam</u>	<u>Not</u>	<u>Mam</u>	<u>Not</u>	<u>Mam</u>	<u>Not</u>	<u>Mam</u>	<u>Not</u>
Recalled - more tests	25		24		19		17	
Biopsied	6		6		6		6	
Ca diagnosed	2	1	3	2	4	2	4	3
Died all causes	1.3	1.3	2.9	3.1	7.4	7.7	20.6	20.8

This table indicates the percentages of healthy women undergoing biennial mammography and those choosing not to be screened, in terms of recall, requiring biopsy, the number of breast cancers diagnosed and the deaths from all causes including breast cancer.

At the other end of the screening spectrum are people who are at high risk of developing a disease and consequently need frequent and sophisticated checking. Women that have first degree relatives with breast cancer or the BRCA gene mutation fall into this category and require complex follow up. Because many are premenopausal with dense breast tissue, routine x-ray mammography may be inadequate. The latest report from the UK suggests that contrast enhanced magnetic resonance imaging is more sensitive than mammography for cancer detection in this ultra-high-risk group (MARIBS study group Lancet 2005;365:1769-78).

Rhesus disease

Kumar & Regan have published an excellent clinical review article called "The management of pregnancies with RhD alloimmunisation ([BMJ 2005;330:1255-8](#)). They reiterate that at least 500 IU of anti-D should be given to non-sensitised Rh negative women at 28 and 34 weeks as well as at delivery. This is highly recommended reading for those who seldom encounter Rh problems.

Hair dyes and cancer

In case any of your patients ask about hair dyes and cancer, you can now reassure them. Recent unconfirmed releases linked the personal use of hair dyes with bladder cancer but a meta-analysis of all the scientific publications available has not confirmed any such association (Takkouche et al [JAMA 2005;293:2516-25](#)).

Contraception USA

The following are the current statistics of contraceptive practice in the United States reproduced in [JAMA 2005;293:2208](#).

- 31% oral contraceptives
- 27% female sterilisation
- 18% condom use
- 9% male sterilisation
- 9% injectable, patches, implants
- 8% all other methods including intrauterine devices

By the way, the latest US infant mortality rates are 7 per 1000.

Ultra diets

Women and men wanting to eat healthily should reduce the amount of fat in their diet, particularly saturated fat. This will reduce cholesterol levels, giving improved low and high density lipoprotein levels. But to really shift these profiles, plenty of fruit, vegetables and whole grains should be added with 5 portions per day still being the most widely quoted recommendation.

This "low-fat plus" diet was rigorously tested on Americans with body mass indices of less than 30 and moderate hyper-cholesterolaemia and shown to be effective in only four weeks. With all the fad diets being punted recently, it is reassuring that this medically backed model at least has a scientific foundation ([Ann Int Med 2005;142:725.33](#)).

UK hysterectomy trends

Half of women referred for secondary care with menorrhagia express a preference for a hysterectomy. However, the newer less invasive procedures and medical management provide viable alternatives, so are trends changing?

Yes, say Reid & Mukri ([BMJ 2005;330:938-9](#)) who noted a one third decrease in the number being carried out in the last decade. They believe it is not due to endometrial ablation increase, nor patients making use of private sector facilities but perhaps the advantages offered by the Mirena which has proven so effective to date. We shall see.

JOURNAL ARTICLE SUMMARY SERVICE

15 Greenfields, Pinewood Road, Rondebosch 7700, Cape Town, South Africa

June 2005

Dear Colleague

Contraception, breast cancer, osteoporosis and screening have dominated the journals in the last month. There is a wealth of new data – most of it reassuring – that proves we are on the right track medically, but suggesting vigilance about jumping on board screening bandwagons.

Fiona Godlee is the BMJ's new Editor and she holds forth on the question of who should receive health care – the sick or the healthy? This is a provocative line but an appropriate debate in our speciality.

Certainly the practice of Gynaecology is becoming less surgically dominated and more health proactive. We have a major role in guiding and allowing women to be born and survive in optimal health.

We request all those postal subscribers with email addresses to send us an email message and we will send them JASS electronically rather than by post – even if this is just experimentally.

Yours sincerely

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QUESTIONS JUNE 2005

- | | True / False |
|--|--------------|
| 1. Wider availability of emergency contraception leads to inappropriate use of standard contraceptive measures and increases sexually transmitted infections | _____ |
| 2. After two missed oral contraceptive pills, additional contraceptive measures are advised | _____ |
| 3. Physical activity <u>after</u> treatment for breast cancer decreases mortality rates | _____ |
| 4. Mortality rates for early stage breast cancer survival have remained static over the last decade | _____ |
| 5. Maternal betamethasone in pregnancy to prevent respiratory distress leads to increased susceptibility to cardiovascular disease in their offspring thirty years later | _____ |
| 6. There are data to show that routine episiotomy decreases perineal trauma | _____ |
| 7. Subcuticular drains at caesarean section reduce wound morbidity in obese women | _____ |
| 8. Antidepressants in the third trimester can give rise to withdrawal effects in the neonate | _____ |
| 9. Oral contraceptives are the most popular form of family planning in the United States | _____ |
| 10. Hysterectomy rates in the United Kingdom have remained steady over the last ten years | _____ |

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