Women's Health Research Review

Making Education Easy

Issue 25 – 2017

In this issue:

Abbreviations used in this issue
BMI = body mass index
COC = combined oral contraceptive
DHEA = dehydroepiandrosterone
IUS = intrauterine system
WHI = Women's Health Initiative

PHARMACY GUILD OF NEW ZEALAND

NZMA New Zealand Medical Association

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

This month we report a WHI analysis that shows that menopausal hormone therapy for 5–7 years does not increase the long-term risk of all-cause mortality, and an ancillary study of the KEEPS trial shows that transdermal estradiol may improve sexual function in postmenopausal women with low sexual function. Finnish investigators assess the feasibility of fast-tract initiation of levonorgestrel-releasing IUS contraception after medical termination of pregnancy, and a *post hoc* analysis of the SMART-2 trial shows that women taking conjugated estrogens/bazedoxifene can expect approximately 50% reduction in hot flush frequency after about 8–10 days, and sustained improvement with continued treatment. We also report an interesting ethical and scientific discussion about current Australian and NZ guidelines for assisted fertility services in obese women, evidence that breastfeeding reduces the likelihood of endometriosis, and a review of current guidelines for recurrent vulvovaginal candidiasis.

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

Kind regards,

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Menopausal hormone therapy and long-term all-cause and cause-specific mortality

Authors: Manson J et al., for the WHI Investigators

Summary: This analysis of data from two WHI trials (Estrogen + Progestin and Estrogen-Alone) investigated the association between the use of menopausal hormone therapy for 5–7 years and long-term mortality. 27,347 postmenopausal women aged 50–79 years were enrolled in the 2 trials in 1993–1998 and followed up through 2014. The women were randomised to conjugated estrogens 0.625 mg/day + medroxyprogesterone acetate 2.5 mg/day or placebo for a median 5.6 years; or to conjugated estrogens alone or placebo for a median 7.2 years. 7489 deaths occurred during the cumulative 18-year follow-up. In the overall pooled cohort, hazard ratios (HRs) for hormone therapy vs placebo were 0.99 for all-cause mortality, 1.00 for cardiovascular mortality, 1.03 for total cancer mortality, and 0.95 for other causes.

Comment (HR): I was in Australia when this came out and there was a lot of excitement in the papers about this publication. Not really sure why as there never really was any increase in mortality from WHI publications – they were presenting increase in incidence. But it is good that women get this message. There is no overall increase or overall benefit in all-cause mortality. The publication cautions that due to multiple comparisons the results for cause specific mortality should be interpreted with caution. There has long been discussion about the possible different cardiovascular disease outcomes when hormone replacement therapy is used at different ages. Looking at data from both studies combined, although women in the 50–59 year age group had lower hazard ratios than older woman for mortality from cardiovascular disease during the intervention phase this was not statistically significant during the cumulative follow-up phase. Specifically looking at breast cancer, overall combined menopausal hormone therapy did not result in an increase but estrogen-only was associated with a decrease in breast cancer mortality that just reached statistical significance. No doubt we will hear more about this in later publications.

Reference: JAMA 2017;318(10):927-38
Abstract

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Independent commentary provided by Associate Professor Helen Roberts
Helen is Associate Professor Women's Health at the University of Auckland and involved with both undergraduate and postgraduate medical education in O&G. **FOR FULL BIO CLICK HERE.**

Independent commentary provided by Dr Anil Sharma
Anil works in gynaecology private practice from Ascot Central and Ascot Hospital. His key interests are in menstrual problems including fibroids, urogynaecology and endometriosis. **FOR FULL BIO CLICK HERE.**

Effects of oral vs transdermal estrogen therapy on sexual function in early postmenopause

Authors: Taylor H et al.

Summary: This ancillary study of the KEEPS trial investigated the effects of oral and transdermal estrogen therapy on sexual function in postmenopausal women. 670 women aged 42–58 years who were within 36 months from their last menstrual period were randomised to receive oral conjugated estrogens 0.45 mg/day, transdermal 17β-estradiol 50 µg/day, or placebo for 4 years. Participants also received oral micronised progesterone 200mg (if randomised to estrogen therapy) or placebo (if randomised to placebo) for 12 days each month. Aspects of sexual function and experience were assessed using the Female Sexual Function Inventory (FSFI). Transdermal estrogen significantly improved FSFI overall score across all time points compared with placebo, but oral estrogen therapy did not. In the individual domains of sexual function, transdermal estrogen treatment was associated with a significant increase in mean lubrication and decreased pain compared with placebo.

Comment (HR): Data for this study were collected at 4 time periods – baseline,18, 36, and 48 months Compared to placebo, transdermal estrogen improved lubrication and decreased pain on penetration across all the time points but desire, arousal, orgasm and sexual satisfaction seemed improved only at 18 months. Compared to oral estrogen, desire and arousal was better with transdermal only at the 18-month time period but overall oral estrogen demonstrated fewer improvements than transdermal compared to placebo. In some ways these results reflect what we do in clinical practice. Oral estrogen is known to increase sex hormone-binding globulin in the liver. This means that there will be less free testosterone available which may decrease libido for some women. Changing to transdermal estrogen (now funded) can improve this. Systemic estrogen used for hot flushes does help with vaginal dryness but we know can make incontinence worse. Many women who are on systemic estrogen for flushes will need vaginal estrogen to really improve vaginal symptoms with the added benefit of helping urgency and urge incontinence. Ovestin® is the funded vaginal estrogen in NZ. The last sentence in the conclusion is important – the study did not look at whether women were distressed by changes in sexual function. As the North American Menopause Society website for women points out, the issue is not the sexual "problem" or condition itself but whether it is bothersome or troubling to the person or partners involved.

Reference: JAMA Intern Med 2017;177(10):1471-79
Abstract

Fast-track vs. delayed insertion of the levonorgestrel-releasing intrauterine system after early medical abortion

Authors: Korjamo R et al.

Summary: This pilot study compared expulsion rates after fast-track or delayed insertion of a levonorgestrel-releasing IUS following mifepristone and misoprostol medical abortion. 108 women at ≤63 days' gestation were randomised to fast-track (≤3 days) or delayed (2–4 weeks) insertion of an IUS after medical termination of pregnancy (MTOP) and were followed up for 1 year. At 3 months, expulsion had occurred in six (12.5%) women after fast-track and 1 (2.3%) woman after delayed insertion (risk ratio [RR], 5.50). By 1 year, expulsion had occurred in 7 (14.6%) and 5 (11.5%) women in the respective groups (RR, 1.28).

Comment (HR): In this study fast-track IUS insertion is within 3 days of an MTOP i.e., on the next working day after giving the misoprostol. Vaginal ultrasound was performed to ensure that gestational sac expulsion had occurred and to exclude remaining products of conception. Delayed IUS insertion was at 2–4 weeks after MTOP. There were more partial expulsions with the fast track. These were mainly at the 2–4 week visit, asymptomatic, and diagnosed with ultrasound. Regarding the 1-year expulsion comparison, the authors noted that a significant difference between long-term levonorgestrel IUS expulsion rates following the fast-track and delayed insertion could not be shown, and limited conclusions could be drawn because of the low number of women and the high loss to follow-up. It is likely that immediate insertion after MTOP will result in more women having the IUS inserted as this has been found to be the case with immediate postplacental insertion after delivery compared to insertion at the 6-week visit. At present we inform women having MTOP to have IUS inserted 2 weeks post termination. It is unlikely at this stage that we can clinically do this earlier in primary health care if ultrasound is going to be a required part of the protocol. Hopefully though we will have further research to guide us.

Reference: Contraception 2017;96(5):344-51
Abstract

CLICK HERE to read previous issues of Women's Health Research Review

Time to transient and stable reductions in hot flush frequency in postmenopausal women using conjugated estrogens/bazedoxifene

Authors: Pinkerton J et al.

Summary: This *post hoc* analysis of data from the SMART-2 trial examined the impact of conjugated estrogens/bazedoxifene on hot flush frequency in postmenopausal women. In the SMART-2 trial, women with at least 7 moderate/severe hot flushes per day or 50 per week were randomised to receive conjugated estrogens/bazedoxifene (0.45mg/20mg or 0.625mg/20mg) or placebo daily for 12 weeks. Participants recorded the frequency of moderate/severe hot flushes in diaries throughout the trial. Median time to a transient 50% reduction in hot flush frequency was 8 days for conjugated estrogens/bazedoxifene 0.45mg/20mg, 9.5 days for 0.625mg/20mg, and 10 days for placebo; median time to a stable 50% reduction was 9, 10, and 38 days in the respective groups. Median time to a transient 90% reduction in hot flush frequency was 32 and 22.5 days for conjugated estrogens/bazedoxifene 0.45mg/20mg and 0.625mg/20mg, respectively, and median time to a stable 90% reduction was 83 and 29 days, respectively.

Comment (HR): Nice to have a time frame to tell women how soon they can expect some flush benefits. This is not likely to be any different though to using conjugated estrogens alone or with a progestogen. It is a pity that this combination wasn't with a transdermal estrogen. This combination is not funded in NZ and although we have data regarding endometrial protection and no effect on breast density after 1 year of use we await data regarding the breast cancer outcomes. Will they be different from WHI data with combined hormone therapy use?

Reference: Menopause 2017;24(9):1011-16
Abstract

Maintaining physiological testosterone levels by adding dehydroepiandrosterone to combined oral contraceptives

Authors: Coelingh Bennink H et al.

Summary: This study evaluated whether adding DHEA to combined oral contraceptives (COCs) maintains physiological levels of free testosterone. 81 healthy women (aged 20–35 years) were randomised to receive 5 cycles of ethinylestradiol (EES) combined with levonorgestrel or drospirenone together with either DHEA 50 mg/day or placebo. After 5 cycles, all participants crossed over to the other treatment arm for an additional 5 cycles. Both COCs decreased the levels of all androgens measured. Significant decreases were found with EES/levonorgestrel and EES/drospirenone for total testosterone (54.5% and 11.3%, respectively) and for free testosterone (66.8% and 75.6%, respectively). Adding DHEA to the COCs significantly increased all androgens compared with placebo. The addition of DHEA restored free testosterone levels to baseline levels in both COC groups and restored total testosterone levels to baseline (EES/levonorgestrel) or above baseline (EES/drospirenone).

Comment (HR): It's hard to know what this study will mean from the point of view of sexual function in women. Female sexual function depends on many factors and really we don't have a strong correlation between free testosterone levels and sexual function. A 2013 systematic review found that although the combined pill decreased free testosterone the majority of women reported no significant change in libido. A 2006 review noted that supplementing the combined pill with androstenedione in women with decreased libido showed no benefit over placebo.

Reference: Contraception 2017;96(5):322-29
Abstract

Comparison of clinical outcomes among users of oral and transdermal estrogen therapy in the Women's Health Initiative Observational study

Authors: Crandall C et al.

Summary: This study analysed data from the WHI Observational study to compare clinical outcomes among users of oral and transdermal estrogen therapy. 45,112 participants in the WHI Observational study (average follow-up 5.5 years) who were taking oral or transdermal estrogens were assessed for time to first global index event (GIE), defined as coronary heart disease, breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, or death. Women taking oral conjugated estrogens <0.625 mg/day + progestogen had a lower risk of a GIE during follow-up than women taking oral conjugated estrogens 0.625 mg/day + progestogen (adjusted hazard ratio [HR], 0.74). GIE risk in women taking oral conjugated estrogens 0.625 mg/day + progestogen was greater with ≥5-year use than <5-year use (adjusted HR, 1.22). In women with prior hysterectomy, compared with women taking oral conjugated estrogens ≤0.625 mg/day for <5 years, GIE risk was similar with oral conjugated estrogens <0.625 mg/day, oral estradiol, and transdermal estradiol, whether used for <5 years or ≥5 years.

Comment (HR): Well this is interesting. Previous observational studies have suggested that transdermal estrogen did not have the increase in venous thromboembolism/stroke risk that exists with oral estrogen – so I would have expected a lower overall GIE risk with transdermal. That lower doses of oral estrogen have lower overall risks makes sense – hence the advice to use the lowest dose possible for symptom relief. The authors suggest that using conjugated estrogens at a dose <0.625 mg/day instead of 0.625 mg/day, limiting the duration of use of conjugated estrogens + progestogen to <5 years, and avoiding the use of conjugated estrogens + progestogen in women with BMI ≥30 could result in fewer adverse events. However, this study did not look at the dose of the transdermal estrogen, and all the observational studies showing less risk of venous thromboembolism/stroke were 50µg patches or less (not 100µg). The authors do go on to say that the results may not apply to the low dose transdermal preparations that we are now using, suggesting that some of these women were likely to have been using higher dose (>50µg) transdermal preparations.

Reference: Menopause 2017;24(10):1145-53
Abstract

Should obese women's access to assisted fertility treatment be limited?

Authors: Tremellen K et al.

Summary: Guidelines from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) suggest that severe obesity (BMI >35 kg/m^2) should be an absolute contraindication to assisted fertility treatment, including *in vitro* fertilisation (IVF). This article challenged the ethical and scientific basis for such a ban, and concluded that it is unwarranted and should be revised.

Comment (AS): A very interesting ethical and scientific discussion paper about current Australian and NZ political and RANZCOG attitudes and guidelines regarding the provision of assisted fertility services (AFS) to obese women. Current NZ guidelines do not allow for provision of publically funded AFS to women with a BMI >32. As you know, obesity is the modern scourge with around 45% of the NZ population having a BMI above 30 (37.5% of Australians). The authors assess all the current postulated reasons why AFS should be denied according to BMI and make a good case for relaxing the rules. For example, success rates for IVF for young obese women are better than for women in their late thirties. Complications of pregnancy are generally lower than we have thought if we are dealing with an obese woman without other morbidity versus with other morbidity. Current guidelines are also felt to discriminate more against women from lower socioeconomic and 'indigenous population' backgrounds in both Australia and NZ. These groups have a 2- to 4-fold higher rate of obesity than others. I feel that the current guidelines particularly for access to publically funded AFS in NZ are too rigid and need individualising and discretionary review.

Reference: Aust NZ J Obstet Gynaecol 2017;57(5):569-74
Abstract

History of breast feeding and risk of incident endometriosis

Authors: Farland L et al.

Summary: This analysis of data from the Nurses' Health Study II investigated the association between breastfeeding and endometriosis. 72,394 women who reported having one or more pregnancies were included, of whom 3296 had laparoscopically confirmed endometriosis. For each pregnancy, women reported breastfeeding duration and postpartum amenorrhoea. The duration of total and exclusive breastfeeding was found to be significantly associated with a decreased risk of endometriosis. There were 453 endometriosis cases/100,000 person years in women who reported a lifetime total length of breastfeeding of <1 month, compared with 184 cases/100,000 person years in women who reported a lifetime total of ≥36 months of breastfeeding. Women experienced an 8% lower risk of endometriosis for every additional 3 months of total breastfeeding per pregnancy, and a 14% lower risk for every additional 3 months of exclusive breastfeeding. Women who breastfed for 3 or more years across their reproductive lifetime had a 40% lower risk of endometriosis than women who never breastfed. The protective association with breastfeeding was strongest in women who gave birth within the past 5 years. The association between breastfeeding and endometriosis was partially influenced by postpartum amenorrhoea.

Comment (AS): Breastfeeding helps women with weight loss and reduction in risk of chronic diseases including ovarian and breast cancer. Whilst the nutritional benefits of breastfeeding for infants and mothers are well known, this study with over 20 years of follow-up thus far, confirmed that breastfeeding reduces the risk of endometriosis. Also, the longer the duration of postpartum amenorrhoea due to breastfeeding, the greater the reduction in cases of endometriosis. For the analysis, only laparoscopically diagnosed cases of endometriosis were considered, not just clinical diagnoses. For example, women who had breastfed for a total of >36 months (across 1 or several pregnancies) had a 40% reduced risk of endometriosis. This study adds further support to the range of health benefits associated with breastfeeding and can help in counselling women regarding this. It is postulated that the benefit is due to less menses (and therefore retrograde menses) but of course effects due to major hormonal changes during breastfeeding may well play a part also.

Reference: BMJ 2017;358:j3778
Abstract

Cost-effectiveness of treatments for heavy menstrual bleeding

Authors: Spencer J et al.

Summary: This study investigated the relative cost-effectiveness of 4 treatment options for heavy menstrual bleeding: hysterectomy, resectoscopic endometrial ablation, nonresectoscopic endometrial ablation, and the levonorgestrel-releasing IUS. A decision tree was formulated that evaluated private payer costs and quality-adjusted life years (QALYs) over a 5-year time horizon for premenopausal women with heavy menstrual bleeding and no suspected malignancy. Total average costs, QALYs, and incremental cost-effectiveness ratios were compared for the 4 treatments. The levonorgestrel-releasing IUS had superior quality-of-life outcomes to hysterectomy, and was cost effective compared with hysterectomy in most scenarios. Both resectoscopic and nonresectoscopic endometrial ablation were associated with lower costs than hysterectomy, but resulted in a lower average quality of life. According to standard willingness-to-pay thresholds, resectoscopic endometrial ablation was cost effective compared with hysterectomy in 44% of scenarios, and nonresectoscopic endometrial ablation was cost effective compared with hysterectomy in 53% of scenarios.

Comment (AS): This paper is essentially a mathematical model of a hypothetical cohort of 100,000 women. From already published research papers, complications and outcomes for hysterectomy (all types), the levonorgestrel-releasing IUS and all types of endometrial ablation were reviewed and a cost analysis (using costs and treatment norms for the US) was undertaken for all outcomes. The levonorgestrel-releasing IUS was not only significantly cheaper than hysterectomy but also superior overall with relation to quality of life. Ablation was superior in terms of costs but less so with quality of life considerations on comparison with hysterectomy. This hypothetical paper again indicates that all options for treatment of heavy menstrual bleeding should be considered and discussed, both for managing resource constraints and for considering/counselling regarding complications and outcomes.

Reference: Am J Obstet Gynecol 2017;217(5):574.e1-574.e9
Abstract

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) Fellows may claim 1 PD point per hour in the 'Self-Education' component of any of the three domain for any self-educational O&G activities completed (including reading of relevant Research Reviews).

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Recurrent vulvovaginal candidiasis: a review of guideline recommendations

Authors: Matheson A & Mazza D

Summary: This study evaluated current guidelines for recurrent vulvovaginal candidiasis (VVC). A search of MEDLINE, SCOPUS, The Cochrane Library and relevant websites identified 5 guidelines for VVC. The identified guidelines were found to be of mixed quality. Current international guidelines for recurrent VVC were consistent in terms of their definition of the condition, diagnostic techniques and utilising induction and maintenance therapy as the treatment of choice. However, most guidelines recommended the use of fluconazole weekly for 6 months, which is not particularly effective (only 42.9% of patients are disease free after 12 months). An alternative regimen suggested by one guideline cites a 77% cure rate after 12 months.

Comment (AS): This is a challenging problem that affects up to 75% of women and around 5–8% get recurrent thrush caused mostly by *Candida albicans*. Risk factors include pregnancy, the combined oral contraceptive pill, frequent antibiosis, and immune compromise. To date, most prolonged therapies for recurrent thrush (4 or more episodes a year) are overall disappointing. The authors set out to compare the various published guidelines which were assessed for quality and robustness. A summary of recommendations was provided. Ideally, diagnosis needs culture and proof of infection; asymptomatic colonisation does not need treatment; use topical therapy if pregnant; and always exclude diabetes and human immunodeficiency virus. Six months of weekly fluconazole 150mg provides an efficacy of around 43% at 12 months. A 1-year regimen of fluconazole 200mg three times a week for one week, followed by once a week for seven weeks then once a fortnight from 3 to 6 months and finally once a month from month 7 until month 12 gave an efficacy of 77%. The authors identified that much more research is needed.

Reference: Aust NZ J Obstet Gynaecol 2017; 57(2):139-45
Abstract