Osteoarthritis at the base of the thumb

R E Anakwe, S D Middleton

Patients with osteoarthritis of the thumb carpometacarpal joint, or base of the thumb, commonly present to primary care practitioners and orthopaedic surgeons because of pain and disability. The prevalence of this condition increases with age and is greatest in postmenopausal women. There is broad agreement regarding the prevalence of base of the thumb osteoarthritis. The largest longitudinal cohort study found a 15% prevalence in adults in Finland, 1 and a smaller British study of postmenopausal women found a prevalence of 33%.2 This is likely to increase as populations age and people stay active for longer. Presentation and diagnosis may be delayed because patients try to adapt by adjusting their hand position, using splints, and adopting preferential hand use to limit disability. For most patients the primary treatment is non-operative and can be delivered effectively by primary care doctors, physiotherapists, and occupational therapists. Patients with symptoms that persist despite conservative treatment require referral to a specialist and possibly surgery.3

Various studies have looked at osteoarthritis at the base of the thumb, including large epidemiological and patient cohort studies; biomechanical research; and smaller case series, observational reports, and randomised patient trials. We review these to provide an evidence based guide to the diagnosis and treatment of osteoarthritis at the base of the thumb.

What is it and who gets it?

Arthritis at the base of the thumb occurs as a result of degenerative changes in the trapeziometacarpal joint (fig 1). It may arise as a consequence of trauma or injury to the joint, or it may be associated with more generalised osteoarthritis. Patients often present with thumb weakness, radial sided hand or wrist pain, and grating or crepitus at the base of the thumb. They may learn to avoid or modify how they perform activities that produce high stresses across the basal thumb joints. Typically, pinch related activities are most uncomfortable for the patient.

The reported age adjusted incidence of osteoarthritis at the base of the thumb is 7% for men and 15% for women, and it is most common in older postmenopausal women.1 2 Several large observational studies have identified differences in epidemiology between men and women.1 2 Postmenopausal hormonal changes may result in laxity and instability of the ligaments at the base of the thumb. It not clear why this site is mostly affected, but it may be related to the large forces that are repeatedly transmitted across the joints at the base of the thumb, particularly during pinch and grasping activities. In addition, men and women show differences in the morphology of the trapeziometacarpal joint with respect to joint congruity, total contact surface area, and point contact stresses.1

How does it develop?

The trapeziometacarpal joint is saddle shaped, with little inherent bony stability, and this allows for the multplanar movement that is characteristic of the thumb. The forces transmitted across this joint are amplified and can be as great as 13 times those at the tip of the thumb, particularly during strong pinching.3 Stability for pinching and grasping is provided by the complex arrangement of ligaments around the trapeziometacarpal joint. The most important of these is the...
How to make a diagnosis

The diagnosis of trapeziometacarpal joint osteoarthritis is based on history, clinical assessment, and plain radiographs. Other possible causes of pain at the base of the thumb include acute injury to the scaphoid bone, scapholunate ligament, or thumb metacarpal; a neglected or unrecognised injury to the thumb or adjacent joints; tenosynovitis; tendinopathy; or instability at the carpometacarpal or metacarpophalangeal joints.

History

Points in the history that help to distinguish osteoarthritis at the base of the thumb from these differential diagnoses are pain at the base of the thumb exacerbated by pinching actions or strong grip. This may be insidious or intermittent.

The absence of trauma is also suggestive, although a minor injury to the thumb can sometimes cause a flare of symptoms or exacerbate longstanding symptoms. It is important to determine whether other joints are symptomatic and to include the possibility of an inflammatory polyarthritis.

Examination

The base of an arthritic thumb may develop a prominent rounded appearance known as “shouldering” (fig 2). This is a result of adjacent muscle wasting, subluxation of the joint, osteophyte formation, and the persistent pull of the abductor pollicis longus tendon on the base of the thumb metacarpal. Localised tenderness at the trapeziometacarpal joint is common. Swelling may also result from synovitis, and muscle atrophy may be caused by disuse. It may be possible to show instability at the trapeziometacarpal joint by using gentle pressure at the base of the metacarpal to move the metacarpal forwards and backwards on the trapezium. The axial grind test (box 1) reproduces pain by transiently increasing the loading forces at the trapeziometacarpal joint. If the manoeuvre elicits pain, this suggests injury or wear within the trapeziometacarpal joint. Look for hyperextension of the metacarpophalangeal joint, which, if present, may represent subtle joint instability or a compensatory adaptation to try to improve function when the trapeziometacarpal joint is stiff and arthritic.

An assessment of the scaphotrapeziotrapezoid joint is important because when symptoms originate from this joint rather than the trapeziometacarpal joint, standard treatments aimed solely at the trapeziometacarpal joint are unlikely to provide full relief. Osteoarthritis of the scaphotrapeziotrapezoid and the trapeziometacarpal joints often coexists, and it can be difficult to distinguish symptoms arising from one or other of these joints, or even both. One comprehensive case series of 37 patients undergoing surgery for osteoarthritis at the base of the thumb established that plain radiographs have a low sensitivity for scaphotrapeziotrapezoid arthritis and may underestimate it. In the same study, skilled examination was poor at distinguishing between symptoms resulting from the trapeziometacarpal or the scaphotrapeziotrapezoid joints.

Radiographic imaging

Typical features of osteoarthritis are usually visible on plain radiographs of the whole hand; these include narrowing of the trapeziometacarpal joint space, sclerosis, cystic change, joint subluxation, and osteophyte formation (fig 3). Radiographic evaluation of all the joints in the hand, including the scaphotrapeziotrapezoid joint, is important to identify arthritic changes as well as evidence of instability or subluxation at the interphalangeal or metacarpophalangeal joints. This may allow for detection of early features of conditions that affect multiple joints, such as rheumatoid arthritis. Radiographs can confirm coexisting trapeziometacarpal and scaphotrapeziotrapezoid joint pathology. Radiographs of the base of the thumb taken in hyperpronation can be used to image both of these joints.

If clinical assessment and imaging are not conclusive, injections of local anaesthetic and corticosteroid may be both diagnostic and therapeutic.
sclerosis, and osteophyte formation mainly in the trapeziometacarpal joint at the base of the thumb; namely, local loss of joint space, narrowing of the thumb joint space, with maintained joint cartilage and widened joint space.

Stage 1: Normal articular cartilage and widened joint space

Stage 2: Narrowing at the thumb carpometacarpal joint space, with maintained joint contours, minimal sclerosis, and joint debris (≤2 mm)

Stage 3: Marked narrowing of the thumb carpometacarpal joint arthritis, with sclerosis, cyst formation, osteophytes, and joint debris (>2 mm)

Stage 4: Severe thumb carpometacarpal joint space deterioration with concomitant scaphotrapezial joint degeneration

Is staging of the disease useful?
Radiographic imaging also allows arthritic disease to be staged. The best known and most widely used staging system for arthritis at the base of the thumb is the modified version of that devised by Eaton and Little (box 2). However, this tool has been criticised for its moderate interobserver reliability and, although it is still widely used to guide treatment, radiographic stage does not reliably correlate with symptom severity.

What are the approaches to treatment?
Non-operative and operative treatments are available and all are aimed at dealing with the patient’s specific symptoms and functional demands. Most patients are initially treated non-operatively, often in primary care. Operative treatments are generally used for more severe disease and for patients with high functional demands. Growing expertise with arthroscopic techniques has encouraged the use of operative interventions for early disease, although the benefits of these treatments are not yet well established.

Non-operative treatments
Non-operative strategies provide good functional results and high levels of patient satisfaction, although they may not be curative. One well designed prospective study reported on 33 patients with trapeziometacarpal osteoarthritis treated with hand therapy, splints, and analgesia while awaiting surgery. Symptoms were so much improved in 70% of these patients that they refused surgery after seven months of non-operative treatment. At seven years, only two of them had undergone surgery.10

When both the trapeziometacarpal and scaphotrapezial-trapezoid joints are affected, analgesia, activity modification, injection, and splinting may be used to treat both joints.

Activity modification and pain control
Simple modifications of activity by the patient can effectively reduce pain and disability in trapeziometacarpal joint osteoarthritis. Treatment is mainly based on educating patients to ensure that they rest the joint and modify how they perform specific tasks to minimise stresses across the base of the thumb. Relative rest is therefore achieved by reducing the functional demands placed on the thumb, using the other hand, minimising or avoiding specific tasks, or more formal splinting. These methods offer good symptom relief, although symptoms commonly recur when provocative activities are resumed. Tailor the period of rest or frequency with which it is needed to the patient, the level of symptoms, and the benefit achieved. Offer to escalate treatment if such functional limitations are unacceptable to the patient or they provide little symptomatic benefit.

Behavioural measures can be supplemented with the use of simple analgesics or non-steroidal anti-inflammatory drugs. Simple analgesics have a safer risk to benefit profile, but non-steroidal anti-inflammatory drugs will also treat concurrent inflammation. Neither treatment is known to be superior, and in view of the potential side effects of non-steroidal anti-inflammatory drugs, prescription should be on the basis of symptomatic relief, patient tolerance, and other patient health factors.

Specific exercises and physiotherapy are also advocated and good results have been reported, although it is unclear how these work.11,12 It seems intuitive that instability at the base of the thumb might be improved by strengthening the intrinsic thenar and extrinsic thumb musculature. Hand stretches, particularly directed at the first web space, can help to prevent thumb adduction contractures often seen in late disease. These measures are secondary treatments for trapeziometacarpal osteoarthritis and are unlikely to provide complete symptom relief or prevent disease progression; however, they are often used by experienced hand therapists to target specific problems and symptoms (box 3).

Splinting
Positional splinting in a thumb brace or wrist splint with thumb abduction can offload degenerate areas of the joint surface and provide effective pain relief. Splinting is widely used because it is non-invasive and relatively simple, but evidence to support it is limited. One multicentre randomised controlled trial that recruited 112 patients with basal thumb arthritis found that positional splinting resulted in reduced pain at one year.13 Although not curative, this offers a simple solution, particularly when the patient finds surgery or other treatments unpalatable. Short term splinting also provides a functional solution for intermittent use, especially when symptoms are provoked by specific activities.

A well applied splint limits movement and enforces rest. When used for extended periods, it may encourage the joint to stiffen or stabilise in the splinted functional position. The optimal splinted position should incorporate...
palmar abduction, flexion, and pronation of the thumb metacarpal.\textsuperscript{15} Splints can incorporate the wrist or isolate the base of thumb. When choosing the type of splint to use considerations include the degree of support needed at the trapeziometacarpal joint; whether the splint is to be worn for specific activities or for night-time support; and whether the metacarpophalangeal joint is symptomatic, unstable, or needs to be splinted also. The success of splinting depends on carefully assessing each of these factors so that the splint is acceptable to the patient and adherence is maximised. Custom made splints are directly moulded for each patient by hand therapists or orthotists using thermoplastic materials, but no evidence is available to show that these are superior to “off the shelf” commercial designs (fig 4). Splinting helps reduce pain and can reduce the need for surgery,\textsuperscript{10 11 14} but objective measures, such as grip or pinch strength, have not been shown to improve after splinting, although functional outcome scores may improve.\textsuperscript{14}

\section*{Intra-articular injection}

\textbf{Corticosteroid}

Injection of corticosteroid into the trapeziometacarpal joint space can be performed in the outpatient or primary care setting (box 4). A small but well structured randomised controlled trial of intra-articular corticosteroid injection versus placebo for base of thumb arthritis from 2004 found no benefit of corticosteroid over saline.\textsuperscript{15} However, a recent observational study of 83 patients found that two thirds of patients reported good, although usually temporary, pain relief for all grades of basal thumb osteoarthritis when radiologically guided injections were used.\textsuperscript{16} Another recent prospective cohort study of 41 patients treated for arthritis in 43 thumbs found that 31 patients (76%) reported short term benefit from joint injection, but just as many (76%) had recurrence of or persisting pain at longer term follow-up. Nevertheless, 24 patients (59%) were satisfied with the long term outcome and only 12 of 43 thumbs (28%) had been operated on at three years.\textsuperscript{17}

In practice, non-operative treatments are often combined. A prospective patient cohort study reported the results of a single steroid injection at the trapeziometacarpal joint combined with three weeks of thumb splinting.\textsuperscript{18} In this study, the combination of splinting and injection provided short term pain relief for 13 of 30 patients, 12 of whom still had symptomatic benefit at final review after around two years. Patients with no short term benefit did not subsequently improve. This study also suggested that less severe disease was more amenable to these non-operative measures, although this has not been corroborated in more recent work, which showed that patients with all grades of osteoarthritis can obtain some, albeit temporary, relief.\textsuperscript{16 17}

In vitro studies have raised concerns about the potential chondrotoxic effects of corticosteroid on articular cartilage, particularly when used with local anaesthetics.\textsuperscript{19} Clinicians currently have no good evidence to guide them on how many injections may be safely given over what time period. Repeated injections may jeopardise the viability of articular cartilage and increase the risk of septic arthritis, while providing less effective symptom relief over time. Repeated intra-articular steroid injections are therefore not recommended as a definitive treatment for trapeziometacarpal osteoarthritis, and repeated requests for injection or reducing efficacy may be an indication to escalate treatment. The available evidence suggests that the judicious use of corticosteroid injections can effectively treat pain and may defer or avoid the need for surgery in selected patients, particularly when combined with splinting. Where

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig4}
\caption{Splints commonly used to treat basal thumb arthritis. These may be long in design, including the wrist, or short, leaving the wrist free, depending on the level of support needed. (A) Commercial off the shelf long Velcro thumb splint; (B) custom-made moulded short thermoplastic splint}
\end{figure}

\begin{box}
<table>
<thead>
<tr>
<th>Referral to a therapist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early referral should be made to a therapist with an interest in hand disorders</td>
</tr>
<tr>
<td>Treatments include exercises, splinting, education, and adaptive devices for activities of daily living</td>
</tr>
<tr>
<td>An experienced therapist may escalate and adapt these treatments depending on patient symptoms and functional requirements</td>
</tr>
</tbody>
</table>

\begin{box}
<table>
<thead>
<tr>
<th>Prescribing exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercises aim to:</td>
</tr>
<tr>
<td>- Improve thenar muscle strength and therefore thumb stability</td>
</tr>
<tr>
<td>- Improve the range of movement of the joint and soft tissue pliability</td>
</tr>
<tr>
<td>- Prevent contracture, especially of the first (thumb) web space</td>
</tr>
<tr>
<td>Exercises should not produce protracted pain or discomfort (lasting longer than an hour or two)</td>
</tr>
<tr>
<td>A painful or inflamed joint should be treated with initial rest, splinting, or local injections (or a combination thereof)</td>
</tr>
<tr>
<td>Hand function is improved by preserving the breadth of the thumb web space, and simple stretches are taught to maintain this</td>
</tr>
</tbody>
</table>

\begin{box}
<table>
<thead>
<tr>
<th>Prescribing splints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Define the problem—pain, inflammation, instability?</td>
</tr>
<tr>
<td>Define the use of the splint; is it to improve function and allow work or recreation, to improve the sleeping position, or to reduce joint inflammation and pain during rest?</td>
</tr>
<tr>
<td>Define the patient’s needs and preferences—short or long splints (incorporating the wrist); custom made or commercial off the shelf designs?</td>
</tr>
<tr>
<td>Splints that are aimed at improving function are usually for long term use and those aimed at reducing local inflammation and symptoms designed for use over shorter periods (6-8 weeks)</td>
</tr>
<tr>
<td>Consider concurrent corticosteroid injection; evidence shows that the combination of injection and splinting provides good pain relief</td>
</tr>
</tbody>
</table>
\end{box}
Box 4 | Intra-articular injections
Before injecting the carpometacarpal joint we carefully identify the joint by palpation. An aseptic technique is used. Occasionally a palpable overhanging osteophyte or “shouldering” at the base of the metacarpal is seen and we find an antegrade approach from proximal to distal to be most reliable while abducting the thumb. In this way, the joint is easily identified from the dorsoradial aspect of the thumb metacarpal base. A small gauge needle (25F) is routinely used to introduce up to 2 mL of combined corticosteroid and local anaesthetic. Warn patients that symptoms may flare up during the next 24-48 hours.

Accurate localisation of the joint is difficult, injection can be performed under radiographic guidance.17

Hyaluronate
A few studies have reported the use of hyaluronate injection, which is more commonly used for knee and hip arthritis than for osteoarthritis at the base of the thumb.20-23 However, no good evidence is available to suggest that it is superior to intra-articular steroid injection or to support its routine use for this condition.

Operative treatments
An unacceptable impact on quality of life or failure to control symptoms using non-operative means should prompt referral to a surgeon. Patients are selected for surgery on the basis of an assessment of symptoms, functional demands, and the results of non-operative treatment. Surgery can be tailored towards symptoms, which may predominantly relate to pain, weakness, or instability. Although there is no rigid formula to define patient selection for surgery, it is important to clarify the main problem and the cause of dissatisfaction with non-operative treatments tried so far, and to establish the degree of arthritic disease present at the trapeziometacarpal joint. The goals of surgery are symptom control where non-operative treatment has failed, improved function or ability, and deferred disease progression. How these aims are best achieved will vary between patients, and a tailored approach from a range of options may be needed.

Abduction-extension osteotomy
Osteotomy of the first metacarpal involves a carefully planned and iatrogenic fracture. A small wedge of the bone is then removed so that the metacarpal can be realigned. This redistributes the forces at the trapeziometacarpal joint and aims to reduce the load on degenerate areas of the joint surface. This technique has been used in patients with early trapeziometacarpal osteoarthritis,24 but patients often present with degenerative changes within the joint that are too advanced for osteotomy to be helpful. A small retrospective study with long term follow-up suggested that in selected patients with early disease, osteotomy can provide symptom relief for as long as 13 years.25 Identifying patients with early stage disease whose symptoms are severe enough to need surgery remains a challenge and would perhaps improve the practical value of this procedure.

Trapeziectomy and modified or augmented trapeziectomy
Trapeziectomy is the most commonly performed surgical procedure for osteoarthritis of the trapeziometacarpal joint. The trapezium is excised at the base of the thumb to remove the arthritic joint. This operation relieves pain but has been associated with a loss of thumb strength and stability, which is thought to result from collapse and shortening of the thumb metacarpal into the space left by the excised trapezium and the joint.26

The trapeziectomy procedure has been repeatedly modified since it was first described to try to resolve these problems.27 Modifications include metacarpophalangeal joint stabilisation, haematoma arthroplasty or distraction pinning of the first metacarpal, tendon interposition, and palmar beak ligament reconstruction. Surgeons often use combinations of these procedures to augment simple trapeziectomy, with the aim of achieving reliable pain relief and a stable strong thumb.

The large number of variations of trapeziectomy suggests that the best treatment is still not clear. A recent review examined the evidence from several randomised trials, prospective series, and observational studies. It concluded that no commonly used surgical procedure was superior, although simple trapeziectomy resulted in fewer complications than other approaches.28 Subsidence of the thumb can occur after trapeziectomy, although it seems not to cause serious problems in most patients, perhaps because older patients are able to live with the limitations. For patients with higher functional requirements, an arthrodesis may provide more reliable thumb strength and stability, although it sacrifices joint movement.

Arthrodesis
The indications for arthrodesis as a treatment for trapeziometacarpal osteoarthritis include failure of non-operative treatments, isolated trapeziometacarpal joint arthritis, and high functional demand. Clinicians might consider arthrodesis for patients for whom strength, pain relief, and joint stability are a higher priority than joint preservation. It is often the preferred surgical option for younger manual workers with high functional demands for whom loss of movement at the trapeziometacarpal joint is offset by relief of pain and improved stability. It has also been used suc-
A PATIENT’S PERSPECTIVE
I had been experiencing aches around my thumb for several months before I mentioned it to my general practitioner. I only mentioned it because I had been struggling with my needlecraft, which I enjoy. The pain was bearable, but I was gradually having to give up the things I enjoy and some of the things I don’t enjoy, like peeling potatoes. The pain would come and go but recently it had been more constant and was throbbing. I went to see a surgeon who examined me and took some radiographs. He told me that I had arthritis and he offered me a steroid injection into the thumb joint. The relief was incredible and I was able to use my thumb normally again for a while. I hadn’t realised how much I had been protecting the thumb. After a few months the pain came back and I went back to see the surgeon. I tried a wrist support for a while but it got in the way, so eventually I had an operation to remove my trapezium. I have been pain free ever since.

Joint replacement surgery
Trapeziometacarpal joint replacement surgery has been available in some form for more than 50 years. Silicone prostheses are no longer used because they have been shown in long-term observational studies to fail owing to their susceptibility to mechanical wear. A study of long term outcomes for patients treated with the cemented metallic Caffinière prosthesis showed that 72% of 77 implants survived at 16 years, with a rate of aseptic loosening of 44%. Despite its relatively high rate of loosening, this prosthesis may still be considered because of its reliable pain relief, particularly for older patients with low demands.

Developments in joint arthroplasty and biomaterials have led to the use of synthetic interpositional materials, and these may be used more often in the future. These new implants may not be designed to load bear but instead to act as simple spacers. The longevity of interpositional implants has not yet been established, and dramatic failures have been reported, although some early results suggest excellent pain relief and functional outcomes were encouraging. No good evidence is currently available to support their use over trapeziectomy or arthrodesis.

Arthroscopic surgery
Innovation and expertise now allow for arthroscopic debridement or synovectomy within the trapeziometacarpal joint to provide pain relief, although this option is useful only for early arthritis disease. Partial and total trapeziectomy have also been performed arthroscopically, but as yet no evidence is available of the superiority of these techniques over open surgical ones for advanced trapeziometacarpal arthrosis. One small series of patients treated with arthroscopic hemi- trapeziectomy reported similar outcomes as reported for open trapeziectomy. Few long term results are available for this specialist area of surgery.

Treating the scaphotrapeziotrapezoid joint
Because it can be difficult to localise the scaphotrapeziotrapezoid joint for injection, this is usually done under radiographic guidance and this is difficult to do in the community. Where non-operative treatment has failed, scaphotrapeziotrapezoid arthrosis is best treated with local fusion. Complications are common, however, and this operation does not necessarily halt the development of progressive radiocarpal degenerative change. Failure to treat symptomatic scaphotrapeziotrapezoid joint, either with operative or non-operative measures, may reduce the efficacy of any surgery for trapeziometacarpal arthrosis.

Contributors
Both authors wrote, reviewed, and edited the manuscript. REA is guarantor.

Funding
No special funding received.

Competing interests
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review
Not commissioned; externally peer reviewed.

Patient consent obtained.


Accepted: 25 October 2011

ANSWERS TO ENDGAMES, p 1174

For long answers go to the Education channel on bmj.com

CASE REPORT
A woman with forgetfulness and falls

1. Given the patient’s fluctuating forgetfulness and alertness, the differential diagnosis must include causes of delirium and dementia. The most common causes of delirium in this age group are infection, metabolic and nutritional disturbances (including hypoxia and hypoglycaemia), cerebral haematomas caused by trauma, intoxication, endocrinopathies (including thyroid and parathyroid disorders), space occupying lesions, and side effects or interactions of drugs. The syndrome of dementia has four main types: Alzheimer’s disease, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. A corroborative history from a family member or carer is essential when making a diagnosis.

2. No simple blood test is available to screen for dementia. Blood tests are important in helping to rule out delirium but are also used in the investigation of dementia—such as reversible causes of dementia—and specialist memory clinics should undertake full neuropsychological profiling along with appropriate brain imaging.

3. After baseline investigations in primary care, we referred our patient to local specialist memory services for neuroimaging, neuropsychological assessment, and consideration of pharmacotherapy. A thorough assessment of current needs and future goals should be made with the patient and carers, and appropriate referral should be made to members of the multidisciplinary care team, with planned regular review.

PICTURE QUIZ
Abnormal chest radiograph in pregnancy

1. The risks to the developing fetus are very small. For most diagnostic medical procedures the associated risks of developing childhood cancer or other complications are very low.

2. The radiograph shows a right apical mass within a cavity. The differential diagnosis is aspergilloma, lung abscess, pneumonia, tuberculosis, and malignant tumour.

3. The clinical diagnosis is an acute infective exacerbation of asthma or other obstructive airways disease.

4. She should be treated with nebulised bronchodilators, oral antibiotics, and corticosteroids for the acute exacerbation of asthma. Consider antifungal treatment, such as oral itraconazole or intravenous amphotericin B, or surgery (or both) after delivery.

STATISTICAL QUESTION
The placebo effect

Answer c best quantifies the placebo effect.