Women's Health Research Review

RESEARCH REVIEW 10 YEARS
MAKING EDUCATION EASY SINCE 2006

Making Education Easy

Issue 20 – 2016

In this issue:

Abbreviations used in this issue
ADHB = Auckland District Health Board
GP = general practitioner
IUD = intrauterine device
OR = odds ratio
UTI = urinary tract infection
VTE = venous thromboembolism
WHO = World Health Organisation

PHARMACY GUILD OF NEW ZEALAND

NZMA New Zealand Medical Association

Welcome to the latest issue of Women's Health Research Review.

We report an analysis of the ELITE trial that examined the cardiovascular effects of postmenopausal hormone therapy with regard to the timing of therapy initiation, and a NZ study that evaluated the clinical pathway for investigating postmenopausal bleeding. Other NZ research includes a report of the Jadelle® contraceptive implant, and a discussion of the barriers to contraception for Māori teenage mothers. We also report that sexual function improves after endometrial ablation, and ibuprofen may reduce the need for antibiotics in women with mild UTI.

We hope you find these and the other selected articles interesting, and welcome any feedback you may have.

Kind regards,

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Vascular effects of early versus late postmenopausal treatment with estradiol

Authors: Hodis H et al., for the ELITE Research Group

Summary: This analysis of the ELITE study evaluated the cardiovascular effects of postmenopausal hormone therapy with regard to the timing of therapy initiation. 643 healthy postmenopausal women were stratified according to time since menopause (early postmenopause [<6 years] or late postmenopause [≥10 years]) and were randomised to receive placebo or oral estradiol ± progesterone vaginal gel. The primary outcome was the rate of change in carotid artery intima media thickness (CIMT). After a median 5 years, the effect of estradiol ± progesterone on CIMT progression differed between the early and late postmenopause strata (p=0.007). Among women in the early postmenopause group, the mean CIMT increased by 0.0078 mm/year in the placebo group compared with 0.0044 mm/year in the estradiol group (p=0.008). Among women in the late postmenopause group, the rates of CIMT progression in the placebo and estradiol groups did not differ significantly.

Comment (HR): The accompanying editorial regarding this study gives good advice (Keaney et al., *NEJM* 2016;374:1279-80). "The Elite trial assessed only surrogate measures of coronary heart disease (CHD) and was not designed or powered to assess clinical outcomes. The occurrence of CHD involves not only atherosclerotic plaque formation but also plaque rupture and thrombosis and any changes in these would not be captured in this study. This is of particular interest given that (oral) hormone therapy promotes thrombosis. In light of the available data from randomized trials, guidelines from various professional organizations currently caution against using postmenopausal hormone therapy for the purpose of preventing cardiovascular events. Although the ELITE trial results support the hypothesis that postmenopausal hormone therapy may have more favorable effects on atherosclerosis when initiated soon after menopause, extrapolation of these results to clinical events would be premature and the present guidance remains prudent."

Reference: N Engl J Med 2016;374:1221-31
Abstract

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For more information, please go to www.medsafe.govt.nz

Management of postmenopausal bleeding by general practitioners in a community setting

Authors: Stravens M et al.

Summary: This NZ study evaluated the safety and effectiveness of a clinical pathway for investigating postmenopausal bleeding, managed primarily by GPs. Data for 216 women with postmenopausal bleeding were reviewed retrospectively over a 5-year follow-up period. Transvaginal ultrasound showed 121 women had endometrial thickness (ET) <5mm, 83 had ET ≥5mm, and 12 had an endometrial polyp. In women with ET ≥5mm, 38 underwent a pipelle biopsy in primary care, 36 were referred directly to secondary care, and 9 declined further investigations. Only 17 pipelle biopsies performed in primary care provided sufficient tissue, and the remaining 21 women were referred to secondary care. Seven cases of endometrial cancer were identified (4 by pipelle biopsy and 3 by hysteroscopy). 68% of the study cohort were managed solely by their GP to the point of diagnosis.

Comment (HR): The study discussion says "However, of the 38 pipelles attempted by general practitioners, 21 (55%) did not allow histological diagnosis due to 7 technical failures and 14 yielding insufficient tissue, thereby requiring referral to secondary care and a small delay in diagnosis. This relatively high rate of inadequate biopsies is greater than that reported by other studies for primary care clinicians which range between 13–31%. This high rate may reflect, in part, the fact that biopsies are often more difficult to obtain in post-menopausal women, mainly because of endometrial atrophy". So one of the problems we have in various parts of NZ is how do GPs obtain training for performing pipelles, intrauterine device and Jadelle® insertions? Middlemore Hospital does have a dedicated clinic to teach these skills but the GP training clinic that was at ADHB some years ago is now no longer present. I am often asked to teach these procedures at GP conferences using models but that doesn't replace real clinic training.

Reference: NZ Med J 2016;129:1434
Abstract

Independent commentary provided by Associate Professor Helen Roberts

After my medical degree at Trinity College Dublin, I worked at the Rotunda Hospital and then King's College Hospital in London. In 1983 I came to New Zealand and joined Family Planning, becoming the Medical Director and National Medical Spokesperson from 1988-1992. In 1991 I completed the MPH at Yale University in New Haven and on my return took up an academic position in the Department of Obstetrics and Gynaecology, University of Auckland. At present I am Associate Professor Women's Health at the University of Auckland and am involved with both undergraduate and postgraduate medical education in O&G. My clinical and research interests and publications have been mainly in the areas of contraception, menopause and HPV vaccine.

Risk of venous thromboembolism associated with local and systemic use of hormone therapy in peri- and postmenopausal women and in relation to type and route of administration

Authors: Bergendal A et al.

Summary: This Swedish case-control study assessed the risk of VTE associated with systemic hormone therapy according to the type and route of administration. 838 cases of VTE and 891 matched controls (mean age 55 years) were included. Logistic regression analysis adjusted for confounding factors showed that current use of any hormone therapy was associated with an increased risk of VTE (OR, 1.72). For estrogen in combination with progestogen the OR was 2.85, and for estrogen only the OR was 1.31. For orally administered estrogen combined with progestogen, the OR was slightly higher among users of medroxyprogesterone acetate (2.94) than among norethisterone acetate users (2.55). Transdermal estrogen combined with progestogen was not associated with VTE risk; nor was locally administered estrogen.

Comment (HR): We would not expect vaginal estrogen to affect VTE risk but this study also showed that transdermal delivery, unlike oral, also did not increase VTE risk. The study was too small and not sufficiently powered, hence the borderline significance of this result. However, we do have a series of other observational studies showing that transdermal estrogen (50µg or less) does not increase VTE risk and also does not increase the risk of stroke .The progestogen used seems also to be important for those women who have a uterus and the addition of oral micronised progesterone (Utrogestan®) is the choice rather than medroxyprogesterone acetate or norethisterone. This has important implications for those women who have long term flushes and feel they need to continue with hormone therapy even into their 60s. These women should be changed to this regimen to lower their VTE and stroke risk. We have just heard that transdermal estrogen is soon to be subsidised in NZ.

Reference: Menopause 2016;23(6):593-99
Abstract

New Zealand women's experience during their first year of Jadelle® contraceptive implant

Authors: Roke C et al.

Summary: This study evaluated women's experiences of the Jadelle® contraceptive implant in NZ. 252 women who had a Jadelle® implant inserted at a Family Planning clinic were followed-up for 12 months and asked about their bleeding patterns, satisfaction, and views on implant use. The 3 most common bleeding patterns reported were regular periods, amenorrhoea and irregular bleeding. 18% of the women had their implant removed within the first year. More than half of the women who requested removal because of bleeding problems had experienced prolonged episodes of bleeding. Some women requested removal for both bleeding and hormonal problems, and a few women had their implant removed because of local effects such as tingling and pain. At least 80% of women who were contacted gave a positive response at each time point.

Comment (HR): We started this follow-up study in Family Planning because we were seeing women coming back with bleeding problems and we wondered if this was happening more with our cohort of women compared to the rates in the published literature. We ended up showing that our figures were pretty much the same with about 1 in 10 women having their implant removed for irregular bleeding. The Jadelle® data sheet gives a figure of 14% of removals for this reason. Irregular bleeding can often be sorted with the addition of a combined oral contraceptive pill for some months given with continuous hormone taking. Indeed some women like to continue on the pill on top of the Jadelle® to sort out their bleeding. It seems best to help women sort out the bleeding pattern as early as possible as there seems to be a therapeutic window of opportunity after which women feel they cannot tolerate the irregular bleeding and just want the implant removed.

Reference: J Prim Health Care 2016;8(1):13-19
Abstract

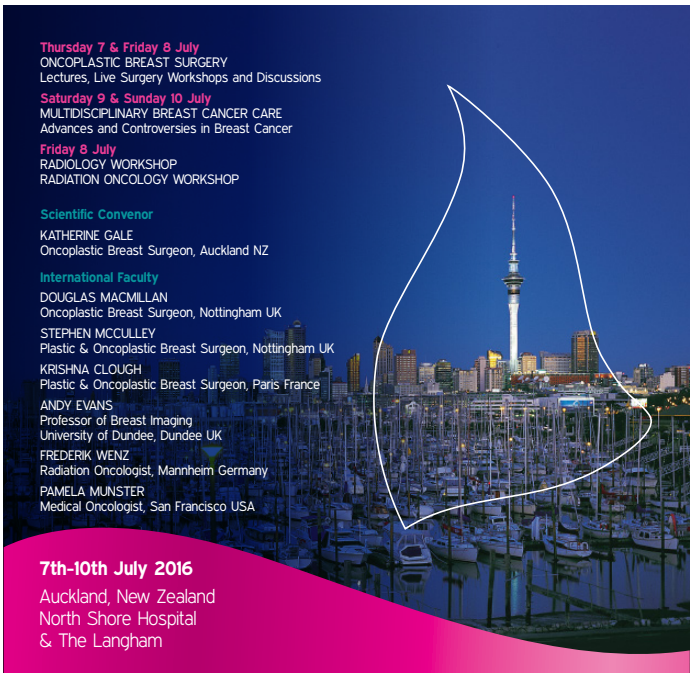
Maternal use of oral contraceptives and risk of birth defects in Denmark

Authors: Charlton B et al.

Summary: This study investigated whether the use of oral contraceptives around the time of pregnancy onset is associated with an increased risk of major birth defects. Data on oral contraceptive use and major birth defects were collected for 880,694 live births in Denmark in 1997–2011. Women were divided into 4 groups according to oral contraceptive use: never users, used >3 months before pregnancy onset (reference group), used 0–3 months before pregnancy onset (recent use), and used after pregnancy onset. The prevalence of major birth defects (per 1000 births) was consistent across each oral contraceptive exposure group: 25.1, 25.0, 24.9, and 24.8, respectively. No increase in prevalence of major birth defects was seen with oral contraceptive exposure among women with recent use before pregnancy or use after pregnancy onset compared with the reference group.

Comment (HR): This is the same finding as other studies – the rate of birth defects is no different from the normal background risk. The same applies to DepoProvera® and Jadelle® implant use at the time of pregnancy. Also, we are aware that if the emergency contraceptive pill fails and the woman gets pregnant after use there is no effect on the pregnancy.

Reference: BMJ 2016;352:h6712
Abstract



E Hine: access to contraception for indigenous Māori teenage mothers

Authors: Lawton B et al.

Summary: This analysis of the E Hine study examined barriers and facilitators to contraception for Māori teenage mothers. In E Hine, 44 Māori women aged 14–19 years were followed through pregnancy and the birth of their babies until their babies' first birthday. Pre-pregnancy, most participants accessed contraception or advice but contraception use was compromised by a lack of information, negative side effects, and limited follow up. All subsequent pregnancies were unplanned. Participants gave considerable thought to post-pregnancy contraception, but many were left without timely effective contraception because of a lack of integrated care between midwives and other primary care services. They also reported financial barriers and negative contraceptive side effects.

Comment (HR): This study adds to others that have been done in NZ over the last few years. They all seem to show that women are not receiving contraception early or immediately in the postnatal period. This also applies to women with severe acute maternal morbidity. Jane MacDonald's study (*Contraception* 2015;92:308-12) carried out in 4 DHBs showed that the majority of women with conditions that pose a significant health risk in pregnancy left hospital with no contraceptive advice. We have a systematic review from the WHO reassuring us that progestogens given immediately postnatally do not affect breast feeding or the quality of breast milk (*Contraception* 2010;82:17-37). The studies also show that once women go home with a new baby they find it hard to organise an appointment at 6 weeks for contraceptive advice – one study showed that this was not just an organisational problem but also a financial one. At present I am involved with a series of lectures for the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) talking about immediate postnatal contraception. One of the ways of facilitating this is to train midwives. We are doing this at ADHB with midwives doing Jadelle® insertion before women leave hospital. Other DHBs may want to look at similar training.

Reference: J Prim Health Care 2016;8(1):52-59
Abstract

Female sexual function improves after endometrial ablation

Authors: Marnach M et al.

Summary: This study determined whether sexual function in women improves after endometrial ablation for heavy menstrual periods. Validated surveys (Female Sexual Function Index [FSFI], Female Sexual Distress Scale [FSDS], and Short-Form Health Survey [SF–12]) were administered to 136 women before and 6 months after endometrial ablation. A total of 97 women completed the FSFI and FSDS surveys. Mean full-scale FSFI score increased from 26.5 to 28.8 ($p<0.001$), with improvement in 5 of 6 FSFI domains. Mean FSDS score decreased from 13.6 to 9.7 ($p<0.001$), showing decreased personal distress regarding sexual function. In assessing quality of life, SF–12 scores improved for global physical function ($p<0.001$) and mental function ($p=0.002$).

Comment (AS): It is known from existing prospective studies that hysterectomy can lead to improvement in sexual function, although some retrospective studies report low libido also. As endometrial ablation becomes an increasingly attractive minimally invasive option for heavy periods for many women, this study adds to knowledge to allow further comparisons with hysterectomy. At least 2 validated surveys were conducted, at baseline and 6 months postoperatively (at least 31 items in the surveys). Of the women (mean age 44) who completed both sets of surveys, there was a significant improvement in sexual function and quality of life. In fact the heavier periods before ablation were associated with greater improvement across several sexual function questions. Surprisingly (or not, given the complexity of sexual function and the factors that affect it), the factors showing improvement included better lubrication and less pain which would not be logically concluded as being caused by heavy periods. The study is small and it may be possible that the patients with the most improvement in bleeding or other symptoms were more likely to complete the second set of surveys. However, the information could be used to offer more detailed counselling for women considering the various secondary care options for the management of heavy menstruation.

Reference: J Womens Health 2016;25(2):149-54
Abstract

Acupuncture for menopausal hot flashes

Authors: Ee C et al.

Summary: This study evaluated the efficacy of acupuncture in women with menopausal hot flashes. 327 women were randomly assigned to acupuncture or sham acupuncture and received 10 treatments over 8 weeks. Mean hot flashes scores at the end of treatment were 15.36 in the acupuncture group and 15.04 in the sham group (p=NS).

Comment (AS): Around 75% of menopausal women get vasomotor symptoms (hot flashes/flushes and night sweats) for an average of 5 years. Conventional hormone replacement therapy, selective serotonin re-uptake inhibitors and complementary therapies have their own pros and cons, risks and benefits and public-purse and individual financial costs. Acupuncture is widely available for menopausal symptoms and, for example in Sydney, acupuncturists are the second most consulted therapists by menopausal women. Acupuncture is more effective for vasomotor symptoms than no treatment. This traditional Chinese acupuncture versus sham acupuncture (no skin prick with the needles but a sensation of this) trial looked at 327 women (mainly Caucasian and all with natural menopause). They had 10 treatments over 8 weeks for at least 7 moderate hot flushes a day. Assessment continued for 6 months post-treatment and the study took place in Victoria and Queensland. Non-insertional sham acupuncture was as effective as Chinese medicine skin-pricking acupuncture for moderately severe hot flashes/flushes. These 2 interventions both led to around 40% improvement in symptoms which is also consistent with known placebo rates.

Reference: Ann Intern Med 2016;164(3):146-54
Abstract

CONGRATULATIONS TO

Anne Brinkman

Professional Nursing Advisor at NZNO.

Anne won an iPad mini 3 by taking part in our recent Subscriptions Update promotion.

Independent commentary provided by Dr Anil Sharma MB ChB DGM Dip Legal Med FRANZCOG FRCOG

Having delivered over 5,000 babies, Anil now works in gynaecology and colposcopy from Ascot Central and Ascot Hospital. His key interests are menstrual problems including fibroids, urogynaecology and endometriosis. He undertakes complex hysteroscopic, laparoscopic and traditional surgery. He also undertakes day-case endometrial ablation. Anil's training was based in the UK and NZ and he co-founded the South Wales MRCOG Clinical course. He is a member of the Australasian Gynae Endoscopy Society and the International Urogynae Association. He strives to keep his practice current and evidence-based and involves patients in decision-making and informed consent having a long held interest and qualification in medical law. Whilst being academically published, his real passion is at the interface of academic evidence and clinician practice. He looks forward to every issue of Research Review. Anil's interest in medical education has continued with GP and Nurse CME, and he is a current speaker at the Goodfellow Conference. Anil lives in Auckland with his wife (who is a GP) and their 3 daughters, enjoying as much of the outdoors as they can. He also loves classic cars and stand-up comedy.

Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women

Authors: Gágyor I et al.

Summary: This German study investigated whether treatment with ibuprofen can reduce the need for antibiotics without increasing symptoms, recurrences or complications in women with uncomplicated UTI. 494 women aged 18–65 years with typical symptoms of UTI and without risk factors or complications were randomly assigned to treatment with fosfomycin 3g daily for 3 days or ibuprofen 3x400mg daily for 3 days in a double-blind, double-dummy design. In both groups, additional antibiotic treatment was prescribed if needed for persistent, worsening, or recurrent symptoms. During 28 days of follow-up, the ibuprofen group received significantly fewer course of antibiotics (incidence rate reduction, 66.5%; p<0.001). However, this strategy resulted in a higher burden of symptoms on days 0–7, and more cases of pyelonephritis.

Comment (AS): This German (primary care) randomised trial treated women with symptoms that could be an uncomplicated UTI. The women were given either a single dose (3g) of fosfomycin (broad spectrum antibiotic not readily available in NZ) or 3x400mg ibuprofen for 3 days. Subsequent additional antibiotics were prescribed if needed for symptoms, and the urine was cultured. The ibuprofen group had significantly fewer courses of antibiotics overall (94 vs 243), but a higher 'burden of symptoms' and more pyelonephritis (5 vs 1 cases) and febrile UTI (3 vs 0 cases). The group who had ibuprofen had a higher incidence of 'impaired activity' (30 vs 20 women) and 1 case of gastrointestinal bleeding (the patient also had 'alcohol disease'). 65% of women who had presented to their GP with uncomplicated UTI symptoms subsequently recovered with just ibuprofen without antibiotics. Whilst the data did not provide enough robust evidence to reject initial antibiotics for ibuprofen as a primary treatment for all, it was felt that there was enough evidence for this plan in cases of mild to moderate symptoms in a 'shared-with-patient decision making approach'. This could potentially also help reduce unnecessary antibiotic prescribing and possible drug resistance. The questions raised by this small trial include 'is it worthwhile initially treating women who could have an uncomplicated UTI with just ibuprofen (if not contraindicated) to avoid antibiotics for those who wish to avoid them?'

Reference: BMJ 2015;351:h6544
Abstract

Selection of key recommendations for the management of women with endometriosis by an international panel of patients and professionals

Authors: Schleedoorn M et al., on behalf of the EndoKey Group

Summary: An international panel of patients and professionals developed a set of key recommendations for the management of women with endometriosis. 10 patients and 11 medical professionals from 9 different European countries rated and prioritised 83 recommendations from the European Society of Human Reproduction and Embryology (ESHRE) guidelines for endometriosis. A representative set of 17 key recommendations was selected, covering all dimensions of endometriosis care, including diagnosis, treatment of endometriosis-associated pain, treatment of endometriosis-associated infertility and miscellaneous topics such as prevention, menopause and relationship with cancer.

Comment (AS): This Dutch paper concerns the outcomes when 10 patients and 11 medical professionals came to an agreement (3 rounds of meetings) after considering existing ESHRE guidelines regarding endometriosis. I have summarised those pertaining to primary care.

- Endometriosis can cause dysmenorrhoea, non-cyclical pelvic pain, deep dyspareunia, infertility and fatigue in the presence of any of the above.
- Endometriosis can cause non-gynaecological cyclical symptoms (dyschezia, dysuria, haematuria, rectal bleeding, shoulder pain).
- Transvaginal sonography is useful to diagnose or exclude an ovarian endometrioma.
- If symptoms suggest, consider ureteric, bladder and bowel imaging to prepare for management.
- Treat women with endometriosis-associated pain with adequate analgesics, the combined oral contraceptive pill, or progestogens as these can all help.

The study was interesting in that all the patients on the panel had endometriosis (all had long delays in diagnosis, all had surgery and all were on special interest groups for patients). It was felt that the different perspectives that were able to be considered led to improved management guidelines. Additionally, women who present with hitherto undiagnosed abdominopelvic pain, often with recurrent episodes over months or years, should be referred to a gynaecologist.

Reference: Hum Reprod 2016;31(6):1208-18
Abstract