Women's Health Research Review

Making Education Easy

Issue 26 – 2018

In this issue:

Abbreviations used in this issue

FDA = Food and Drug Administration

IUD = intrauterine device

LNG-IUS = levonorgestrel-intrauterine system

RCOG = Royal College of Obstetricians and Gynaecologists

VTE = venous thromboembolism

PHARMACY GUILD OF NEW ZEALAND

NZMA New Zealand Medical Association

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

This month we report that neither prescribed vaginal oestradiol tablets nor over-the-counter vaginal moisturisers provide additional benefit over placebo in reducing postmenopausal vulvovaginal symptoms, a systematic review for the US Preventive Services Task Force advises against the use of hormone therapy for primary prevention of chronic conditions in postmenopausal women, and a Danish cohort study evaluates the association between hormonal contraceptives and breast cancer risk. US investigators provide good information on amenorrhoea for women considering a Mirena® for contraception, the desogestrel progestogen-only pill shows promise in women with migraine, and conservative surgery is shown to be a feasible option in patients with large deep endometriosis infiltrating the rectum.

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

Kind regards,

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Efficacy of vaginal estradiol or vaginal moisturizer vs placebo for treating postmenopausal vulvovaginal symptoms

Authors: Mitchell C et al.

Summary: This placebo-controlled US study compared the use of a low-dose vaginal oestradiol tablet and a vaginal moisturiser in women with moderate to severe postmenopausal vulvovaginal symptoms. Women were randomised to use a vaginal oestradiol 10µg tablet (daily for 2 weeks, then twice weekly) plus placebo gel (n=102), placebo tablet plus vaginal moisturiser (n=100), or dual placebo (n=100) for 12 weeks. The most commonly reported 'most bothersome symptom' at baseline was pain with vaginal penetration (60%), followed by vulvovaginal dryness (21%). All treatment groups had similar mean reductions in most bothersome symptom severity over 12 weeks. Female Sexual Function Index score improvement was also similar in all groups.

Comment (HR): It took me a few readings to see what was being looked at here but this is a randomised, double-blind, placebo-controlled, multisite trial of low dose Vagifem® 10µg (not available in NZ) and placebo vaginal gel vs Replens® and placebo vaginal tablets vs dual placebo. Neither Vagifem® nor Replens® seemed to perform better than placebo gel for any outcomes, except that Vagifem® improved the vaginal maturation index, which may not have any clear clinical relevance. So women in all allocation groups reported substantial improvement in their most bothersome vulvovaginal symptom over 12 weeks (a 2-standard deviation decrease, from moderate to severe at baseline to none or mild at follow-up). The authors conclude by suggesting "Our results suggest that most women can achieve greater than 50% reduction in symptom severity with regular, consistent use of a vaginal gel with lubricant properties and do not see added symptom improvement with vaginal estradiol". Treatment decisions about postmenopausal vulvovaginal symptoms should be "based on cost and formulation preference". An editorial comment on the study takes this further, suggesting "initial trial of the cheapest moisturizer or lubricant available over the counter". Vagifem® 10 has had 2 industry studies showing benefit over placebo. The authors of the present study point out that "the largest difference between our trial and others is the magnitude of symptom improvement in our placebo group. Our placebo was quite different from placebo creams and tablets used in other trials of vaginal estrogen, and meets many of the criteria outlined in a recent review as optimal for vaginal moisturizing products". So what is the optimal vaginal product then? A study in *Climacteric* suggests that a vaginal moisturiser or lubricant should have an acidic pH and osmolality below the WHO ideal recommendation of 380 mOsm/kg. However we also need to remember that in NZ some of these lubes and moisturisers are quite expensive and that Ovestin® is subsidised.

Reference: JAMA Intern Med 2018;178(5):681-90
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).

Hormone therapy for the primary prevention of chronic conditions in postmenopausal women

Authors: Gartlehner G et al.

Summary: This systematic review for the US Preventive Services Task Force evaluated the benefits and harms of hormone therapy (HT) for the prevention of chronic conditions in postmenopausal women. A search of MEDLINE, Cochrane Library, EMBASE, and trial registries identified 18 randomised clinical trials (n = 40,058) that were suitable for inclusion. Women using oestrogen-only therapy were found to have significantly lower risks of diabetes and fractures than those using placebo. However, risks were significantly increased for gall bladder disease, stroke, VTE, and urinary incontinence. Women using oestrogen + progestogen had significantly lower risks of colorectal cancer, diabetes, and fractures than those using placebo, but significantly increased risks of invasive breast cancer, dementia, gall bladder disease, stroke, urinary incontinence, and VTE.

Comment (HR): This updated evidence report gives the same advice as all the previous ones – no HT to prevent chronic conditions. A good editorial by Deborah Grady regarding this reminds us that "since age is the major predictor of disease, the absolute risk of all of the outcomes is much lower in symptomatic women near the menopause, and the estimated net harm is small. Of note, there is no evidence that use of HT for 5–7 years increases overall mortality. When adequately informed, women with moderate to severe symptoms and without contraindications should be able to take such small risks if HT improves symptoms and quality of life". So for a woman aged 50–59 years there is an absolute increase of breast cancer diagnosis of 5/10,000 women per year, an extra 2/10,000 women per year for stroke and an extra 11/10,000 women per year for VTE for combined HT use – the figures for oestrogen-only being an extra 3/10,000 women per year for stroke and an extra 4/10,000 women per year for VTE.

Reference: JAMA 2017;318(22):2234-49
Abstract

Contemporary hormonal contraception and the risk of breast cancer

Authors: Mørch L et al.

Summary: This Danish cohort study investigated the association between hormonal contraception and the risk of invasive breast cancer. All women in Denmark aged 15–49 years who had not had cancer or VTE and who had not received treatment for infertility were included. A total of 1.8 million women were followed for a mean 10.9 years, during which time 11,517 cases of breast cancer were reported. Compared with women who had never used hormonal contraception, the relative risk of breast cancer among current and recent users was 1.20. The risk increased from 1.09 with <1 year of use to 1.38 with >10 years of use (p=0.002). After discontinuation of hormonal contraception, the risk of breast cancer was still higher among women who had used hormonal contraceptives for ≥5 years than among women who had not used them. Women who currently or recently used the progestogen-only IUS also had a higher risk of breast cancer than women who had never used hormonal contraceptives (relative risk, 1.21).

Comment (HR): This was a nationwide prospective study involving 1.8 million Danish women who were followed for almost 11 years. The authors remind us that "the estimated number of additional breast cancers among premenopausal women that were attributable to hormonal contraception is likely to be low. This risk should be weighed against important benefits of hormonal contraceptives such as good contraceptive efficacy and reduced risks of ovarian, endometrial, and perhaps colorectal cancer (at least for combined oral contraceptives that were commonly used in the 1970s and 1980s)". The UK RCOG Faculty of Sexual and Reproductive Health documents remind us that previous research from the Collaborative Group on Hormonal Factors in Breast Cancer study (a re-analysis of 54 studies) reported a slightly increased risk of breast cancer associated with current or recent use of hormonal contraceptives and found there was no evidence of an increased risk ≥10 years after stopping use. Their intrauterine device document (2015) stated that evidence does not support a link between breast cancer and use of the LNG-IUS. However non-hormonal contraception is most appropriate for women with a history of breast cancer.

Reference: N Engl J Med 2017;377:2228-39
Abstract

Amenorrhea rates and predictors during 1 year of levonorgestrel 52mg intrauterine system use

Authors: Darney P et al.

Summary: This study evaluated amenorrhoea patterns and predictors during the first year after placement of a 52mg LNG-IUS. The cohort comprised 1714 women who received a Liletta® IUS as part of a multicentre trial to evaluate efficacy and safety for up to 8 years. 148 women had used a LNG-IUS prior to the study and 1566 women had not. Prior users averaged 50 months of use before IUS placement; 38.4% of them reported amenorrhoea at 12 months. Amenorrhoea rates for non-prior-users at 3, 6, 9 and 12 months were 0.2%, 9.1%, 17.2% and 16.9%, respectively. 29 (1.7%) women discontinued for bleeding irregularities during the first 12 months but none of the women discontinued for amenorrhoea. The only significant predictor of amenorrhoea at 12 months was self-reported baseline duration of menstrual flow of <7 days vs ≥7 days (18.2% vs 5.2%; adjusted odds ratio, 3.70).

Comment (HR): It's good to be able to give women some information here – as many women seem to think that they will not have periods at all with Mirena®. This is interesting – in this study the only significant predictor of amenorrhoea at 12 months was self-reported baseline duration of menstrual flow – if periods were <7 days then 18.2% of the women had no periods and if periods were previously 7 or more days in duration then only 5.2% of women had no periods. The UK RCOG intrauterine contraception document gives us the figure that 23.6% women at 3 years have no periods with Mirena® compared with 12.7% of women with the smaller Jaydess® device.

Comment (AS): This study provides some important data for counselling women who have a 52mg LNG-IUS (called Mirena® in NZ) for contraception and not for heavy periods. Whilst the definition of amenorrhoea was strict (no bleeding or spotting in the previous 3 months), rates at 3, 6, 9 and 12 months were 0.2%, 9.1%, 17.2% and 16.9%. The removal rate for erratic bleeding at 12 months (1.7%) seems low and no mention was made of other hormonal side effects leading to removal e.g. mood issues or headaches. These figures will be useful for women considering the device for contraception.

Reference: Contraception 2018;97(3):210-14
Abstract

Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study

Authors: Crandall C et al.

Summary: This analysis of data from the Women's Health Initiative Observational Study determined the association between vaginal oestrogen use and breast/endometrial cancer and cardiovascular events. 45,663 women aged 50–79 years who used vaginal oestrogen (but not systemic oestrogen) during a median follow-up of 7.2 years were included in the analysis. Among women with an intact uterus, the risks of stroke, invasive breast cancer, colorectal cancer, endometrial cancer, and pulmonary embolism/deep vein thrombosis did not differ significantly between vaginal oestrogen users and nonusers. However, the risks of coronary heart disease, fracture, and all-cause mortality were lower in users than in nonusers. Among hysterectomised women, the risks did not differ significantly between users and nonusers.

Comment (HR): This confirms what we have been telling women but it evaluates multiple clinical outcomes in approximately10-fold more women than in any randomised trial of vaginal oestrogen therapies to date. Use of vaginal oestrogen products was determined by self-assessment questionnaires. Women were asked at baseline, and then annually from years 3 through 8 and then year 4 of the extension study, whether they had used "vaginal creams or suppositories" (yes or no), and the duration of use. On average, the duration of vaginal oestrogen use was 2–3 years, at least twice as long as prior trials. So, very reassuring regarding the overall safety of vaginal oestrogen therapies. We are all aware that the package insert for vaginal oestrogen gives the same risk profile as systemic oestrogen. Whether this new evidence will be adequate for the FDA to justify the desired label change, however, still remains a question.

Reference: Menopause 2018;25(1):11-20
Abstract

Effectiveness of the progestin-only pill for migraine treatment in women

Authors: Warhurst S et al.

Summary: This systematic review and meta-analysis evaluated the effectiveness of progestogen-only contraceptives for migraine treatment. A search of MEDLINE, EMBASE and Cochrane Libraries identified 4 studies of progestogen-only treatments for migraine in non-menopausal women. Pooled analysis of the data demonstrated that the desogestrel 75 µg/day progestogen-only pill significantly but modestly reduced the number of migraine attacks and migraine days. It also decreased the intensity and duration of migraines, reduced analgesic and triptan use, and improved headache-related quality of life.

Comment (HR): I see that one of the authors of this research is from Timaru Hospital. As they say in the conclusions the current evidence is low quality and observational from only 4 studies and we need further randomised studies. Migraines commonly occur with menstruation for about 60% of women so may be hormone-related menstrual migraines. We have some data from a recent systematic review that the combined pill can be of benefit for migraines but as one-third of women have migraine with aura the combined oral contraceptive is contraindicated. Prevention of ovulation may be one of the pathways for improvement in migraine. The clinical implications stated are that this progestogen-only pill (Cerazette®) is associated with a modest reduction in migraine frequency and duration in most women, with reduced use of analgesia after 180 days of use. However it is not funded in NZ and is quite expensive.

Reference: Cephalalgia 2018;38(4):754-64
Abstract

Independent commentary provided by Honorary Associate Professor Helen Roberts MB, MPH, FAChSHM

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. I was Associate Professor Women's Health until my retirement at the end of 2017. At present I continue my contraception and menopause clinic at Greenlane clinical centre and work as a certifying consultant at Epsom Day Unit.

Cardiovascular and metabolic morbidity after hysterectomy with ovarian conservation

Authors: Laughlin-Tommaso S et al.

Summary: This study determined the long-term risk of cardiovascular disease and metabolic conditions in women undergoing hysterectomy with bilateral ovarian conservation. 2,094 women who underwent hysterectomy with ovarian conservation for benign indications in 1980–2002 in Olmsted County, Minnesota, were identified using the Rochester Epidemiology Project records-linkage system. Each woman was age-matched to a referent woman residing in the same county who had not undergone prior hysterectomy or oophorectomy. Over a median follow-up of 21.9 years, women who underwent hysterectomy experienced increased risks of *de novo* hyperlipidaemia, hypertension, obesity, cardiac arrhythmias, and coronary artery disease. Women who underwent hysterectomy before 35 years of age had a 4.6-fold increased risk of congestive heart failure and a 2.5-fold increased risk of coronary artery disease.

Comment (AS): This was a case-control study of 2,094 women with a median follow up of 21.9 years. Relative risks in parentheses were hyperlipidaemia (1.14), obesity (1.18), cardiac arrhythmias (1.17) and coronary heart disease (1.33). Women who had hysterectomies at age ≤35 had a 4.6-fold increased risk of congestive cardiac failure and a 2.5-fold increased risk of coronary heart disease. It is notable that women undergoing the hysterectomy with ovarian conservation were already more likely to have pre-existing hyperlipidaemia. One postulation is that the effects are mediated by changes to ovarian blood flow. Whilst causality cannot be established, these findings support discussing other options for benign gynaecological conditions (especially for younger patients) given that there are relatively good alternatives available.

Reference: Menopause 2018;25(5):483-92
Abstract

Conservative surgery versus colorectal resection in deep endometriosis infiltrating the rectum

Authors: Roman H et al.

Summary: This study evaluated the differences in functional outcome after conservative vs radical rectal surgery in patients with large deep endometriosis infiltrating the rectum. 60 patients were randomised to either conservative surgery (shaving or disc excision) or radical rectal surgery (segmental resection) and were followed up for 2 years. Among the 27 patients in the conservative surgery arm, two were converted to segmental resection (7.4%). 48.1% of women in the conservative surgery group and 39.4% of women in the radical surgery group presented with at least 1 functional problem (constipation, frequent bowel movements, defaecation pain, anal incontinence, dysuria or bladder atony requiring self-catheterisation) at 24 months after surgery (odds ratio, 0.70; 95% CI 0.22–2.21). Segmental resection was associated with a significant risk of bowel stenosis.

Comment (AS): This randomised controlled trial looked at the differences in outcome between conservative surgery (shaving off endometriosis or resecting a disc of endometriosis) versus more radical surgery (i.e. bowel resection). The 60 patients had large deep endometriosis lesions affecting the rectum. There was no major difference in outcome in a functional (symptomatic) way between the two arms. The radical surgery arm had around a 15% risk of rectal stenosis requiring further surgery. The overall presentation with recurrent symptomatic problems was around 40% in each group within 2 years. Whilst there was no significant difference in efficacy between the 2 types of surgery, it is likely that for smaller rectal lesions, conservative surgery will be better. It would seem that conservative surgery was better overall.

Reference: Hum Reprod 2018;33(1):47-57
Abstract

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.

Association of hysteroscopic vs laparoscopic sterilization with procedural, gynecological, and medical outcomes

Authors: Bouillon K et al.

Summary: This French nationwide cohort study compared adverse events associated with hysteroscopic and laparoscopic sterilisation. Women aged 30–54 years receiving a first hysteroscopic or laparoscopic sterilisation in 2010–2014 were followed-up through December 2015. Of the 105,357 women included, 67.7% underwent hysteroscopic sterilisation and 32.3% underwent laparoscopic sterilisation. Women undergoing hysteroscopic sterilisation had a lower risk of surgical complications (0.13% vs 0.78%) and medical complications (0.06% vs 0.11%), but a higher risk of sterilisation failure (4.83% vs 0.69%). In addition, 5.65% of women who underwent hysteroscopic sterilisation required gynaecological reoperation compared with 1.76% of women who underwent laparoscopic sterilisation.

Comment (AS): With the ongoing recent adverse outcomes and publicity attributed to hysteroscopic sterilisation, this is one of several timely papers that looked at complications of hysteroscopic sterilisation compared with the long established technique of laparoscopic sterilisation. Failure of sterilisation in the first year after hysteroscopic vs laparoscopic sterilisation was 4.83% vs 0.69%; a need for gynaecological reoperation was 5.65% vs 1.76%; medical outcomes (i.e. medical not surgical issues) were similar in both groups; and there was a lower risk of intraoperative complications with hysteroscopic sterilisation (0.13% vs 0.78%). The FDA has ordered the manufacturer to conduct a randomised controlled trial comparing hysteroscopic and laparoscopic sterilisation (results expected in 2023). Pending these more detailed studies and the passage of time it would continue to seem appropriate that vasectomy or an LNG-IUS device be offered first for women who desire reliable contraception. If, after consideration, these are declined the next best option is probably laparoscopic sterilisation. Bilateral salpingectomies can also be considered for sterilisation, and reduce the long term risks of ovarian cancer significantly.

Reference: JAMA 2018;319(4):375-87
Abstract

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