# Obs & Gyn

### Uncomplicated urinary tract infection treatment

Uncomplicated lower urinary tract infections (UTIs) are common but usually self-limiting. Often antibiotics are provided simply for quicker symptom relief but antibiotic overuse is a global problem that contributes to resistance. Previous studies have shown some benefit of using ibuprofen for symptom management in uncomplicated UTI. Researchers have now investigated if the use of ibuprofen in uncomplicated UTIs is non-inferior to antibiotic use. If so then the use of ibuprofen in this setting may be a safe option to help reduce the burden of antibiotic over-use. Nearly 400 female patients presenting with uncomplicated UTIs were randomised to receive three days of either ibuprofen or the antibiotic pivmercillinam. A day 4 symptom report revealed that 39% of ibuprofen patients reported feeling well versus 74% who were given antibiotics. Moreover, the ibuprofen receiving group were significantly more likely to go on to develop pyelonephritis, of these patients (n=7) all recovered with the help of antibiotics. These findings do not support the use of ibuprofen alone in uncomplicated UTIs.

Vik I, Bollestad M, Grude N, et al. Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women—A double-blind, randomized non-inferiority trial. PLoS Med 2018: 15(5): e1002569. https://doi.org/10.1371/journal.pmed.1002569

### Polycystic ovary syndrome and liver disease

Polycystic ovary syndrome (PCOS) is common, affecting 10% of women. It involves chronic anovulation, polycystic appearance of the ovaries and an androgen hormone excess. It also linked to a lifelong metabolic disorder, encompassing an increased risk of type 2 diabetes, hypertension and cardiovascular events. Non-alcoholic fatty liver disease (NAFLD) is a condition that can progress to irreversible cirrhosis of the liver. It is associated with conditions such as type 2 diabetes and increased weight, and now there is some talk of its association with PCOS. A retrospective study has analysed data including over 63,000 women with PCOS in the United Kingdom. Women with PCOS were found to have an increased rate of NAFLD. This increased risk was also found in PCOS patients with normal weight. The study authors urge further investigation into whether androgen excess is also linked with the complications of NAFLD - fibrosis and cirrhosis. The researchers rationalise that the androgen excess seen in PCOS may be a contributing factor for NAFLD and argue that women with PCOS should be screened for NAFLD.

Kumarendran B, O'Reilly MW, Manolopoulos KN, et al. Polycystic ovary syndrome, androgen excess, and the risk of non-alcoholic fatty liver disease in women: A longitudinal study based on a United Kingdom primary care database. PLoS Med 2018; 15(3): e1002542. https://doi.org/10.1371/journal.pmed.1002542

### Foetal exposure to selective serotonin inhibitors

The use of selective serotonin inhibitors (SSRIs), for conditions such as depression and anxiety, is increasing amongst pregnant women. Previously, animal studies have demonstrated that perinatal SSRI use can alter brain pathways linked to the development of anxiety and depressive-like behaviours in the infant's teen years. A study has now looked at the associations between prenatal SSRI exposure and brain development through magnetic resonance imaging (MRI). The study included infants with in-utero SSRI exposure (n=16), in-utero maternal depression that was untreated (n=21), and healthy controls (n=61). Infants were given MRI scans at a mean age of 3 weeks old. In particular, grey matter volume was compared between the infant groups. In SSRI exposed infants, regions of the brain associated with emotional processing were altered compared to both the healthy controls and the infants exposed to untreated maternal depression. Prenatal SSRI exposure may be associated with foetal brain development. The authors recommend further research on potential long-term behavioural and psychological outcomes.

Lugo-Candelas C, Cha J, Hong S, et al. Associations Between Brain Structure and Connectivity in Infants and Exposure to Selective Serotonin Reuptake Inhibitors During Pregnancy. JAMA Pediatr. 2018;172(6):525–533. doi:10.1001/jamapediatrics.2017.5227

### Acupuncture and IVF success rates

Women undergoing in vitro fertilisation (IVF) are often recommended to simultaneously receive acupuncture therapy as many believe that it can help success rates. The actual evidence base for the efficacy of this is conflicting. A randomised trial has compared efficacy of acupuncture in this setting with a sham acupuncture procedure. Female participants included in the study were undergoing a fresh IVF cycle (n=848) in Australia and New Zealand. The sham acupuncture consisted of noninvasive needle placed at sites away from true acupuncture sites. The main outcome was successful live births at greater than 20 weeks' gestation or birth weight of at least 400g. The first treatment was given prior to and following embryo transfer. Live births occurred in 74 of 405 (18.3%) women who received acupuncture and 72 or 404 (17.8%) women who were in the sham acupuncture group, a non-significant difference. These findings do not support the use of acupuncture as an aide to improve success in women undergoing IVF.

Smith CA, de Lacey S, Chapman M, et al. Effect of Acupuncture vs Sham Acupuncture on Live Births Among Women Undergoing In Vitro Fertilization A Randomized Clinical Trial. JAMA 2018;319(19):1990–1998. doi:10.1001/jama.2018.5336

# Cardiology

### Fluoroquinolone use and aortic dissection

Fluoroquinolone antibiotics are some of the most commonly used antibiotics globally. This group of antibiotics has already been associated with an increased risk of tendon disorders through mechanisms involving the degradation of collagen which is part of their antimicrobial action. Two recent studies have observed a potential link between fluoroquinolone use and aortic aneurysm and dissection which has prompted interest in further investigation into this. A historical cohort study has now looked at data on over 360,000 treatment episodes in Sweden involving fluoroquinolones, the majority of which were ciprofloxacin. Data analysed looked at first episodes of aortic aneurysm diagnosis or episodes of aortic dissection that occurred within 60 days from the start of treatment. The study compared fluoroquinolone related events with amoxicillin, a different group of antibiotic. The use of fluoroquinolone was associated with a 66% increased rate of aortic aneurysm

or dissection versus use with amoxicillin. The researchers urge further work to confirm what exactly rives this and whether there are in-group differences between fluoroquinolones.

Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. BMJ 2018; 360 :k678

### Atopic eczema and cardiovascular outcomes

Up to 10% of adults are affected by atopic eczema and its prevalence is increasing worldwide. It is caused by several mechanisms and the inflammatory component of which has been associated with cardiovascular outcomes. One group has looked further into this link by investigating whether adults with atopic eczema are specifically at an increased risk of myocardial infarction, unstable angina, heart failure, atrial fibrillation, stroke and cardiovascular death. Over 380,000 atopic eczema patients were matched with 1.5 million controls in a population-based cohort study and were followed up for an average of 5 years. Severe atopic eczema was associated with a 20% increased risk of stroke, a 40-50% increased risk in myocardial infarction, unstable angina, atrial fibrillation and cardiovascular death, and a 70% increased risk of heart failure. Active, severe atopic eczema in adults is associated with an increased risk in several cardiovascular outcomes.

Silverwood RJ, Forbes HJ, Abuabara K, et al. Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. BMJ 2018; 361 :k1786

### Risk of stroke in resolved atrial fibrillation

Atrial fibrillation is one of the commonest causes of stroke. This risk can be reduced with the use of anticoagulants and atrial fibrillation itself can be treated with pharmaceutical or electrical cardioversion. Patients are considered resolved of atrial fibrillation either by the above-mentioned treatment or via spontaneous resolution. Although, treatment success rates are not 100% and fibrillation can re-occur. A group has investigated if the risk of stroke or transient ischaemic attack (TIA) remains high in patients with resolved atrial fibrillation. Participants without a history of previous stroke or TIA were included in the retrospective cohort study. Resolved atrial fibrillation participants were compared with controls with atrial fibrillation and controls without a history of or current atrial fibrillation (AF). Active AF participants had the highest risk of stroke. Once resolved AF patients who had recurrent AF were excluded from the study, the risk of stroke or TIA for resolved AF patients was 1.45 versus the controls without AF. The authors encourage the continued use of anticoagulants in patients with resolved atrial fibrillation.

Adderley NJ, Nirantharakumar K, Marshall T. Risk of stroke and transient ischaemic attack in patients with a diagnosis of resolved atrial fibrillation: retrospective cohort studies. BMJ 2018; 361 :k1717

### Strategies for deciding blood pressure treatment

Traditionally, guidance for blood pressure treatment is based on thresholds of systolic blood pressure. Another way of deciding who is treated for blood pressure is with cardiovascular disease (CVD) risk predictors. Simulation studies have previously shown benefits of using CVD risk in guiding treatment decisions. A study has now compared the efficacy of predicted CVD risk assessment with standard blood pressure thresholds on cardiovascular outcomes. Data were taken from over 47,800 participants across 11 trials and an average of 4 years follow up. Analysis revealed that more CVD events could be avoided using CVD risk assessment versus blood pressure thresholds. At systolic blood pressures equal to or greater than 150 mmHg, CVD risk strategy would treat 29% fewer persons to prevent the same number of CVD events. However, the risk assessment strategy was not found to be more beneficial in patients with diabetes or existing cardiovascular disease. Cardiovascular disease risk assessment may be a better indicator for blood pressure treatment guidance than systolic blood pressure targets in primary prevention.

Karmali KN, Lloyd-Jones DM, van der Leeuw J, et al. Blood pressure-lowering treatment strategies based on cardiovascular risk versus blood pressure: A meta-analysis of individual participant data. PLoS Med 2018; 15(3): e1002538.

### Coronary artery graft stenting

Coronary artery bypass grafts are one of the commonest surgical procedures in the USA and Europe. One complication is bypass graft failure, this is seen particularly with saphenous vein grafts (SVG), and many of these failed grafts will need to undergo percutaneous coronary intervention. In this scenario, either bare-metal stents (BMS) or drug-eluting stents (DES) are implanted, with the latter previously demonstrating improved outcomes for graft survival. One study has further investigated the risks and benefits of the use of BMS and DES in de-novo SVG lesions. Nearly 600 patients with at least one significant de-novo SVG lesion were randomised (1:1) to receive either BMS or DES. AT 12 months, target vessel failure was 19% with BMS and 17% with DES, a non-significant difference. There were no between group differences in serious adverse events or stent thrombosis. This demonstrates economic significance as the less expensive BMS can be considered both efficacious and safe in areas where DES stents have high prices.

Brilakis ES, Edson R, Bhatt DL, et al. Drug-eluting stents versus bare-metal stents in saphenous vein grafts: a double-blind, randomised trial. Lancet 2018; 391:1997-2007

## Paediatrics

### Antiretroviral uptake in children

The World Health Organisation is one of several global health stakeholders that has addressed the need for better access for children to antiretroviral therapy for (ART). The 90-90-90 target, set in 2015 for 2020, aims for 90% of people with HIV to know their status, 90% to receive ART and 90% of people on treatment to be virologically suppressed. A comprehensive AIDS database was used to collect information on percentages of children aged 0-19 years receiving ART within 2 years. Data were taken from Asia-Pacific, sub-Saharan Africa, and Latin America and was completed in 2015. A total of 135,000 HIV-1 infected children who were ART-naïve were included. The global probability of starting ART within 2 years was just 68 per cent. Of the remainder, 2% died before treatment initiation and 20% were lost to follow up which may indicate higher deaths than accounted for. The worst ART uptake rates were for children <1 year and the age groups 15-19 years. More needs to be done to combat the low levels of HIV infected children receiving antiretroviral therapy.

Desmonde S, Tanser F, Vreeman R, et al. (2018) Access to antiretroviral therapy in HIV-infected children aged 0–19 years in the International Epidemiology Databases to Evaluate AIDS (IeDEA) Global Cohort Consortium, 2004–2015: A prospective cohort study. PLoS Med 2018; 15(5): e1002565. https://doi.org/10.1371/journal.pmed.1002565

### Vitamin D and premature infant wheezing outcomes

Recurrent wheezing during infancy is a common complication found in black infants that were born prematurely. The use of vitamin D supplementation might be beneficial in reducing wheezing amongst this infant group. A United States based study has compared the efficacy of 2 different vitamin D dosing strategies in infants born between 28 and 36 weeks' gestation. The main outcome of the study was to see if there was any difference between continued vitamin D supplementation (n=153) or dietary vitamin D plus placebo (n=147) on premature infant's rates of recurrent wheezing. Vitamin D supplementation was with cholecalciferol given at 400IU/d. The infants were randomised to either group and treated for 6 months adjusted age, and they were then followed up at 12 months adjusted age. Recurrent wheezing was found in 31% of the continued supplementation group and 41% of the diet-limited group. Sustained vitamin D supplementation resulted in significantly reduced wheezing in black premature infants, versus dietary vitamin D supplementation alone.

Hibbs AM, Ross K, Kerns LA, et al. Effect of Vitamin D Supplementation on Recurrent Wheezing in Black Infants Who Were Born Preterm The D-Wheeze Randomized Clinical Trial. JAMA 2018;319(20):2086–2094. doi:10.1001/jama.2018.5729

### Genetic target for sudden infant death syndrome

Sudden infant death syndrome (SIDS) is a complicated and devastating event. It is the leading cause of infant death in high-income countries. One of the main mechanisms appears to be central respiratory system depression. A gene that is involved in the excitation of skeletal respiratory muscle has now been implicated. The SCN4A gene that encodes the sodium channel NaV1.4 has disruptive variants that are associated with paralysis, congenital myopathy, myotonia, myasthenic syndrome and has also been found in infants with life-threatening apnoea and laryngospasm. A study has now investigated if variants in this gene are found in infants who have died from SIDS. The case-control study included 278 SIDS cases and 729 matched controls. Rare variants of the SCN4A gene were found in 1.4% of the SIDS cohort compared with none (0%) of the control group, a significant difference (p=0.0057). Genetic variants that alter NaV1.4 function may contribute to a small proportion of SIDS cases. This is potentially due to alteration in respiratory muscle membrane excitability. These findings highlight muscle sodium channel dysfunction as a potential therapeutic target.

Mannikko R, Wong L, Tester D, et al. Dysfunction of NaV1.4, a skeletal muscle voltage-gated sodium channel, in sudden infant death syndrome: a case-control study. Lancet 2018. 391; 1483-1492.

### Allergies and autism spectrum disorder

In the United States, prevalence of autism spectrum disorder (ASD) has increased over recent years. The cause for increase is not known but many argue that it is the result of increased recognition and diagnosis. Moving on from the neuro-social implications of ASD, much research interest is now focusing on its medical associations. We have already seen an increased prevalence of gastrointestinal disorders within children with ASD. A study group have decided to investigate if there is any potential link between ASD and various allergies. The population based, cross-sectional study examined data from the US National Health Interview Survey from children aged 3-17 years over the time period 1997-2016. Nearly two hundred thousand children were included in the analysis which revealed that reported food, respiratory and skin allergies were all found at higher rates in children with ASD versus children without. Common allergies, in particular those that are food related, are found at higher rates amongst US children with autism spectrum disorder than those without.

Xu G, Snetselaar LG, Jing J, et al. Association of Food Allergy and Other Allergic Conditions With Autism Spectrum Disorder in Children. JAMA Network Open. 2018;1(2):e180279. doi:10.1001/jamanetworkopen.2018.0279

## Infection

### Combining hypertension management with HIV clinics

The commonest cause for death worldwide is cardiovascular disease, the leading risk factor for which is hypertension, a non-communicable disease. Sub-Saharan Africa (SSA) has a high dual burden of communicable and non-communicable diseases. The leading cause of death in SSA remains to be AIDS but successful antiretroviral therapy (ART) regimens are helping reduce burden of HIV. One group have looked at the potential of combining HIV clinics with blood pressure clinics. The researchers argue that HIV clinics can provide a platform to offer non-communicable disease interventions, such as that of blood pressure management. This experiment was conducted in Malawi, home to a high prevalence of hypertension. Standard treatment protocols were used for hypertension. The additional burden of hypertension drugs did not affect the participants ART adherence. Some logistical problems were run into with government funded clinics, mainly due to inconsistencies in medicine supplies. The authors hope that larger scale efforts will be put in place to integrate health services for communicable and non-communicable diseases.

Patel P, Speight C, Maida A, et al. Integrating HIV and hypertension management in low-resource settings: Lessons from Malawi. PLoS Med 2018. 15(3): e1002523. https://doi.org/10.1371/journal.pmed.1002523

### Mosquito saliva and the human immune system

Each year, roughly three-quarters of a million people die from mosquito borne infections. This number may rise in the coming decades with climate change due to an increase of hosting capabilities by various species of mosquitos. Understanding the immune mechanisms at play in mosquito borne infections is key to providing a foundation for tackling the burden of mosquito borne diseases. Mosquitos act as a vector for many pathogens, which are transmitted into human blood stream via the mosquito's saliva. The saliva alone may be important in human responses, but so far only animal models have been used to investigate this. The effects of proteins in mosquito saliva have now been investigated in mice with humanised immune systems. Compared to previous animal models, mosquito saliva lone affects a much larger number of immune cells in humanised models. Some responses were detected for up to 7 days post-bite. Mosquito saliva alone is responsible for immune changes in humanised models. Further research on these proteins and immune responses may help development of vaccine targets.

Vogt MB, Lahon A, Arya RP, et al. Mosquito saliva alone has profound effects on the human immune system. PLoS Negl Trop Dis 2018. 12(5): e0006439. https://doi.org/10.1371/journal.pntd.0006439

### Cardiac findings in congenital Zika syndrome

The neurological manifestations of antenatal exposure to Zika virus are becoming well described. However, it has been reported that the effects of the disease are not limited to the brain. A previous study has reported a link between antenatal Zika exposure and non-severe congenital heart defects seen in infants born with congenital Zika syndrome. A study has further investigated this by performing a cross sectional study of cardiology assessments on infants with confirmed vertical exposure to Zika virus, in Rio de Janeiro, Brazil. The study included 120 eligible children. Vertical exposure to Zika virus (ZIKV) was confirmed by PCR from maternal, foetal and infant specimens. Using ECHO imaging, 40% of the cohort were found to have cardiac defects. Just over 10% had major cardiac defects including atrial septal defect, ventricular septal defect, and patent ductus arteriosus. No defects were found to be severe. Antenatal Zika exposure is associated with an increased incidence of structural heart disease but not of severe structural defects. The authors recommend that postnatal ECHO imaging should be as for the general new-born population.

Orofino DHG, Passos SRL, de Oliveira RVC, et al. Cardiac findings in infants with in utero exposure to Zika virus- a cross sectional study. PLoS Negl Trop Dis 2018;12(3): e0006362.

## Miscellaneous

### Surgical versus conservative management in hip impingement

Non-arthritic hip pain in young adults is commonly caused by femoroacetabular impingement syndrome. This syndrome is often associated with a particular hip shape. Increasingly arthroscopic hip surgery, via keyhole, is being used. This can involve the reshaping of the hip and repairing cartilage and labral tears which occur with repeated impingement. An alternative is a conservative approach that is personalised and physiotherapist-led. A trial has compared clinical efficacy of these two approaches across 23 hospitals in the United Kingdom. Participants with femoroacetabular impingement were randomly allocated to receive either surgery (n=171) or conservative personalised hip therapy (n=177). Efficacy (hip related quality of life) was determined by the patient-reported International Hip Outcome Tool (iHOT-33) at 12 months after randomisation. Both measures were shown to improve hip-related quality of life in patients with femoroacetabular impingement syndrome but surgical intervention with hip arthroscopy had significantly better outcomes. The authors argue for more follow up studies to demonstrate if the more expensive surgical option is cost-effective in the long term.

Griffin D, Dickenson E, Wall P, et al. Hip arthroscopy versus best conservative care for the treatment of femoroacetabular impingement syndrome (UK FASHIoN): a multicentre randomised controlled trial. Lancet 2018: 391; 2225-2235

### Management of resistant primary biliary cholangitis

Primary biliary cholangitis is often managed with ursodeoxycholic acid. Patients who do not respond to this therapy are at high risk for disease progression. Bezafibrate is a class of drug that has been shown to provide potential benefit in this scenario when combined with ursodeoxycholic acid. A double-blind, placebo-controlled, phase 3 trial, has assessed the efficacy of this drug combination in refractory primary biliary cholangitis patients (n=100). Patients were randomly assigned a daily dose of 400mg of bezafibrate (n=50) or placebo (n=50), both on a background of continued ursodeoxycholic acid therapy. The investigation's primary outcome was complete biochemical response at 24 months, measured by levels of total bilirubin, alkaline phosphatase, aminotransferases, and albumin. This was achieved in 31% of the treatment patients and 0% of the placebo group. Alkaline phosphatase returned to normal in 67% of the treatment group versus 2%. Myalgia was more common in the bezafibrate group. The addition of bezafibrate to ursodeoxycholic acid resulted in significantly improved outcomes in patients with primary biliary cholangitis with inadequate responses to ursodeoxycholic acid alone.

Corpechot C, Chazouilleres O, Rousseau A, et al. A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis. NEJM 2018; 378:2171-2181

### Omega-3 fatty acids and dry eye disease

Those suffering from dry eye disease can experience ocular discomfort and disturbance that can seriously impact ones quality of life. Patients are often recommended to use omega-3 fatty acid (n-3 fatty acid) supplements to help relieve the symptoms. A double-blind clinical trial has assessed the efficacy of this approach. Patients with moderate to severe dry eye disease were randomly assigned to receive a daily oral dose of 3000mg fish-derived omega-3 fatty acid supplement (n=349) or an olive oil placebo (n=186). The primary outcome was mean change in baseline score via the Ocular Surface Disease Index (OSDI) rating. There was no significant difference between mean OSDI score's in the supplement and placebo cohorts at 6 and 12 months. Patients suffering from dry-eye disease may not benefit from relived symptoms with omega-3 fatty acid supplementation despite their encouraged use.

The Dry Eye Assessment and Management Study Research Group. n–3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease. NEJM 2018; 378:1681-1690. DOI: 10.1056/NEJMoa1709691

### Gene therapy in β-thalassaemia

Individuals with β-thalassaemia have to undergo life-long frequent blood transfusions, which can have harmful effects. Allogeneic haematopoietic-cell transplant is another option but it is limited by donor availability and transplantation-related risks. Now, gene therapy is being considered in patients with β–thalassaemia. Gene transfer of a β-globin gene (βA-T87Q) has been shown to substitute for blood transfusions. The safety and efficacy of this therapy has now been investigated in two phase 1-2 studies including 22 participants with different types of β-thalassaemia via transfer of autologous CD34+ cells. At an average of 26 months follow up post gene-infusion, in participants who had non-β0/ β0 genotype of β-thalassaemia, 12 out of 13 patients were able to stop receiving red-cell infusions. In the β0/ β0 group the average annual red blood cell transfusion volume was reduced by 73% and transfusions were completely stopped in 3 patients. The safety profile of this therapy was similar to that of stem cell transplants. Gene therapy for beta-thalassaemia reduced or eliminated need for long term red cell transfusions without serious adverse events.

Thompson A, Walters M, Kwiatkowski J, et al. Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia. NEJM 2018; 378:1479-1493 DOI: 10.1056/NEJMoa1705342