Women's Health RESEARCH REVIEW™

Making Education Easy

Issue 29 – 2019

In this issue:

Abbreviations used in this issue

ACOG = American College of Obstetricians and Gynecologists
BSO = bilateral salpingo-oophorectomy
EC = emergency contraception
HR = hazard ratio
HRT = hormone replacement therapy
IUD = intrauterine device
IUS = intrauterine system
LMP = last menstrual period
NSAID = non-steroidal anti-inflammatory drug
SAVE U = sacrospinous fixation versus vaginal hysterectomy in treatment of uterine prolapse ≥2
UPSI = unprotected sexual intercourse
WHI = Women's Health Initiative

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

In this issue, a large meta-analysis estimates the excess breast cancer risk associated with HRT in postmenopausal women, findings from the WHI study suggest that oestrogen-only HRT may have a mortality benefit in women with early menopause, and we present useful information on different bleeding patterns associated with various levonorgestrel IUSs. We also report a 5-year follow-up of the SAVE U study that supports the use of uterine-preserving surgery in women undergoing treatment for prolapse, a Cochrane review assesses the effectiveness of cyclical oral progestogen regimens for heavy menstrual bleeding, and a meta-analysis evaluates the prevalence of dysmenorrhoea in young women and its impact on their academic performance.

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

Kind regards,

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Type and timing of menopausal hormone therapy and breast cancer risk

Authors: Beral V et al., on behalf of the Collaborative Group on Hormonal Factors in Breast Cancer

Summary: This meta-analysis evaluated the risk of breast cancer associated with different types of HRT in postmenopausal women. Individual participant data from published and unpublished prospective studies were included. Current users were included up to 5 years after last-reported HRT use. During prospective follow-up, 108,647 postmenopausal women developed breast cancer at a mean age of 65 years; 51% of them had used HRT. Every type of HRT except vaginal oestrogens was associated with excess breast cancer risk. Risk increased steadily with duration of use and was greater for oestrogen-progestogen than oestrogen-only preparations. Among current users, the excess risk emerged during the first 4 years of treatment and doubled during years 5–14. Some excess risk persisted for more than 10 years after stopping HRT; the magnitude of risk depended on the duration of previous use.

Comment (HR): This large analysis examined data from 58 studies regarding HRT and breast cancer. It found that the breast cancer risk (for 5 years of HRT use) was 6.3% for no HRT, 6.8% for oestrogen-only therapy, 7.7% for sequential progesterone therapy, and 8.3% for continuous combined use. The risk was greater for oestrogen-receptor positive than oestrogen-receptor negative disease and was similar for oral and transdermal oestrogen. It was not affected by the type of progestogen. There was no increase in risk with 1 year of use and also no increase with vaginal oestrogen. The same authors also published data on HRT and breast cancer mortality (*Beral et al., Lancet 2019*) from the Million Woman Study. They found that 0.8% of women died from breast cancer (0.74% of never users and 0.85% of combined users). Past users with less than 5 years of prior use did not have excess mortality. How do these results compare with the data from randomised WHI studies? The breast cancer risk with combined therapy was less but there was some increased risk even after stopping. The WHI study showed no risk with oestrogen-only therapy and the large WHI 18-year follow-up study showed no increased risk of mortality. From the point of view of HRT prescribing, the usual advice still applies – use for the shortest period of time that is needed for symptom relief.

Reference: Lancet 2019;394(10204):1159-68
Abstract

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Menopausal estrogen-alone therapy and health outcomes in women with and without bilateral oophorectomy

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

Summary: This subgroup analysis of the WHI study evaluated health outcomes associated with oestrogen-only menopausal therapy in women with and without BSO. 9939 women aged 50–79 years with prior hysterectomy and known oophorectomy status were randomised to receive conjugated equine oestrogens 0.625 mg/day or placebo for a median 7.2 years. End-points included coronary heart disease, invasive breast cancer, all-cause mortality, and a "global index" (these 3 end-points plus stroke, pulmonary embolism, colorectal cancer, and hip fracture). The effects of conjugated oestrogens alone did not differ significantly according to BSO status during the intervention phase and 18-year cumulative follow-up. However, age modified the effect of conjugated oestrogens in women with prior BSO. During the intervention phase, conjugated oestrogens treatment was associated with a net adverse effect (HR for global index, 1.42) in women aged ≥70 years, but not in younger women. During cumulative follow-up, women aged 50–59 years with BSO had a treatment-associated reduction in all-cause mortality (HR, 0.68), whereas older women with BSO did not. There was no significant association between conjugated oestrogens and outcomes in women with conserved ovaries.

Comment (HR): This is an interesting subgroup analysis of the WHI study and the 18-year follow-up for women. Age at assignment to conjugated equine oestrogen strongly influenced the effect of treatment. Younger women (aged 50–59 years) with BSO who were randomly assigned to conjugated oestrogens experienced a statistically significant 32% reduction (47 less events per 10,000 women/years) in all-cause mortality during 18 years of cumulative follow-up (i.e. time taking HRT plus the time they were followed up after stopping HRT). Younger women without BSO and older women with or without BSO did not have a reduction. The associated reduction in all-cause mortality experienced by younger women with BSO taking oestrogen was most apparent among those who had had this procedure before age 45. Other individual outcomes such as coronary heart disease or invasive breast cancer did not show any reduction. Expert opinion has always been that women with an early menopause should use HRT till the age of menopause. It is useful to now have a randomised study suggesting that there may well be some health benefit with use of oestrogen alone for those women with an early surgical menopause.

Reference: Ann Intern Med 2019;171(6):406-14
Abstract

Comparing bleeding patterns for the levonorgestrel 52 mg, 19.5 mg, and 13.5 mg intrauterine systems

Authors: Goldthwaite L & Creinin M

Summary: This study compared bleeding patterns in users of various doses of levonorgestrel IUS products. Data were extracted from published sources for levonorgestrel 52mg IUS (n=1700), levonorgestrel 19.5mg IUS (n=1566) and levonorgestrel 13.5mg IUS (n=1531). Amenorrhoea rates were significantly higher 6 months after insertion of the 52mg IUS (11%) than after the 19.5mg (5%) or 13.5mg (3%) IUS, and infrequent bleeding rates were significantly higher in users of the 52mg IUS by the end of the first year (31% vs 26% and 20%, respectively). Irregular bleeding rates were higher at 3 months in women using the lower dose products, and remained higher at the end of the first year. Frequent and prolonged bleeding patterns remained similar over the first 2 years for all products, and were higher for the levonorgestrel 13.5mg IUS than for the 19.5mg or 52mg IUS.

Comment (HR): This information on the different bleeding patterns with these devices will be useful to give to women. From November 1 this year the Mirena® and the smaller Jaydess® will be funded for women. Mirena® has levonorgestrel 52mg and Jaydess® 13.5mg. Mirena® gives 5 years of contraception and Jaydess® 3 years. How will we know which device a woman needs? Before insertion of any IUD we do a pelvic examination. This tells us whether the uterus is anteverted or retroverted – obviously important to know the insertion direction to avoid perforation. The uterus is then sounded so we know what size it is. The white plastic disposable sounds are now used in preference to metal sounds. Jaydess® will be used for those women who have a uterus that sounds less than 6.5cm.

Comment (AS): This study looked mainly at the effects on frequent and prolonged bleeding rates in users of the 3 types of IUS with different doses of levonorgestrel. The findings confirmed expectations that a higher dose device worked better. For example, for amenorrhoea as an outcome, the 52mg device had a 36.4% result by 36 months of use versus 11.6% for the 13.5mg device. Therefore if women wish to reduce bleeding maximally they should use the 52mg device. There was no mention of other outcomes or satisfaction rates overall. The 52mg levonorgestrel-releasing IUS (Mirena®) has just become fully funded for prescription in NZ. The indications for this 5-year device include for the use of heavy menstrual bleeding, endometriosis and endometrial hyperplasia without atypia. A lower dose 3-year device (Jaydess®) was also fully funded at the same time (indicated for contraception only). Jaydess® has been anecdotally used for women (especially younger age groups) with smaller uteri as some specialists believe that the side effect of cramping/dysmenorrhoea for them is lower; the smaller dose device is also smaller sized. However, one must weigh this up with other indications that the patient may have (such as heavy menstrual bleeding or endometriosis) which might make the larger device more suitable.

Reference: Contraception 2019;100(2):128-31
Abstract

Copper intrauterine device placement 6–14 days after unprotected sex

Authors: Thompson I et al.

Summary: This study evaluated the contraceptive efficacy of a copper IUD (CuT380A) when inserted 6–14 days after unprotected sex. 134 women who had a copper IUD inserted 6–14 days after unprotected intercourse were included. 95 (71%) women had a urine pregnancy test 2–4 weeks after IUD placement and the other 39 women were followed for 6 months after IUD placement to assess pregnancy status. None of the women reported a pregnancy within 4 weeks of copper IUD placement.

Comment (HR): Copper IUDs (not Mirena®) can be used as a post-coital contraceptive. The day of intercourse is not the important information we need. What we need to work out is the day of likely ovulation. As the luteal phase is fixed this is 14 days before the next period is due. So a woman who has a 28-day cycle will ovulate on day 14. She could have had sex on day 9 and as long as she has had the IUD placed by day 19, i.e. 5 days after ovulation it will work as a post-coital device. Any fertilised egg will still be in the tubes and not in the uterus as it takes at least 6 days for implantation to occur. This means that inserting the IUD before then will stop implantation. The Faculty of Sexual and Reproductive Healthcare gives the following information on post-coital use of an IUD … "A Cu-IUD can be inserted up to 5 days after the first UPSI in a cycle. Given that the earliest implantation is believed to occur 6 days after ovulation (and over 80% of implantations occur 8–10 days after ovulation), a Cu-IUD can also be inserted up to 5 days after ovulation, before the process of implantation has begun. Ovulation occurs about 14 days prior to onset of menstruation. It is established practice that the earliest likely ovulation date is estimated as the date of the start of the LMP plus the number of days in the shortest cycle minus 14. LMP must be accurately known and cycles must be regular in order to make the estimation. A Cu-IUD can be inserted for EC in good faith up to 5 days after this date (e.g. until day 19 of a regular, 28-day cycle)". Women included in this study had to have a negative pregnancy test. They excluded participants with cycle lengths that were irregular or likely to be misreported (<20 and >35 days). So I am not sure how the IUD worked as a post-coital device with some scenarios. For example a woman with say a 30-day cycle will ovulate on day 16. If they had sex on day 15 and the IUD put in day 29 (i.e. 14 days after the sex and 13 days after potential ovulation) the fertilised egg would have already implanted, given that implantation happens 8–10 days after ovulation. I think I've got this right! I will probably stick with the Faculty advice.

Reference: Contraception 2019;100(3):219-21
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**

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Topical estrogen prescribing patterns for urogenital atrophy among women with breast cancer

Authors: Richter L et al.

Summary: This study evaluated physicians' attitudes about topical oestrogen use in women with urogenital atrophy and a history of breast cancer. A cross-sectional survey of breast surgeons, urogynaecologists, and gynaecologists was distributed via their professional societies. A total of 820 physicians completed the survey. 84% of them (regardless of specialty) were comfortable prescribing vaginal oestrogen to women with a history of oestrogen receptor-negative cancer. 65.7% were comfortable prescribing for women with oestrogen receptor-positive breast cancer no longer on endocrine therapy (51.3% were comfortable prescribing for women taking an aromatase inhibitor [AI] and 31.4% for women taking tamoxifen [TMX]). Urogynaecologists were more comfortable than breast surgeons prescribing vaginal oestrogen for the lowest risk patients, whereas breast surgeons had the highest level of comfort for women taking endocrine therapy.

Comment (HR): Clinically we often start with Replens® for vaginal symptoms in women with previous breast cancer. If this is not beneficial we use the subsidised vaginal oestrogen in NZ – Ovestin® (oestriol) with very low absorption in preference to Vagifem® (oestradiol) with higher systemic absorption. The commentary in this paper is helpful for our prescribing: "Although providers expressed higher comfort prescribing topical estrogen for women on AIs compared with those on TMX, we would, however, have expected the opposite to be the case. Because AIs inhibit the peripheral conversion of androgens to estrogens to reduce circulating estradiol levels, their efficacy is dependent on near-total suppression of estrogen. It has been suggested that even small increases in systemic estrogen may be detrimental in this population. In fact, the ACOG Committee Opinion has indicated that more data is needed before vaginal estrogen can be recommended for women on AIs. Unlike AIs, treatment with TMX, because of its competitive interaction with the estrogen receptor, does not seem to be affected by low or temporary increases in plasma estrogen suggesting that the use of vaginal estrogens may be more appropriate for women on TMX". Tamoxifen has some oestrogenic action in the vagina compared to AIs – so women may have less vaginal dryness. Tamoxifen though may cause more flushes than AIs.

Reference: Menopause 2019;26(7):714-9
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.

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Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding

Authors: Rodriguez M et al.

Summary: This meta-analysis evaluated the effects of NSAIDs on heavy menstrual bleeding compared with other treatments. A search of various databases identified 19 randomised controlled trials (n=759) that were suitable for inclusion. Overall, NSAIDs were more effective than placebo at reducing heavy menstrual bleeding but less effective than tranexamic acid, danazol and the levonorgestrel IUS. Danazol was associated with a shorter duration of menstruation and more adverse events than NSAIDs, but is not usually recommended for heavy menstrual bleeding. There was no clear evidence of a difference between NSAIDs and other treatments such as oral luteal progestogen, ethamsylate, an older progesterone-releasing IUS, and the oral contraceptive pill, but most studies were underpowered. There was no evidence of a difference between the NSAIDs naproxen and mefenamic acid in reducing heavy menstrual bleeding.

Comment (HR): Not sure really why luteal phase progestogen is mentioned here as it is not seen as being at all effective for heavy menstrual bleeding and the most recent Cochrane review also gives that opinion. The decision of what treatment to use will often depend on whether the woman would also like contraception in which case Mirena® or the combined pill would be the options. The pill can be given in the usual 21/7 with the hormone withdrawal bleed in the pill-free interval being lighter than the woman's normal period. Even better it can be taken with continuous hormones with no bleed and giving better contraception. The old guidelines for heavy menstrual bleeding are still available and cover the topic well with NSAIDs taken during the period delivering a 29% reduction in blood loss. This compares to Mirena® (94% reduction), norethisterone 15mg on days 5–25 (87% reduction), tranexamic acid (47% reduction), and the combined pill (43% reduction). The pamphlet for women is available on the Auckland District Health Board website.

Reference: Cochrane Database Syst Rev 2019;9:CD000400
Abstract

Sacrospinous hysteropexy versus vaginal hysterectomy with uterosacral ligament suspension in women with uterine prolapse stage 2 or higher

Authors: Schulten S et al.

Summary: This 5-year follow-up of the SAVE U trial evaluated the long-term effectiveness of uterine-preserving sacrospinous hysteropexy as an alternative to vaginal hysterectomy with uterosacral ligament suspension for the surgical treatment of uterine prolapse. 204 of 208 women who had been randomised to sacrospinous hysteropexy or vaginal hysterectomy with uterosacral ligament suspension in the initial SAVE U trial were followed annually for 5 years after surgery. At 5 years, surgical failure of the apical compartment with bothersome bulge symptoms or repeat surgery occurred in 1 patient (1%) after sacrospinous hysteropexy compared with 8 patients (7.8%) after vaginal hysterectomy with uterosacral ligament suspension. 87% of patients in the sacrospinous hysteropexy group and 76% in the vaginal hysterectomy group achieved the composite outcome of success (no prolapse beyond the hymen, no bothersome bulge symptoms, and no repeat surgery or pessary use for recurrent prolapse) at 5 years.

Comment (AS): This study adds to the body of opinion that has formed regarding uterine-preserving surgery when surgery for prolapse is undertaken. This is overall gaining in popularity not just for the sake of preservation of the organ but to reduce additional morbidity if a hysterectomy is carried out. This study also confirmed an 87% success with the uterine-preserving approach (during surgery for prolapse). This is a useful additional resource when surgeons discuss management options with patients but in my opinion the study should have had a third arm, namely a group who underwent vaginal hysterectomy with sacrospinous fixation. This would have been comparing apples with apples as the study, as useful as it is, seems to be comparing two quite different operations. For the uterine-preservation group it would probably be useful to assess the endometrium concurrently as there was at least 1 case of endometrial cancer arising after uterine-preserving surgery.

Reference: BMJ 2019;366:l5149
Abstract

Independent commentary provided by Dr Anil Sharma

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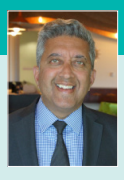

Anil's Obstetrics days are now behind him. He works as a gynaecological surgeon from Ascot Central with special interests including menstrual problems, urogynaecology, endometriosis and postgraduate education. **FOR FULL BIO CLICK HERE**

Cyclical progestogens for heavy menstrual bleeding

Authors: Bofill Rodriguez M et al.

Summary: This Cochrane review assessed the effectiveness of two different regimens of oral progestogen therapy for reducing ovulatory heavy menstrual bleeding. A search of Cochrane Gynaecology and Fertility's specialised register, CENTRAL, MEDLINE, Embase, CINAHL and PsycInfo identified 15 randomised controlled trials (n=1071) of cyclical oral progestogens that were suitable for inclusion. Short-cycle progestogen therapy during the luteal phase (medroxyprogesterone acetate or norethisterone for 7–10 days from day 15–19) was inferior to tranexamic acid, danazol and a progestogen-releasing IUS with respect to reduction of menstrual blood loss and number of bleeding days. Long-cycle progestogen therapy (medroxyprogesterone acetate or norethisterone from day 5–26) was inferior to the levonorgestrel-releasing IUS, tranexamic acid and ormeloxifene, but similar to the combined vaginal ring with respect to reduction of menstrual blood loss. The evidence supporting these findings was limited by low or very low gradings of study quality.

Comment (AS): This 2019 mainly Auckland University Cochrane review looked at 15 randomised controlled trials (none versus placebo) and over 1000 women with heavy menstrual bleeding. The aim was to investigate oral progestogens which are the most frequently prescribed medications for women with heavy menstrual bleeding. Whether the women took short-cycle medroxyprogesterone acetate or norethisterone (day 15–19 of the cycle) or long cycle (day 5–26), the drugs were inferior when compared with both the levonorgestrel-releasing IUS and tranexamic acid. The analysis included number of bleeding days, side effects and satisfaction rates. The overall quality of the studies was felt to be low (mainly due to lack of placebo and subject bias as the women generally knew which treatment they were on). Whilst it is difficult to draw firm conclusions from this detailed review giving the quality of evidence available, I will continue to use tranexamic acid and the levonorgestrel-releasing IUS as ongoing 'first-line' treatment when resources and side effects and patient choice allow. Of course the surgical managements are available too. I would suggest that progestogens still have a place in the initial management of heavy bleeding e.g. a course that will stop most episodes within a week and then tapers off over the next couple of weeks. This will enable time and resources to be directed at more efficacious and acceptable management options.

Reference: Cochrane Database Syst Rev 2019;8:CD001016
Abstract

The prevalence and academic impact of dysmenorrhea in 21,573 young women

Authors: Armour M et al.

Summary: This systematic review and meta-analysis examined the prevalence of dysmenorrhoea in young women and its impact on their academic performance and other school-related activities. A search of MEDLINE, PsychINFO, Embase, and Cumulative Index to Nursing and Allied Health Literature identified 38 studies involving 21,573 young women that were suitable for inclusion. Meta-analysis of the data found that the prevalence of dysmenorrhoea was 71.1%. Rates of dysmenorrhoea were similar between school students (72.5%) and university students (74.9%). 20.1% of the women reported absence from school or university because of dysmenorrhoea and 40.9% reported a negative impact on classroom performance or concentration.

Comment (AS): Dysmenorrhoea in women under 25 years is a major problem with a prevalence of 71%, absence rates from educational establishments of around 20% and adverse effects on academic performance in around 40%. This meta-analysis, from 38 cross-continental studies included over 21,000 young women. It is worth mentioning that severity of dysmenorrhoea was not analysed and pain was frequently 'normalised' and probably led to an underestimation of both 'any pain' and in the severity of pain. What is clear is that the problem needs addressing with more resources and clinical pathways to evaluate and treat the underlying cause, whether it be endometriosis, 'primary dysmenorrhoea' or 'other'.

Reference: J Womens Health (Larchmt) 2019;28(8):1161-71
Abstract