# Ob & Gyn

# Moderate alcohol consumption and fertility

There is an established relationship between alcohol intake during pregnancy and foetal outcomes. One Danish prospective cohort study wanted to investigate the effect alcohol intake has on fertility considering the significant role that alcohol often has in the social lives of women at child-bearing age.

Over 6000 women who were trying to conceive were included in the study. Alcohol intake was self-reported over a period of a maximum 12 menstrual cycles or until pregnancy was achieved.

During the follow-up around 70% of women achieved a pregnancy. A fecundability ratio was established for the participants compared to those with no alcohol consumption.

The adjusted fecundability ratios for alcohol consumption of 1–3, 4–7, 8–13, and 14 or more servings of alcohol per week were 0.97, 1.01, 1.01 and 0.82, respectively. It is worth noting that the study did not distinguish between regular and binge drinking.

This Danish study has shown that consumption of less that 14 servings of alcohol per week did not significantly affect fertility in women.

Mikkelsen EM, Riis AH, Wise LA, et al. Alcohol consumption and fecundability: prospective Danish cohort study. *BMJ* 2016; 354: i4262.

#### Abaloparatide for postmenopausal osteoporosis

Osteoporosis in post-menopausal women is a prevalent condition with a large public health burden. The ACTIVE study group wanted to determine the safety and efficacy of abaloparatide, a parathyroid hormone type 1 receptor activator. This phase 3 double bind randomised control trial was designed to compare the efficacy of abaloparatide against placebo in preventing new vertebral fractures in postmenopausal women.

For 18 months' participants were given daily subcutaneous injections of placebo (n=821), abaloparatide (n=824) or open label teriparatide (an established anti-osteoporotic) (n=818). The primary endpoint was rate of new vertebral fracture which occurred in less than 1% of the abaloparatide group compared to over 4% of the placebo group, a significant difference. However, only 77% participants completed the study. Non-vertebral

fractures were also lower in the abaloparatide group compared to placebo and teriparatide. Hypercalcaemia was significantly lower with abaloparatide compared to teriparatide.

For post-menopausal women with osteoporosis abaloparatide successfully reduced rate of vertebral and non-vertebral fractures compared to placebo.

Miller PD, Hattersley G, Riis B, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA 2016; 316: 722–733.

#### Maternal obesity, folate and childhood metabolism

Maternal obesity is often associated with offspring obesity and existing reports link maternal pre-pregnancy obesity to low folate concentrations.

A group of US researchers investigated if maternal folate concentration, alone or combined with maternal overweight, would have a significant effect on a child's metabolic health, including risk of overweight or obesity (OWO).

A prospective cohort study was conducted at Boston Medical Centre in the US from 1998 to 2012 and 1527 mother-child participants were recruited and followed up until 2014.

The study found that the highest risk factor for OWO in children was having an obese mother with a low folate concentration when compared to normal-weight mothers. When obese mothers had adequate folate concentrations there was an associated significant 43% reduction in risk of childhood OWO compared to low folate mothers (p=0.03).

There is a link between folate levels and childhood metabolism, highlighting the importance of mothers in maintaining an optimum folate concentration.

Wang G, Hu FB, Mistry KB, et al. Association between maternal pre-pregnancy body mass index and plasma folate concentrations with child metabolic health. *JAMA Pediatr* 2016; 170 (8): e160845. DOI: 10.1001/jamapediatrics.2016.0845.

#### Azithromycin for caesarean delivery

Caesarean delivery is associated with an infection rate 5 to 10 times that found with vaginal delivery. Prophylactic antibiotics are routine, but infection remains a risk. A study has looked at the potential benefits of adding the antibiotic azithromycin to the existing prophylaxis course.

The trial was conducted at 14 centres across the US, recruiting over 2000 pregnant women who were then randomly assigned to receive a

standard prophylaxis course of antibiotics, plus either azithromycin (n=1019) or placebo (n=994) before undergoing non-elective caesarean. Primary outcomes included endometritis and wound infection at six weeks.

Women receiving azithromycin experienced the primary outcome 6% of the time compared to 12% in the placebo cohort (p<0.001). Rates of endometritis, wound infection and serious adverse events were all significantly lower in the azithromycin treatment group compared to placebo. No significant differences were observed in adverse neonatal outcomes between the groups.

Extended prophylaxis with azithromycin may be helpful in further reducing post-caesarean risk of infection.

Tita ATN, Szychowski JM, Boggess K, et al. Adjunctive azithromycin prophylaxis for cesarean delivery. *N Engl J Med* 2016; 375: 1231–1241.

# Respiratory

# Transvenous neurostimulation for central sleep apnoea

Central sleep apnoea occurs with failures of neural output from respiratory control centres resulting in disrupted breathing and subsequent interruption of oxygen homeostasis. There is an implantable device, the remedè system, that stimulates diaphragmatic contraction via transvenous neurostimulation producing a response similar to normal breathing. One prospective, multicentre, randomised study evaluated the safety and efficacy of this method in patients with central sleep apnoea. The primary endpoint was proportion of patients with a 50% or more reduction in apnoea activity measured via apnoea-hypnoea index (AHI) evaluated by polysomnography at six months. Patients were implanted with the device and assigned (1:1) stimulation (n=73) or no stimulation (n=78).

Significantly more patients in the treatment group experienced a 50% or greater reduction in AHI from baseline at six months. At 12 months no serious adverse events were reported in over 90% of total participants.

The severity of central sleep apnoea was significantly reduced in patients having transvenous neurostimulation and this should be considered a safe and encouraging treatment option for such patients.

Costanzo MR, Ponikowski P, Javaheri S, et al. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. *The Lancet* 2016; 388: 974–982.

#### Benralizumab for eosinophilic asthma

Benralizumab is an anti-interleukin-5 receptor α monoclonal antibody that causes rapid depletion of eosinophils. Safety and efficacy of this drug as an add-on therapy for those with severe, uncontrolled asthma that presents with elevated eosinophils has been tested in the phase 3 CALIMA study. Patients across 11 countries with a history of 2+ exacerbations in the prior year were randomly assigned to receive either a placebo (n=440) or benralizumab at 30mg either every four weeks (n=425) or eight weeks (n=441) over a 56-week period. Endpoints assessed were rate of annual exacerbations and pre-bronchodilator forced expiratory volume in one second (FEV.).

Benralizumab significantly reduced annual exacerbations in both the treatment settings compared to the placebo. Both treatment settings also significantly improved FEV,.

The adverse event most commonly reported was nasopharyngitis in 21% of the four-week group and placebo and 18% of eight-week group.

Benralizumab is a generally well tolerated drug that can significantly reduce annual asthma events in patients with elevated eosinophilic, uncontrolled asthma.

FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor  $\alpha$  monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet* 2016; DOI:10.1016/S0140-6736(16)31322-8.

## Triple therapy efficacy in chronic obstructive pulmonary disease

Poor symptom management in chronic obstructive pulmonary disease (COPD) by standard therapy means patients are often stepped up to a 'triple therapy' of combined inhaled corticosteroid, a long-acting β2 agonist, and a long-acting muscarinic antagonist. The TRILOGY randomised, double-blind trial was designed to assess the efficacy of the 'triple therapy' single-inhaler combination of beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) compared to beclometasone dipropionate and formoterol fumarate (BDP/FF) treatment. Study endpoints were pre-dose FEV<sub>1</sub>, 2h post-dose FEV<sub>1</sub>, and transition dyspnoea index (TDI) focal score, measured at 26 weeks. Over 1300 COPD patients received either BDP/FF/GB (n=687) or BDP/FF (681).

A significant improvement was seen in the BDP/FF/GB group for both pre-dose FEV<sub>1</sub> and 2h post-dose FEV<sub>1</sub>. There was no significant difference between the groups for TDI score. A 23% reduction in exacerbations was seen in the BDP/FF/GB group compared with BDP/FF.

Triple therapy from a single inhaler may provide clinical benefit for COPD patients.

Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus longacting  $\beta$ 2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *The Lancet* 2016. 388: 963–973.

# **Psychiatry**

## Behavioural activation therapy for depression

Clinical depression is a common and debilitating condition. Medication and cognitive behavioural therapy (CBT) are the two major treatment options and both have a wealth of literature concerning their efficacy. However, medications may have many side effects and CBT can be costly and must be provided by highly trained specialists. There is an alternative therapy, behavioural activation (BA) that is much simpler than CBT and can be provided by junior mental health workers.

In the COBRA study, a randomised non-inferiority trial, participants from the UK who met the criteria for major depressive disorder were assigned either CBT (n=221) or BA (219) to assess if BA could provide a similar depression management to CBT. The primary outcome measured was depression symptoms at 12 months.

There was found to be no difference in proportion of patients from each group who responded to treatment.

BA was found to be non-inferior to CBT and provides a cost-effective alternative intervention for depression.

Richards DA, Ekers D, McMillan D, et al. Cost and outcome of behavioural activation versus cognitive behavioural therapy for depression (COBRA): a randomised, controlled, non-inferiority trial. *The Lancet* 2016; 388: 871–880.

## Comparing mood-stabilisers in bipolar

The UK's four most prescribed drugs for mood-stabilisation in bipolar disorder have well documented side effects, but there is less known about the relative risks of adverse events between the drugs.

A cohort study has investigated the relative risks of several common side

effects in patients prescribed lithium (n = 2148), valproate (n = 1670), olanzapine (n = 1477) or quetiapine (n = 1376) as maintenance treatment.

The study found that lithium was associated with the highest risk of renal failure and hypercalcaemia. Thyroid disease rates were highest in those on lithium compared to valproate and olanzapine, but not quetiapine. Rates of greater than 15% weight gain were higher in valproate, olanzapine, and quetiapine compared to lithium.

The use of lithium as a mood-stabiliser was associated with higher risk for renal and endocrine side effects compared to the other three drugs, but the risk for weight gain was reduced for lithium.

These findings highlight the importance of collaborative doctor-patient discussions to help find a suitable treatment regimen for the patient.

Hayes JF, Marston L, Walters K, et al. Adverse renal, endocrine, hepatic, and metabolic events during maintenance mood stabilizer treatment for bipolar disorder: a population-based cohort study. *PLoS Med* 2016; 13 (8): e1002058. DOI:10.1371/journal. pmed.1002058.

#### Phenotype associated with naltrexone response

Researchers have linked a sweet-taste liking (SL) phenotype to the hedonistic response that is often associated with alcohol dependency. It has a sweet disliking alternative (SDL) and is a stable and heritable characteristic that researchers theorise could be associated with familial risk for alcohol dependency. One team hypothesised that the SL phenotype might influence a patient's response to naltrexone, a drug commonly used to help treat alcohol dependence.

This double-blind placebo-controlled trial took 80 alcohol dependent patients who were either SL phenotypic (n=22) or SDL (n=58) and randomised them by phenotype and pre-treatment high (n=40) or low alcohol (n=40) craving. Patients were given brief weekly counselling, plus either naltrexone 50 mg daily or placebo. For heavy drinkers, the SL phenotype plus naltrexone significantly reduced heavy drinking days and increased abstinent days. The SL phenotype plus naltrexone was particularly strong in reducing drinking in those with pre-treatment high craving.

The SL/SDL phenotype may be a helpful identifier of alcohol dependent patients who could be sensitive to treatment with naltrexone.

Garbutt JC, Kampov-Polevoy AB, Kalka-Juhl LS, et al. Association of the sweet-liking phenotype and craving for alcohol with the response to naltrexone

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treatment in alcohol dependence: a randomized clinical trial. *JAMA Psychiatry* 2016; DOI:10.1001/jamapsychiatry.2016.2157.

## Medication for children with depression

There is some controversy surrounding the best treatment option for children and adolescents with major depressive disorder, particularly regarding pharmacological intervention. However, this is one of the most common forms of mental health issue within this population age-group and so it is of high importance that there are clear treatment regimens on offer.

A meta-analysis was conducted to rank the efficacy of several major interventions. Over 30 trials were eligible for analysis, including more than 5200 patients and 14 different anti-depressants. Primary outcomes included efficacy and tolerability.

When compared to placebo, only fluoxetine was found to have a significantly higher efficacy of treatment. Fluoxetine was also found to have a higher tolerability than two other drugs, duloxetine and imipramine.

The meta-analysis conducted did not show a clear advantage for children and adolescents in taking anti-depressants. However, fluoxetine appears to be the best option if pharmacological treatment is preferred.

Cipriani A, Zhou X, Del Giovane C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *The Lancet* 2016; 388: 881–890.

#### Infection

#### Sex differences in tuberculosis

Tuberculosis (TB) is reported at a higher incidence in men than in women and indeed globally more men die from the illness.

A systematic review has investigated the sex differences found in the prevalence of TB.

Random-effects meta-analyses were used to identify male-to-female (M:F) ratios, as well as prevalence-to-notification (P:N) ratios for TB positive cases.

Over 50 surveys reviewed found M:F prevalence ratios of 2.21 and 2.51 for bacteriologically- and smearpositive TB, respectively. More than 30 studies found the P:N ratio as 1.55 for M:F. The results indicate that men take a longer time to access TB care and therefore a longer time until diagnosis and appropriate treatment. This is of

particular importance as undiagnosed TB is one of the main transmission drivers within communities.

Strategies must be put in place to ensure that men's access to TB services is improved. If this happens successfully, undiagnosed case rates could fall, spread could decrease, and the gender gap could lessen, overall reducing the global burden of TB.

Horton KC, MacPherson P, Houben R, et al. Sex differences in tuberculosis burden and notifications in low- and middle-income countries: a systematic review and meta-analysis. *PLoS Med* 2016; 13 (9): e1002119. DOI: 10.1371/journal.pmed.1002119.

#### Maternal immunisation of influenza vaccine

The risk of influenza for infants is high, although this vaccination is not recommended in those younger than six months old.

A phase 4 trial has been conducted to assess the safety and efficacy of maternal vaccination in protecting infants from influenza during their first six unvaccinated months.

This observer-blind trial, conducted in Mali, gave pregnant women in their third trimester (≥28 weeks' gestation) either an inactivated influenza vaccine or a meningococcal vaccine. Over 1700 infants from each group were followed up for six months.

Vaccine efficacy was 33% in women vaccinated at any time pre-partum and 37% in those vaccinated at least 14 days' pre-partum. However, efficacy appeared to diminish after four months.

The vaccine programme may provide benefit for around four months and in a resource-constrained country it provides a feasible approach to battling influenza in infants who are too young to have their own vaccine.

Tapia MD, Sow SO, Tamboura B, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. *The Lancet Infectious Diseases* 2016; 16: 1026–1035.

# Common infections with glucocorticoids

Glucocorticoids, often prescribed for inflammatory and autoimmune diseases, have immunosuppressive properties. We know that there is an increased overall risk of infection following exposure to glucocorticoids, but there is a gap in the literature concerning the risk regarding specific infections.

Researchers conducted a population-based cohort study to find out more detail of these infections. Elec-

tronic medical records identified over 270 000 adults in the UK that had been prescribed oral glucocorticoids, alongside a random sample of individuals with the same underlying illnesses but no drug exposure.

Those exposed to glucocorticoids had a significantly higher risk of several common infections, including cutaneous cellulitis, candidiasis and a six-fold higher risk for lower respiratory tract infections. There was also an increased risk of infection observed for those on higher drug doses, diabetics, and patients with low albumin levels.

Certain infections are more common when patients are prescribed glucocorticoids. The link between low albumin is currently unclear and the researchers urge more work into understanding this.

Fardet L, Petersen I, Nazareth I. Common infections in patients prescribed systemic glucocorticoids in primary care: a population-based cohort study. *PLoS Med* 2016; 13 (5): e1002024. DOI:10.1371/journal.pmed.1002024.

## Disease burden from injecting drug use

Injecting drug use (IDU) is a key mechanism in the spreading of diseases such as HIV and chronic viral hepatitis B and C (HBV, HCV).

Estimates using historical data have been provided as part of the Global Burden of Disease (GBD) Study 2013 to evaluate the risk of disease burden due to IDU. Data were extracted from sources, including the United Nations records and estimates of IDU-associated disease burden were calculated as disability-adjusted life-years (DALYs).

Over 10 million DALYs were attributable to previous exposure to HIV, HBV and HCV through IDU in 2013 – four times the amount seen in 1990. IDU-associated HIV was highest in lower-middle-income countries, whereas for IDU-associated HCV the burden was highest in high-income countries. In 2013 IDU was estimated to cause 1% of DALYs through HBV, 4% of DALYs through HIV, and nearly 40% of DALYs due to HCV.

Both historical and current IDU contribute majorly to the global burden of disease and more interventions should be in place to help combat this.

Degenhardt L, Charlson F, Stanaway J, et al. Estimating the burden of disease attributable to injecting drug use as a risk factor for HIV, hepatitis C, and hepatitis B: findings from the Global Burden of Disease Study 2013. *The Lancet Infectious Diseases* 2016; DOI: http://dx.doi.org/10.1016/S1473-3099(16)30325-5.

#### Glycaemic control and tuberculosis risk

In low- and middle-income countries where there is high burden of tuberculosis (TB), there is also an increasing prevalence of diabetes — a known risk-factor for TB. So far there have been inconsistent results concerning the association between glycaemic control and TB risk. To investigate this relationship one group assembled a cohort of over 123 000 individuals from a community-based health screening service in northern Taiwan. Glycaemic control was measured via fasting plasma glucose (FPG) and over several years the cohort was followed up for risk of TB.

In total 327 cases of TB were reported over nearly four years. Diabetics with a high FPG (indicating poor glycaemic control) had a significantly higher risk of TB compared to non-diabetics. There was no significant difference in the risk of TB in diabetics with a good glycaemic control compared to a population of non-diabetics. The study estimated that 7.5% of its TB occurrences could be attributed to poor glycaemic control.

Good glycaemic control could reduce risk of TB among diabetic patients. Lee PH, Fu H, Lai TC, et al. Glycaemic control and the risk of tuberculosis: a cohort study. *PLoS Med* 2016; 13(8): e1002072. DOI:10.1371/journal. pmed.1002072.

# Surgery

## Laparoscopic versus retropubic prostatectomy

There is a gap in uro-oncology literature comparing outcomes of laparoscopic prostatectomy with open radical retropubic prostatectomy for prostate cancer patients.

A phase 3 trial aimed to compare results on functional and oncological outcomes between these two surgical approaches.

Patients with newly diagnosed prostate cancer were randomly assigned either radical retropubic surgery (n=151) or a robot-assisted laparoscopic procedure (n=157). Urinary outcome, sexual function and oncological outcome were the primary outcomes measured at six and 12 weeks.

There was no significant difference between post-surgical urinary function in both groups at six weeks (p=0.09) or 12 weeks (p=0.48). No significant differences were seen for sexual function at six weeks (p=0.45) or 12 weeks (p=0.18). Fourteen patients (9%) in the retropubic group versus 4% of the

laparoscopic group experienced postoperative complications (p=0.052). Superiority tests determined there was no significant difference between oncological surgical margin outcomes.

There are similar outcomes from both surgical prostatectomy interventions, and patients may find more comfort in choosing a surgeon they trust over a specific surgical approach.

Yaxley JW, Coughlin GD, Chambers SK, et al. Robotassisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. The Lancet 2016; 388: 1057–1066.

#### Regional anaesthesia for arteriovenous fistula patency

For end-stage renal failure the optimum form of vascular access is through arteriovenous fistulae. This, however, has a high early failure rate. Researchers investigated if the use of regional compared to local anaesthesia may improve the arteriovenous fistula patency based on the idea that regional anaesthesia causes a greater vasodilatation and subsequent increase in blood flow compared to local.

In this randomised controlled trial patients across three Glasgow university hospitals who were undergoing radiocephalic or brachiocephalic arteriovenous fistula creation were randomly assigned (1:1) to receive either local anaesthesia (n=63) or regional brachial plexus block (BPB) (n=63).

At three-months follow-up primary patency was significantly higher in the BPB group (84% vs 62% of patients; p=0.005), and was also greater in radiocephalic fistulae conditions compared to brachiocephalic.

Regional BPB anaesthesia significantly improved patency at three months for patients with end-stage renal disease undergoing arteriovenous fistula creation compared to local anaesthesia.

Aitken E, Jackson A, Kearns R, et al. Effect of regional versus local anaesthesia on outcome after arteriovenous fistula creation: a randomised controlled trial. *The Lancet* 2016; 388: 1067–1074.

# Mapping spatial access to surgical care

The majority of disability-adjusted life-years that are attributed to surgical conditions could be prevented by improving surgical access in low- and middle-income countries. One group wanted to assess population-level spatial access to essential surgeries in Ghana. Bellwether procedures including caesarean section, laparotomy and

open fracture repair, were used as a marker of essential surgeries and their performance rate was used to map the access to essential surgeries. A total of 123 (79.4%) of Ghana Health Service managed hospitals reported data to the study. In 2014 over 75% of the hospitals surveyed did not have capacity to perform all three of the bellwether procedures. Around 20% could perform 1–11 of each procedure and only 3% could perform at least 12. The study concluded that nearly 30% of Ghanaians do not have spatial access to safe and essential surgeries within two hours.

The use of bellwether procedure performance rates may provide a useful monitor for surgical access evaluation, and could be used with the aim to improve access to surgical care.

Stewart BT, Tansley G, Gyedu A, et al. Mapping population-level spatial access to essential surgical care in Ghana using availability of bellwether procedures. *JAMA Surg* 2016; DOI: 10.1001/jamasurg.2016.1239.



CPD Challenge

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