Obs & Gyn

Intervention for menopausal hot flush

Hot flushes experienced by menopausal women can be activity limiting, affecting the quality of life for those experiencing them. Hormone replacement is effective but oestrogen exposure carries risk. Neurokinin B is a signalling pathway implicated in menopausal hot flushes. A double-blind phase 2 study has looked at the efficacy of an oral neurokinin 3 receptor antagonist, MLE4901, in reducing hot flushes in menopausal women. The participants (n=28) were healthy women with moderate-to-severe hot flushes, and no period for more that 12 months. Participants received four weeks of drug therapy and four weeks of placebo, in random order, with a two-week wash out period. The primary outcome was number of hot flushes experienced in the final week of both treatment and placebo periods. The MLE4901 drug significantly reduced final hot flush numbers by 45 percentage points versus placebo and was well tolerated. This drug represents a potentially practice changing strategy for safely and effectively reducing hot flush symptoms without need for oestrogen exposure.

Prague JK, Roberts RE, Comninos AN, et al. Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flushes: a phase 2, randomised, double-blind, placebo-controlled trial. *The Lancet* 2017; 389: 1809–1820.

Tranexamic acid for post-partum bleeding

Worldwide, bleeding following childbirth is a major cause of maternal death. The drug tranexamic acid is known to reduce the incidence of death following bleeding in trauma patients and its efficacy in reducing postpartum bleeding related deaths has now also been assessed. A randomised, double-blind study has compared efficacy of 1g intravenous tranexamic acid versus placebo plus usual care in women clinically diagnosed with postpartum haemorrhage following vaginal or caesarean births. This study included over 20 000 women across 21 countries and nearly 200 hospitals. Tranexamic acid significantly reduced the risk of death from bleeding in participants compared to placebo. The benefit was especially prominent when given to women within three hours or giving birth. There was no difference in all-cause mortality or adverse events between groups. Intravenous tranexamic acid can help reduce deaths due to bleeding in women with postpartum bleeding.

Shakur H, Roberts I, Fawole B, et al. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with postpartum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *The Lancet* 2017; 389: 2105–2116.

Surgical approaches in hysterectomy for endometrial cancer

Standard care for women with early-stage endometrial cancer includes the surgical removal of ovaries, ovarian tubes, uterus and lymph nodes. There are two main surgical approaches for doing this, total abdominal hysterectomy (TAH) and total laparoscopic hysterectomy (TLH). A trial has investigated if the laparoscopic approach is equivalent and therefore an appropriate alternative to the total abdominal approach for women with early stage endometrial cancer. Over 750 women with untreated stage I endometrial cancer were randomised to undergo either TAH or TLH in this multinational trial. Participants were followed up for an average of 4.5 years and the primary outcome assessed was disease-free survival. At follow-up, disease-free survival was found in 81.3% of the TAH cohort and 81.6% of the TLH group. These results met the studies pre-specified margin for equivalence. Secondary outcomes of recurrence and overall survival were also similar between groups. Laparoscopic hysterectomy is an appropriate intervention for women with stage I endometrial cancer.

Janda M, Gebski V, Davies LC, et al. Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with stage I endometrial cancer: A randomized clinical trial. *JAMA* 2017; 317 (12): 1224–1233. DOI: 10.1001/jama.2017.2068

Treatment for endometriosis pain

Endometriosis is a chronic, inflammatory condition that causes dysmenorrhea and pelvic pain, affecting the quality of life of its sufferers. A gonadotropin-releasing hormone antagonist, elagolix, has been shown to supress oestrogen in previous studies, and now researchers have investigated if this drug can reduce the oestrogen-driven symptoms in endometriosis. Two similar, randomised, double-blind, studies were set-up comparing the efficacy of elagolix at two different doses, a low dose group of 150 mg once daily, and a higher dose group of 200 mg twice daily, both compared with placebo. Over 800 surgically-diagnosed endometriosis patients were randomised in each study and followed up for three months to assess the primary outcomes of dysmenorrhoea and clinical response of non-menstrual pelvic pain. By three months, both treatment receiving groups achieved a significantly higher rate of clinical response. Participants in the treatment groups did report a greater incidence of hypoestrogenic symptoms, including hot flush. Both low and higher doses of elagolix resulted in improved clinical responses to dysmenorrhoea and pelvic pain by three months and this was sustained at six months.

Taylor HS, Giudice LC, Lessey BA, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *NEJM* 2017. DOI: 10.1056/NEJMoa1700089

Gastroenterology

Pathway inhibitor for Crohn's disease

Risankizumab is a monoclonal antibody that has been developed to target a specific subunit (p19) of interleukin-23, the pathway of which has been implicated in the pathogenesis of Crohn's disease. A double-blind, randomised phase 2 study has compared the efficacy of this drug, at two doses, against placebo. Participants (n=121) had been diagnosed with moderate-to-severe Crohn's for at least three months upon screening. Following a 1:1:1 randomisation, participants were intravenously given either 200 mg risankizumab, 600 mg risankizumab, or placebo at zero, four, and eight weeks. Primary outcome of clinical remission, according to Crohn's Disease Activity Index (CDAI), was assessed at 12 weeks. Of the total number of treatment-receiving patients, 31% achieved clinical remission versus 15% of the placebo group, a significant difference. When separated into doses, only the 600 mg group achieved a significant result. Adverse events were similar across all three groups, with nausea and worsening of Crohn's most common. Risankizumab, and therefore selective blockade of interleukin-23 subunit p19, may be a promising avenue for therapeutic intervention of moderate-to-severe Crohn's disease.

Feagan BG, Sandborn WJ, D'Haens G, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. *The Lancet* 2017; 389: 1699–1709.

Tofacitinib for ulcerative colitis

Tofacitinib is a janus kinase inhibitor drug that has previously been shown to have efficacy as induction therapy for ulcerative colitis (UC) in a phase 2 trial. A further study has been conducted to assess its efficacy as induction and maintenance therapy. The phase 3, randomised, double-blind trial compared efficacy of induction therapy with eight weeks of 10 mg twice daily tofacitinib with placebo in two induction trials, both with over 500 moderate-to-severe UC patients. Both induction trials demonstrated a significantly higher remission rate in UC patients given tofacitinib versus the placebo groups. The maintenance trial included nearly 600 patients who demonstrated clinical response to induction therapy and were randomly assigned maintenance therapy with tofacitinib at 5 mg or 10 mg twice daily, or placebo, for 52 weeks. Again, both tofacitinib groups had a significantly higher rate of remission versus placebo (34% with 5 mg and 40% with 10 mg vs 11% with placebo). However, tofacitinib was associated with higher risks of certain events such as infection and increased lipid levels. Tofacitinib is more effective then placebo for induction and maintenance therapy in ulcerative colitis.

Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *NEJM* 2017; 376: 1723–1736.

Dexamethasone for postoperative nausea

Nausea and vomiting are the most common postoperative complications, occurring in more than 30% of patients. A randomised trial has been conducted on over 1300 patients undergoing elective bowel surgery to assess if pre-operative dexamethasone administration reduces post-operative nausea and vomiting incidence. Participants were given a single dose of 8 mg intravenous dexamethasone (n= 674) at the time of anaesthesia induction or standard care (n=676). The primary outcome was reported vomiting within 24 hours. Primary outcome was reported in 25% of the dexamethasone group versus 33% of the standard care group. A significantly higher number of participants requested additional antiemetic therapy in the standard care group versus the dexamethasone group. Risk of complication did not increase in the dexamethasone group. Additional single dose of 8 mg of dexamethasone given at anaesthesia induction can significantly reduce postoperative nausea and vomiting with no increase in adverse events.

Abbott S, Hwang M, Karim A, Luke, DP, et al. Dexamethasone versus standard treatment for postoperative nausea and vomiting in gastrointestinal surgery: randomised controlled trial (DREAMS Trial). *BMJ* 2017; 357: j1455.

Time to follow-up colonoscopy and cancer risk

The faecal immunochemical test (FIT) is a common screening assessment for colorectal cancer. If a positive test is identified, a colonoscopy is required to follow-up for further investigation. A study has investigated if the time interval between positive FIT and follow-up colonoscopy is associated with an increased risk of colorectal cancer. The retrospective cohort study included over 70 000 patients with a positive FIT result aged 50–70 years who were eligible for colorectal screening. Risk of any colorectal cancer or advanced disease were not increased with follow-up at two months, three months, four to six months, or seven to nine months when compared to risk with follow-up within eight to 30 days. However, when colonoscopy follow-up was extended to 10–12 months, and 12 plus months, risk of any colorectal cancer and advanced stage disease were significantly higher. Positive FIT results followed up with colonoscopy at 10 or more months are associated with a higher risk of colorectal cancer compared to earlier follow-up.

Corley DA, Jensen CD, Quinn VP, et al. Association between time to colonoscopy after a positive fecal test result and risk of colorectal cancer and cancer stage at diagnosis. *JAMA* 2017; 317 (16): 1631–1641. DOI: 10.1001/jama.2017.3634

Respiratory

New target for severe asthma

Those with severe asthma are found to have mast cells present in their airways regardless of glucocorticoid intervention, serving as a marker of poor asthma control. Mast cell homeostasis is largely involved with stem cell factor and its receptor, KIT. A trial has been conducted to assess the benefits of inhibiting KIT in severe asthma. The double-blind trial lasted 24 weeks in which participants were randomised to receive the KIT inhibitor imatinib, or placebo. Airway hyperresponsiveness levels were the primary endpoint assessed. Imatinib significantly reduced airway hyperresponsiveness versus placebo in asthmatics. It was also found that serum tryptase, a marker of mast cell activation, was significantly reduced with imatinib. However, muscle cramps were reported at a greater incidence in the imatinib group. For those with severe asthma, imatinib was found to significantly reduce airway hyperresponsiveness, mast cell count and tryptase release. These results suggest KIT pathways and mast cells are contributors to the pathogenesis of severe asthma and this helps identify them as potentially promising therapeutic targets.

Cahill KN, Katz HR, Cui J, et al. KIT Inhibition by imatinib in patients with severe refractory asthma. *NEJM* 2017; 376: 1911–1920.

Improving outcomes for chronic obstructive pulmonary disorder exacerbations

For sufferers of chronic obstructive pulmonary disorder (COPD), exacerbations of the disease are often associated with poor outcomes. A study group has looked into potential interventions to prevent these poor outcomes and a study has now been conducted to assess if the addition of home non-invasive ventilation (NIV) to home oxygen therapy can improve outcomes in those with severe COPD and hypercapnia post-hospital admission for acute COPD exacerbation. Patients were randomised to receive home oxygen alone (n=59) or home oxygen plus home NIV (n=57). Main outcomes included time to readmission or death during a 12–month period. In the home oxygen plus home NIV group the median time to readmission was just over four months compared to 1.4 months in the home oxygen alone group. There was an absolute risk reduction of readmission or death in the home oxygen plus home NIV group of 17%. For patients with hypercapnia following an acute COPD exacerbation, the addition of home non-invasive ventilation to home oxygen significantly improved outcomes.

Murphy PB, Rehal S, Arbane G, et al. Effect of home non-invasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA* 2017. DOI: 10.1001/jama.2017.4451

Fixed triple therapy for COPD

A study has been conducted to assess the efficacy of triple therapy with two long-acting bronchodilators and an inhaled corticosteroid in patients with COPD. The double-blind, randomised trial compared 52 weeks of single inhaler treatment with tiotropium, fixed

triple therapy (extrafine beclometasone dipropionate (BDP), formoterol fumarate (FF), and glycopyrronium bromide), and open triple therapy (BDP/FF plus tiotropium).

Eligible COPD patients were randomised and assessed for the primary endpoint of moderate-to-severe COPD exacerbation rate by week 52. Exacerbation rates in the tiotropium (n=1075), fixed triple (n=1078), and open triple (n=538), settings were 0.57, 0.46, and 0.45, respectively. The fixed triple regime was superior to tiotropium for exacerbation rates and fixed triple was superior to tiotropium for improving forced expiratory volume in one second (FEV_1) and non-inferior to open triple. In this study, single inhaler treatment with fixed triple therapy of extrafine beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide, provided clinical benefit compared to tiotropium for patients with symptomatic COPD.

Vestbo J, Papi A, Corradi M, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *The Lancet* 2017; 389: 1919–1929.

Glucocorticoid-sparing therapy in severe asthma

Oral glucocorticoid treatment is necessary for many severe asthmatics to manage their disease. Benralizumab is a monoclonal antibody that targets the interleukin-5 receptor and is known to reduce asthma exacerbations. One study has investigated if the simultaneous use of benralizumab can help reduce the dose of glucocorticoid needed for maintenance therapy in severe asthma. This 28-week randomised trial gave patients either placebo or benralizumab every four weeks or eight weeks, and assessed glucocorticoid dose change from baseline. A total of 220 participants were involved in the study. Both benralizumab dosing regimens significantly reduced oral glucocorticoid doses by an average of 75% compared to 25% with placebo. The four-weekly benralizumab regimen also reduced annual exacerbation rate by 55% compared to placebo, and the eight-weekly rate was 70% lower than with placebo. By week 28 there was no significant change seen in forced expiratory volume in one second (FEV_1) compared with placebo for either benralizumab regime. Benralizumab provides the option for a glucocorticoid-sparing therapy in severe asthmatics.

Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. *NEJM* 2017. DOI: 10.1056/NEJMoa1703501

Paediatrics

Childhood lead exposure and cognitive outcomes

Lead is a known developmental neurotoxin, but currently the long-term effects of childhood exposure on cognitive and socioeconomic outcomes are uncertain. To ascertain these outcomes, a prospective cohort study has been conducted in New Zealand where childhood lead exposure was not related to socioeconomic status of the time. Participants IQ's were assessed at 38-years-old following lead blood level testing at 11 years of age. High blood levels were found in children from all socioeconomic backgrounds. At 38 years of age, greater childhood lead levels were associated with a greater decline in IQ from childhood to adulthood. Cognitive function and socioeconomic mobility were also assessed in this study using the Wechsler Adult Intelligence Scale-IV and New Zealand Socioeconomic Index-2006, respectively. Socioeconomic status was associated with a downward social mobility from childhood to adult, mediated by cognitive decline from childhood. This study highlights that exposure to lead in childhood may have long-term cognitive and socioeconomic consequences.

Reuben A, Caspi A, Belsky DW, et al. Association of childhood blood lead levels with cognitive function and socioeconomic status at age 38 years and with IQ change and socioeconomic mobility between childhood and adulthood. *JAMA* 2017; 317 (12): 1244–1251.

Childhood adversity and risk of suicide

Whilst overall suicide rates begin to fall, the rate of suicide among adolescents is increasing and accounting for one of the leading causes of death for 15–29 year olds. To help understand this, a cohort study has looked at the relationship between childhood adversity and suicide risk in adolescence. Swedish medical and population registers provided information from over half a million individuals born between 1987–91 and pooled information on adversity during ages 0–14. Rate ratios for suicide risk at adolescence ranged from 1.4 for parental separation, 1.6 for residential instability and public welfare assistance, 1.9 for parental substance misuse and death in family, 2.0 for parental psychiatric disorder, 2.3 for parental criminality, and 2.9 for suicide in the family. There was also an accumulated adversity relationship and those exposed to one adversity with a risk of 1.1 versus two and three adversities, which carried risks of 1.9 and 2.6, respectively. The identification of these adversities in childhood may better help identify those at risk of suicide so that effective interventions can be put in place.

Björkenstam Charlotte, Kosidou Kyriaki, Björkenstam Emma. Childhood adversity and risk of suicide: cohort study of 548 721 adolescents and young adults in Sweden. *BMJ* 2017; 357: j1334.

Maternal antidepressant use and offspring outcomes

Adverse outcomes have been associated with prenatal antidepressant exposure. One study has investigated if first-trimester maternal antidepressant use is associated with poor offspring outcomes, including birth and neurodevelopmental problems. This retrospective cohort study included over 1.5 million Swedish offspring and analysed maternal self-reported first-trimester antidepressant use and offspring health data for up to 17 years. When adjusted for confounding factors, maternal first-trimester antidepressant use was not associated with increased risk in small for gestational age, autism spectrum disorder or attention deficit disorder in offspring. However, first-trimester antidepressant exposure was associated with increased preterm birth with an odds ratio of 1.34 in a sibling comparison analysis. Following adjustment for confounding factors, first-trimester antidepressant exposure was associated with an increased risk of preterm birth compared to those with no exposure.

Sujan AC, Rickert ME, Öberg AS, et al. Associations of maternal antidepressant use during the first trimester of pregnancy with preterm birth, small for gestational age, autism spectrum disorder, and attention-deficit/hyperactivity disorder in offspring. *JAMA* 2017; 317 (15): 1553–1562. DOI: 10.1001/jama.2017.3413

Patent ductus arteriosus ligation in preterm infants

Previous observational studies have associated surgical ligation of patent ductus arteriosus (PDA) in preterm infants with adverse neonatal outcomes and neurodevelopmental impairment. However, one group of researchers has argued that these previous studies did not account for confounding biases, including pre-ligation morbidity. A retrospective cohort study has now been

conducted to account for these potential biases to generate more accurate information on adverse outcomes. Over 750 extremely preterm infants (28 weeks gestation and under) with PDA were included in this study that compared surgical ligation with medical management of PDA and looked at death and neurodevelopmental impairment at 18–24 months of corrected age. After adjusting for pre-ligation morbidities, the researchers found no difference in the risk of death or neurodevelopmental impairment. In fact, ligation was associated with lower odds of mortality than medical management. Patent ductus arteriosus in extremely premature infants was not associated with higher risk of death or neurodevelopmental impairment than medical management, contrary to previous studies.

Weisz DE, Mirea L, Rosenberg E, et al. Association of patent ductus arteriosus ligation with death or neurodevelopmental impairment among extremely preterm infants. *JAMA Pediatr* 2017; 171 (5): 443–449. DOI: 10.1001/jamapediatrics.2016.5143

Cardiovascular

Gluten intake and cardiovascular health

Sufferers of coeliac disease are advised to avoid gluten in their diets as it can trigger inflammation and gastrointestinal damage. There are groups of non-coeliac sufferers who also follow this practice due to un-validated beliefs of possible health benefits. A prospective cohort study has used food information questionnaires to follow-up over 100 000 participant's gluten intake over 26 years and analyse for any association with coronary heart disease. Questionnaires were updated every four years until 2010. Participants in the highest fifth of gluten intake had a lower incidence of coronary heart disease compared to participants in the lowest fifth of gluten intake (277 versus 352 events per 100 000 person years, respectively), but, with risk adjustments, no significant associations were found between gluten intake and risk of coronary heart disease. However, researchers added that a reduction in gluten intake may coincide with a reduced intake of whole grains, which itself may compromise cardiovascular health. Therefore, the recommendation of gluten-free diets for those without coeliac disease should not be promoted.

Lebwohl B, Cao Y, Zong G, et al. Long term gluten consumption in adults without celiac disease and risk of coronary heart disease: prospective cohort study. *BMJ* 2017; 357: j1892.

Active commuting and health outcomes

Over the past decade, commutes to work have become increasingly inactive, contributing to the worldwide decline in physical activity, which has major health implications. To help combat this and increase daily physical activity, active commuting has been recommended.

A prospective cohort study has assessed the health benefits of active commuting, including the use of cycling and walking. Commutes considered active (cycling and walking) were assessed for association between incidence of cardiovascular disease (CVD), cancer, and all-cause mortality. Over 260 000 participants in the UK were analysed for their commute activity to work on a typical day and the above-mentioned health outcomes. Those who commuted by cycling were found to have a significantly lower risk of CVD, cancer, and all-cause mortality. Walking to work was associated with a significantly lower risk of CVD. Active commuting to work was associated to better health outcomes compared to non-active commuters and should be encouraged to help reduce the burden inactivity places on chronic conditions.

Celis-Morales C, Lyall DM, Welsh P, et al. Association between active commuting and incident cardiovascular disease, cancer, and mortality: prospective cohort study. *BMJ* 2017; 357: j1456.

Body weight fluctuations and cardiovascular outcomes

In those without cardiovascular disease, fluctuating body weight is a known risk factor for death and poor coronary outcomes. One study has set out to investigate if this relationship also exists in those with existing coronary artery disease. Over 9500 participants were included in the study which measured weight at baseline and again at follow-up visits. The primary outcome assessed was any coronary event, including death from coronary heart disease and angina, among others. Secondary outcomes were any cardiovascular event. The study found that an increase of one standard deviation (SD) in body weight was associated with a significantly increased risk in any coronary event, any cardiovascular event (secondary outcome), and death. Patients with the highest variation in body weight had a 64% higher risk of coronary event, 124% higher risk of death, 117% higher risk of myocardial infarction, and a 136% higher risk of stroke than those in the lowest variation group.

For participants with existing coronary artery disease, increased fluctuation in body weight increases risk of mortality and cardiovascular morbidity.

Bangalore S, Fayyad R, Laskey R, et al. Body-weight fluctuations and outcomes in coronary disease. *NEJM* 2017: 376: 1332–1340.

HIV infection and heart failure

In the antiretroviral era of HIV, the improved survival of patients has come with the added complication of increased rates of heart failure (HF). One study has set out to clarify if HIV infection increases risk of HF, including HF with reduced ejection fraction (HFrEF), HF with preserved EF (HFpEF), or both. This cohort study comprised of nearly 100 000 veterans, including HIV positive veterans, matched with uninfected veterans by age, sex, and ethnicity. Individuals with HIV infection were subject to a 61% increased risk of HFrEF, 21% increased risk of HFpEF, and a 37% increased risk of borderline HFpEF. These results remained significant even after adjusting for confounding factors. Risk of HFrEF was pronounced in veterans who were younger than 40 at baseline. Increased risk of HFrEF was seen in people with higher viral counts (500 plus copies /mL versus less than 500 copies /mL). HIV infected individuals have an increased risk of heart failure, both with preserved and reduced ejection fractions, compared to uninfected individuals. This is important to consider so that focus can be put on prevention strategies for HIV infected individuals.

Freiberg MS, Chang CH, Skanderson M, et al. Association between HIV infection and the risk of heart failure with reduced ejection fraction and preserved ejection fraction in the antiretroviral therapy era: Results from the veterans aging cohort study. *JAMA Cardiol* 2017; 2 (5): 536–546. DOI: 10.1001/jamacardio.2017.0264