Obs & Gyn

Antimalarials in first trimester pregnancy

Artemisinin combination therapies (ACTs) are the most efficacious antimalarials available, yet animal embryotoxicity data, alongside the scarcity of safety data in human pregnancies, have prevented them from being recommended for malaria treatment in the first trimester of pregnancy, except in lifesaving circumstances. One meta-analysis used data from prospective observational studies across six sites in sub-Saharan Africa to determine whether ACTs carry an increased risk in the first trimester of pregnancy compared with quinine. It found that artemisinin treatment in the first trimester was not associated with an increased risk of miscarriage or stillbirth. Furthermore, while the data was limited, they indicate no difference in the prevalence of major congenital abnormalities between treatment groups either. The authors conclude that the benefits of three-day ACT therapy regimens to treat malaria in early pregnancy are likely to outweigh the adverse outcomes of partially treated malaria, which can occur with oral quinine because of the known poor adherence to seven-day regimens.

Dellicour S, Sevene E, McGready R, et al. First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-analysis of observational studies. *PLOS Med* 2017; 14(5): e1002290. DOI: 10.1371/journal.pmed.1002290

Brexanolone in post-partum depression

Post-partum depression is a serious mood disorder consistently observed in an estimated 10–20% of all mothers who give birth in countries worldwide. One phase 2 study investigated brexanolone (SAGE-547 injection), an intravenous formulation of allopregnanolone (a positive allosteric modulator of γ-aminobutyric acid (GABAA) receptors), for the treatment of post-partum depression. In a double-blind, randomised, placebo-controlled trial, 21 women with severe post-partum depression (Hamilton Rating Scale for Depression [HAM-D] total score ≥ 26) were assigned to the brexanolone (n=10) and placebo (n=11) groups. At 60 hours the mean reduction in HAM-D total score from baseline was 21 points in the brexanolone group, compared with 8.8 points in the placebo group (difference -12.2, 95% CI -20.77 to -3.67; p=0.0075). No deaths, serious adverse events, or discontinuations because of adverse events were reported in either group. A pivotal clinical programme for the investigation of brexanolone in patients with post-partum depression is now in progress.

Kanes S, Colquhoun H, Gunduz-Bruce H, et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. *The Lancet* 2017; 390(10093): 480–489.

Anxiety and the birth process

The rate of interventions during childbirth has increased dramatically during the last decades. Maternal anxiety might play a role in the progress of the labour process and interventions. One prospective cohort study aimed to identify associations between anxiety in the first half of pregnancy and the birth process, including any interventions required during labour. The prevalence of high general anxiety (State-Trait Anxiety Inventory state >= 43) and pregnancy-related anxiety (Pregnancy-Related Anxieties Questionnaire (PRAQ) >=P90) were self-reported in the first half of pregnancy as 30.9% and 11.0%, respectively. In nulliparae, both general anxiety and pregnancy-related anxiety were found to be associated with pain relief and/or sedation; in multiparae, general anxiety was associated with induction of labour (odds ratio (OR) 1.53), and pregnancy-related anxiety was associated with primary caesarean section (OR 1.66). Overall, high levels of general and pregnancy-related anxiety in early pregnancy are shown to contribute modestly to more interventions during the birth process, with some differences between nulliparae and multiparae.

Koelewijn J, Sluijs A, and Vrijkotte T. Possible relationship between general and pregnancy-related anxiety during the first half of pregnancy and the birth process: a prospective cohort study. *BMJ Open* 2017; 7: e013413. DOI: 10.1136/bmjopen-2016-013413

Gestational weight gain and outcomes

Body mass index (BMI) and gestational weight gain are increasing globally. In 2009, the Institute of Medicine provided specific recommendations regarding the ideal gestational weight gain, however, the association between gestational weight gain consistent with the guidelines and pregnancy outcomes is unclear. One study undertook a systematic review and meta-analysis of 1 309 136 pregnancies to evaluate this association. They found gestational weight gain below recommendations (in 23% of women) was associated with higher risk of small for gestational age (odds ratio [OR], 1.53) and preterm birth (OR, 1.70), and lower risk of large for gestational age (OR, 0.59) and macrosomia (OR, 0.60). Gestational weight gain above recommendations (47%) was associated with lower risk of small for gestational age (OR, 0.66) and preterm birth (OR, 0.77), and higher risk of large for gestational age (OR, 1.85), and caesarean delivery (OR, 1.30). The authors conclude that gestational weight gain greater or less than guideline recommendations, compared with weight gain within recommended levels, was associated with higher risk of some adverse maternal and infant outcomes.

Goldstein R, Abell S, Ranasinha S, et al. Association of Gestational Weight Gain With Maternal and Infant Outcomes. A Systematic Review and Meta-analysis. *JAMA* 2017; 317 (21): 2207–2225. DOI:10.1001/jama.2017.3635

Infection

HIV control

The Joint United Nations Programme on HIV/AIDS 90–90–90 targets require that, by 2020: 90% of those living with HIV know their status; 90% of known HIV-positive individuals receive sustained antiretroviral therapy (ART); and 90% of individuals on ART have durable viral suppression. The HPTN 071 (PopART) trial is carrying out a large community-randomised trial over three years in 21 communities in Zambia and South Africa to measure the impact of a universal testing and treatment intervention on HIV incidence. This is delivered house-to-house by trained lay health workers. At one year, the trial reports a high uptake of HIV testing, with an estimated 78% of men and 87% of women who were HIV-positive knowing their HIV status. Among known HIV-positive adults, around 73% were on ART by the end of the annual round. Achieving higher test uptake in men and more rapid linkage to care will be key objectives during the second round of the intervention.

Hayes R, Floyd S, Schaap A, et al. A universal testing and treatment intervention to improve HIV control: One-year results from intervention communities in Zambia in the HPTN 071 (PopART) cluster-randomised trial. *PLOS Medicine* 2017; 14 (5): e1002292. DOI: 10.1371/journal.pmed.1002290

Enhanced prophylaxis for advanced HIV

In sub-Saharan Africa, among patients with advanced HIV infection, the rate of death from infection shortly after initiation of antiretroviral therapy (ART) is approximately 10%. One study sought to determine whether enhanced antimicrobial prophylaxis improved outcomes in patients with advanced HIV and starting ART for the first time, compared with standard prophylaxis. Enhanced antimicrobial prophylaxis consisted of continuous trimethoprim-sulfamethoxazole, plus at least 12 weeks of isoniazid-pyridoxine, 12 weeks of fluconazole, five days of azithromycin, and a single dose of albendazole, compared with trimethoprim-sulfamethoxozale alone for standard prophylaxis. They found that, at 24 weeks, the rate of death with enhanced prophylaxis was lower than with standard prophylaxis (8.9% vs 12.2%). Patients in the enhanced prophylaxis group had significantly lower rates of tuberculosis (p=0.02), cryptococcal infection (p=0.01), oral or oesophageal candidiasis (p=0.02), death of unknown cause (p=0.03), and new hospitalisation (p=0.03). However, there was no significant between-group difference in the rate of severe bacterial infection (p=0.32). The authors conclude that enhanced antimicrobial prophylaxis combined with ART resulted in reduced rates of death without compromising viral suppression or increasing toxic effects.

Hakim J, Musiime V, Szubert AJ, et al. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. *NEJM* 2017; 377: 233–245.

Primaquine and *Plasmodium Vivax*

Recent efforts in malaria control have resulted in great gains in reducing the burden of *Plasmodium falciparum*, but *Plasmodium vivax* has been more refractory. Further, there are concerns over declining efficacy for chloroquine (CQ) in endemic areas. One study undertook a randomised controlled trial in Ethiopia to compare artemether-lumefantrine (AL) and CQ with and without primaquine (PQ), the only currently available hypnozoiticide, for the treatment of *P. vivax*. They found that, despite evidence of CQ resistance in Ethiopia, the risk of recurrence by day 28 and 42 was greater following AL than CQ. Moreover, the addition of PQ to either CQ or AL reduced the risk of recurrence three-fold by day 42, and two to three-fold over one year. The authors conclude that PQ radical cure should be included in the treatment schedule in Ethiopia and other areas with high relapse risk to reduce relapsing infection and transmission, but further work is needed to improve adherence to the current 14–day regimen to ensure maximum public health impact.

Abreha T, Hwang J, Thriemer K, et al. Comparison of artemether-lumefantrine and chloroquine with and without primaquine for the treatment of Plasmodium vivax infection in Ethiopia: A randomized controlled trial. *PLOS Medicine* 2017; 14 (5): e1002299. DOI: 10.1371/journal.pmed.1002299

Prophylactic platelet transfusion and dengue

Dengue is the commonest vector-borne infection worldwide. It is often associated with thrombocytopenia, and prophylactic platelet transfusion is widely used despite the lack of robust evidence. One study undertook an open-label, randomised, superiority trial to assess the efficiency and safety of prophylactic platelet transfusion in the prevention of bleeding in adults with dengue and thrombocytopenia. They found that clinical bleeding by day seven or hospital discharge occured in 21% of patients in the platelet transfusion group (n=187), and 26% of patients in the control group (n=182) (relative risk 0.81; p=0.16). Adverse events occurred 13 times in the transfusion group, including three cases of urticaria and one case each of anaphylaxis, chest pain, pruritus and maculopapular rash, and two occurred in the control group (relative risk 6.26; p=0.0064). The authors conclude that prophylactic platelet transfusion for patients with uncomplicated dengue is not recommended. Further studies should focus on children with dengue and patients with severe dengue.

Lye D, Archuleta S, Syed-Omar S, et al. Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial. *The Lancet* 2017; 389 (10079): 1611–1618.

Paediatrics

Iron-deficiency anaemia

Iron-deficiency anaemia (IDA) affects millions of persons worldwide, and is associated with impaired neurodevelopment in infants and children. Ferrous sulfate is the most commonly prescribed oral iron, yet iron polysaccharide complex preparations may be prescribed due to their potentially improved tolerability and better taste. One study undertook a double-blind, superiority randomized clinical trial of infants and children aged nine to 48 months with nutritional IDA to compare the effect of these two iron agents on haemoglobin concentration within this group. From baseline to 12 weeks, mean haemoglobin increased from 7.9 to 11.9g/dL (ferrous sulfate group) vs. 7.7 to 11.1g/dL (iron complex group), a greater difference of 1.0g/dL (p<0.001) with ferrous sulfate. The proportion with a complete resolution of IDA was also higher in the ferrous sulfate group (29% vs 6%; p=0.04). The authors conclude that once daily, low-dose ferrous sulfate should be considered for children with nutritional iron-deficiency anaemia.

Powers J, Buchanan G, Adix L, et al. Effect of Low-Dose Ferrous Sulfate vs Iron Polysaccharide Complex on Hemoglobin Concentration in Young Children With Nutritional Iron-Deficiency Anemia. *JAMA* 2017; 317 (22): 2297–2304. DOI: 10.1001/jama.2017.6846

Maternal serotonergic antidepressants and autism

Previous observations have identified a higher risk of child autism spectrum disorder with serotonergic antidepressant exposure during pregnancy. However, these findings may have been confounded. As such, one study sought to evaluate the association by undertaking a retrospective cohort study of 35 906 births in Ontario, Canada. They found no statistically significant association between exposure to serotonergic antidepressants compared with no exposure in inverse probability of treatment analysis. The association was also not significant when exposed children were compared with unexposed siblings. The authors conclude that while a causal relationship cannot be ruled out, the previously observed association may be explained by other factors. These findings are consistent with other recent studies looking at maternal antidepressant exposure and adverse outcomes more generally.

Brown H, Ray J, Wilton A, et al. Association between serotonergic antidepressant use during pregnancy and autism spectrum disorder in children. *JAMA* 2017; 317 (15): 1544–1552. DOI: 10.1001/jama.2017.3415

Faster urine collection from infants

Urinary tract infections are common in young children, but obtaining urine for analysis from pre-continent children can be difficult and time consuming. One non-invasive method is clean

catch urine collection, which involves waiting for a nappy-free child to void spontaneously. One study undertook a randomised control trial to determine if the Quick-Wee method, which involves gentle suprapubic cutaneous stimulation using a gauze soaked in cold fluid, increases the rate of infant voiding for clean catch urine. The Quick-Wee method was found to result in a significantly higher rate of voiding within five minutes compared with standard clean catch urine (31% vs. 12%, P<0.001). It also had a higher rate of successful urine sample collection (30% v 9%, P<0.001) and greater parental and clinician satisfaction. The number needed to treat was 4.7 to successfully collect one additional urine sample within five minutes. The Quick-Wee method requires minimal resources, and the authors conclude that it presents a simple way to trigger faster voiding for clean catch urine from infants.

Kaufman J, Fitzpatrick P, Tosif S, et al. Faster clean catch urine collection (Quick-Wee method) from infants: randomised controlled trial. *BMJ* 2017; 357: j1341.

Diabetes

Prevalence of type 2 diabetes in Nigeria

While many studies have reported increasing prevalence of type 2 diabetes mellitus (T2DM) globally, there is not yet a comprehensive evidence-based epidemiological report on T2DM in Nigeria. One meta-analysis aimed to estimate country-wide and zonal prevalence, hospitalisation and mortality rates of T2DM in Nigeria, with 42 studies, a total population of 91 320, meeting the selection criteria. They found that the age-adjusted prevalence rates of T2DM in Nigeria among persons aged 20–79 years increased from 2.0% in 1990, to 5.7% in 2015, accounting for over 874 000 and 4.7 million cases, respectively. The pooled prevalence rate of impaired glucose tolerance was 10.0%, and 5.8% for impaired fasting glucose. Hospital admission rate for T2DM was 222.6 per 100 000 population, with hyperglycaemic emergencies, diabetic foot and cardiovascular diseases being the most common complications. The overall mortality rate was 30.2 per 100 000 population. These findings suggest an increasing burden of T2DM in Nigeria, with many persons currently undiagnosed, and few known cases on treatment.

Adeloye D, Ige J, Aderemi A, et al. Estimating the prevalence, hospitalisation and mortality from type 2 diabetes mellitus in Nigeria: a systematic review and meta-analysis. *BMJ Open* 2017; 7: e015424. DOI: 10.1136/bmjopen-2016-015424

Diabetes in pregnancy and expressing breastmilk

Infants of women with diabetes in pregnancy are at increased risk of hypoglycaemia, admission to a neonatal intensive care unit (NICU), and not being exclusively breastfed. Many clinicians encourage women with diabetes in pregnancy to express and store breastmilk in late pregnancy, yet no evidence exists for this practice. One study aimed to determine the safety and efficacy of antenatal expressing in women with diabetes in pregnancy by undertaking a multicentre, two-group, unblinded, randomised controlled trial. The primary outcome was the proportion of infants admitted to the NICU. They found that the proportion of infants admitted to the NICU did not differ between groups (46 [15%] of 317 assigned to antenatal expressing vs 44 [14%] of 315 assigned to standard care; adjusted relative risk 1.06, 95% CI 0.66 to 1.46). The authors conclude that there is no harm in advising women with diabetes in pregnancy at low-risk of complications to express breastmilk from 36 weeks' gestation.

Forster D, Moorhead A, Jacobs S, et al. Advising women with diabetes in pregnancy to express breastmilk in late pregnancy (Diabetes and Antenatal Milk Expressing [DAME]): a multicentre, unblinded, randomised controlled trial. *The Lancet* 2017; 389 (10085): 2204–2213.

Treatment for proliferative diabetic retinopathy

Proliferative diabetic retinopathy is the most common cause of severe sight impairment in people with diabetes, and it has been managed by panretinal laser photocoagulation (PRP) for the past 40 years. One study sought to determine the clinical efficacy of an alternative treatment: intravitreal aflibercept. This was a phase 2b, single-blind, non-inferiority trial on adults with type 1 or 2 diabetes and active proliferative retinopathy. Patients were randomly assigned (1:1) to repeated intravitreal aflibercept, or PRP standard care, and the primary outcome was a change in best-corrected visual acuity at 52 weeks. They found aflibercept to be non-inferior and superior to PRP in both the modified intention-to-treat population (mean best corrected visual acuity difference 3.9 letters; p<0.0001) and the per-protocol population (4.0 letters; p<0.0001). Further, there were no safety concerns. The authors conclude that aflibercept is an effective treatment for active proliferative diabetic retinopathy, and it might be adopted as an alternative option to PRP.

Sivaprasad S, Prevost A, Vasconcelos J, et al. (2017). Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *The Lancet* 2017; 389 (10085): 2193–2203.

Gastroenterology

NSAID use in high risk patients

Present guidelines are conflicting for patients at high risk of both cardiovascular and gastrointestinal events who continue to require non-steroidal anti-inflammatory drugs (NSAIDs). One study undertook a double-blind, double-dummy, randomised trial to determine whether celecoxib (a cyclooxygenase-2-selective NSAID) plus esomeprazole (a proton-pump inhibitor) is superior to naproxen (a non-selective NSAID), plus esomeprazole for the prevention of recurrent ulcer bleeding in concomitant users of aspirin with previous ulcer bleed. Recurrent upper gastrointestinal bleeding, the primary endpoint, occurred in 14 patients in the celecoxib group, and 31 patients in the naproxen group. The cumulative incidence of recurrent bleeding in 18 months was 5.6% in the celecoxib group, and 12.3% in the naproxen group (p=0.008). The authors conclude that in patients at high risk of both cardiovascular and gastrointestinal events who require concomitant aspirin and NSAID, celecoxib plus proton pump inhibitor is the preferred treatment to reduce the risk of recurrent upper gastrointestinal bleeding. Naproxen should be avoided despite its perceived cardiovascular safety.

Chan F, Ching J, Tse Y, et al. Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic diseases and arthritis after upper gastrointestinal bleeding (CONCERN): an industry-independent, double-blind, double-dummy, randomised trial. *The Lancet* 2017; 389 (10087): 2375–2382.

Helicobacter pylori infection diagnosis

Several detection methods for *Helicobacter pylori* have already been developed, such as culture, histological staining, the urea breath test (UBT) and the *H. pylori* stool antigen test

(HpSA), but a simple, non-invasive, inexpensive and accurate diagnostic test remains the goal. Preliminary studies have explored the diagnostic accuracy of testing for anti-*H. pylori* antibodies in urine, and one study undertook a meta-analysis to systematically measure the potential diagnostic value of this method. The study found a pooled sensitivity of 0.83, specificity of 0.89, positive likelihood ratio of 8.81, and a negative likelihood ratio of 0.13. Subgroup analyses showed that diagnostic accuracy of the urine IgG assay was no different in age, region, study population and assay method. The authors conclude that anti-*H. pylori* IgG in urine might serve as a good marker in diagnosing *H. pylori* infection. However, further validation based on a larger sample is still required.

Gong Y, Li Q, Yuan Y. Accuracy of testing for anti-*Helicobacter pylori* IgG in urine for *H. pylori* infection diagnosis: a systematic review and meta-analysis. *BMJ Open* 2017; 7: e013248. DOI: 10.1136/bmjopen-2016-013248

Anti-MAdCAM antibody for ulcerative colitis

Ulcerative colitis is an inflammatory condition of the colon that has a great global burden. Despite its prevalence many patients do not respond well to classic therapies. PF-00547659 is a fully human monoclonal antibody that binds to human mucosal addressin cell adhesion molecule-1 (MAdCAM-1) to selectively reduce lymphocyte homing to the intestinal tract. One phase 2, randomised, double-blind, placebo-controlled trial aimed to assess the efficacy and safety of PF-00547659 in patients with moderate to severe ulcerative colitis. Patients were randomly assigned to receive placebo (n=73) or one of four PF-00547659 doses. Remission rates at week 12 were significantly greater in three of four active treatment groups than in the placebo group (2.7%): 7.5mg (11.3%), 22.5mg (16.7%), 75mg (15.5%), 225mg (5.7%). The authors conclude that PD-00547659 was safe and well tolerated in this patient population, and better than placebo for induction of remission in patients with moderate to severe ulcerative colitis. The greatest clinical effects were observed with the 22.5mg and 75mg doses. A large phase 3 programme is now underway.

Vermeire S, Sandborn W, Danese S, et al. Anti-MAdCAM antibody (PF-00547659) for ulcerative colitis (TURANDOT): a phase 2, randomised, double-blind, placebo-controlled trial. *The Lancet* 2017; 390 (10090): 135–144.

Misc

Vitamin D and atopic disease

Low circulating vitamin D levels have been associated with risk of asthma, atopic dermatitis, and elevated total immunoglobulin E (IgE). These epidemiological associations, if true, would have public health importance, since vitamin insufficiency is both common and correctable. One study aimed to test these associations, using Mendelian randomization (MR) to control bias owing to confounding and reverse causation. The study identified four 25-hydroxyvitamin D (25OHD)-lowering alleles and found that none of them were associated with asthma, atopic dermatitis, or elevated IgE levels ($p \geq 0.2$). The MR odds ratio per standard deviation decrease in log-transformed 25OHD was 1.03 ($p=0.63$) for asthma, and 1.12 ($p=0.27$) for atopic dermatitis, and the effect size on log-transformed IgE levels was -0.40 ($p=0.54$). These findings suggest efforts to increase vitamin D are unlikely to reduce risks of atopic disease. However, the findings do not exclude an association with 1.25-hydroxyvitamin D, the active form of Vitamin D, and this is the main limitation of the study.

Manousaki D, Paternoster L, Standl M, et al. Vitamin D levels and susceptibility to asthma, elevated immunoglobulin E levels, and atopic dermatitis: A Mendelian randomization study. *PLOS Medicine* 2017; 14 (5): e1002294. DOI: 10.1371/journal.pmed.1002294

Barriers to evidence-based acute stroke care

Despite major advances in research on acute stroke care interventions, relatively few stroke patients benefit from evidence-based care due to multiple barriers. Yet current evidence of such barriers is predominantly from high-income countries. One study sought to understand stroke care professionals' views on the barriers which hinder the provision of optimal acute stroke care in Ghanaian hospital settings. They identified four key barriers, and 12 subthemes of barriers. These include barriers at the patient (financial constraints, delays, sociocultural or religious practices, discharge against medical advice, denial of stroke), health system (inadequate medical facilities, lack of stroke protocol, limited staff numbers, inadequate staff development opportunities), health professionals (poor collaboration, limited knowledge of stroke care interventions) and broader national health policy (lack of political will) levels. Perceived barriers varied across health professional disciplines and hospitals. The authors conclude that barriers from low- and middle-income countries differ substantially from those in high-income countries, and the contrasts and uniqueness in these barriers must be considered when designing interventions.

Baatiema L, de-Graft Aikins A, Sav A, et al. Barriers to evidence-based acute stroke care in Ghana: a qualitative study on the perspectives of stroke care professionals. *BMJ Open* 2017; 7: e015385. DOI: 10.1136/bmjopen-2016-015385

Informed health choices primary school intervention

Claims about what improves or harms our health are ubiquitous, and people need to be able to assess the reliability of these claims. One study aimed to evaluate an intervention designed to teach primary school children in Uganda to assess claims about the effects of treatments. In a cluster-randomised controlled trial, the study gave the intervention group the Informed Health Choices primary school resources, including textbooks, exercise books, and a teachers' guide, as well as an introductory workshop for teachers. The primary outcome was the mean score on a test covering all 12 concepts taught, with a mean score of 62.4% recorded for the intervention schools, and 43.1% for the control schools (adjusted mean difference 20.0%; $p<0.00001$). The authors conclude that the use of the Informed Health Choices learning resources led to a large improvement in the ability of children to assess claims about the effects of treatments. Future studies should look at effects on actual health choices, and address how to scale-up the use of these resources.

Nsangi A, Semakula D, Oxman A, et al. Effects of the Informed Health Choices primary school intervention on the ability of children in Uganda to assess the reliability of claims about treatment effects: a cluster-randomised controlled trial. *The Lancet* 2017; 390 (10092): 374–388.