GUIDELINES

Fertility (update): summary of NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Further information about the guidance, a list of members of the guideline development group, and the supporting evidence statements are in the full version on bmj.com.

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- Recognition and management of psychosis and schizophrenia in children and young people: summary of NICE guidance (*BMJ* 2013;346:f150)
- Ectopic pregnancy and miscarriage: summary of NICE guidance (*BMJ* 2012;345:e8136)
- Assessment and management of psoriasis: summary of NICE guidance (*BMJ* 2012;345:e6712)
- Diagnosis of active and latent tuberculosis: summary of NICE guidance (*BMJ* 2012;345:e6828)
- Prevention and management of neutropenic sepsis in patients with cancer: summary of NICE guidance (*BMJ* 2012;345:e5368)

Infertility affects about one in seven couples in the United Kingdom[1] and can have a severe psychological impact.[2] Since publication in 2004 of the original fertility guideline by the then National Institute for Clinical Excellence (NICE),[3] more people are now having fertility treatment, which is increasingly successful.[4 5] It is mandatory that this care is appropriate. This article summarises the recommendations relevant to general clinicians from the recent update of NICE's fertility guideline.[6]

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

Information on conception

- Inform people who are concerned about their fertility that:
  - Over 80% of couples in the general population will conceive within one year if the woman is aged under 40 years and they have regular sexual intercourse without contraception
  - Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate over 90%)
  - Vaginal sexual intercourse every two to three days optimises the chance of pregnancy.
- For people who are unable to, or would find it very difficult to, have vaginal intercourse, offer an initial consultation to discuss other options for attempting conception (such as in vitro fertilisation (see definitions box)). (New recommendation.)
- Female fertility declines with age. Use a woman's age as an initial predictor of her overall chance of success through natural conception or with in vitro fertilisation. (New recommendation.)
- Take a lifestyle and sexual history to identify people who are less likely to conceive:
  - Inform men that the following factors may reduce the likelihood of conception: excessive alcohol intake, smoking, raised scrotal temperature. (However, whether wearing loose fitting underwear improves fertility is uncertain)
  - Inform women that the following factors may reduce the likelihood of conception: smoking and passive smoking, body mass index of ≥30 in women who are not ovulating, and body mass index of <19 in women who have irregular menstruation or who are not menstruating.
- Couples who have problems in conceiving should be seen as a couple because both partners are affected by decisions about investigation and treatment.
- Inform both partners that stress in the male and/or female partner can affect the couple's relationship and is likely to reduce libido and frequency of intercourse, in turn contributing to fertility problems.
- Inform people who experience fertility problems
  - That they may find it helpful to contact a fertility support group, and
  - Offer counselling as fertility problems can cause psychological stress.

Defining infertility and referral for specialist assessment and/or treatment

- Define infertility as the period of time people have been trying to conceive without success after which formal investigation is justified and possible treatment implemented. (New recommendation.)
- If a woman has not conceived after a year, offer further clinical assessment and investigation, along with her partner. (New recommendation.)
- If a woman who is using artificial insemination (see definitions box) has not conceived after six cycles of treatment, offer further clinical assessment and investigation. When artificial insemination is using partner sperm, the referral should include her partner. (New recommendation.)
- Offer an earlier referral for specialist consultation when (new recommendation):
  - The woman is aged ≥36 years
  - There is a known cause of infertility or a history of predisposing factors for infertility
  - Investigations show there is apparently no chance of pregnancy with expectant management (see definitions box) and IVF is the only effective treatment.

Assessment options

- Offer men semen analysis, comparing results with the World Health Organization values (see definitions box). If the result is abnormal, a repeat test should be offered and undertaken within three months. (Updated recommendation.)
- Offer women:
  - A blood test to measure serum progesterone in the mid-luteal phase of the cycle (day 21 of a 28 day cycle) to confirm ovulation.
  - A blood test to measure serum gonadotrophins (follicle stimulating hormone and luteinising hormone) if menstrual cycles are irregular
  - Hysterosalpingography or hysterosalpingo-contrast ultrasonography to women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy, or endometriosis). Offer laparoscopy and dye in women who are thought to have comorbidities.
- Do not routinely offer women other tests

Definitions box

Expectant management—When a health professional supportively offers an individual or couple information and advice about the regularity and timing of intercourse and any lifestyle changes that might improve their chances of conceiving. It does not involve active clinical or therapeutic interventions

Artificial insemination—A medical alternative to sexual intercourse; the introduction of semen into a woman's vagina, cervix, or uterus. It includes intrauterine insemination

Intrauterine insemination—Artificial insemination involving delivery of sperm via the vagina into the uterine cavity

In vitro fertilisation (IVF)—A technique whereby eggs are collected from a woman and fertilised with a man's sperm outside the body. A single embryo is usually transferred (sometimes two) with the aim of starting a pregnancy

Full cycle—A full IVF treatment, which should include one episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s)

Intracytoplasmic sperm injection—An IVF procedure in which a single sperm is injected directly into an egg

Ovulation induction—Stimulation of ovulation by medication to reverse anovulation or oligoovulation, usually by ovarian stimulation but can also mean triggering oocyte release from mature ovarian follicles

Ovarian stimulation—Stimulation of the development of ovarian follicles to produce oocytes

Classification of ovulatory disorders

The World Health Organization classifies ovulation disorders into three groups:

- Group I: hypothalamic pituitary failure (hypothalamic amenorrhoea or hypogonadotrophic hypogonadism)
- Group II: hypothalamic-pituitary-ovarian dysfunction (predominately polycystic ovary syndrome)
- Group III: ovarian failure

Semen analysis

The WHO reference values for semen analysis:

- Semen volume: ≥1.5 mL
- Semen pH: ≥7.2
- Sperm concentration: ≥15 million spermatozoa per mL
- Total sperm number: ≥39 million spermatozoa per ejaculate
- Total motility (percentage of progressive motility (sperm that move forward) and non-progressive motility (sperm that move but do not progress forward)): ≥40% motile or ≥32% with progressive motility
- Vitality: ≥58% live spermatozoa
- Sperm morphology (percentage of normal forms): 4%

- Do not use basal body temperature charts to predict ovulation

Treatment options

- Inform couples that the effectiveness of complementary therapies for fertility problems has not been properly evaluated and that further research is needed.
- For women with unexplained infertility (new recommendation):
  - Do not routinely offer intrauterine insemination (see definitions box)
  - Do not offer oral ovarian stimulation agents (such as clomifene citrate, anastrozole, or letrozole)
  - Offer IVF treatment to women who have not conceived after two years of regular unprotected sexual intercourse (this can include up to one year before their fertility investigations).
- For people with mild endometriosis or "mild male factor infertility" who are having regular unprotected sexual intercourse (new recommendation):
  - Do not routinely offer intrauterine insemination (see definitions box)
  - Advise them to try to conceive for a total of two years (this can include up to one year before their fertility investigations) before IVF will be considered.
- For women with WHO Group I ovulation disorders (see definitions box), offer pulsatile administration of gonadotrophin releasing hormone or gonadotrophins with luteinising hormone activity to induce ovulation.
- For women with WHO Group II anovulatory infertility (including polycystic ovary syndrome), offer one of the following treatments (new recommendation):
  - Clomifene citrate (for ovulation induction and ovarian stimulation (see definitions box))
  - Metformin
  - A combination of the above.
- Inform women who are offered ovulation induction that (new recommendation):
  - No direct association has been found between these treatments and invasive cancer
  - No association has been found in the short to medium term between these treatments and adverse outcomes (including cancer) in children born from ovulation induction
  - Information about long term health outcomes in women and children is still awaited.
- Inform couples who are considering IVF treatment (new recommendation):
  - The chance of a live birth after IVF treatment falls with rising female age
  - IVF treatment is more effective in women who have previously been pregnant or had a live birth
  - Of the risks and benefits of IVF treatment and subsequent pregnancy in accordance with the current Human Fertilisation and Embryology Authority code of practice[7]
  - Although the absolute risks of long term adverse outcomes from IVF treatment, with or without intracytoplasmic sperm injection (see definitions box), are low, a small increased maternal risk of borderline ovarian tumours cannot be excluded
  - The absolute risks of long term adverse outcomes in children born as a result of IVF are low.
- When IVF is used (new recommendation):
  - Offer three full cycles to women aged under 40 years. If a woman reaches the age of 40 during treatment, do not offer further full cycles
  - Offer one full cycle to women aged 40–42 years, provided these three criteria are fulfilled:
    - They have never previously had IVF treatment
    - There is no evidence of low ovarian reserve
    - There has been a discussion of the additional implications of IVF and pregnancy at this age.
- When IVF is used and a top quality blastocyst is available, use single embryo transfer. (New recommendation.)

Overcoming barriers

To maximise the chance of pregnancy while minimising medical intervention, the guideline recommends against routinely using intrauterine insemination for people with unexplained infertility, mild endometriosis, or mild male factor infertility. This will change practice in the UK.

NHS funding for IVF in the UK varies widely. The updated guideline aims to remedy this by clarifying when IVF should be offered, to whom, and what appropriate management comprises.

Currently double embryo transfer in IVF is the most commonly used strategy in the UK. However, to maximise the chance of pregnancy while minimising the risk of a multiple pregnancy, the guideline recommends using a single fresh embryo and subsequently any frozen and thawed embryos.

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EASILY MISSED?

Chronic exertional compartment syndrome

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realize or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic for this series, please email us at easilymissed@bmj.com.

A 31 year old woman with no medical history of note presented with bilateral lower leg pain on running. The pain was absent when she started running; gradually built after the first kilometer, forcing her to stop; then resolved shortly after stopping. She tried not running for several weeks, but the pain returned when she started again. Physical examination at rest was normal, with no swelling or focal tenderness. The differential diagnosis included muscle strain, medial tibial stress syndrome, stress fracture, chronic exertional compartment syndrome (CECS), and popliteal artery entrapment syndrome. Dynamic intracompartmental pressure measurements confirmed the diagnosis of CECS.

What is CECS?

CECS is an ischaemic condition that occurs when a fascial compartment is unable to accommodate the increase in volume associated with muscle contraction and swelling. The increased volume increases intracompartmental pressure and reduces perfusion of the tissues within the fascial compartment. The condition is most common in the lower leg but has also been described in the thigh, forearm (gymnasts and climbers), and foot (runners and during aerobic training). Symptoms depend on the fascial compartment affected and the nerve or structures contained within (figure).

KEY POINTS

Patients typically have no pain at rest but develop pain after a set duration and intensity of activity; symptoms subside with a short period of rest

Tenderness is usually elicited in the middle of the muscle compartment, not on the bone; pain near the bone should alert the clinician to alternative or associated diagnoses, such as tibial stress fractures or medial tibial stress syndrome

If chronic exertional compartment syndrome (CECS) is suspected, obtain intracompartmental pressure measurements at rest and after exertion

For patients with confirmed CECS and no associated problems, conservative treatment rarely allows the athlete to return to competition. If this fails or is unsuitable, subcutaneous fasciotomy should be performed.

HOW COMMON IS CECS?

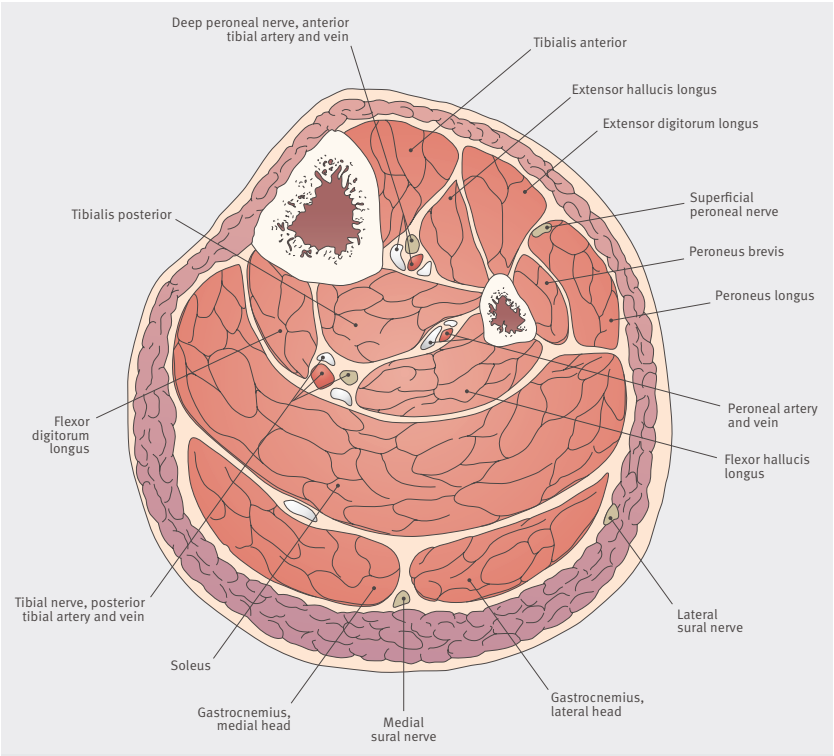
- Prevalence depends on the population studied
- Runners and endurance athletes have a higher risk than sedentary populations or those who engage in upper extremity dominant sports.[1] In a prospective study of exercise active people (not formally defined as athletes) who had exercise induced leg pain, 49% were diagnosed as having the syndrome.[2] In a case series of athletes with exercise induced leg pain, the incidence of pressure confirmed CECS was 27%[3]
- People with diabetes may be at increased risk, even with minimal exertional activity[2]
- Prevalence is similar in men and women, and median age of onset is about 20 years[4]

Why is CECS missed?

The diagnosis is often missed because patients are asymptomatic at rest with minimal findings on physical examination. It may be confused with other conditions. For example, in a case series of 42 patients with diabetes who were thought to have claudication, but who had normal pedal pulses and ankle brachial indexes, 38 were found to have CECS.[5] Clinicians need to be aware of the potential diagnosis and be willing to challenge patients with exertional tests to reproduce the symptoms. In addition, CECS may co-occur with other diseases, including stress fractures or medial tibial stress syndrome (tenderness over the posterior medial border of the tibia related to traction from muscular attachments or diffuse overuse of periosteum and medial border of tibia), which can make diagnosis more difficult.[6] The diagnosis may also be missed owing to overuse of the non-specific label of "shin splints." Clinicians need to make a specific and anatomic diagnosis that leads to targeted treatment.

Why does this matter?

When the diagnosis is missed, patients may undergo myriad failed treatments that target symptoms but not



Cross sectional anatomy of the leg midway between the knee and ankle, including muscles and neurovascular structures in each of the four leg compartments

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- Myasthenia gravis (*BMJ* 2012;345:e8497)
- Klinefelter's syndrome (*BMJ* 2012;345:e7558)
- Perilunate dislocation (*BMJ* 2012;345:e7026)
- Hirschsprung's disease (*BMJ* 2012;345:e5521)
- Pre-eclampsia (*BMJ* 2012;345:e4437)

the cause of the problem. Athletes may give up their sport completely. Rarely, CECS converts to an acute compartment syndrome as athletes continue competing despite pain. In such cases, pressures build and do not resolve with rest. Acute compartment syndrome is a surgical emergency that can cause permanent impairment, muscle loss, paralysis, or limb loss if left untreated.

How is CECS diagnosed?

Clinical features

Despite a lack of data on the predictive value of specific symptoms, expert consensus is that history plays an important role in diagnosis. Patients are typically symptom free at rest. Exertion causes a dull achy pain and tightness. The pain begins in a typical manner after a set duration. It gradually increases in severity, forcing the patient to stop the activity. Pain and tightness subside within a few minutes of cessation. When symptomatic, the compartment may be palpably tense, like a drum. Some patients also have neurologic symptoms including numbness, tingling, or weakness corresponding to the nerve in the affected compartment. If the lower leg is affected, anterolateral pain is most common, with a palpable tight fascial over the anterior or lateral compartments. If present, paresthesias occur over the dorsal aspect of the foot. If the anterior compartment is affected, ankle dorsiflexion may be weak. If the lateral compartment is affected, ankle eversion may be weak. If the deep compartment is affected, toe flexion may be weak, with numbness on the planar aspect of the foot. In contrast, patients with stress fractures or medial tibial stress syndrome have localized pain over the bone and not the soft tissues. In addition, athletes with stress fractures and medial tibial stress syndrome have pain at rest and pain with first impact but no delay in onset.

Investigations

Pre-exertion and postexertion intracompartmental pressure testing, in which a large bore needle is inserted into the compartment, is the gold standard for confirming the diagnosis. Although it is unclear whether the examiner should assess all four compartments, both legs, or also assess 10 minutes after exertion, assessing the effect of exertion is essential.[6-8] Pressure can be measured using a needle manometer, a slit catheter, the microtip pressure method, a wick catheter, or microcapillary infusion. Some techniques can measure pressures during exercise, whereas others require repeated needle placement before and after exertion. The Stryker Intra-Compartmental Pressure Monitor (Stryker Corp) is a handheld battery powered system with good reproducibility between examiners.[9]

Use of the following criteria results in less than a 5% incidence of false positives: resting pressure ≥15 mm Hg plus a one minute post-exercise pressure ≥30 mm Hg or a five minute postexercise pressure ≥20 mm Hg.[10] Around 42% of orthopedic surgeons in the United Kingdom use a pressure of greater than 35 mm Hg after exercise (sensitivity of 77% and specificity of 83%).[11] Most surgeons insist on a positive pressure test before proceeding with surgery for CECS. Recent systematic reviews have questioned these thresholds and recommended a more rigorous standardized process.[8 12]

Alternative methods to confirm the diagnosis include near infrared spectroscopy and magnetic resonance imaging. Although not routinely available, near infrared spectroscopy non-invasively measures tissue oxygen saturation in the relevant anatomic compartment; tissue oxygen saturation less than 50% has a sensitivity of 78% and a specificity of 67%.[13] Magnetic resonance imaging measures changes in the T2 signal intensity at rest and after exertion. Unfortunately, this non-invasive approach has had poor diagnostic results compared with intracompartmental measurements and near infrared spectroscopy.[13]

How is CECS managed?

If associated diagnoses, such as stress fractures or medial tibial stress syndrome, are present, conservative treatment should be tried initially, although evidence for its effectiveness has not been validated in evidence based literature or comparative studies. This may include reducing or stopping the inciting activities—together with non-steroidal anti-inflammatory drugs, bracing, stretching, or orthotics as indicated—to target alignment anomalies, inflammation, or stress fracture that may push an asymptomatic exertional compartment syndrome to a symptomatic one. Once symptoms resolve, the athlete can gradually return to activity to assess whether symptoms recur.

In our experience, however, conservative treatment is ineffective in most patients with CECS confirmed by pressure measurements because they eventually require surgi-

cal intervention unless they give up sport entirely. Surgery usually entails subcutaneous fasciotomy via one or two small incisions. We find that this offers good to excellent results in 80-90% of patients, although the success rate decreases to 73% in cases of revision.[14] More guarded outcomes might be expected in patients with diabetes, inconsistent symptoms, associated diseases, or deep posterior compartments.[2 14-19] Fasciectomy or excision of a band of fascia is reserved for resistant or recurrent cases.

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ANSWERS TO ENDGAMES, p 38

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STATISTICAL QUESTION

Sample size: how many participants are needed in a trial?

Statements *a*, *b*, *c*, and *d* are true, whereas *e* is false.

CASE REPORT

Postpartum fever and shortness of breath

1 The most likely cause is shock owing to puerperal sepsis. Other causes of severe illness postpartum are severe pre-eclampsia, postpartum haemorrhage, acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, amniotic fluid embolism, massive pulmonary embolism, disseminated herpes simplex infection, viral or bacterial pneumonia, catastrophic antiphospholipid syndrome, phaeochromocytoma, severe thyrotoxicosis, adrenal insufficiency, and maternal pulmonary hypertension.
2 Left ventricular dysfunction might have been caused by sepsis related cardiomyopathy or peripartum cardiomyopathy (PPCM).
3 The risk of deterioration in left ventricular function and death in any subsequent pregnancy is high. The degree of risk depends on the degree of recovery of left ventricular function.
4 Management of peripartum cardiomyopathy requires a multidisciplinary team approach involving midwives and an obstetrician, cardiologist, anaesthetist, paediatrician, and intensive care doctor. Diuretics, digoxin, β blockers, hydralazine, and nitrates can all be used safely during pregnancy. Anticoagulation with low molecular weight heparin should be used if LVEF is less than 35%. Dopamine agonists may have a role in treatment and possibly prevention of peripartum cardiomyopathy.

PICTURE QUIZ

An 81 year old man with a blistering rash

1 The main differential diagnoses are bullous pemphigoid, linear IgA disease, and epidermolysis bullosa acquisita. This patient had bullous pemphigoid, the most common autoimmune subepidermal blistering disorder. It mainly affects older patients and presents with tense fluid filled blisters that can appear anywhere on the body, including the mucous membranes. It typically occurs over the limbs, groin, and abdomen.
2 Diagnosis of bullous pemphigoid is based on clinical presentation. It is confirmed by histology and direct and indirect immunofluorescence.
3 Bullous pemphigoid is mainly associated with conditions of ageing: Parkinson's disease, cerebrovascular disease, and some neurological disorders. Bullous pemphigoid often coexists with other autoimmune disorders, but studies have shown there is no significant association. Drugs such as diuretics and neuroleptics have been found to be more commonly used in patients with bullous pemphigoid.
4 Mild, moderate, or localised bullous pemphigoid may be treated with highly potent topical steroids. Tetracyclines used alone or in combination with nicotinamide can be useful in mild to moderate disease. Oral steroids are the mainstay of treatment for moderate to severe disease. Immunosuppressants should be considered in severe or unresponsive disease.