

Obs & Gyn

Endometrial scratching in IVF

Endometrial scratching is a technique used to enhance embryo implantation and increase success rates of pregnancies in women undergoing in vitro fertilisation (IVF). An open-label, multicentre, randomised trial has been conducted to assess the efficacy of this technique. Women undergoing IVF were randomised in a 1:1 ratio to receive either endometrial scratching as an adjunct to their IVF treatment, or no further intervention than standard IVF. The primary outcome assessed was successful live birth. The rate of live birth in the endometrial scratching group was 26.1% (180 of 690 women), and in the control group the rate was also 26.1% (176 of 674 women). No significant differences were observed between groups regarding rates of ongoing pregnancy, clinical pregnancy, multiple pregnancy, ectopic pregnancy, or miscarriage. Out of a score of 10 being the worst pain, endometrial scratching averaged a pain score of 3.5. Endometrial scratching did not add any benefit to women undergoing IVF.

Lensen S, Osavlyuk D, Armstrong A, et al. A randomised trial of endometrial scratching before in vitro fertilisation. *NEJM* 2019; 380:325-334

Valproate linked with attention deficit disorder

The effects of the use of valproate in pregnancy are well documented, these include congenital malformations and adverse neurodevelopment in offspring. Women of childbearing age prescribed valproate are already counselled for these reasons and are advised to consider stopping or switching to other medicine prior to trying for pregnancy. Research has now looked into the potential association between valproate use and risk of offspring with attention deficit/hyperactivity disorder (ADHD). The population-based cohort study included over 900,000 children in Denmark. Prenatal exposure to valproate and other anti-epileptic medications was assessed using the Danish National Prescription Registry and all children with ADHD were identified using other database sources. The study found that prenatal exposure to valproate was associated with a 48% increased risk of ADHD compared to children with no exposure. No other anti-epileptic drugs assessed in the study were found to have any association with ADHD. Women of

childbearing age using valproate should also be counselled on risk of ADHD in potential offspring.

Christensen J, Pedersen LH, Sun Y, et al. Association of Prenatal Exposure to Valproate and Other Antiepileptic Drugs With Risk for Attention-Deficit/Hyperactivity Disorder in Offspring. *JAMA Netw Open*. 2019;2(1):e186606.

Prepubertal androgens, breast development and cancer

Sex hormones are strongly linked with breast cancer, in particular oestrogen is associated with post-menopausal breast cancer. The relationship between testosterone and breast cancer is less studied, but high levels of testosterone in females have been linked with the development of pre- and post-menopausal breast cancer. A study has asked if serum concentrations of androgens in prepubertal girls is associated with a family history of breast cancer. The study included 104 prepubertal girls (age range 6-13 years at baseline). The study found that girls with prepubertal androstenedione concentrations above the median began breast development 1.5 years earlier than girls with concentrations below the median and similar results were found with total and free testosterone. Girls with a first degree family history of breast cancer (their mother) were found to have a 240% higher androstenedione concentration, 10% higher total testosterone, and 92% higher free testosterone concentrations versus girls without breast cancer family history. Familial clustering of breast cancer may be associated with elevated androgen concentrations in adolescent girls with a first degree family history of breast cancer.

Houghton LC, Knight JA, Wei Y, et al. Association of Prepubertal and Adolescent Androgen Concentrations With Timing of Breast Development and Family History of Breast Cancer. *JAMA Netw Open*. 2019;2(2):e190083.

Respiratory

Culture-negative pulmonary tuberculosis

Culture-negative pulmonary tuberculosis (PTB) is considered an early stage of infection that may advance to culture-positive PTB disease when left untreated. It is important to know how this group of patients may differ in presentation versus those with culture-positive TB and what proportion of PTB patients are culture-negative. Participants (n=796) included patients aged 18 and

over with signs of pulmonary disease and sputum culture results and those co-infected with HIV were excluded. Culture-negative PTB was considered those who had clinical and radiographic presentation consistent with TB, 3 negative sputum culture results, and improvement following anti-tuberculosis treatment. The proportion of participants who were culture-negative PTB was 15 per cent. Culture-negative PTB patients were more likely to be female and presented with significantly lower frequency of cough, weight loss, and cavitation (both on X-ray and chest computed tomographic scans). The authors argue that culture-negative PTB may be underdiagnosed and as such there should be an effort to find better tools for early diagnostics to help reduce the world wide burden.

Nguyen MH, Levy NS, Ahuja SD, et al. Factors Associated With Sputum Culture-Negative vs Culture-Positive Diagnosis of Pulmonary Tuberculosis. *JAMA Netw Open*. 2019;2(2):e187617.

Are electronic cigarettes leading to cigarette use?

In recent years, the use of electronic cigarettes (e-cigarettes) has grown exponentially, becoming a successful adjunct for traditional cigarette smoking cessation. However, whilst tobacco cigarette use declines in adults, there appears to be a trend for young tobacco-naïve adolescents to start smoking e-cigarettes. A prospective cohort study has now further investigated the patterns of e-cigarette smoking in youths to ascertain whether tobacco-naïve youths who take up e-cigarette smoking are then more likely to start smoking traditional cigarettes. Of the sample population (n=6123, mean age 13.4 years), 8% reported e-cigarettes were their first exposure to tobacco use whereas 3% reported using traditional cigarettes first. Compared with those with no prior tobacco use, smoking e-cigarettes was associated with more than 4 times the odds of any cigarette use and 3 times the odds of current cigarette use. This study supports the notion that e-cigarette use is associated with increased risk for initiation and use of traditional cigarette smoking among youths.

Berry KM, Fetterman JL, Benjamin EJ, et al. Association of Electronic Cigarette Use With Subsequent Initiation of Tobacco Cigarettes in US Youths. *JAMA Netw Open*. 2019;2(2):e187794.

Changing views on asthma pathophysiology

The pathophysiology of asthma is most commonly described as a process of

inflammation in the airways that leads to bronchial hypersensitivity and poor lung function. However, results from a recent study challenge this paradigm. A study has found that children who go on to develop asthma have reduced lung function before asthma symptoms develop and diagnosis is made. The study included information from a high-risk cohort of over 350 children born from mothers with asthma. The participants had their lung function repeatedly measured using mixed methods from the age of 1 month up to 13 years. In children who would go on to develop asthma, airway obstruction and bronchial hyperreactivity developed before the symptoms of asthma. This did not worsen the longer asthma symptoms were present for nor did they recede when participants went into remission. These results suggest low lung function begins in early childhood prior to the development of airway inflammation in children who develop asthma.

Hallas HW, Chawes BL, Rasmussen MA, et al. Airway obstruction and bronchial reactivity from age 1 month until 13 years in children with asthma: A prospective birth cohort study. *PLoS Med* 2019;16(1): e1002722.

Inflammatory markers and lung cancer

Lung cancer is a leading cause of death worldwide and is strongly linked with smoking behaviour. Convenient and cost-effective strategies for early detection of lung cancer are needed to help reduce the burden of lung cancers. The role of inflammation in lung cancer is becoming a point of interest for researchers. A study has investigated the association of inflammatory markers with incidence of lung cancer. High sensitivity C reactive protein (hsCRP) is a marker for systemic inflammation and it is low cost and widely available as a point-of-care test. A nested case-control study has analysed prospectively measured circulating hsCRP concentration with risk of lung cancer overall, according to smoking status (never, former, and current), and histological subtype. Former and current smokers with high hsCRP had higher incident risk of lung cancer overall versus never smokers. High hsCRP was associated with increased risk of all histological subtypes, excluding adenocarcinoma for which there was little association regardless of smoking status. Circulating hsCRP may be a helpful pre-diagnostic maker for lung cancer.

Muller DC, Larose TL, Hodge A, et al. Circulating high sensitivity C reactive protein concentrations

and risk of lung cancer: nested case-control study within Lung Cancer Cohort Consortium *BMJ* 2019; 364 :k4981

Inhaled marijuana and pneumomediastinum

Inhalation of marijuana is associated with respiratory symptoms such as chronic cough, sputum production, dyspnoea and hoarseness. More recently it has been associated as a risk factor for chronic bullous lung disease and secondary pneumothorax. A study has now investigated if inhalational marijuana use is associated with spontaneous pneumomediastinum (SPM – free air in the mediastinum). This study used a retrospective chart review over a one year period to identify patients who had presented with SPM in the absence of trauma, malignancy or any other iatrogenic cause. Of the 21 cases identified (64% male, average age 22.5 years), daily use of inhalational marijuana was reported in 50% of cases. Other SPM risk factors were concurrent vomiting and coughing. Unfortunately, only two cases had details of the mechanism of smoking. The authors suggest that air leakage around the bronchovascular sheaths during successive inhalation through a high-resistance smoking apparatus or forced exhalation against a closed glottis may precede the development of spontaneous pneumomediastinum. The authors urge further research into the safe use of smoking devices and techniques.

Weiss ZF, Gore S, Foderaro A. Pneumomediastinum in marijuana users: a retrospective review of 14 cases *BMJ Open Respiratory Research* 2019;6:e000391. doi: 10.1136/bmjresp-2018-000391

Paediatrics

Effects of screen time on children's wellbeing

Public discussion is increasing surrounding the potential ill effects of children's exposure to screen time. As a result, expert groups and governing bodies have considered setting guidelines that recommend limiting screen time. However, some of these guidelines have come under fire for not being evidence based. To better help inform policy, a group have conducted a systematic review to answer the question 'what is the evidence for health and well-being effects of screentime in children and adolescents?'. The studies included

addressed body composition, diet, mental health, cardiovascular health, fitness, sleep, pain and asthma.

Analysis found moderately strong evidence for associations between screentime and greater obesity and depressive symptoms. There was moderate evidence for screentime and higher energy intake, less healthy diet and poorer quality of life. There was weak evidence for associations with behavioural problems, anxiety, poorer well-being, cardiorespiratory fitness and poor sleep. No evidence was found for association with asthma or pain. High levels of screentime is associated with a variety of health harms for children and young people. Stiglic N, Viner RM. Effects of screentime on the health and well-being of children and adolescents: a systematic review of reviews *BMJ Open* 2019; 9:e023191.

Adult antisocial behaviour linked with childhood mistreatment

In recent years there has been a move to reduce harsh punishments on children. one notable example is spanking which has been made illegal in some countries. A study has looked at whether harsh physical punishment (including pushing, grabbing, slapping and hitting), child maltreatment (including physical, sexual and emotional abuse), combined or alone might contribute to antisocial behaviours in adulthood. Of over 36,000 participants from the general United States population, the prevalence of harsh physical punishment and maltreatment was 18% and 46%, respectively. The study found that harsh punishment alone, maltreatment alone and harsh punishment with maltreatment were all associated with antisocial behaviours in adulthood. It was estimated that harsh physical punishment and child maltreatment might account for just under half of antisocial behaviours among men and women in the United States. This study adds evidence to the already extensive pool of literature documenting the ill effects of mistreating children. Preventing harsh physical punishment and child maltreatment may help decrease adult antisocial behaviours in the general population.

Atifi TO, Fortier J, Sareen J, Taillieu T. Associations of Harsh Physical Punishment and Child Maltreatment in Childhood With Antisocial Behaviors in Adulthood. *JAMA Netw Open*. 2019;2(1):e187374. doi:10.1001/jamanetworkopen.2018.7374

Steroid regimens for very preterm infants

Dexamethasone is often given to preterm infants in the first week of life to reduce the rate of death or bronchopulmonary dysplasia (BPD). This is an effective intervention but there are some long term adverse effects seen in very preterm infants. Increasingly, hydrocortisone is being used as an alternative but there is little literature to support its use in this scenario. A randomised trial has assessed the effect of hydrocortisone initiated in these preterm infants. Participants were of less than 30 weeks' gestation, or <1250g birthweight, who were ventilator dependent between days 7 and 14 of life. Infants were randomised to receive either a 22 day course of hydrocortisone (n=182) or placebo (n=190). There was no significant difference seen in the composite of death or BPD between those given hydrocortisone versus placebo (70.7% versus 73.7 %, respectively) at 36 weeks' postmenstrual age. But there was significance in reduced rates of death alone at 36 weeks' (a secondary outcome). Additionally, hyperglycaemia requiring insulin was significantly higher in the hydrocortisone group (18.2% vs 7.9%).

Onland W, Cools F, Kroon A, et al. Effect of Hydrocortisone Therapy Initiated 7 to 14 Days After Birth on Mortality or Bronchopulmonary Dysplasia Among Very Preterm Infants Receiving Mechanical Ventilation: A Randomised Clinical Trial. *JAMA*. 2019;321(4):354–363.

Lifestyle

Breakfast consumption and weight loss

Dietary advice is a pillar to managing weight loss and preventing and reducing obesity. Many dietary plans advise inclusion of a regular breakfast, based on presumptions (fed from observational studies) that skipping breakfast may lead to energy overcompensation later in the day. To aid the discussion, a meta-analysis and systemic review has looked at randomised trials comparing breakfast versus no breakfast consumption on body weight and energy intake in adults from high-income countries. Meta-analysis revealed a small difference in weight that favoured participants who had skipped breakfast and participants assigned breakfasts had higher total daily calorie intake. However, the

authors remarked that there was inconsistency across trial results, many trials were at risk of bias, and follow-up was only short term. The results suggest addition of breakfast may not be a good strategy for weight loss, regardless of established breakfast habit. However, these results should be taken with caution due to poor quality of existing data. The authors urge further randomised trials of high quality are needed to better examine the role of breakfast eating in weight management.

Sievert K, Hussain SM, Page M et al. Effect of breakfast on weight and energy intake: systematic review and meta-analysis of randomised controlled trials *BMJ* 2019; 364 :l42

Renal cell carcinoma risk and obesity

The incidence of renal cell carcinoma (RCC) has already been linked to obesity-related factors, but it has been hard to disentangle the independent risk factors from this pool. A genome-wide association study (GWAS) was used to identify several genetic variants associated with obesity, blood pressure, type 2 diabetes, lipids, glucose and insulin. These variants were used as proxies for risk factors of RCC using the GWAS pool which included data on 10,000 RCC patients and twice as many controls. The study found little association between RCC and systolic blood pressure, circulating lipids, overall diabetes, or fasting glucose. However, associations were found between diastolic blood pressure, multiple obesity measures (including body mass index and waist-to-hip ratios), and insulin. The authors state that this research offers novel evidence for the role of insulin in RCC risk. This study provides confirmatory evidence for the independent role obesity-related factors, perhaps mediated through insulin and diastolic blood pressure, have on an increased risk of renal cell carcinoma.

Johansson M, Carreras-Torres R, Scelo G, et al. The influence of obesity-related factors in the etiology of renal cell carcinoma—A mendelian randomization study. *PLoS Med* 2019; 16(1): e1002724. <https://doi.org/10.1371/journal.pmed.1002724>

Obesity and psoriasis

Obesity as a risk factor for disease has been investigated in another genetics based study. This time, exploring the association of obesity with psoriasis. Psoriasis is a common inflammatory skin disorder, which in its severe forms

it can manifest significant physical and mental health impairment. Observational studies have already linked obesity and psoriasis but causality has not been established. The study analysed data from two large population-based studies as well as published data from genome-wide association studies (GWAS). Analysis found that higher body mass index (BMI) causally increases the odds of psoriasis at an increased risk of 9% per 1 unit increase in BMI, supporting existing observational study data. In contrast, analysis did not support a causal role for psoriasis genetics on risk of raised BMI. These findings suggest obesity contributes to pathogenesis of psoriasis. The authors suggest further studies into lifestyle modification to evaluate the efficacy of BMI reduction as an intervention for psoriasis.

Budu-Aggrey A, Brumpton B, Tyrrell J, et al. Evidence of a causal relationship between body mass index and psoriasis: A mendelian randomization study. *PLoS Med* 2019; 16(1): e1002739.

Moderate alcohol consumption benefit in heart failure

There is a complex relationship between alcohol consumption and heart failure - on one hand high alcohol consumption is linked with alcoholic cardiomyopathy and subsequent heart failure but there is also an association of moderate alcohol consumption with reduction in heart failure incidence. A prospective cohort study has investigated the relationship of alcohol consumption on survival in those with heart failure. Participants (n=5888) were aged 65 and over. Of these, 393 developed heart failure and were included in the study. Alcohol consumption was categorised into: abstainers (never drinkers), former drinkers, 7 or fewer drinks per week, and more than 7 per week. After controlling for other variables, consumption of 7 or fewer alcoholic drinks was associated with a significantly increased mean survival of over one year, compared with abstinence from alcohol. Consumption of 10 drinks per week was associated with the longest survival after heart failure diagnosis. These finding suggest that older adults diagnosed with heart failure need not abstain from moderate levels of alcohol consumption.

Sadhu JS, Novak E, Mukamal KJ, et al. Association of Alcohol Consumption After Development of Heart Failure With Survival Among Older Adults in the Cardiovascular Health Study. *JAMA Netw Open*. 2018;1(8):e186383.

Miscellaneous

Sex work laws and health inequality

Sex workers face health and social inequalities, this combined with poor access to services that might otherwise mitigate these further potentiates such inequalities. These poor outcomes have been associated with the criminalisation of sex work. Researchers compiled a mixed-methods review, including both qualitative and quantitative studies, to highlight the extent to which sex work laws and policing practices might negatively impact sex workers. Repressive policing practices were associated with increased risk of sexual and physical violence from clients or other partners, as shown in nine studies with over 5,200 total participants. Repressive policing was also linked with increased risk of sexually transmitted infections, HIV and condomless sex. Analysis of qualitative studies showed that from criminalisation or repressive policing of sex workers, there is disruption of support networks, reduced use of risk reduction strategies, and reduced access to health and justice services. Quantitative and qualitative evidence demonstrates that there is extensive harm associated with the criminalisation of sex work. The authors urge the need for reform in sex-work related law.

Platt L, Grenfell P, Meiksin R, et al. Associations between sex work laws and sex workers' health: A systematic review and meta-analysis of quantitative and qualitative studies. *PLoS Med* 2018; 15(12): e1002680.

Ethical standards of transplant research

Researchers have investigated if papers on Chinese transplant recipients comply with international professional standards and now the authors are now calling for mass retraction of over 400 research papers. The standards mentioned aim to exclude publication of research that (1) involves any biological material from executed prisoners; (2) lacks Institutional Review Board (IRB) approval and (3) lacks consent from donors. Papers included (n= 445 studies) were published in English-language peer-reviewed journals and reported on research outcomes of recipients of transplanted hearts, livers or lungs (n= 85477 transplants) in mainland China. Over 90% of papers did not report whether or not organs were sourced from executed prison-

ers. Standard (2) analysis revealed that 73% of papers did report IRB approval. Whereas standard 3 (report of consent from donor) was not reported in 99% of these papers. The authors conclude that the transplant research community has failed to implement ethical standards of banning publication of research on material from executed prisoners and as such there is a large body of unethical research that now contributes to transplant literature.

Rogers W, Robertson MP, Ballantyne A, et al. Compliance with ethical standards in the reporting of donor sources and ethics review in peer-reviewed publications involving organ transplantation in China: a scoping review *BMJ Open* 2019;9:e024473. doi:10.1136/bmjopen-2018-024473

Enhancing productivity in the emergency department

An Australian study has looked at whether the use of scribes to assist consultants and final year registrars in the emergency department alters productivity. In this randomised, multicentre trial, scribes were trained and randomly allocated to senior emergency physicians. The role of the scribe included clerical work such as locating notes, consultation documentation, information retrieval, facilitating investigations, post-initial consultation tasks, and discharge preparation. The study included over 580 scribed shifts with over 5,000 patients and over 3,200 non-scribed shifts with 23,800 patients. The presence of scribes significantly improved physician's productivity by increasing number of patients seen per hour and there was also significant reduction in patient length of stay in the emergency department. The paper reported that the best gains were seen when the scribes were placed with doctors at triage. Cost-benefit analysis revealed savings even when the scribe was trained and paid by the hospital. The use of scribes may be a cost-effective means to enhance senior physician productivity in the emergency department.

Walker K, Ben -Meir M, Dunlop W, et al. Impact of scribes on emergency medicine doctors' productivity and patient throughput: multicentre randomised trial *BMJ* 2019; 364 :1121

Optimising stable ankle fracture management

Traditionally, stable Weber type B ankle fractures are managed conservatively with a below-the-knee cast for six weeks. The rationale behind this comes from recognition that it takes approximately six weeks for optimum bone union with safe weight bearing.

However, the longer a cast is left on the higher the risk of deep vein thrombosis and increased ankle stiffness and so there is desire to shorten and optimise non-operative fracture healing strategies. A non-inferiority study has taken place across two major trauma centres in Finland, involving patients aged sixteen and over with skeletal maturity, presenting with isolated Weber B fibula fractures. Participants were randomised to conventional six week cast immobilisation (n= 84) or three week treatment in a cast (n= 83) or in a simple orthosis (n= 80). Immobilisation for three weeks in cast or orthosis was non-inferior to conventional six week cast immobilisation and three week immobilisation had significantly improved incidence of DVT and plantar flexion. Three week immobilisation is non inferior to conventional six week immobilisation in the treatment of isolated, stable Weber B fractures.

Kortekangas T, Haapasalo H, Flinkkilä T, et al. Three-week versus six-week immobilisation for stable Weber B type ankle fractures: randomised, multicentre, non-inferiority clinical trial *BMJ* 2019; 364 :k5432

Injuries associated with standing electric scooters

There has been a rapid increase in the use of standing electric scooters in cities. They are considered an easy, inexpensive and eco-friendly means of transportation and many cities have adopted daily rental service platforms. A United States based study has been conducted to characterise the injuries associated with electric scooter use. The study used retrospective medical record reviews of all patients presenting at 2 urban emergency departments following standing electric scooter incidents over the course of one year. A total of 249 patients presented due to scooter associated injuries, over ninety per cent of these were riders and the rest were non-riders. Frequent injuries included fractures (31%), head injury (40%) and contusions, sprains, and lacerations without fracture or head injury (27%). Two patients ended up in intensive care. Only four per cent were documented as wearing a helmet. Due to the increasing prevalence of standing electric scooter use the authors suggest using these findings to help inform local public policy surrounding their use.

Trivedi TK, Liu C, Antonio ALM, et al. Injuries Associated With Standing Electric Scooter Use. *JAMA Netw Open*. 2019;2(1):e187381. doi:10.1001/jamanetworkopen.2018.7381



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