education

FROM THE JOURNALS Edited highlights of weekly research reviews

There's no place like home

Older patients with acute illness are often on the borderline between needing admission and being able to manage at home. When talking through these options with them, we often cite the risk of adverse events from hospital admission (hospital acquired infections, pressure sores, deconditioning, and so on) as one good reason to stay at home.

A cluster randomised controlled trial of a structured, ward based, improvement programme called "Eat Walk Engage" sought to reduce hospital acquired complications among older people. No such reduction was observed in the patients on the four wards that received the intervention (aimed at improving nutrition, hydration, mobility, and cognitive and social engagement). The overall rates give a sense of how big a consideration this is for patients: of the over 65 year olds admitted to the study wards for at least three days, 49% suffered delirium, disability, incontinence, fall, or pressure injury associated with their hospitalisation.

JAMA Intern Med doi:10.1001/jamainternmed.2021.7556

The cost of living

The £9.35 prescription charge in England is enough to put many people off collecting their prescriptions—an estimated 800 000 a year according to a 2008 Ipsos MORI poll. How much higher would this be if those over 60 years old weren't exempt from prescriptions charges and if their annual prescriptions costs were over £1000?

In the US, researchers calculated "out-of-pocket" costs for patients who use Medicare—the federal health insurance for people aged 65 or older. The good news was that costs for patients with common chronic conditions who were prescribed medications recommended by guidelines has gone down slightly between 2009 and 2019. And the bad news? For an older adult with COPD, hypertension, osteoarthritis, osteoporosis, and type 2 diabetes enrolled in any Medicare prescription drug plan, the median out-of-pocket cost in 2019 was $1999 a year.

JAMA Intern Med doi:10.1001/jamainternmed.2021.7457

Gene genie

How often does the plan to await some test results roll over from one ward round to the next? A team at Stanford University collaborating with Google shows that it doesn't have to be that way, even if you're awaiting genetic sequencing that can take weeks. Twelve patients in critical care with a clinical presentation consistent with a genetic disease were selected to pilot ultrarapid nanopore genome sequencing. Diagnostic variants were found in five of the 12 patients, and the shortest time from the blood sample arriving in the lab to an initial diagnosis from genome sequencing was just 7 hours 18 minutes. The report demonstrates that we have the technology to do amazing things very quickly; it's the limited capacity and overstretched resources that often delay diagnostic testing and keep those ward round plans stuck.

N Engl J Med doi:10.1056/NEJMc2112090

GLP-1 agonists for obesity management

Might we soon see more drugs licensed for treating obesity? In 2020, NICE approved the GLP-1 agonist liraglutide, but only under narrow conditions—including being under the care of a specialist multidisciplinary tier 3 weight management service, having non-diabetic hyperglycaemia, and being at high cardiovascular risk.

Another weight loss drug, the appetite suppressant phentermine-topiramate isn't licenced in the EU and UK because of safety concerns. A new meta-analysis concludes: "In adults with overweight and obesity, phentermine-topiramate and GLP-1 receptor agonists proved the best drugs in reducing weight; of the GLP-1 agonists, semaglutide might be the most effective." The study estimated weight reduction with lifestyle modification alone at 3.38% a year, with an extra 11.41% weight fall when semaglutide is added. However, the researchers found high levels of gastrointestinal side effects, and semaglutide has to be given as a once weekly injection.

Lancet doi:10.1016/S0140-6736(21)01640-8

Semaglutide and liraglutide go head to head

Hot on the heels of the *Lancet* meta-analysis, the STEP 8 randomised clinical trial of once weekly semaglutide injections versus once daily oral liraglutide (both in combination with diet and lifestyle counselling) for weight loss has appeared in *JAMA*.

The main headline is that weight loss with semaglutide seems greater: 15.8% mean body weight change versus 6.4% with liraglutide after 68 weeks. Participants were adults with body mass index of ≥30, or ≥27 with one or more weight related comorbidities, without diabetes. How the 338 participants for this study were recruited isn't described in the paper or study protocol. A 16-week dose titration for semaglutide (from 0.25 mg to 2.4 mg) and monthly counselling on diet and activity will be challenges to applying this intervention to clinical practice, and the ›80% incidence of gastrointestinal side effects may translate to higher discontinuation rates than the 19.8% seen here.

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Tom Nolan is a GP in London and clinical editor at *The BMJ*

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10-MINUTE CONSULTATION

Chronic anal fissure in adults

Artaza Gilani,[1] Gillian Tierney[2]

[1]UCL Research Department of Primary Care and Population Health, University College London Medical School
[2]Royal Derby Hospital; University of Nottingham
Correspondence to: Artaza Gilani artaza.gilani@ucl.ac.uk

This is part of a series of occasional articles on common problems in primary care. *The BMJ* welcomes contributions from GPs.

CPD READING
0.5 HOURS

An otherwise healthy 24 year old schoolteacher presents with a three month history of sharp, severe anal pain on defecation. There is bright red blood on wiping and an intense burning pain that persists for several hours after bowel movements. He is on sick leave because the pain is so extreme.

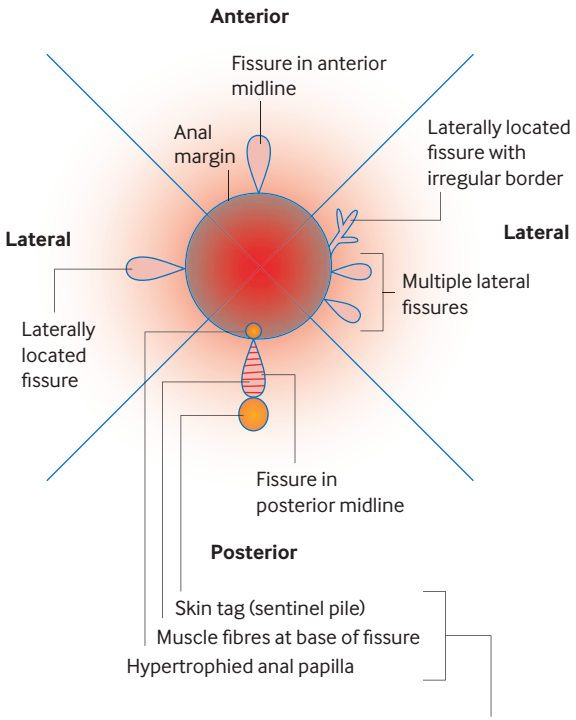
An anal fissure is a tear in the skin of the anal canal.[1] Anal fissures are common, particularly in middle aged adults, children, and infants.[2] There is no consensus on the timeframe that makes a fissure chronic, but most sources consider the cut-off to range from four to 12 weeks.[3] Presentation to primary care is commonly delayed due to embarrassment, despite the often highly distressing symptoms. Topical treatments can be effective, although side effects are common. This article outlines a primary care consultation with an adult presenting with symptoms of a chronic anal fissure.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The article was discussed with a patient, who commented that they wished they had known that a topical treatment for fissures was available that did not cause a headache as a side effect. The topical treatment least likely to cause headache is discussed further in the pharmacological measures section of the article.

WHAT YOU NEED TO KNOW

- Anal fissure generally causes extreme pain that may be debilitating—severe, sharp pain during defecation and significant post-defecation pain
- Less common causes (such as inflammatory bowel disease and malignancy) need to be considered, especially if the fissure is irregular, recurrent, multiple, persistent or non-healing, or located laterally
- Most primary fissures heal with lifestyle and pharmacological (topical glyceryl trinitrate or diltiazem) measures. Botulinum toxin and surgical options may be explored in secondary care



Triad of features that suggest fissure is chronic: hypertrophied papilla at proximal end, sphincter muscle fibres at base, and skin tag at distal margin. Any combination of this triad may be visible during bedside examination

Diagram showing different locations (anterior, posterior, or lateral) and types of fissure (such as irregular, multiple, lateral). Primary or typical fissures are usually singular and tend to occur in the posterior midline (less commonly in the anterior midline). Laterally located fissures or those that are irregular or multiple regardless of location tend to be secondary

What you should cover

History

Symptoms of painful defecation and rectal bleeding are strongly suggestive of an anal fissure. Conditions may coexist—for example, haemorrhoids and anal fissure. The patient's history should be broad enough to account for this. Many differentials share similar presenting features (box 1). Key to diagnosis is the nature of pain (with or without bleeding) and its relationship to defecation.

Is defecation painful? Pain from a fissure is typically severe and sharp (common descriptions include knife-like, passing broken glass, tearing, or splitting). A burning pain may persist for several hours after defecation.

Is there rectal bleeding? Bright red blood on wiping or on the surface of the stool often occurs with a fissure.[1] Other types of bleeding, such as darker blood or blood mixed with the stool, may indicate a more proximal cause (such as colitis or cancer). Some patients (such as those

Box 1 | Common causes of perianal symptoms*

Anal fissure—Pain on defecation likened to passing broken glass, and bright red bleeding is seen on wiping (compare with haemorrhoids, which, in contrast to fissure, typically cause painless, rather than painful, rectal bleeding on defecation). Symptoms of a fissure may wax and wane.

Haemorrhoids—Typically painless bright red bleeding on defecation, perianal itch, and occasional prolapse. Pain, dull in nature, is an uncommon feature and usually seen with thrombosis or strangulation.

Anal abscess—A tender perianal lump with dull, throbbing pain which may be associated with systemic symptoms such as fever. Blood, mixed with pus may be seen if the abscess bursts

Anal fistula—Sometimes follows an anal abscess and usually presents with bloody/purulent discharge, perianal itch, and discomfort. Patients may report a damp patch in their underwear

Anal cancer—May present with a tender ulcerated or non-ulcerated mass with pain, bleeding, and weight loss. Can be an incidental finding on inspection

Rectal cancer—May present with change in bowel habit, urgency, bleeding, and tenesmus, as well as other red flag symptoms, including unintentional weight loss

Proctitis—May present with blood mixed with stool, urgency, and perianal discomfort. Other systemic features of inflammatory bowel disease may be present

Functional —This complex group of conditions may present with bleeding and anal pain. Examples include

- Levator ani syndrome (regular, long lasting aching or pressure in the rectum, worsened by sitting and relieved by walking)
- Solitary rectal ulcer syndrome (a misnomer for an uncommon condition in which ulcers are not always present and has broad and varied symptoms, including pain, rectal bleeding, and a sense of incomplete evacuation)
- Proctalgia fugax (recurrent sudden, severe cramping rectal pain which often occurs at night)

Sexually transmitted infection—May present with anal pain and bleeding in combination with other genitourinary symptoms such as urethral discharge

* The list is not prescriptive because symptoms are not always present or absent in all cases, and conditions can coexist or present atypically

who require help with personal care or who have a visual impairment) may be unaware of bleeding, and a collateral history may be useful.

How long have symptoms been present? Most acute fissures heal within one to two weeks.[4] There is no consensus on how long a fissure needs to be present to be classified as "chronic," but most cut-offs range from four to 12 weeks.[3]

Is there incontinence? Continence is not usually affected. Establish baseline continence to guide future management options.

Has this happened before? This may help identify patients who could be offered referral for recurrent anal fissure, which may be a sign of an underlying condition such as inflammatory bowel disease.

What impact have symptoms had on day-to-day life? Quality of life and mental health may be affected.[5] Fearful of pain, patients may avoid opening their bowels, predisposing to constipation, and forming a vicious cycle. Pain may make it difficult to work, exercise, socialise, or even sit.

Consider underlying causes (box 2). Ask about unintentional weight loss, a change in bowel habit, tenesmus, loss of appetite, abdominal pain, fevers, night sweats, rashes, and family and sexual history. Primary causes are usually the result of local trauma (including constipation) rather than an underlying medical condition. Secondary causes are less common and tend to improve as the underlying medical condition improves.

Examination

Explain to the patient that their symptoms may be due to an anal fissure—a tear at the edge of the anus—and that examination can help confirm this. Seek consent and offer a chaperone. During the initial assessment, inspect the perianal area. If there are no red flags and symptoms are typical of a fissure, we recommend deferring digital rectal examination (to exclude other serious anorectal conditions) to a follow-up appointment when the patient's pain has improved.

- An acute fissure appears as a superficial laceration with well demarcated edges (like a paper cut).
- Chronic fissures are wider and deeper than acute fissures, and have raised edges that may be swollen. Sphincter muscle fibres may be visible at the base of a chronic fissure. At the proximal end of a chronic anal fissure may be hypertrophied anal papillae, while at the distal margin may be a skin tag (sentinel pile).
- Primary, or typical, fissures are usually singular. They generally occur in the posterior midline; they occur less commonly in the anterior midline, but more so in women.[1 3] Atypical fissures (multiple, laterally located. or with irregular borders) may indicate a secondary cause (figure).
- A fissure isn't always visible and does not need to be seen for diagnosis to be made. For instance, anal spasm and/or pain may make it difficult to visualise the fissure. Asking the patient to strain can sometimes reveal the fissure. Gentle pressure on the anal margin may produce pain.

Box 2 | Common causes of anal fissure[6]*

Primary causes

- Constipation†
- Diarrhoea†
- Vaginal delivery
- Anal trauma
- Anal surgery

Secondary causes

- Inflammatory bowel disease—Anal fissures are more common in Crohn's disease than ulcerative colitis[7]
- Granulomatous diseases—Such as extrapulmonary tuberculosis, sarcoidosis
- Malignancy—Such as squamous cell anal cancer, leukaemia
- Communicable diseases—Such as HIV infection, syphilis, chlamydia

*In additional to the factors listed, primary fissures may also have no clear underlying cause

†Consider the underlying cause of these

Ask about unintentional weight loss, a change in bowel habit, tenesmus, loss of appetite, abdominal pain, fevers, night sweats, rashes, and family and sexual history

What you should do

For patients with a chronic anal fissure who are unlikely to have a secondary cause, explain what an anal fissure is and how they come about. We explain a fissure is a tear in the lining of the anus, that the underlying cause is usually unclear, but may be related to local trauma caused by constipation or diarrhoea, although in many cases neither of these are present. We emphasise the vicious circle of pain and spasm, which prevent healing. Hence, the aims of treatment are to relieve spasm and improve blood supply to the fissure, which should help alleviate symptoms and heal the fissure.

Dietary and lifestyle changes

These should continue long term. Stool should be soft, passed easily and without straining. Suggest minimising delay between getting the urge to defecate and going to the toilet. Not more time than is needed should be spent on the toilet. Recommend regular exercise (150 minutes of moderate intensity activity per week), weight management (if relevant), good hydration and a balanced diet, including adequate dietary fibre (~30 g a day for adults[8]). Highlight that soluble fibre is good for constipation, but fibre in general also reduces risk of a range of illnesses, including cardiovascular disease, type 2 diabetes, and colorectal and breast cancer.[9] Increase fibre intake gradually to avoid flatulence and bloating.

Sitting in a warm, shallow bath that bathes the perineum (sitz bath) is often recommended, but evidence is weak.[10 11] Other measures such as bidets, or therapeutic local heat application may be more practical, but data for these measures are lacking.

Pharmacological management

A topical anaesthetic (such as lidocaine ointment) applied externally to the anal area may relieve pain on defecation. It may take 30 minutes to work. Avoid long term use. Suggest regular paracetamol and/or ibuprofen for post-defecatory pain. Avoid opioids (such as codeine and tramadol) as they cause constipation, unless pain cannot be managed with the aforementioned measures.

Topical glyceryl trinitrate (GTN) and diltiazem promote healing of anal fissures (through vasodilatation and improving blood supply to the fissure) and are analgesic, although fissure recurrence may occur. In the UK, 0.4% GTN is licensed for relief of pain associated with chronic fissure, whereas diltiazem is currently unlicensed. Evidence of comparative efficacy is limited, but, when used for chronic anal fissure, they are considered equally effective, with initial efficacy approximately 70%.[12]

The Association of Coloproctology of Great Britain and Ireland and the American Society of Colon and Rectal Surgeons currently recommend topical diltiazem as the first line pharmacological agent for chronic fissure.[13 14] Conversely, the NICE commissioned Clinical Knowledge Summary suggests GTN 0.4% ointment as first line treatment in adults who have had symptoms of a primary anal fissure for ≥1 week without improvement.[15] GTN commonly causes headache, so we recommend taking paracetamol before applying it, and applying it with clingfilm wrapped around the finger to reduce systemic absorption, and, therefore, risk of headache.

Diltiazem may cause perianal itch, dermatitis, and headache, but headache is 85% less likely to occur with diltiazem than GTN, so diltiazem may be better tolerated.[12 16] Topical diltiazem should be kept refrigerated and used within four weeks of opening (so prescribe two tubes per treatment course), whereas topical GTN needs to be used within eight weeks. Advise patients to complete the 6-8 weeks treatment course even if symptoms resolve before then.

Follow-up

We recommend reviewing all patients with anal fissure no later than 6-8 weeks after start of treatment. This is to ensure that symptoms have resolved and to re-examine the perianal area and conduct a digital rectal examination (especially if this was not done at the first visit) to help confirm that the fissure has resolved and to assess for any coexisting anorectal pathology.

Investigations and when to refer

Consider referral for elderly patients (in whom primary fissures are uncommon and there is higher chance of malignant causes); patients with non-healing or recurrent fissures, atypical features (lateral location, irregular margins, multiple fissures), or red flags; and patients who have tried topical treatment for 6-8 weeks without adequate response.

Investigations in secondary care depend on the clinical scenario but may include colonoscopy, flexible sigmoidoscopy, examination under anaesthesia, biopsy, and culture. If primary fissure is confirmed, botulinum toxin injection may be offered. The operative management of anal fissure is reviewed elsewhere.[17 18]

The aims of treatment are to relieve spasm and improve blood supply to the fissure, which should help alleviate symptoms and heal the fissure

EDUCATION INTO PRACTICE

- Do you have local prescribing guidelines about topical treatments for anal fissure?
- How could you optimise the care of patients with anal fissure who are awaiting secondary care review?

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Management and outcomes of extreme preterm birth

CPD READING
0.5 HOURS

Andrei S Morgan,[1 2 3] Marina Mendonça,[4 5] Nicole Thiele,[6] Anna L David[2 7]

[1]Université de Paris, Epidemiology and Statistics Research Center/CRESS, INSERM, Paris
[2]Elizabeth Garrett Anderson Institute for Women's Health London, University College London
[3]Department of Neonatal Medicine, Maternité Port-Royal, Association Publique des Hôpitaux de Paris (APHP), Paris
[4]Department of Psychology, University of Warwick, Coventry
[5]Department of Neuroscience, Psychology and Behaviour, University of Leicester
[6]European Foundation for Care of the Newborn Infant, Munich
[7]National Institute for Health Research, University College London Hospital Biomedical Research Centre

Correspondence to: AS Morgan andrei.morgan@inserm.fr

Extreme preterm birth, defined as birth before 28 weeks' gestational age,[1] affects about two to five in every 1000 pregnancies, and varies slightly by country and by definitions used (box 1, bmj.com). Severe maternal morbidity, including sepsis and peripartum haemorrhage, affects around a quarter of mothers delivering at these gestations.[2] For the babies, survival and morbidity rates vary, particularly by gestational age at delivery but also according to other risk factors (birth weight and sex, for example) and by country.[3 4] In this update, we focus on high income countries and provide a broad overview of extreme preterm birth epidemiology, recent changes, and best practices in obstetric and neonatal management.

WHAT YOU NEED TO KNOW

- Overall survival of babies born extremely preterm has improved in recent years, but evidence for improvements in longer term neurodevelopmental outcomes is limited
- Recent changes in obstetric care include how, when, and to whom to administer steroids, surfactant, and new treatments such as antenatal magnesium sulphate or delayed cord clamping and placental transfusion
- Active participation of parents in treatment may positively influence bonding as well as longer term outcomes for child and family
- Variability in provision of care for extreme preterm birth has an impact on morbidity and mortality outcomes
- Extreme preterm birth has a social impact on mothers, fathers, children born preterm, and their families; the value of investing early in life to prevent later complications is now widely recognised

Rates of extreme preterm births, survival, and associated morbidities

Estimates from vital statistics data suggest that globally between 9% and 12% of births occur before 37 weeks' gestation, resulting in around 14.84 million preterm births a year. Extreme preterm births constitute around 0.42% of all births.[5]

Perinatal survival in extreme preterm birth

Perinatal survival has improved in recent years. In European countries, rates of stillbirth at 24 to 27 weeks' gestation fell between 2004 and 2015 from 0.97 to 0.70 per 1000 births. Below 24 weeks, rates have remained similar over time at 0.55 per 1000 births (95% confidence interval (CI) 0.40 to 0.70) in 2004 and 0.53 per 1000 births (95% CI 0.41 to 0.66) in 2015.[9] These trends are matched in the latest UK data.[6] However, variability is seen between countries,[6 9] in part because of differences in the definition of stillbirth[10] (box 2) and recording of data, but even between countries with similar approaches, differences remain with no obvious reason why.[9] Improvements over time in neonatal survival are described,[6-8] albeit with marked variation between countries at different weeks of gestation (fig 1, bmj.com).[4]

Longer term morbidities

Marked survival differences are not clearly related to longer term morbidities.[4] Higher intensities of perinatal[13 14] and neonatal[15] care are related to improved survival without increasing proportions of survivors with neurodevelopmental impairment at 1.5 to 2.5 years, suggesting that more aggressive treatment does not cause increased morbidity. Yet despite such differences and improvements in survival over time, results are more mixed for longer term neurological outcomes such as cognition, which have not improved in more recent cohorts.[16 17] Comparisons of children from the English EPICure (born in 1995) and EPICure-2 (born in 2006) cohorts at age 11, for example, showed no improvement in moderate to severe disability (which affected 55% of survivors born at 22-25 weeks' gestation in both cohorts using imputed data to account for loss to follow-up), with no change either in cognition (difference in mean mental processing index score 0.1, 95% CI -0.3 to 0.5).[18]

Postnatal environment is also likely important in modifying outcomes into childhood and later life.[3] For example, a recent meta-analysis of European preterm cohorts showed that, compared with families in which mothers had a bachelors or higher degree, standardised mean differences of cognitive scores for children born extremely preterm were 0.24 (95% CI 0.02 to 0.46) lower in families in which mothers had an upper secondary or short tertiary level of education, and 0.57 (95% CI 0.34 to 0.76) lower when mothers had only primary or lower secondary education.[20]

Box 3 | Recommendations for best practice obstetric management

- Transfer the mother antenatally to a tertiary centre that can provide appropriate care to optimise outcome
- Tocolysis may be useful if it is safe for mother and baby to delay delivery short term and allow timely administration of antenatal corticosteroid treatment
- Administer antenatal corticosteroids to facilitate fetal lung maturation
- Provide peripartum magnesium sulphate infusion to reduce neurological injury (as recommended by the National Institute for Health and Care Excellence (NICE) in the UK and various professional societies)[24 25]
- Caesarean section is indicated for risks to the mother's life or when an agreement has been made to resuscitate the neonate and labour would be detrimental to outcome
- Perform delayed cord clamping of at least 60 seconds to facilitate placental transfusion to the newborn[24-29]

Box 2 | Stillbirth

No agreed international definition of stillbirth exists, and the recording of fetal deaths at extreme preterm gestations varies by country. European recommendations are that all births from 22 weeks' gestational age should be officially recorded,[10] but some countries define stillbirth using higher thresholds or birth weight. For example, stillbirth is defined as fetal death from 24 weeks in the UK and by the World Health Organization, 180 days in Italy, and 28 weeks in Bulgaria; in Austria, Belgium, Czech Republic, Germany, and Poland, fetal deaths are recorded at 500 g and above.

Management options

Shared decision making and counselling

Careful counselling is important to enable women and their families to be partners in clinical decision making.[21] Appropriate consideration should be given to personal and religious beliefs, as well as social factors.[22] Advice from practitioners outside the hospital environment who know the family may be helpful in reaching decisions.

Antenatally, counselling should cover risks to the mother as well as longer term outcomes affecting the child: more than a quarter of women in a recent study from a regional referral centre for extreme preterm birth experienced labour or delivery complications such as sepsis and haemorrhage.[2] Predicting outcomes for children born extremely preterm is challenging, however. The child's long term prognosis is likely to change during the course of the neonatal hospitalisation, particularly if the child experiences major events such as severe brain injury or the need for surgery.[23]

Obstetric management

Best management practices in preparation for extreme preterm birth are shown in box 3. Magnesium sulphate infusion peripartum is advised,[24 25] and delayed cord clamping is now recommended when appropriate.[24-27] During preterm labour, cardiotocograph (CTG) monitoring of the fetal heart rate is difficult owing to frequent instances of signal loss associated with the small size of the fetus. Additionally, as the fetal autonomic nervous system is not mature, fetal heart rate patterns which may be typical at later gestations are not present. Only low quality evidence from small case control or cohort studies supports the use of CTG in preterm birth; no studies show benefit from monitoring specifically at extreme preterm gestations, however abnormal baseline variability and the presence of late, prolonged, and variable decelerations are associated with fetal hypoxia.[24]

Mode of delivery is more controversial. The one systematic review of randomised controlled trials (RCTs) for mode of delivery in extreme preterm birth is inconclusive.[30] Caesarean section may be indicated for maternal reasons (such as maternal haemorrhage) or fetal (such as severe fetal growth restriction), or when there is an agreed decision to resuscitate the neonate and labour would be detrimental to the outcome. Following delivery, delayed cord clamping facilitates placental transfusion to the newborn. "Milking" of the cord should be avoided as an RCT showed an association with a secondary outcome of increased intraventricular haemorrhage at extreme preterm gestations (risk difference 16%, 95% CI 6% to 26% compared with delayed cord clamping alone).[31] Delayed cord clamping is both well evidenced[28 29] and acceptable to parents,[32] although may not always be appropriate, for example with placental abruption.[33] Mobile resuscitation trolleys to facilitate bedside resuscitation with the umbilical cord intact are available and acceptable to parents.[32 34]

Neonatal management

Babies may be offered compassionate (palliative, also known as "comfort focused") or survival focused ("active") care following delivery. If compassionate care is provided, care objectives are to avoid painful stimuli or maternal-infant separation. Advise parents that babies may show signs of life, but respiratory support should not be used.[21] Conversely, most babies receiving active care are likely to require some form of respiratory support. Current evidence suggests early non-invasive continuous positive airway pressure is preferred to intubation and ventilation.[35] Transfer to the neonatal intensive care unit should follow stabilisation; parents should be able to accompany the baby, especially for inter-hospital transfer.

During hospitalisation, parent-baby closeness should be promoted, particularly through skin-to-skin contact as well as involvement in providing routine care such as feeds or nappy changes, as such closeness enhances neurobehavioural outcomes. Ward rounds led by parents provide valuable opportunities for this, and have recently been shown to be feasible.[36] Optimal management of neonates is hugely debated, with many questions outstanding. These include if, when, and how exogenous surfactant therapy should be used.[37] Similarly, early initiation of feeding is thought to decrease necrotising enterocolitis and late onset neonatal sepsis, but precise strategies relating to the quantity, frequency, and rate of increase of feeds still need to be determined.[38] Debate also exists for other areas of neonatal

management, including use of prophylactic antibiotics, management of a patent ductus arteriosus, and strategies for controlling pain and discomfort.

Approaches to early developmental care, such as the Newborn Individualized Developmental Care and Assessment Program[39] are increasingly used because of concerns about potential long term effects of the intensive care environment.[40]

Challenges for children and their families

Many children born extremely preterm have happy fulfilling lives, but they have an increased risk of a wide range of health, learning, and social difficulties compared with those born at higher gestational ages.[41] Specialist follow-up with appropriate multidisciplinary input enables potential problems to be identified early and thus mitigates risks.

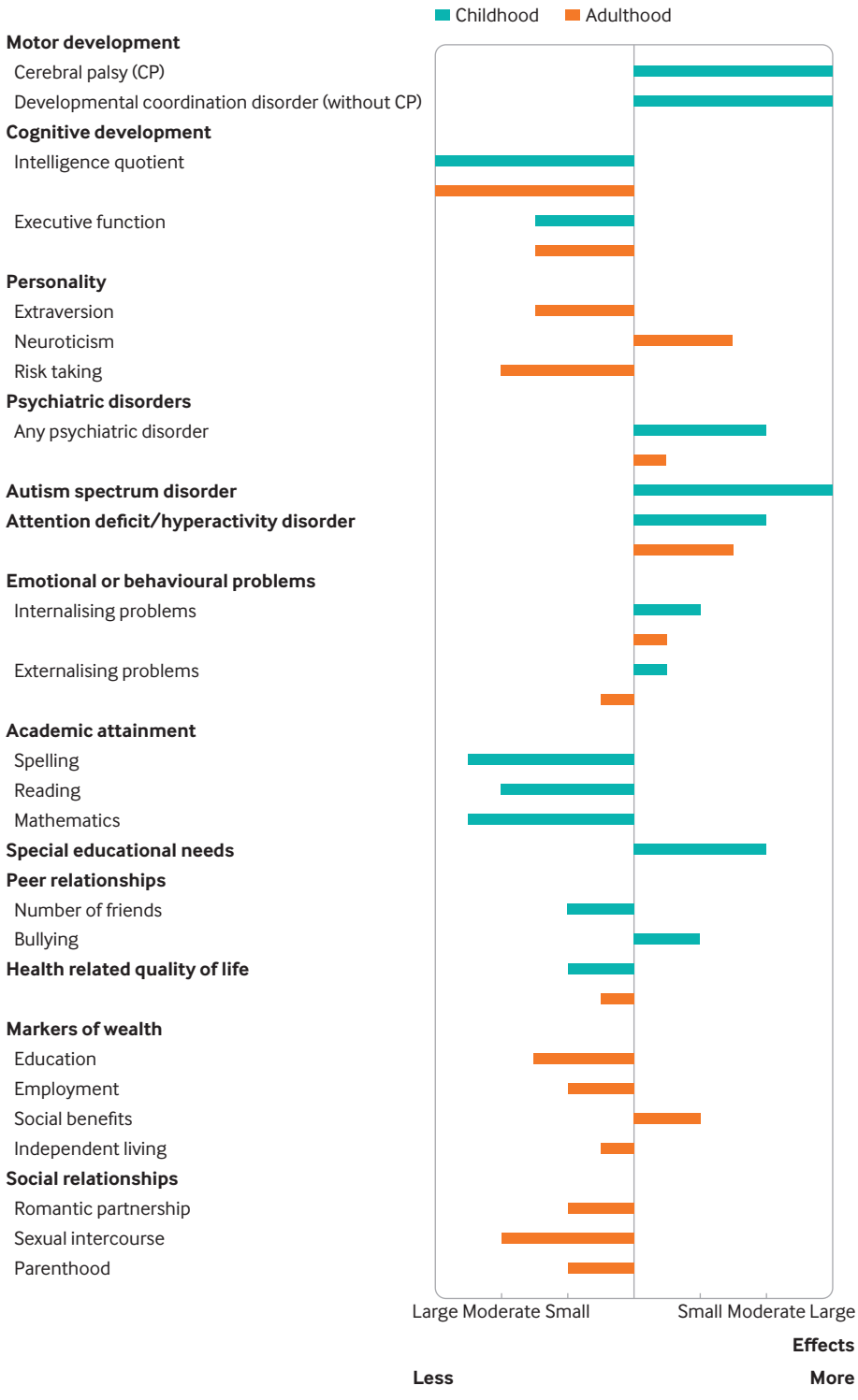

Fig 2 | Approximate effect sizes for the impact of very preterm birth (<32 weeks' gestation) on long term outcomes (compared with birth at term; zero vertical line). Effect sizes are defined as small (odds ratio (OR) 1.48 or inverted 0.67; Cohen's d between means 0.2), moderate (OR 3.45 or 0.29, Cohen's d 0.5), or large (OR 9.00 or 0.11, Cohen's d 0.8).[60] Outcomes assessed in childhood and adolescence are shown in orange and outcomes assessed in adulthood in turquoise. ADHD=attention deficit/hyperactivity disorder; ASD=autism spectrum disorder; DCD=developmental coordination disorder; HRQoL=health related quality of life; IQ=intelligence quotient; SEN=special educational needs. Figure and caption adapted from Wolke et al, 2019[41]

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

None of the authors are patients. Nicole Thiele is Vice Chair of the Executive Board of the European Foundation for Care of the Newborn Infant, the first pan-European organisation and network to represent the interests of preterm and newborn infants and their families. The manuscript was shown to parents who have experienced extreme preterm birth.

Children born extremely preterm are more likely to experience ADHD, anxiety, depression, difficulties with social interaction, and are more likely to have autistic characteristics than their peers

EDUCATION INTO PRACTICE

- How does your practice signpost women and families who have experienced extreme preterm birth to multi-agency support?
- Think about a family in your practice that has been affected by extreme preterm birth; what challenges do you think they might experience?
- What do you know about the birth circumstances of child and adult patients in your practice who experience problems potentially related to extreme preterm birth?

Motor problems

Motor development may be disrupted following extreme preterm birth, from minor delays in sitting or walking, to severe neuromotor impairment, such as cerebral palsy, which is the main motor disorder and affects around 10% to 20% of individuals born extremely preterm.[18-45] Rates of cerebral palsy have remained relatively stable over time in cohort studies of children born extremely preterm (for example, at age 8 they were 13%, 11%, and 14% in the 1991-92, 1997, and 2005 VICS cohorts, respectively)[18 19]; however, findings from a study of registries that included nearly all children with cerebral palsy in Victoria, Australia[45] indicate that cerebral palsy rates have decreased from 102.5 per 1000 neonatal survivors in 1992-2000 to 70.6 per 1000 in 2001-2009. Hence, findings for temporal trends in cerebral palsy among children born extremely preterm are conflicting, which may be partly attributable to the variety of assessment tools used (making comparison difficult) or other methodological issues (eg, differences in baseline populations, outcome definitions, ages at assessment, or follow-up rates).[3]

Regarding motor problems without cerebral palsy, such as deficits in coordination, balance, gross and fine motor control (also referred to as developmental coordination disorder, DCD), evidence from the VICS study show that rates of DCD have increased over time, with a respective prevalence of 13%, 15%, and 26% for extreme preterm babies born in 1991-92, 1997, and 2005.[17]

Cognitive and academic performance

Meta-analyses of childhood IQ show that children born extremely preterm score on average 11 to 13 IQ points lower than term born children.[46 47] No evidence of improvement in mean difference in IQ is seen over time,[47] nor of developmental catch-up by individuals as they grow older.[19]

Mental health and social interactions

Findings from a systematic review and meta-analysis which included summary data on mental outcomes from 41 studies show that children born extremely preterm are more likely to experience attention deficit/hyperactivity disorder (ADHD), internalising problems (eg, anxiety, depression), difficulties with social interaction, and are more likely to have autistic characteristics than their peers born at term.[49] The size of these associations varied between moderate (internalising problems, social problems, autistic characteristics) to large (ADHD, which is four times more likely in extremely preterm children than in term born peers[50]) in childhood. Overall, children born extremely preterm struggle more with social interaction, tend to be shyer, have fewer friends, are more socially withdrawn,[51] and are more likely to be bullied than term born peers.[52 53] The prevalence of autistic spectrum disorders is 8% higher among those born extremely preterm compared with term born children,[54] with persistence of increased autistic traits through to early adulthood.[55]

Although children born extremely preterm are at increased risk of psychiatric disorders,[56] this does not mean that individuals will necessarily develop mental problems—only that the risk is higher when compared with those born at term. Evidence suggests that ADHD and internalising symptoms persist into adulthood,[49] but clinical diagnoses of disorders seem to reduce,[57] suggesting that adults who were born extremely preterm may overcome earlier mental health problems.

How do early life circumstances affect adults born extremely preterm?

Recent meta-analyses show that adults born preterm have greater risks of socioeconomic problems than adults born at term. Risks increase with decreasing gestational age. For example, adults born extremely preterm were 67% less likely to be in a relationship and 69% less likely to be parents than adults born at term[58]; they also had fewer educational qualifications, lower employment rates, and were more frequently in receipt of social benefits.[59] Furthermore, indicators of lower wealth and poorer social relationships were found at different ages and in both sexes, suggesting they are persistent and that difficulties found in childhood can contribute to social and economic inequalities in adulthood. Figure 2 shows approximate effect sizes[60] for the impact of very preterm birth on the social and wealth outcomes reported in these meta-analyses.[41]

Cross generational fertility loss can be another consequence: as well as adults born preterm being less likely to become parents, women delivering extremely preterm are less likely to have further children.[61] Little evidence exists on how best to tackle these problems, but it is important to encourage early social interaction and to provide educational support.

What are the consequences of extreme preterm birth for parents?

In women who deliver extremely preterm, and particularly in those who give birth by caesarean, risks include haemorrhage, infection, and admission to the intensive care unit.[2 64] A midline uterine incision or "classic" caesarean section, which has a higher chance of scar dehiscence in subsequent labours than lower segment caesarean section, is more frequently performed, and women are therefore advised against having future vaginal deliveries. Pregnancy related conditions that are associated with extreme preterm birth are also associated with increased risks of disease in the mother. Women with pre-eclampsia are twice as likely to be diagnosed with cardiovascular disease or stroke as women with uncomplicated pregnancies, and approximately half of women with gestational diabetes mellitus develop type 2 diabetes within 10 years.[65]

Extreme preterm birth is stressful for both parents. Debriefing from healthcare professionals with specialised knowledge and with access to results of placental histopathology and details of any vaginal infection is recommended, particularly to plan management of any future pregnancy. Following second trimester pregnancy loss (16 to 27 weeks' gestation), recurrent second trimester delivery is around 7%,[66] and the risk of any preterm birth around 25-35%.[67] Anxiety, depression, post-traumatic stress disorder, and poorer overall wellbeing are increased in mothers and fathers.[68]

Prevention

Societal measures to prevent preterm birth include legislation to make air free of cigarette smoke, a measure associated with reductions in preterm birth rates of 10.4% (95% CI 2.0 to 18.8).[73] Advice for women is shown in box 4 (bmj.com). Paternal health is also important: obesity is linked with preterm birth and other adverse pregnancy outcomes.[83]

Competing interests: None declared.

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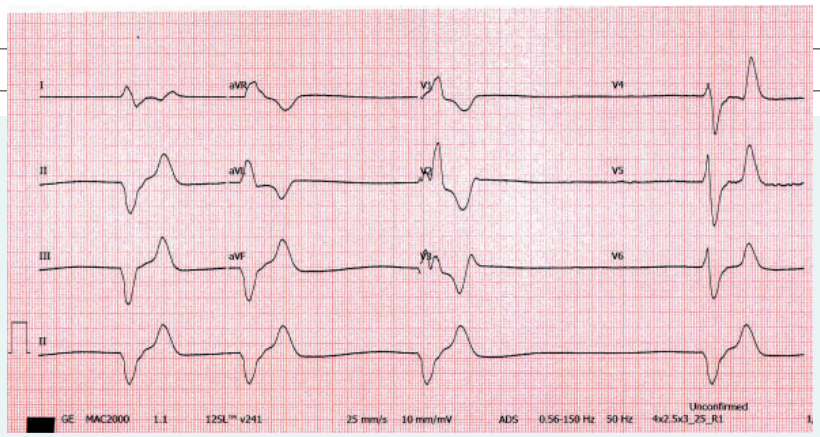
Find the full version with references at doi: 10.1136/bmj-2021-055924

CASE REVIEW

A tropical electrocardiogram wave

Laboratory test results on presentation to emergency department

Investigation	Result	Normal range
Blood analytes		
Sodium (mmol/L)	126	133-146
Potassium (mmol/L)	9.5	3.5-5
Urea (mmol/L)	32	2.5-7.8
Creatinine (µmol/L)	228	60-105
Haemoglobin ($\times 10^9$/L)	92	130-180
Mean corpuscular volume (fL)	86	80-102
White blood cells ($\times 10^9$/L)	5.38	4.0-11.0
Blood film	No fragments	–
Cortisol: am (nmol/L)	528	172-497
Creatine kinase (U/L)	154	24-195
Arterial blood gases		
pH	7.22	7.35-7.45
Partial pressures:		
Carbon dioxide (kPa)	3.9	4.3-6.4
Oxygen (kPa)	12.6	11.6-14.4
Bicarbonate (mmol/L)	12	22-28
Lactate (mmol/L)	1.0	0.5-1.7
Glucose (mmol/L)	7.0	3.0-7.7
Chloride (mmol/L)	111	96-106
Base excess (mmol/L)	−7.2	−2 to 2
Other		
Abdominal ultrasonography	Normal sized kidneys and no evidence of urinary tract obstruction	
Inflammatory markers, bone profile, liver and thyroid function	Within normal range	



Electrocardiogram on admission to emergency department showing severe bradycardia with a ventricular rate of 24 beats/min. Broad QRS complexes are fused with tall tented T waves in a "sine wave" configuration. Absent p waves and an irregular ventricular rhythm are also present

A man in his 70s on holiday from Ghana presented to the emergency department with a one week history of lethargy. On arrival he was bradycardic (heart rate 20 beats/min) and hypotensive (88/55 mm Hg).

He had a history of cardiac failure (left ventricular ejection fraction 35%), atrial fibrillation, chronic kidney disease stage G3aA3, hypertension, and stroke.

Over the past six months his daily dietary intake had comprised a large proportion of tropical fruits (including mangoes, bananas, and pineapples) and two litres of fresh orange juice. He was taking amlodipine 10 mg daily, allopurinol 100 mg daily, atorvastatin 20 mg daily, bumetanide 2 mg twice a day, carvedilol 6.25 mg twice a day, quinine sulphate 200 mg every night, ramipril 2.5 mg daily, spironolactone 25 mg daily, and warfarin.

The table shows the results of electrocardiography (figure), ultrasonography, and key laboratory tests on admission to the emergency department.

1 What are the most likely diagnoses?

2 What are the possible causes?

3 What investigations are needed?

Submitted by Simon Findlay, Katharine Nelson, and Ian Logan

Patient consent obtained.

Cite this as: *BMJ* 2022;376:e065769

answers

CASE REVIEW **A tropical electrocardiogram wave**

1 What are the most likely diagnoses?

- Severe hyperkalaemia—indicated by blood test results, and electrocardiographic findings of broad QRS complexes fused with tall tented T waves in a "sine wave" configuration and severe bradycardia
- Hyponatraemia
- BRASH syndrome (bradycardia, renal failure, AV blockade, shock, hyperkalaemia)

All these conditions can cause bradycardia.

Absent p waves and an irregular ventricular rhythm are consistent with atrial fibrillation.

2 What are the possible causes?

Tropical fruits and orange juice are rich in potassium and natural acids. The patient's diet, reduced renal function and use of ramipril, spironolactone, and bumetanide account for the hyperkalaemia and hyponatraemia.

Other causes of severe hyperkalaemia include renal failure; rhabdomyolysis; haemolysis; metabolic acidosis including ketoacidosis; hypoaldosteronism; pseudohypoaldosteronism; and pseudohyperkalaemia.

3 What investigations are needed?

Investigations to determine the cause include a full blood count; urea, creatinine, and electrolytes; arterial blood gas; and blood glucose and ketones. Other investigations may include creatine kinase, digoxin, cortisol, aldosterone, and hormonal precursor.

Consider renal ultrasonography if renal tract obstruction is suspected.

Repeat test for serum potassium immediately to confirm the hyperkalaemia and again at one hour to assess the efficacy of treatment.

When serum potassium levels indicate moderate to severe hyperkalaemia, perform 12 lead electrocardiography for conduction disturbance, and continuous cardiac monitoring.

PATIENT OUTCOME

See bmj.com.

LEARNING POINTS

- A comprehensive history, including drugs and dietary intake, helps determine the cause of hyperkalaemia.
- Grossly abnormal findings might be evident on electrocardiograms in severe hyperkalaemia and need urgent investigation and treatment.

CPD READING
0.5 HOURS

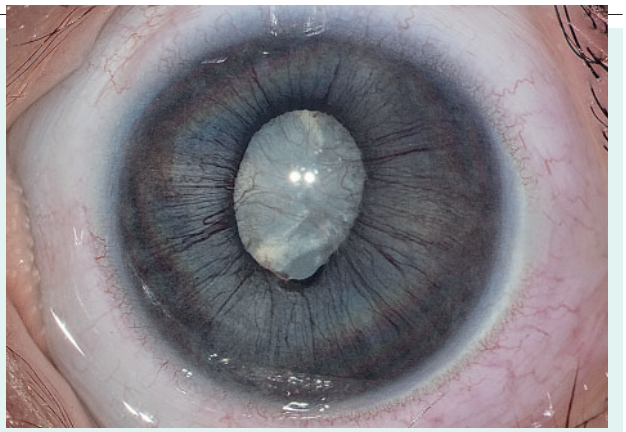
You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.

LEARNING MODULE

Articles with a "learning module" logo have a linked BMJ Learning module at http://learning.bmj.com.

MINERVA

Vascularised iris in an infant



This is leucocoria (white pupil) and tunica vasculosa lentis (fine vascular network) suggestive of persistent fetal vasculature (PFV) in the left eye of a 3 month old infant.

The infant had an uneventful birth and was brought to the clinic by her mother who noticed a white left pupil. On examination, the left eye was smaller than right (axial length 17.29 mm *v* 19.56 mm), with poor fixation and absent red reflex. Tunica vasculosa lentis projected radially from the pupil and extended from the iris to the anterior surface of the lens, giving the appearance of a white pupil. Examination of the right eye was unremarkable. PFV in the left eye was diagnosed.

PFV is a congenital developmental disorder that occurs when vascular structures fail to regress during the development of the eye, and these can present as leucocoria. Visual prognosis is poor even after surgical intervention, but early treatment can rescue residual vision.

Referral to an ophthalmologist should not be delayed in infants presenting with leucocoria. Other differentials include congenital cataract and retinoblastoma, the most common intraocular tumour of childhood, which can be fatal.

Zhaotian Zhang; Xiaoyan Ding (dingxiaoyan@gzzoc.com), Zhongshan Ophthalmic Centre, Sun Yat-sen University, Guangzhou 510060, China

Parental consent obtained.

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If you would like to write a Minerva picture case, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx

Prediabetes and mortality risk

Prediabetes is a label applied to people with evidence of impaired glucose metabolism but whose glucose or HbA_{1c} levels aren't high enough to meet diagnostic criteria for diabetes. An umbrella review reckons that prediabetes is associated with a 6% to 25% increase in mortality from all causes, and a higher incidence of cardiovascular disease, chronic kidney disease, cancer, and dementia. Mind you, many of the individual meta-analyses covered by the review were judged at high risk of bias (*Diabetologia* doi:10.1007/s00125-021-05592-3).

Long term outcomes of diabetes prevention

On the same subject, a long running investigation reports that neither lifestyle changes nor metformin made much difference to outcomes over 21 years of follow-up. More than 3000 adults at high risk for type 2 diabetes were randomly assigned to an intensive lifestyle intervention, metformin, or placebo. When the trial ended, the lifestyle intervention was offered to all participants and metformin was continued in those originally allocated to it. Although metformin and lifestyle modification reduced the occurrence of diabetes, they failed to reduce mortality from all causes, cancer, or cardiovascular disease (*Diabetes Care* doi:10.2337/dc21-1046).

A trial found no benefit from 5 years of vitamin D supplementation

Pain after surgery

Persistent pain at the site of the incision following surgery is surprisingly common. Among 15 000 patients having non-cardiac surgery, around one in 30 reported incisional pain a year later. More than half found the pain severe enough to require analgesia. Risk factors for persistent pain included surgery for fracture, a history of chronic pain, and female sex (*Anesthesiology* doi:10.1097/ALN.0000000000003951).

Treatment of hypertrophic cardiomyopathy

β blockers are widely used for symptomatic patients with obstructive hypertrophic cardiomyopathy but, until now, no supporting evidence from randomised controlled trials has been available. A small crossover trial confirms their value. Compared with placebo, metoprolol reduced left ventricular outflow tract obstruction, provided symptom relief, and led to improved quality of life (*J Am Coll Cardiol* doi:10.1016/j.jacc.2021.07.065).

Covid-19 and outcomes of pregnancy

A retrospective study carried out during the first wave of the pandemic in France reports that women who had been hospitalised with a diagnosis of covid-19 during pregnancy experienced poorer obstetric outcomes and higher maternal morbidity. Adverse outcomes included preterm birth, pre-eclampsia, peripartum haemorrhage, and caesarean section. However, women with a diagnosis of covid-19 were older and more likely to be obese (*PLOS Med* doi:10.1371/journal.pmed.1003857).

Covid-19 in elite sportsmen

Professional footballers are young and fit and one would expect them to make a rapid recovery after infection with SARS-CoV-2. Nonetheless, an analysis of the on-pitch performance of 257 positive cases among players in the German Bundesliga and the Italian Serie A finds lingering effects of the virus. The time played and the number of completed passes declined relative to uninfected players and did not return to normal for months (www.economist.com/graphic-detail/2022/01/08/for-elite-footballers-the-effects-of-covid-19-linger-for-months).

Vitamin D supplementation

Observational studies have suggested links between low levels of vitamin D and an increased risk of several chronic diseases. However, a large randomised controlled trial from Finland finds no benefit from five years of vitamin supplementation. The incidence of cardiovascular events and invasive cancer was no lower among people taking daily vitamin D3 supplements than in those allocated to placebo (*Am J Clin Nutr* doi:10.1093/ajcn/nqab419).

Cite this as: *BMJ* 2022;376:o77