Women's Health Research Review™

Making Education Easy

Issue 28 – 2019

In this issue:

Abbreviations used in this issue
COC = combined oral contraceptive
OR = odds ratio
RANZCOG = Royal Australian and NZ College of Obstetricians and Gynaecologists
VTE = venous thromboembolism

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, Finnish investigators suggest that long-term use of systemic hormone therapy (but not vaginal oestradiol) increases the risk of Alzheimer disease in postmenopausal women, UK data confirm that transdermal treatment is the safest type of hormone replacement therapy with regard to VTE risk, and Danish researchers show that contemporary combined hormonal contraceptives reduce the risk of ovarian cancer in women of reproductive age. US investigators report that simple ovarian cysts are not associated with an increased risk of ovarian cancer, a randomised controlled trial finds little difference in outcomes between surgical excision and ablation of endometriosis for chronic pelvic pain, and a survey evaluates current management practices for pelvic organ prolapse in Australia and NZ.

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

Kind regards,

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Dr Anil Sharma
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Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland

Authors: Savolainen-Peltonen H et al.

Summary: This Finnish nationwide case-control study evaluated the risk of Alzheimer disease (AD) in women taking postmenopausal hormone therapy. 84,739 postmenopausal women who were diagnosed with AD in 1999–2013 were matched by age and hospital district with 84,739 postmenopausal women without AD. Use of systemic hormone therapy was associated with a 9–17% increased risk of AD. The risk did not differ significantly between users of oestrogen-only therapy and users of oestrogen-progestogen. The increased risk in users of oestrogen-progestogen therapy was not related to different progestogens. In women aged <60 years at hormone therapy initiation, increases in risk were associated with hormone therapy exposure >10 years, but not the age at initiation of treatment. Exclusive use of vaginal oestradiol did not affect the risk of AD.

Comment (HR): This large observational study found that women taking hormone therapy had a 9–17% higher risk of developing AD. In women who began taking hormone therapy before age 60, this increased risk was tied to long-term use of a decade or longer. This means 9–18 excess diagnoses of AD per year will be detected in 10,000 women aged 70–80, especially in those women who had used hormone therapy for over 10 years. Nearly all of the women with AD were diagnosed after 60. More than half were over 80 at the time of diagnosis. The study didn't find a difference in AD risk based on the formulation of hormone therapy. The risk was similar whether women took oestrogen alone, or oestrogen and progesterone together. Exclusive use of vaginal oestradiol was not related to risk of AD. For shorter treatment durations (<10 years), the risk of AD was not increased among those who initiated either oestrogen therapy or oestrogen plus progesterone therapy before age 60. We need to remember that observational studies can however show only associations between hormone therapy use and the risk of AD, not causation. The only randomised trial of postmenopausal hormone therapy for prevention of AD, the Women's Health Initiative Memory Study (WHIMS), showed a doubling of the risk of all-cause dementia with oestrogen plus progestin. In this study, hormone therapy was initiated for women older than 65, many years after the onset of menopause. This observational study was a registry study and the accompanying editorial points out the limitations common to all registry studies, including the lack of information on potential confounding factors, including apolipoprotein E4 genotype, and other risk factors for dementia. The editorial concludes that for women in early menopause, with bothersome vasomotor symptoms, no compelling evidence exists of cognitive concern from randomised trials.

Reference: BMJ 2019;364:l665
Abstract

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Use of hormone replacement therapy and risk of venous thromboembolism

Authors: Vinogradova Y et al.

Summary: This UK study analysed data from the QResearch and Clinical Practice Research Datalink databases to evaluate the risk of VTE associated with different types of hormone replacement therapy. 80,396 women aged 40–79 years with a primary diagnosis of VTE in 1998–2017 were matched by age, general practice, and index date to 391,494 female controls. Overall, 7.2% of women who had VTE and 5.5% of controls had been exposed to hormone replacement therapy in the 90 days before the index VTE date. Within these two groups, 85% and 78% of women used oral therapy, which was associated with an increased risk of VTE compared with no exposure (adjusted odds ratio [OR], 1.58). The increased risk was found for both oestrogen-only preparations (OR, 1.40) and combined preparations (OR, 1.73). Oestradiol was associated with a lower VTE risk than conjugated equine oestrogens for oestrogen-only preparations (OR, 0.85) and combined preparations (OR, 0.83). Transdermal preparations were not associated with VTE risk.

Comment (HR): This large observational study found that oral menopausal hormone therapy was associated with a 70% increased risk of VTE while the transdermal route had no increase. Information regarding the VTE safety profile of transdermal oestrogen has been around since 2003 when the French national cohort study, ESTHER, was published and there have been other observational studies since then showing similar results. New information in this study showed a neutral effect with both low dose (50 mcg or less) and high dose (>50 mcg) transdermal preparations. The highest risk was with the oral conjugated equine oestrogens and medroxyprogesterone acetate combination. Different oral progestogen preparations were noted to have different risks, the lowest noted with dydrogesterone which was not associated with a significant increase in thrombotic risk. The French study found the same with the combination of transdermal oestrogen and micronised progesterone. In NZ the transdermal patch has been funded for some years. In addition to no VTE risk, other studies have also shown no increased risk of stroke. The oral progesterone – Utrogestan® 100mg capsules – is however not funded.

Reference: BMJ 2019;364:k4810
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Association between contemporary hormonal contraception and ovarian cancer in women of reproductive age in Denmark

Authors: Iversen L et al.

Summary: This Danish nationwide cohort study investigated the association between contemporary combined hormonal contraceptives and ovarian cancer. 1,879,227 women aged 15–49 years in 1995–2014 were categorised as never users, current/recent users (≤1 year after stopping), or former users (>1 year after stopping) of different hormonal contraceptives. 1249 incident ovarian cancers occurred during 21.4 million person-years of follow up. Compared with never users, reduced risks of ovarian cancer were seen with current/recent use (relative risk [RR], 0.58) and former use (RR, 0.77) of any hormonal contraception. Relative risks among current/recent users decreased with increasing duration of use (from 0.82 with ≤1 year's use to 0.26 with >10 years' use; p<0.001 for trend). Progestogen-only contraceptives were not associated with ovarian cancer risk.

Comment (HR): Previous research relating to the use of older and higher dose preparations of oestrogen-containing contraceptives has shown a reduced risk of ovarian cancer in users of combined oral hormonal contraceptives. This reduced risk has been shown to persist for many years after stopping use. In contrast with most previous research, this large prospective population-based study included women aged 15–49 years, most of whom will have been premenopausal and who used lower dose combined pills. Contemporary combined hormonal contraceptives are still associated with a reduced risk of ovarian cancer in women of reproductive age, with patterns similar to those seen with older combined oral products. The reduced risk seems to persist after stopping use, although it is not yet known how long for. Presently, there is insufficient evidence to suggest similar protection among exclusive users of progestogen-only products. The reduced risk associated with hormonal contraception was seen with nearly all types of ovarian cancer. Recent evidence (2015) from long term observations of hundreds of thousands of women, in 10 European countries, demonstrated that the use of oral contraceptives reduces overall mortality by roughly 10%.

Reference: BMJ 2018;362:k3609
Abstract

Association of risk for venous thromboembolism with use of low-dose extended- and continuous-cycle combined oral contraceptives

Authors: Li J et al.

Summary: This analysis of the US Sentinel Distributed Database investigated the risk of VTE in women taking continuous (84/7) or extended (365/0) combined COCs containing ethinyloestradiol and levonorgestrel compared with cyclic (21/7) COCs. 210,691 initiators of continuous/extended COCs were compared with 522,316 initiators of cyclic COCs. After propensity-score matching, the risk of VTE was higher in women taking continuous/extended COCs vs cyclic COCs (HR, 1.32; 95% CI 1.07–1.64). However, the absolute risk difference between the 2 groups was low and may not translate into clinically significant risk differences.

Comment (HR): This is good news as we are advocating to women about talking their pills with continuous hormones and no break with placebo pills. Over a period of time this will mean taking more hormones however the findings of this study are not unexpected as the increase in hormone use is small. Most VTEs occur in the first years of use with the pill. Our historical method of teaching women to take pills 21/7 did not really make good contraceptive sense. Why would you put the ovaries to sleep for 3 weeks then wake them up again for a week then put them to sleep again etc. So much better to get ongoing good ovarian suppression with continuous hormones which gives better contraception. With this method of pill taking, one would need to miss more than 8 pills in a row to get potential ovulation – unlikely even with poor pill takers. Also, continuous hormones mean relief for those women who get hormone withdrawal symptoms such as headaches in the pill-free interval. The other real benefit is there is no hormone-withdrawal bleed (period). There does not seem to be any increase in spotting with continuous hormone use compared to taking the pill with the placebo break. If it does occur the advice is to take 4 days off, let the unstable endometrium come away, and restart taking pill hormones continuously.

Reference: JAMA Intern Med 2018;178(11):1482-8
Abstract

Sociodemographic factors associated with attitudes towards abortion in New Zealand

Authors: Huang Y et al.

Summary: The 2016–2017 New Zealand Attitudes and Values Study used a survey to assess support for legalised abortion in NZ (19,973 respondents). Overall, there was moderate-to-high support for legalised abortion regardless of the reason, and strong support for abortion when the woman's life is endangered. Respondents who were religious, lived in a more deprived neighbourhood and had more children were less likely to support both measures of abortion. Men were less supportive of abortion for any reason, but had high support for legalised abortion when the woman's life is endangered.

Comment (HR): With the first reading and passing of the bill on Thursday 8th August we may be on our way to modernise the laws on abortion, by removing it from the Crimes Act and treating abortion as a health issue. If the bill is accepted then women will be able to self-refer to an abortion service provider. There will obviously be a lot of work required to enable this to happen. How will women know where to go, will each District Health Board be responsible for providing a service, will good contraceptive advice and provision be available? It would be great if this means that more women present earlier for advice and are able to have an early medical termination of pregnancy. But who will provide this service and advice is still unclear.

Reference: NZ Med J 2019;132:1497
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.

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).

Vaginal estrogen use and chronic disease risk in the Nurses' Health Study

Authors: Bhupathiraju S et al.

Summary: This analysis of the Nurses' Health Study (1982–2012) examined the risk of multiple health outcomes in postmenopausal women using vaginal oestrogen. Over 18 years of follow up, the risks of cardiovascular disease, cancer, and hip fracture did not differ between users and nonusers of vaginal oestrogen, and there was no significant increase in risk of any health outcome with vaginal oestrogen.

Comment (HR): Vulvovaginal atrophy and atrophic vaginitis affects a substantial proportion of postmenopausal women with estimates ranging from as low as 25% to as high as 70%. It is likely to be underdiagnosed as women may not discuss this unless asked about the symptoms when taking the history. Signs and symptoms include genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or dyspareunia; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections. Unlike vasomotor symptoms, symptoms do not resolve over time, are chronic, and can become progressively worse without treatment. Current advice is that low-dose vaginal oestrogen does not confer the risks of systemic treatment. This large prospective study of postmenopausal nurses gives us information regarding the safety profile for longer durations of use. After a period of 18 years of follow up, they found that users and nonusers of vaginal oestrogen did not have different risks for major cardiovascular outcomes (including total myocardial infarction, stroke, pulmonary embolism/deep vein thrombosis), cancer outcomes (total invasive cancer, invasive breast, ovarian, endometrial, or colorectal cancer), or hip fracture. This makes sense as the substantial increases in blood hormone levels seen with systemic oestrogen treatment are not observed in treatment with the recommended low doses of vaginal oestrogen.

Reference: Menopause 2019;26(6):603-10
Abstract

Risk of malignant ovarian cancer based on ultrasonography findings in a large unselected population

Authors: Smith-Bindman R et al.

Summary: This nested case-control study of patients enrolled in Kaiser Permanente Washington quantified the risk of ovarian cancer based on ultrasonographic characteristics of ovarian masses in a large unselected population. Participants were 72,093 women who underwent pelvic ultrasonography in 1997–2008, 1043 of whom had ultrasonographic evidence of ovarian masses. 210 women were diagnosed with ovarian cancer (49 were aged <50 years, and 161 were ≥50 years). The risk of cancer was significantly elevated in women with complex cysts or solid masses, with likelihood ratios ranging from 8–74 relative to women with normal ovaries. In contrast, women with simple cysts did not have an increased risk of ovarian cancer.

Comment (AS): This study sought to quantify the risks of ovarian cancer depending on characteristics of ovarian cysts on ultrasonography. The researchers also tried to identify 'benign' features on cysts so that ongoing surveillance was not necessary. The study involved around 120,000 sonograms over a 10-year period. The sonographic findings were characterised according to cyst size, simple versus complex (locules, septations, nodules, any solid areas). Of the 72,093 women involved, 210 were subsequently diagnosed with ovarian cancer (75% of the women with ovarian cancer were over 50 years of age). Over 75% of the total women were under 50 years of age. In over 15,000 with a simple cyst, only 1 was diagnosed with ovarian cancer within 3 years of the scan (likelihood ratio of 0.06). With a complex cyst in women younger than 50 years, the 3-year risk of ovarian cancer was 9.4–11 cases per 1000 women. In women older than 50 years with a complex cyst the risk was 65.2–429.8 per 1000 women. The clear messages from this study are that, where high quality ultrasonography has been undertaken, complex ovarian cysts should lead to referral to a specialist to manage whilst simple cysts can be managed conservatively. Whilst ongoing surveillance of simple cysts is the norm (due to poor prognosis of ovarian cancer and the fear of this 'silent' disease), the study provides further support for reassurance and non-surveillance for smaller simple cysts (under 5cm). At the least, one should consider ending surveillance for smaller simple cysts after several scans over a 2- to 3-year period.

Reference: JAMA Intern Med 2019;179(1):71-7
Abstract

Surgical excision versus ablation for superficial endometriosis associated pain

Authors: Riley K et al.

Summary: This randomised controlled trial compared surgical excision versus ablation of endometriosis for treatment of chronic pelvic pain. 73 women with minimal to mild endometriosis undergoing laparoscopy at a tertiary care hospital were randomised intraoperatively to excision or ablation of endometriosis. Those who underwent ablation had improved dyspareunia at 6 months but not at 12 months, whereas dysmenorrhoea was improved at 6 and 12 months. No significant improvements were seen after surgical excision at 6 or 12 months. The only significant difference between groups was the improvement in dyspareunia at 6 months in women who underwent ablation.

Comment (AS): It is a commonly held belief that surgery involving excision for endometriosis is more effective than ablative surgery. This trial followed up with assessment of changes in pain symptoms (painful periods, non-period pain, pain on intercourse and pain on defaecation). Quality of life was also assessed at 6 and 12 months. The study involved 37 patients in each arm using robotic assisted laparoscopic methods (only if superficial endometriosis was found). The groups were balanced in terms of whether they received a Mirena® at the time or not and for other medical treatments. The results showed that neither approach seems to improve dyschezia whilst both modalities helped with dysmenorrhoea. For dyspareunia, ablation was better at 6 months but not sustained to 12 months. These findings are useful as there is a paucity of robust studies comparing these methods. It is also technically easier to undertake ablation compared with excision and in theory this means more surgeons can treat superficial endometriosis. However the corollary to this is that less skilled surgeons should perhaps not treat endometriosis. Larger robust studies are needed.

Reference: J Minim Invasive Gynecol 2019;26(1):71-7
Abstract

Recent trends in the management of pelvic organ prolapse in Australia and New Zealand

Authors: Miller B et al.

Summary: This study examined current practices in the management of female pelvic organ prolapse in Australia and NZ in the light of the 2015 withdrawal of the Prolift® and Prosima® mesh kits. 403 out of 2506 RANZCOG trainees and fellows participated in the survey (16% response rate). Native tissue repair was reported to be the procedure of choice for prolapse (primary and recurrent) of the anterior and posterior vaginal wall. 45% of anterior recurrences and 25% of posterior recurrences were treated using an implant. Vaginal hysterectomy and repair were the procedures of choice for uterovaginal prolapse, and 41% of respondents said that sacrospinous hysteropexy was their uterine preservation procedure of choice. 65% preferred sacrospinous colpopexy and vaginal repair for post-hysterectomy vault prolapse. There was a substantial decline in use of implants across all indications between 2007 and 2015, except for midurethral slings and sacrocolpo/hysteropexy. 42% of respondents changed their practice as a result of the withdrawal of Prolift® and Prosima® mesh kits in 2015.

Comment (AS): This study, based on a questionnaire sent to 2506 RANZCOG members (with a low 16% response rate) mirrored what is happening with common local clinical practice. In essence there is a significant return to non-mesh (native tissue) repair surgery. Other findings suggested that most surgeons are using vaginal surgery versus laparoscopic or open. Why this is relevant is the rapidly changing clinical practice environment fuelled by an overall higher than expected complication rate with polypropylene meshes for transvaginal repair surgery. To the best of my knowledge, these mesh repair operations are no longer undertaken in NZ. For marked (stage 3) prolapse, most respondents preferred vaginal surgery and an apical non-mesh support procedure such as sacrospinous fixation. Current clinical practice allows for translaparoscopic/transabdominal sacrocolpopexy mesh which (given current problems and international litigation trends) may be best reserved for recurrent prolapse after failed primary non-mesh repair surgery. With regard to mid-urethral polypropylene slings/tapes, these are cleared for ongoing use in NZ but, given the England and Wales 'surgical pause pending investigation' (July 2018), many local surgeons (including this one) have become much more cautious about using them. The investigation concludes in the next few months. However, urinary incontinence causes major morbidity and there are many non-surgical and surgical options available.

Reference: Aust NZ J Obstet Gynaecol 2019;59(1):117-22
Abstract

Independent commentary provided by Dr Anil Sharma

MB ChB DGM Dip Legal Med FRANZCOG FRCOG

Having delivered over 5000 babies, Anil now works as a gynaecological surgeon from Ascot Central. His key interests are menstrual problems including fibroids, urogynaecology (all non-mesh, prolapse and incontinence) and endometriosis. He undertakes complex hysteroscopic, laparoscopic and traditional surgery. He also undertakes day-case endometrial ablation. 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. Anil's interest in medical education has continued with GP and Nurse CME. Anil lives in Auckland with his wife (who is a GP) and their 3 daughters, enjoying the outdoors. He also loves classic cars and stand-up comedy.

Who can afford a Mirena® for contraception?

Authors: Murray C & Roke C

Summary: This NZ study evaluated the socio-economic status and ethnicity of women choosing a nonsubsidised Mirena® for contraception compared with a subsidised long-acting contraceptive (copper intrauterine device [IUD] or Jadelle® implant) or who qualify for a Special Authority Mirena® (funded by Pharmac for women with heavy menstrual bleeding). All 1410 Mirena®, Jaydess®, IUD and Jadelle® insertions at Family Planning clinics in Wellington in 2015 were reviewed. Of the self-funded levonorgestrel-releasing intrauterine systems (LNG-IUSs) inserted, 5% were for women living in the most deprived areas of Wellington (quintile 5) and 28% were for women living in the least deprived areas (quintile 1). Of the Special Authority Mirena® inserted, 24% were for women living in quintile 5 areas and 19% were for women living in quintile 1 areas. 2.5% of Māori women and no Pacific women chose self-funded LNG-IUSs, compared with 21% of NZ European women. 9.5% of Māori women, 9.6% of Pacific women and 4% of NZ European women received a Special Authority Mirena®.

Comment (AS): This timely article from the NZ Family Planning group in Wellington adds further to what is already well known in medical circles and even beyond. Namely that safe effective contraception is a necessity in any society that wishes to be considered civilised. The study looked at the 1410 devices utilised. Of the self-funded devices, only 5% were for women in the most deprived parts of the Wellington region. However 24% of the devices that were used under Special Authority (Pharmac criteria) were for this group of women. The study also found that when looking at self-funded Mirena® the uptake from Māori women (2.5%) and Pacific women (0%) was very low. There are many robust studies that support the economic benefits of long acting reversible contraceptives (Mirena®) for women. These have shown favourable reductions in morbidity, economic benefits from fewer sick days, reduction in more major surgery, cost effectiveness and of course the benefits to women and health in general from the consequences of unplanned pregnancy. As the patent and exclusivity licences for Mirena® come closer to expiry, there should be room for negotiations on cost as well.

Reference: J Prim Health Care 2018;10(3):201-6
Abstract

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