Women's Health Research Review

Making Education Easy

Issue 23 – 2017

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Abbreviations used in this issue

HPV = human papillomavirus
IUD = intrauterine device
LARC = long-acting reversible contraception
LPP = luteal phase pregnancy
RCT = randomised controlled trial

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NZMA New Zealand Medical Association

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

This month we report that cervical lidocaine-prilocaine cream may alleviate IUD insertion pain, the risk of luteal phase pregnancy is low after any-cycle-day insertion of contraceptive implants, and there is no weight gain with long-acting reversible contraceptives. Australian researchers show that outpatient hysteroscopy may well be the new gold standard for abnormal uterine bleeding or post-menopausal bleeding, and US investigators report no association between IUDs and the acquisition or clearance of HPV infection.

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

Kind regards,

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Effect of cervical lidocaine-prilocaine cream on pain perception during copper T380A intrauterine device insertion among parous women

Authors: Abbas A et al.

Summary: This study evaluated the analgesic effect of cervical lidocaine-prilocaine cream during copper T380A IUD insertion. 120 parous women undergoing copper IUD insertion were randomised to receive lidocaine-prilocaine cream or placebo cream in a double-blind design. Cream was applied to the anterior cervical lip and the cervical canal 7 minutes prior to IUD insertion. Lidocaine-prilocaine cream reduced median visual analogue scale (VAS) pain scores during tenaculum placement, sound insertion and IUD insertion compared with placebo cream (all p=0.0001). A lower ease of insertion score was also reported in women who received the lidocaine-prilocaine cream (p=0.001).

Comment (HR): This is interesting as most previous interventions to alleviate insertion pain have not been successful. Certainly nulliparous women may get more severe pain with IUD insertion (about 17%) as opposed to parous women (11%). A meta-analysis in 2013 found no evidence to recommend prophylactic ibuprofen for insertion pain. Misoprostol 400mg is sometimes given some hours prior to IUD insertion for those women where a previous attempted insertion has failed due to a tight cervix. However the 2013 meta-analysis found no clear evidence that pain was reduced from the woman's perspective but some evidence that misoprostol eases insertion from the provider's perspective. They suggested that if misoprostol is to be used for cervical priming/ripening to improve technical ease in certain groups of women, that a non-steroidal anti-inflammatory (NSAID) is co-administered to manage the prostaglandin-mediated side effects (e.g. uterine cramping). The application of local anaesthetic lignocaine gel before IUD insertion has been evaluated in three RCTs. One study found benefit but limitations of the study included non-blinding of treatment groups and a higher proportion of nulliparous women being allocated to the 'no treatment' group. The study also found no clear evidence from RCTs to recommend routine prophylactic use of local anaesthesia in any form for IUD insertions. However, complications arising from the procedure, need for dilation, and insertion pain are difficult to predict and they advise that injectable local anaesthesia should therefore be at hand for reactive administration, intracervically or paracervically. A useful 2014 article on practical advice for avoidance of pain with IUD insertion is in agreement with the findings of the meta-analysis. Most women tolerate IUD insertion well but paracervical block is useful where sounding the uterus is difficult. We often give NSAIDs to help post-insertion pain but there is currently no evidence to recommend routine prophylactic use because there is no clear evidence of benefit. The conclusion was that there is some evidence to suggest that non-pharmacological interventions might reduce pain levels. Women's anxiety about the procedure may contribute to higher levels of perceived pain during insertion, highlighting the importance of pre-insertion counselling, and 'verbal anaesthesia' and distraction during the procedure to help minimise anxiety. It goes without saying that having skilled inserters is one of the keys issues.

Reference: Contraception 2017;95(3):251-56
Abstract

Independent commentary provided by Associate Professor Helen Roberts

Helen is Associate Professor Women's Health at the University of Auckland and involved with both undergraduate and postgraduate medical education in O&G.

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Independent commentary provided by Dr Anil Sharma

Anil has a background in medical education with interests in clinical practice, teaching and informed consent. **FOR FULL BIO CLICK HERE.**

Risk of luteal phase pregnancy with any-cycle-day initiation of subdermal contraceptive implants

Authors: Richards M et al.

Summary: This retrospective study determined rates of LPP in young women receiving subdermal implants on any day of the menstrual cycle. Young women who presented at an adolescent clinic with a negative pregnancy test were eligible for same-day insertion regardless of cycle day, contraceptive use, or last intercourse. LPP rates were calculated for insertions within manufacturer guidelines (≤5 days of menstrual onset or ≤7 days after stopping hormonal contraception) and outside these guidelines. 1868 out of 3180 insertions (58.8%) were outside recommended guidelines. Women with insertions within guidelines were older (20.2 vs 19.3 years; p<0.001) and more likely to be white (40.4% vs 29.5%). Definitive pregnancy data were documented for 1726 patients: 660 in the within guidelines group, and 1066 in the outside guidelines group. Rates of LPP were 0.3% and 0.9% in the respective groups.

Comment (HR): Although this study did not find definitive pregnancy data for 46% of the patients it is worth thinking about what they propose. The study authors remind us "One concern limiting the use of same-day initiation of LARC is the risk that a patient in the luteal phase of her menstrual cycle may have undergone egg fertilisation or implantation of a pregnancy and not yet have a positive pregnancy test. Because the subdermal contraceptive implant changes bleeding patterns, identification of such an LPP may be delayed. However, the risk of subsequent unintended pregnancy in patients leaving with no method or a short-acting 'bridge' method may be significantly higher than the risk for LPP". There is a new proposed clinical guidance for excluding pregnancy prior to contraceptive initiation. This paper suggests an immediate start for contraception. "Immediate start" (also known as "Quick Start") refers to contraceptive method initiation at the time of the clinic visit, regardless of where the woman is in her menstrual cycle. Immediate start has the potential to reduce the risk of pregnancy, as women do not need to wait until their next menses before starting a contraceptive method. Hormonal methods (other than hormonal IUD), when given accidentally to a woman who is already pregnant, pose no risk to mother or the course of her pregnancy, and babies exposed *in utero* to contraceptive steroids have not been shown to have short- or long-term negative health effects. For this reason, immediate start of combined oral contraceptives, injectable contraceptives and even implants can be considered when pregnancy cannot conclusively be ruled out. In such cases, after initiation of the contraceptive method, women are advised to use condoms or abstain from sex for the first 7 days to protect against pregnancy until contraceptive effect is achieved. A follow-up pregnancy test may be needed if there was unprotected intercourse. In the unlikely event of a positive pregnancy test for a woman who had an implant inserted and who wished to continue the pregnancy, the implant would be removed.

Reference: Contraception 2017;95(4):364-70
Abstract

Changes in body composition in women using long-acting reversible contraception

Authors: Silva Dos Santos P et al.

Summary: This study assessed changes in body composition in women using the levonorgestrel intrauterine system (LNG-IUS), a copper IUD or an etonogestrel (ENG) implant. 149 women were included. Lean body mass increased over 12 months in LNG-IUS and copper IUD users but not in ENG implant users, although changes in bodyweight and body composition did not differ significantly between groups.

Comment (HR): This study confirms what we already know regarding these methods of contraception – no weight gain. This also applies to the Jadelle® implant that we use here in NZ. In addition, we have RCT evidence that there is no weight gain with the pill compared to placebo. With Depo Provera® the Faculty of Sexual and Reproductive Health of the Royal College of Obstetricians and Gynaecologists says that it appears to be associated with weight gain particularly in women under age 18 with a body mass index >30 kg/m^2. It also advises that women who gain more than 5% of their baseline bodyweight in the first 6 months of use are likely to experience continued weight gain.

Reference: Contraception 2017;95(4):382-89
Abstract

CONGRATULATIONS TO **DR ROBIN RUND**
who won an iPad mini 3 by taking part in our recent subscriptions update promotion. Robin is an Anaesthetist at the Bay of Plenty District Health Board.

Early menarche, nulliparity and the risk for premature and early natural menopause

Authors: Mishra G et al.

Summary: This analysis of data from the InterLACE collaboration examined whether parity and timing of menarche are associated with premature and early natural menopause. Data for 51,450 postmenopausal women from 9 observational studies in the UK, Scandinavia, Australia and Japan were reviewed. The median age at final menstrual period was 50 years, with 2% of women experiencing premature menopause (<40 years) and 7.6% early menopause (40–44 years). Women with early menarche (≤11 years, compared with 12–13 years) were at higher risk of premature menopause (relative risk ratio [RRR], 1.80) and early menopause (RRR, 1.31). Nulliparity was associated with increased risk of premature menopause (RRR, 2.26) and early menopause (RRR, 1.32). Women having early menarche and nulliparity had a nearly 6-fold increased risk of premature menopause and a 2-fold increased risk of early menopause compared with women who had menarche at ≥12 years and 2 or more children.

Comment (HR): This study advises preventive health interventions for mitigating the risk of adverse health outcomes associated with early menopause, but does not discuss what the interventions are. Premature ovarian insufficiency (premature menopause) has been associated with increased risk of early cardiovascular disease in a meta-analysis by Muka *et al.* that was published last year. The commentary of this meta-analysis reminds us that we do not know the direction of this association and indeed there are data to support the hypotheses that it is cardiovascular health that contributes to the timing of menopause. Genetic studies have also shown pathways other than hormones in the link between premature ovarian insufficiency and cardiovascular disease (CVD). The Guidelines of the European Society of Human Reproduction and Embryology (ESHRE) say reducing this risk includes advice on not smoking, taking regular exercise and maintaining a healthy bodyweight. These women may have menopausal symptoms and wish to use hormone therapy. Guidelines, including those of the ESHRE, recommend hormone therapy in women with premature ovarian insufficiency to control future risk of CVD but actually there are no longitudinal outcome data to show benefit.

Reference: Hum Reprod 2017;32(3):679-86
Abstract

'Everyone's talking Jadelle': the experiences and attitudes of service providers regarding the use of the contraceptive implant, Jadelle in young people in New Zealand

Authors: Sandle M & Tuohy P

Summary: This NZ study explored the attitudes and experiences of health professionals regarding the use of Jadelle® in teenagers. Ten midwives, doctors and nurses who were providing contraceptive services to young people were interviewed. Jadelle® was seen to be a good contraceptive option because of its effectiveness, discreetness and user independence. Barriers for young people obtaining Jadelle® included cost, access, fear of procedure and lack of appropriate services. Improvements to access were identified, including reduced cost and more youth-friendly services.

Comment (HR): As the authors say – "Previous studies have found that cost, concerns about side effects, fear of procedures and lack of trained providers can be challenges to young people obtaining LARC, and this study also identified these factors as barriers". There are various plans that I am aware of to help Jadelle® training – a Goodfellow module is being put together so that clinicians can access the theoretical knowledge. At Auckland District Health Board (ADHB), most nurses at Epsom Day Unit (abortion medicine clinic) are trained to insert Jadelle® at the time of the abortion. This is free for the woman apart from the $5 cost of Jadelle®. Also at ADHB, midwives are being trained to insert Jadelle® immediately postnatally before the woman is discharged. This is also free. At Greenlane there is a fortnightly midwife-led Jadelle® insertion clinic that lead maternity carers and general practitioners can refer women to for Jadelle® insertion – again this is free. We have NZ data from a Family Planning study regarding side effects. For bleeding between periods – the most evidence-based side effect – the NZ figures compare with the quoted 1 in 7 women who have implant removal for this reason. What we now need is Jadelle® insertion clinics for general practitioners. Family Planning can offer this training but there is a cost involved.

Reference: NZ Med J 2017;130(1454):40-46
Abstract

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Protective effect of hormone therapy among women with hysterectomy/oophorectomy

Authors: Chen L et al.

Summary: This study investigated whether exposure to menopausal hormone therapy (MHT) in mid-aged women alters their risk of cardiovascular disease (CVD) mortality and all-cause mortality. 13,715 women in the mid-aged population-based cohort (born 1946–1951) of the Australian Longitudinal Study on Women's Health were followed from 1998 to 2013. After adjusting for confounding factors, existing users of MHT were found to have a reduced risk of CVD mortality compared with non-initiators (hazard ratio [HR], 0.63) but there was insufficient evidence of an association in initiators of MHT. For all-cause mortality, risks were reduced for both initiators (HR, 0.69) and existing users (HR, 0.80). Subgroup analysis showed that women with hysterectomy/oophorectomy had lower risks of CVD mortality and all-cause mortality in both initiators and existing users.

Comment (HR): This observational study agrees with the findings of the large randomised Women's Health Initiative study. In this, women aged 50–59 years who had taken estrogen on its own for the study duration and then stopped and were followed (13 years of cumulative follow-up) had 11 less CVD events per 10,000 women/yr. This was statistically significant. However there was no statistically significant effect on overall mortality.

Reference: Hum Reprod 2017;32(4):885-92
Abstract

Is outpatient hysteroscopy the new gold standard?

Authors: Ma T et al.

Summary: This study determined the safety, effectiveness and acceptability of outpatient hysteroscopy over an 11-year period at a tertiary hospital in Australia. 990 women underwent outpatient hysteroscopy at the hospital between March 2003 and January 2014. Successful hysteroscopic access was obtained in 94% of cases. 26% of patients needed a second procedure (132 women had endometrial polyps and 33 had submucosal fibroids that were not able to be treated in the outpatient setting). 88% of women said they would be happy to have the procedure again. Provision of the outpatient hysteroscopy service saved theatre time and was calculated to reduce costs by approximately $AU1000 per case.

Comment (AS): Most hysteroscopies in Australia and NZ are performed in theatre under general anaesthesia. They are undertaken for abnormal uterine bleeding or post-menopausal bleeding. This recent paper from Melbourne showed that outpatient hysteroscopy should replace these procedures as a first line option (in appropriate cases). Its safety and efficacy and resource and financial savings are likely considerable. This prospective study looked at 990 women over 11 years and whilst 26% of patients needed a further procedure (polyps and fibroids that needed definitive treatment), around 9/10 women who had the outpatient procedure would have it again if needed. Advances in ultrasonography with better imaging and greater experience along with improved, more affordable equipment should improve the above findings further in the future. Careful patient selection of course helps reduce the need for a two-stage procedure and complications such as vasovagal episodes.

Reference: Aust NZ J Obstet Gynaecol 2017;57(1):74-80
Abstract

The effect of intrauterine devices on acquisition and clearance of human papillomavirus

Authors: Averbach S et al.

Summary: This study evaluated the association between IUD use and cervical HPV acquisition and clearance. The cohort comprised 676 sexually active young women enrolled from family planning clinics in San Francisco; 85 of whom used an IUD at some time during follow-up. After adjusting for potential behavioural confounders, there was no association between IUD use and acquisition or clearance of HPV infection.

Comment (AS): A previous meta-analysis in 2011 showed that women who had ever used an intrauterine contraceptive device (IUCD) had around half the risk of cervical cancer compared with those who had never used one. However, many flaws prevented the acceptance of this meta-analysis. It was postulated and indirectly shown that IUDs may cause inflammation and thereby accentuate an immune response against HPV. The opposite i.e. a harmful effect was also shown! 676 women in San Francisco were followed up with questionnaires, examinations and high risk (hr) HPV tests with an average of 3 visits each. 85 women used an IUD at some time during the nearly 4 years of follow up. This study did not show any significant association between IUD use and either acquisition or clearance of HPV. The research was limited in that no data were collected regarding the type of IUCD which seems a major omission, although it was likely that the majority were levonorgestrel (LNG) releasing types (Mirena®) and not copper. What is not clear as yet (much larger and better designed studies are needed), is whether IUCDs play any role in the prevention of precancerous lesions (CIN) in women with HPV or indeed a role in helping clearance of these. Also a clear distinction between the respective roles of the copper IUCD and the LNG IUD are needed. In the meantime it is thought to be safe to use IUCDs in women with known HPV. However I would add that if there is a cervical smear abnormality, it is advisable to undertake colposcopy and have a treatment or follow-up plan in place prior to placing an IUCD as the threads can limit treatment of CIN where needed and get damaged during treatment.

Reference: Am J Obstet Gynecol 2017;216(4):386.e1-e5
Abstract

Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease

Authors: Mytton J et al.

Summary: This data linkage study compared outcomes after removal of all ovarian tissue versus ovarian conservation at the time of hysterectomy in premenopausal women with benign disease. A retrospective analysis of the English Hospital Episode Statistics database identified 113,679 women aged 35–45 years who had had a hysterectomy for a benign condition in 2004–2014. Hospital admissions and deaths in women with bilateral ovarian removal were compared with those in women who had ovarian conservation (no removal or unilateral ovarian removal). Patients in the ovarian conservation group were less likely to be hospitalised for ischaemic heart disease after hysterectomy (adjusted hazard ratio [HR], 0.85; p=0.001) and were less likely to have a cancer-related post-hysterectomy admission (adjusted HR, 0.83; p<0.001). The rate of all-cause mortality was lower in women with ovarian conservation (adjusted HR, 0.64; p<0.001), as were the rates of heart disease mortality (adjusted HR, 0.50; p=0.02) and cancer mortality (adjusted HR, 0.54; P<0.001).

Comment (AS): This is a retrospective study of women aged 35–45 years who had a hysterectomy (with one or both ovaries conserved or both removed) between 2004 and 2014. The main reason for removal of all ovarian tissue was to attempt to reduce the risk of ovarian cancer (around a 2% lifetime risk). A third of the women had bilateral ovarian removal which conferred a significantly higher risk of mortality from all causes (1.01% vs 0.6%). Admissions for ischaemic heart disease (2.02% vs 1.6%) and for cancer of any type (3.49% vs 2.8%) were also higher. The rate of breast cancer occurring later on in the up to 10-year follow-up was similar in both groups (0.97% in the removal group vs 1.02% in the conservation group). The authors excluded all women who had a history of breast cancer or cancer of the reproductive tract. It is thought that depleting a premenopausal woman of her natural oestrogen leads to these negative outcomes. There is no information in this study on the use of hormone replacement therapy (HRT) after ovarian removal, and one must presume that some women were given HRT. What surprises me is that after the demise of widespread prescribing of HRT in the early 2000s, I was under the impression that most gynaecologists stopped offering prophylactic bilateral salpingo-oophorectomy to premenopausal women at a concurrent hysterectomy (unless there was a family history of ovarian cancer etc). This study has refuted that for the UK in the period 2004–2014, where 1 in 3 women aged 35–45 were still oophorectomised. Follow-up data are planned and will be interesting.

Reference: BMJ 2017;356:j372
Abstract

Perioperative outcomes of total laparoscopic hysterectomy at a regional hospital in New Zealand

Authors: Suisted P & Chittenden B

Summary: This study evaluated outcomes after total laparoscopic hysterectomy (TLH) at a regional public hospital in NZ. 120 cases of TLH over 3 years were reviewed and compared to the same number of abdominal (AH) and vaginal hysterectomy (VH) cases. TLH and AH were mainly performed for heavy menstrual bleeding and VH for prolapse. The largest uteri were in the AH group, followed by TLH then VH. Compared to TLH, both AH and VH cases had shorter mean operating theatre times (126.8 vs 103.2 and 93 min, respectively), longer mean hospital stay (51.3 vs 101.9 and 75.1h, respectively) and increased mean blood loss (153 vs 517 and 244ml, respectively). One TLH was converted to laparotomy and one required interval laparoscopy. Major complications were lowest in the TLH group (2.5%).

Comment (AS): This audit with 120 cases of TLH compared outcomes with the same number of women undergoing abdominal hysterectomy and vaginal hysterectomy. The last two methods had a significantly shorter average operating time but the study put this down to learning curves and training of junior surgeons. The TLH cases had a significantly shorter hospital stay with fewer major and minor complications including less blood loss. A detailed review of NZ hysterectomies is to be welcomed. Most of the findings of this study are in agreement with international findings. The cases of TLH included power morcellation of uterine fibroids until FDA warnings about this (theoretical and possibly real risks of dissemination of undetected leiomyosarcoma in fibroids in 2014 of around 1/300). Interestingly, one case of (low grade) sarcoma was found in the total of 360 hysterectomies. This in my opinion anecdotally supports advice to not (power) morcellate fibroids without detailed informed consent.

Reference: Aust NZ J Obstet Gynaecol 2017;57(1):81-86
Abstract