TEST

Protein S blood test

A protein S blood test measures a natural anticoagulant that helps prevent excessive blood clotting.

WHAT IT MEASURES
Amount or activity of protein S, a natural anticoagulant

SAMPLE
Blood

FASTING NEEDED?
No

HOW LONG IT TAKES
Usually under 10 minutes

RESULTS IN
Several days to two weeks, laboratory-specific

USED FOR
Investigating inherited or acquired protein S deficiency

MAIN LIMITATION
Anticoagulants, pregnancy, and acute illness can mislead results

Overview

Protein S is a protein in your blood that helps control clotting. It works with another natural anticoagulant like warfarin or apixaban called activated protein C to prevent clotting from continuing longer than needed.

A protein S blood test can measure how much protein S is present or how well it works. There are three main measurements:

Only the free form is immediately available to help regulate clotting. Your laboratory may perform one measurement first and add others if the result is unusual.

Low protein S may be inherited because of a change in the PROS1 gene. It can also be acquired later because of pregnancy, illness, medicines, or another medical condition. One low result does not prove that you have an inherited deficiency.

- Protein S activity: how well the protein works
- Free protein S antigen: the amount available to help control clotting

- Total protein S antigen: both free protein S and protein attached to other proteins

Why the test is ordered

The test is usually part of an investigation into an unusual tendency to develop blood clots in veins, known as venous thrombosis . Examples include deep vein thrombosis, usually in a leg, and pulmonary embolism, which is a clot in the lungs.

It may be considered after a clot that occurred at a young age, happened more than once, developed in an unusual vein, or was accompanied by a strong family history. Testing may also be offered when a close biological relative has a confirmed protein S deficiency.

The result is most useful when it could change a decision about treatment, pregnancy planning, contraception, or testing relatives. Protein S testing is not usually used as a general screening test for everyone who has had a blood clot.

Who should have the test

You may be offered testing if your medical history or family history suggests that an inherited clotting tendency is possible. A specialist may help decide whether testing would provide useful information.

Testing everyone in a family is not automatically helpful. The value of testing depends on whether a relative has a confirmed deficiency, your own history, and whether the result would affect future choices.

The timing matters. Testing during a new clot, pregnancy, serious illness, or treatment with certain anticoagulants can produce a low or otherwise misleading result. British Society for Haematology guidance advises delaying testing for natural anticoagulant deficiencies until after the initial treatment period for an acute clot.

Children have age-related protein S levels, so results must be compared with an appropriate paediatric range.

How to prepare

You do not normally need to fast. You can usually eat and drink as normal before the blood draw.

Tell the clinician arranging the test about all medicines and supplements you take. This is

especially important for warfarin, direct oral anticoagulants such as apixaban or rivaroxaban, heparin, oestrogen-containing contraception, and hormone therapy.

Do not stop an anticoagulant yourself. Suddenly interrupting treatment could increase your risk of another clot. If testing off treatment is appropriate, the timing should be planned safely.

Also mention pregnancy, recent childbirth, a recent blood clot, infection, surgery, transfusion, liver or kidney disease, and any known vitamin K deficiency.

What happens during the test

A healthcare professional places a small needle into a vein, usually inside your elbow or on the back of your hand. Blood is collected into a tube containing a substance that prevents it from clotting before analysis.

The needle is removed, and pressure is applied to the area. The appointment usually takes less than 10 minutes, although the blood draw itself often takes only a few minutes.

The sample may be sent to a specialist coagulation laboratory. Results can therefore take several days or occasionally longer.

Understanding your results

Your report should show which type of protein S test was performed and the laboratory's reference range. There is no single universal range. Results and interpretation vary by laboratory, test method, age, sex, pregnancy status, medicines, and clinical context.

A low activity result can mean that protein S is not working normally. However, it can also be caused by anticoagulant treatment, pregnancy, acute illness, or interference with the test.

If activity is low, free and total protein S antigen tests may help clarify the pattern:

These patterns do not confirm an inherited condition by themselves. Repeat testing under more stable conditions is often needed. Testing relatives or examining the PROS1 gene is sometimes considered, but genetic testing is not required or useful in every case.

A high protein S result is generally not known to cause bleeding or to have the same clinical importance as a low result.

- Low activity with low total and free antigen can suggest reduced production
- Low activity with normal antigen can suggest protein that is present but works poorly

- Low activity and free antigen with normal total antigen can reflect reduced available protein

What affects the results

Protein S is particularly sensitive to circumstances present when the sample is taken. These can make a result look low without an inherited deficiency being present.

Important influences include:

Some activity tests are also affected by factor V Leiden, lupus anticoagulant, high factor VIII, or other clotting abnormalities. These may create a false low or false normal result, depending on the test method.

An underfilled collection tube, a clotted sample, or delayed sample processing can also make the result unreliable. Ordinary exercise is not considered a major direct influence, although testing during severe physical stress or acute illness may be less useful.

- Warfarin: lowers protein S because protein S requires vitamin K
- Direct oral anticoagulants and heparin: may interfere with some activity methods
- Pregnancy and the weeks after birth: naturally reduce free protein S
- Oestrogen medicines: including some contraceptives and hormone therapy
- A recent blood clot: can make testing during the acute period difficult to interpret
- Inflammation, severe infection, surgery, or major injury: may alter protein S
- Liver disease or vitamin K deficiency: can reduce protein production
- Disseminated intravascular coagulation: widespread activation of clotting can consume clotting proteins
- Nephrotic syndrome: kidney disease causing major urinary protein loss
- Recent transfusion: donated plasma may temporarily affect the measured level
- Age and sex: expected levels are not identical in every group

Accuracy and limitations

Protein S testing does not have one accuracy rate that applies to every person or laboratory. Different activity and antigen methods have different weaknesses.

Activity tests can identify protein that does not work properly, but they are more vulnerable to

interference from anticoagulants and other clotting factors. Antigen tests are often less affected by these factors, but they can miss a rare situation in which the amount of protein is normal and its function is abnormal.

False low results are a significant concern during pregnancy, acute thrombosis, illness, or warfarin treatment. A false low could suggest a deficiency that is not truly present. Some anticoagulants can instead make a functional result appear normal or high, potentially hiding a deficiency.

For these reasons, an unexpected result is usually checked again when temporary influences have passed. Free protein S antigen testing may be a better next test when an activity assay could be affected by anticoagulants or another clotting abnormality. Genetic testing may help in selected families, but it will not explain every abnormal protein S result.

Risks and complications

A blood draw may cause brief discomfort, a small bruise, or minor bleeding where the needle entered. Some people feel faint, but serious complications are uncommon.

What happens next

A result within the laboratory's range may make a clinically important protein S deficiency less likely, but it does not rule out every inherited or acquired clotting tendency.

A low result is usually reviewed alongside the timing of any clot, your medicines, pregnancy status, illnesses, and family history. The next step may be repeat testing, a different type of protein S measurement, or tests for other causes of abnormal clotting. This is usually routine follow-up rather than an emergency.

The blood test itself does not show whether you currently have a clot. Seek urgent same-day medical assessment for new swelling, warmth, or pain in one leg or arm. Call emergency services for sudden shortness of breath, chest pain, coughing up blood, collapse, or severe unexplained weakness.

Common questions

Can I drink coffee before a protein S blood test?

Yes. Fasting is not normally required, so plain coffee is generally acceptable unless you are

having another test that requires fasting at the same appointment.

Does the time of day matter?

Protein S testing is not usually scheduled for a specific time of day. Your medicines and current health are more important than the hour when the sample is collected.

Can I exercise beforehand?

Normal exercise is not known to have a major direct effect. Avoid testing during severe physical stress, major injury, or an acute illness if the test can safely wait.

Can I have the test while taking warfarin?

A sample can be collected, but warfarin lowers protein S and may make the result unsuitable for diagnosing deficiency. Do not stop warfarin unless the clinician managing your anticoagulation has made a safe plan.

Can I be tested during pregnancy?

Yes, but free protein S naturally falls during pregnancy, making a low result difficult to interpret. If the answer is not needed immediately, testing may be postponed and repeated after pregnancy.

Will one low result mean my family needs testing?

Not necessarily. Temporary causes and test interference should be considered first. Family testing is generally more informative after a persistent deficiency has been confirmed and the result could affect a relative's care.

Sources

- Arachchillage DRJ, Mackillop L, Chandratheva A, et al. "Thrombophilia testing: A British Society for Haematology guideline." British Journal of Haematology . 2022;198(3):443-458.
- Middeldorp S, Nieuwlaat R, Baumann Kreuziger L, et al. "American Society of Hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing." Blood Advances . 2023;7(22):7101-7138.
- ARUP Consult. "Hereditary Thrombophilia-Hypercoagulability." ARUP Laboratories.
- Mayo Clinic Laboratories. "Protein S Activity, Plasma" and "Protein S Antigen, Free, Plasma." Test Catalog.
- National Blood Clot Alliance. "Protein S Deficiency." Patient education resource.