Women's Health RESEARCH REVIEW™

Making Education Easy

Issue 30 – 2021

In this issue:

Abbreviations used in this issue

ADHB = Auckland District Health Board
FSRH = Faculty of Sexual and Reproductive Health
IUD = intrauterine device
LNG = levonorgestrel
IUS = intrauterine system
LMC = lead maternity carer
RANZCOG = Royal Australian and NZ College of Obstetricians and Gynaecologists
TVT = tension-free vaginal tape
WHI = Women's Health Initiative

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

PHARMACY GUILD OF NEW ZEALAND

NZMA New Zealand Medical Association

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

In this issue, a substudy of the REPLENISH trial reports that Bijuva® oral capsules reduce moderate to severe vasomotor symptoms in postmenopausal women, a US study evaluates the efficacy of LNG-IUDs for emergency contraception, an analysis of the ACCESS IUS study finds that fertility returns rapidly after LNG-IUS removal, and the WHI trials report important differences in hormone therapy-related outcomes according to age and time since menopause. Also in this issue, we report several interesting articles on endometriosis (March is Endometriosis awareness month) as well as a randomised controlled trial of TVT surgery versus Bulkamid® in women with stress urinary incontinence.

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

Kind regards,

Associate Professor Helen Roberts
helenroberts@researchreview.co.nz

Dr Anil Sharma
anilsharma@researchreview.co.nz

17β-estradiol/progesterone in a single, oral, softgel capsule (TX-001HR) significantly increased the number of vasomotor symptom-free days in the REPLENISH trial

Authors: Kaunitz AM et al.

Summary: This substudy of the REPLENISH trial evaluated the effects of oral oestradiol/progesterone (Bijuva®) capsules on vasomotor symptoms in postmenopausal women. 726 postmenopausal women aged 40–65 years with an intact uterus and moderate to severe hot flushes (≥7 per day or ≥50 per week) were randomised to receive daily oral oestradiol/progesterone combinations of 1mg/100mg, 0.5mg/100mg, 0.5mg/50mg, 0.25mg/50mg, or placebo. More women taking oestradiol/progesterone had ≥50% and ≥75% reductions in moderate to severe vasomotor symptoms at weeks 4 and 12 compared with those taking placebo ($p<0.05$), and they also had significantly more days per week without moderate to severe vasomotor symptoms at week 12 ($p<0.05$). The number of women without severe hot flushes at week 12 ranged from 43–56% with oestradiol/progesterone compared with 26% with placebo ($p\leq0.01$).

Comment (HR): The REPLENISH trial has been going now for a few years, with previous publication of its findings. It was a multicentre, phase 3 randomised controlled trial that evaluated the safety and efficacy of an oestradiol/natural progesterone combination capsule in postmenopausal women over a 12-month period. The use of the word 'natural' is interesting. The authors point out that the use of compounded hormones has increased since WHI publication with a decrease in use of conventional approved hormone therapy. Other publications from the REPLENISH group have reviewed the observational or intermediate outcome data that suggest that this combination and particularly the use of 'natural' progesterone has a beneficial profile compared to the WHI hormones and this includes a lower risk of breast cancer. Various combinations of hormones were used in the study. Compared with placebo, the 2 highest doses (oestradiol/progesterone 1mg/100mg and 0.5mg/100mg daily) demonstrated significant reductions in the frequency and severity of moderate to severe vasomotor symptoms at weeks 4 and 12, while protecting the endometrium from hyperplasia. In addition, after 12 weeks of treatment, women who received either of these doses had around 3 days per week with no moderate to severe vasomotor symptoms at all, an outcome not previously measured. No combination of oestradiol/progesterone is FDA or European Medicines Agency approved. This formulation would fill this gap.

Reference: Menopause 2020;27(12):1382-7
Abstract

Levonorgestrel vs. copper intrauterine devices for emergency contraception

Authors: Turok DK et al.

Summary: This US study compared the use of LNG-IUDs and copper IUDs for emergency contraception. 638 women who sought emergency contraception after an episode of unprotected intercourse were randomised to receive a 52mg LNG-IUD or a copper T380A IUD. In modified intention-to-treat and per-protocol analyses, 1-month pregnancy rates were 0.3% in the LNG-IUD group and 0% in the copper IUD group. The between-group absolute difference in both analyses (0.3 percentage points) was consistent with the LNG-IUD being noninferior to the copper IUD. Adverse events that necessitated medical care in the first month after IUD placement occurred in 5.2% and 4.9% of patients in the respective groups.

Comment (HR): This randomised trial compared the efficacy of the LNG-IUD and the copper IUD as a postcoital contraceptive and found that both were effective, with pregnancy rates of 0.3% and 0%, respectively. For all the women participating there was a history of regular menstrual cycles (21–35 days), and known date of the last menstrual period (±3 days). On the basis of the menstrual history the menstrual cycle day of unprotected sexual intercourse was calculated. Interestingly, 40% of the participants in the LNG group had multiple episodes of unprotected sexual intercourse, and women who reported having unprotected sexual intercourse more than 5 days before IUD placement were not excluded. However, all women had a negative pregnancy test before the IUD/IUS was inserted. Other research has suggested that it may be safe to insert an emergency IUD at any time during the cycle provided a high sensitivity pregnancy test is negative. Research has shown that oral LNG 1.5mg alone for emergency contraception has not decreased rates of unintended pregnancy. This may be in part due to the fact that it is only useful if given in the first half of the cycle as it works by delaying ovulation and does not cover further unprotected sex in the cycle. However, IUD/IUS insertion would give ongoing contraception. The authors do not go into detail of how the LNG device might work as an emergency contraceptive beyond saying that laboratory data support the potential for LNG to directly interfere with sperm transport, sperm capacitation, the acrosome reaction, and oviduct transport. The FSRH guideline on emergency contraception reminds us that pregnancy begins at implantation and that any intervention given for emergency contraception must act either to prevent fertilisation or to prevent implantation, rather than by disrupting established implantation. This is not the first research into use of the LNG-IUS for postcoital contraception. The main author of this paper (David Turok) has previously looked at the effectiveness of the LNG-IUS used along with oral emergency contraception. Larger studies will no doubt be needed to confirm these findings but it would be excellent to have a further effective postcoital contraceptive method.

Reference: N Engl J Med 2021;384:335-44
Abstract

RACP MyCPD Program participants can claim one credit per hour (maximum of 60 credits per year) for reading and evaluating Research Reviews. **For more information CLICK HERE**

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.

FOR FULL BIO CLICK HERE

The Women's Health Initiative trials of menopausal hormone therapy: Lessons learned

Authors: Manson JAE et al.

Summary: This article summarised the findings of the WHI trials. In the trials, 16,608 women with an intact uterus were randomised to receive oral conjugated equine oestrogens (± medroxyprogesterone acetate) or placebo for a median of 5.6 years, and 10,739 women with a hysterectomy were randomised to receive conjugated oestrogens or placebo for a median of 7.2 years. Both cohorts were followed for 18 years. In the overall study population, neither oestrogen/progesterone therapy nor oestrogen-only therapy prevented coronary heart disease or resulted in a favourable balance of chronic disease benefits and risks. Subgroup analyses suggested that timing of hormone therapy initiation influenced its impact on coronary risk, with more favourable effects reported in women who were younger (<60 years) or recently menopausal (within the previous 10 years).

Comment (HR): This summary of the WHI studies gives us feedback for not only the 5 years of the study but gives us information regarding what happened to these women in the next 13 years of follow-up. The majority of women had given permission for ongoing follow-up so that we have 18 years of information. We need to remember that the WHI was assessing oral conjugated oestrogens taken with or without medroxyprogesterone acetate for the prevention of chronic disease in postmenopausal women aged 50–79 years. In the overall study population (mean age 63 years), neither oestrogen-progestin therapy nor oestrogen-only therapy prevented coronary heart disease or led to a favourable balance of chronic disease benefits and risks. During a cumulative follow-up of 18 years, neither oestrogen-progestin therapy nor oestrogen-only therapy was associated with all-cause, cardiovascular, cancer, or other mortality. With respect to breast cancer mortality, oestrogen-progestin therapy was associated with a borderline significant increase in risk whereas oestrogen-only therapy was associated with significantly reduced risk. The protective effect of oestrogen-only therapy was seen only in women without prior hormone therapy use, those without a first-degree relative with breast cancer, and those at generally lower risk for breast cancer. However, subgroup analyses found more favourable effects in women who were younger (age <60 years) or recently menopausal (within 10 years) than in women who were older or further past the menopausal transition. After 18 years of cumulative follow-up the only significant finding was for those younger women who had used oestrogen-only therapy who had a 32% reduction in all-cause mortality over the long-term follow-up. So for women who had used oestrogen-only therapy for the duration of the trial and were then followed up for 13 years there were 24 fewer cases of all-cause mortality per 10,000 women per year. In the WHI oestrogen-only therapy trial, all participants entered with prior hysterectomy, and 40% also had prior bilateral oophorectomy. Interestingly, it was only younger women with bilateral oophorectomy who experienced a significant 32% reduction in all-cause mortality. On the other hand, in women without bilateral oophorectomy, oestrogen therapy had neutral effects. Older women with bilateral oophorectomy had no reduction. The authors conclude that the WHI's age-stratified findings indicate that the balance of benefits and risks is acceptable, even favourable, for healthy women with and without bilateral oophorectomy who are younger than age 60 years. In postmenopausal women of all ages, low-dose vaginal oestrogen may be used to treat genitourinary symptoms of menopause in the absence of vasomotor symptoms.

Reference: Menopause 2020;27(8):918-28
Abstract

This Research Review has been endorsed by The Royal New Zealand College of General Practitioners (RNZCGP) and has been approved for up to 1 CME credit for the General Practice Educational Programme (GPEP) and Continuing Professional Development (CPD) purposes. You can record your CME credits in your **RNZCGP Dashboard**

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.**

Conception rates in women desiring pregnancy after levonorgestrel 52mg intrauterine system (Liletta®) discontinuation

Authors: Carr BR et al.

Summary: This study evaluated conception rates after removal of a 52mg LNG-IUS (Liletta®) in women desiring pregnancy. 165 women participating in the ACCESS IUS study who had the LNG-IUS removed within 60 months and desired pregnancy were included. 142 (86.1%) of them became pregnant within 12 months (median time to conception 92 days). 12-month conception rates did not differ between nulligravid and gravid women, or between nulliparous and parous women. Multivariable analysis found that obesity was the only factor associated with ability to conceive (adjusted odds ratio 0.3, 95% CI 0.1–0.8).

Comment (HR): The introduction to this study reminds us that nulliparous women have been denied IUD access for decades and that contemporary surveys suggest that providers still consider IUD use in women without children to be inappropriate due to concerns about infertility, pelvic infection, and insertion difficulty. Indeed, a 2014 publication reported survey results from US obstetrician-gynaecologists in which only 67% considered IUDs appropriate for nulliparous women and about 15% considered pelvic infection a major risk of IUD use. We are now aware that it is not the IUD/IUS that causes pelvic infection but the acquisition of a sexually transmitted infection. We have previously not had a lot of data on fertility after discontinuation of contemporary IUDs. This trial included women who received an IUS, of whom more than half had never had children, enabling the potential to follow a relatively large cohort of nulligravid and gravid women for return of fertility after IUS discontinuation. The findings are very reassuring and demonstrate that fertility returns normally in women who discontinue a 52mg LNG-IUS and desire pregnancy, with a 1-year conception rate of 86%. Fertility rates after contraceptive discontinuation in the general population are approximately 83% at 1 year, with multiple factors affecting this rate including age and obesity. The same was true for the women in this study. The most influential factor in failure to conceive was obesity. Duration of IUS use, gravidity, parity and other variables had no significant effect on the ability to conceive. Many women became pregnant quickly and by 3 months the conception rate of 42% is again similar to that reported in the general community. The authors conclude that fertility rates in the year after IUS removal are normal overall which will be helpful for both nulligravid and nulliparous women when providing counselling to women about LNG-IUS use.

Reference: Contraception 2021;103(1):26-31
Abstract

Management of women affected by endometriosis: Are we stepping forward?

Authors: Guardo FD et al.

Summary: This article discussed the management of endometriosis, an oestrogen-dependent chronic disease affecting up to 15% of women of reproductive age. It is one of the most common gynaecological causes of severe pelvic pain, and its main symptoms are dysmenorrhoea and deep dyspareunia. Medical treatments such as progestin, oral contraceptives and gonadotropin-releasing hormone agonists provide symptomatic relief, whereas laparoscopic surgery may be more effective. Radical surgery appears to be associated with better pain relief, but may also be associated with higher recurrence rates.

Comment (AS): It is appropriate (not least given that March is Endometriosis awareness month) to add some pertinent learning points from this review article. Recent Ministry of Health guidelines and a focus on this debilitating disease has led to a more rational approach in the management of endometriosis. The most common symptoms are dysmenorrhoea, dyspareunia and chronic non-menstrual pain. In rarer presentations (extra-pelvic) of the condition, certain symptoms (e.g. thoracic cyclical symptoms of chest pain or in severe cases pneumothorax and even shortness of breath) should raise the suspicion of endometriosis. As should bleeding per rectum, dyschezia or alternating bowel habit. Renal function should also be considered as ureteral obstruction can (rarely) occur with minimal symptoms, so that where indicated, a renal ultrasound at the time of pelvic ultrasound could be considered. And finally to reiterate the link with infertility, endometriosis should be at least considered in every case.

Reference: J Endometr Pelvic Pain Disord 2019; 11(2):77-84
Abstract

That one doctor . . . Qualitative thematic analysis of 49 women's written accounts of their endometriosis diagnosis

Authors: Fernley N

Summary: This study analysed women's online written accounts of their endometriosis experience. 49 original accounts were included. 40 of the women experienced endometriosis symptoms before the age of 20 years, and 33 before the age of 15 years. 36 of them had never heard of endometriosis prior to diagnosis, despite repeated presentation to a GP. The women highlighted the positive impact of 'that one doctor' who finally mentioned the word 'endometriosis', and who listened, investigated and provided referral to a specialist.

Comment (AS): At least 1 in 9 women (from this Australian paper) have endometriosis and possibly more. There is a delay of around 9–10 years in diagnosis, and the economic burden on countries is huge. The common misdiagnoses (in 44% of women subsequently diagnosed to have endometriosis) include irritable bowel syndrome, food intolerances, urinary tract infection, psychosexual disorder and appendicitis. In this fascinating study which collated online data including blogs and accounts (no social media were used), 39 out of 49 women had not heard the name endometriosis prior to their diagnosis despite multiple presentations to primary care. Additionally, 21 women had endometriosis dismissed as a likely cause of their symptoms on first specialist review. 27 women took longer than 6 years for diagnosis and 11 women more than 10 years. In general terms, the feelings for all the doctors that missed the diagnosis were very negative and the feelings around the diagnosis and recognition that there was a physical cause for the symptoms very positive. The women want better education for health care workers, patients and more research into endometriosis. There was also much talk of 'that one doctor', the one that helped them research the condition and diagnose or treat it. Of course this is not a standard piece of medical research but it does raise many questions and adverse findings. There is no reason that we cannot all be 'that one doctor'.

Reference: J Endometr Pelvic Pain Disord 2021; published online Jan 4
Abstract

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

Anil's Obstetrics days are now behind him. He works as a gynaecological surgeon from Ascot Central with special interests including menstrual problems, urogynaecology, endometriosis and postgraduate education. **FOR FULL BIO CLICK HERE**

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).

Quality of life and sexual function after TVT surgery versus Bulkamid injection for primary stress urinary incontinence

Authors: Itkonen Freitas AM et al.

Summary: This study investigated 1-year changes in quality of life (QoL) and sexual function after TVT surgery versus polyacrylamide hydrogel (PAHG) injection in women with stress urinary incontinence (SUI). 234 women with primary SUI were randomised to undergo TVT surgery or PAHG injection. Urinary incontinence and health-related QoL were assessed at baseline and 1 year using the Urogenital Distress Inventory, Incontinence Impact Questionnaire (short form), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire and RAND-36 Item Health Survey. Both TVT and PAHG treatments improved QoL and sexual function at 1 year. However, incontinence and health-related QoL scores were better in the TVT group.

Comment (AS): Transurethral PAHG (Bulkamid®) has been used for over 10 years in the management of SUI in women. With the negative issues with regards to mesh vaginal surgery and despite the great efficacy of retropubic TVT, many women prefer non-mesh surgery for stress incontinence and will accept lower efficacy. Ideally, all should initially be referred to a pelvic physiotherapist prior to surgery. At 1 year post-op in this randomised controlled trial, the various urinary distress symptoms (including incontinence, frequency, and urgency) were all less common in the TVT group (pain was greater but did not reach statistical significance). There was improvement in both groups when looking at sexual health questions. Furthermore, there was significant improvement in QoL scores with both but the TVT group fared better. At this short-term follow-up of 1 year, TVT was better overall but one must bear in mind potential longer-term complications with polypropylene and therefore informed consent remains imperative.

Reference: Int Urogynecol J 2021;32(3):595-601
Abstract

Is provision of contraception at discharge following delivery associated with postpartum visit attendance?

Authors: Chiruvella M et al.

Summary: This retrospective cohort study examined whether provision of contraception at discharge after delivery is associated with lower rates of postpartum visit attendance. Of 1015 women who received pregnancy care at a Midwestern medical centre in 2013 and met inclusion criteria, 55% had been provided with contraception (or had been sterilised) upon discharge following delivery. Poisson regression models adjusted for confounding factors found no association between provision of contraception at discharge after delivery and subsequent postpartum visit attendance.

Comment (HR): FRSH guidelines recommend that women should receive contraception after delivery before discharge. This is also the recommendation for RANZCOG and indeed for the ADHB. The reason for this is that much of the research shows only a 50% attendance for the postnatal 6-week check. Factors that may impact on this include cost and availability of transportation, lack of support from family and friends, childcare responsibilities, and a lack of perceived benefit of attending the visit relative to these barriers. There is ongoing effort now to make sure that contraception is discussed in the antenatal period and once the woman has chosen her preferred method this is documented on the hospital record so that it can be delivered after birth. Many of our ADHB midwives are now trained in Jadelle® insertion, and the updated Medsafe document has finally removed breastfeeding as a contraindication. This research, a retrospective cohort study, looked at whether having been given contraception before discharge affected whether the woman would turn up for the postpartum 6-week check. In NZ this check with the GP is mainly for the baby's immunisation as the LMC provides the postnatal check for the mother. They found no evidence of a statistically or clinically meaningful association between provision of contraception at discharge following delivery and attendance. They conclude that "this finding may reassure providers that contraception provision does not act as a deterrent to receiving postpartum follow up". However, the attendance in this study was remarkably low since only one-third of the patients returned for a visit in the expected time frame.

Reference: Contraception 2021;103(2):103-6
Abstract

Levonorgestrel intrauterine system (IUS) in a patient with uterine didelphys

Authors: Goldman AR & Gerber SR

Summary: This case report described the use of a single 13.5mg LNG-IUS for contraception in a patient with uterine didelphys.

Comment (HR): This is an interesting case review of a 20-year-old nulliparous woman who presented requesting removal and replacement of a 13.5mg LNG-IUS (Jaydess® in NZ). She reported that at the time of placement 3 years prior at a different facility, she was told she had a 'split uterus'; she had wanted a copper IUD, but was advised that a single hormonal IUS would provide adequate contraception. She reported she had not used any other contraceptive method during the 3-year period. The doctor ordered a transvaginal ultrasound which revealed a fused duplication of the uterus and cervix with 1 vaginal compartment. The IUS was in the left side. Through shared decision-making, she opted to use a contraceptive implant and the IUS was removed without difficulty, intact. So what does the FSRH of the Royal College of Obstetricians and Gynaecologists say regarding IUD placement in this circumstance? It states that the insertion of an IUD/IUS into any congenital or acquired uterine abnormality distorting the uterine cavity is designated a UKMEC 3. This is "a condition where the theoretical or proven risks usually outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable". However, it goes on to say that in some women with a distorted uterine cavity it may be appropriate to attempt insertion of an IUS after discussion. Actually, previous reports describe the use of hormonal IUS for noncontraceptive reasons, primarily management of abnormal uterine bleeding (AUB) in uterine didelphys and bicornuate uterus. One report described where a Mirena® was put into each horn, and one described where it was placed into 1 horn only. Both options fully resolved the episodes of AUB. A third report described Mirena® use for menstrual suppression in a 14-year-old with severe developmental delay and uterine didelphys. Imaging after placement of the IUS demonstrated correct placement in the right uterine cavity and complete resolution of the left haematometra, suggesting an adequate progestin effect throughout both uterine bodies for control of AUB. The authors comment that this case report "substantiates the pressing need to expand collaborative research efforts to better define IUS efficacy and safety in women with congenital uterine anomalies to allow for access and equitable use of this form of contraception".

Reference: Contraception 2021;103(2):134-5
Abstract