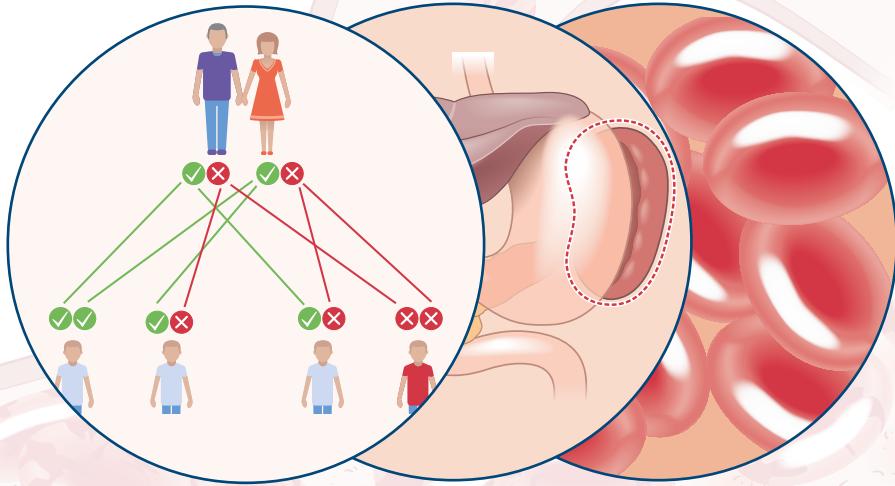




Pyruvate Kinase Deficiency

A rare genetic disease that affects red blood cells

Authored by hematologist
Dr Rachael Grace



Q. What does pyruvate kinase do?

A. Makes energy for red blood cells

First, the facts ...

- 1** Pyruvate kinase deficiency is a rare genetic disease that causes red blood cells to break apart easily (hemolysis).
 - 2** Some patients have no or few symptoms; others have severe **hemolytic anemia** (a low red blood cell count or low hemoglobin level) that needs treatment with regular red blood cell transfusions.
 - 3** **Hemolytic anemia** is associated with complications that need monitoring, including the development of gallstones, iron overload and low bone density.
 - 4** Common supportive treatments for pyruvate kinase deficiency include blood transfusions, removal of the spleen (splenectomy) and medications to remove excess iron from the blood (chelation therapy).
 - 5** Research into new treatments for pyruvate kinase deficiency is very promising.
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To get the best outcome, you must equip yourself with the best information possible and ask the right questions. The space throughout this booklet is for you and your doctors, nurses and family to use as you see fit to get the answers and support you need. Let this booklet help you get organized.

My main concerns

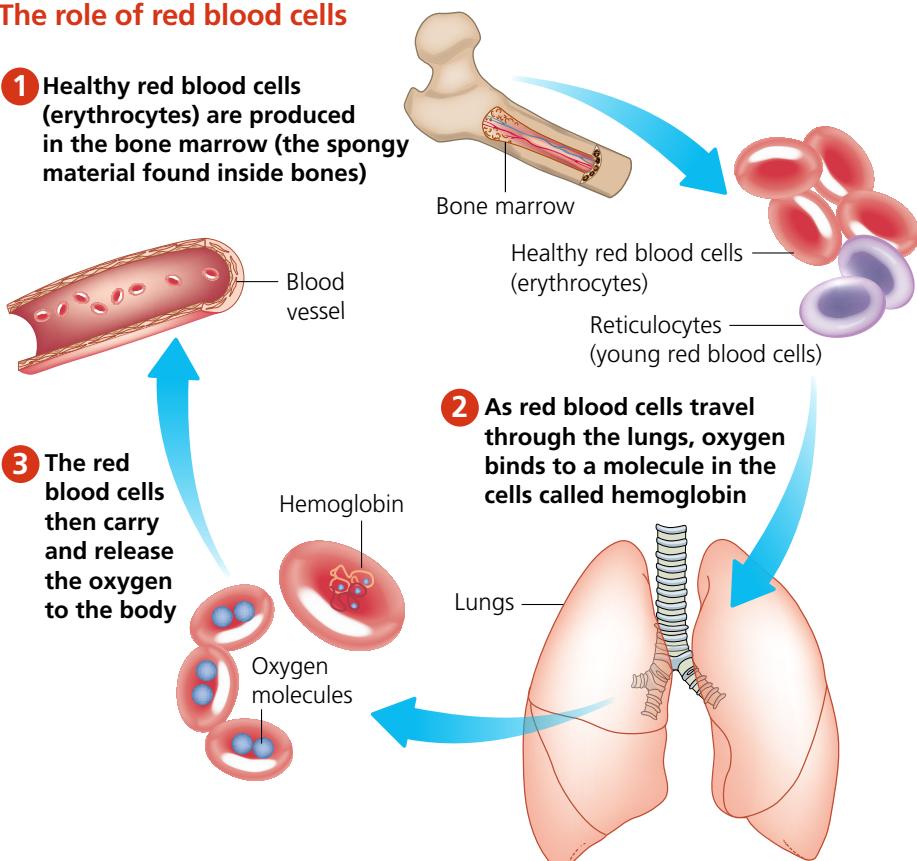
Make a note of anything you want to discuss with your doctor here ...

What is pyruvate kinase deficiency?

Pyruvate kinase (PK) deficiency is a rare genetic disease that affects red blood cells. Everyone who has PK deficiency is born with it, even if they are diagnosed later in life. To understand how PK deficiency affects you, you need an understanding of the role of healthy red blood cells and pyruvate kinase, and what happens to red blood cells in PK deficiency.

The role of red blood cells

- 1 Healthy red blood cells (erythrocytes) are produced in the bone marrow (the spongy material found inside bones)

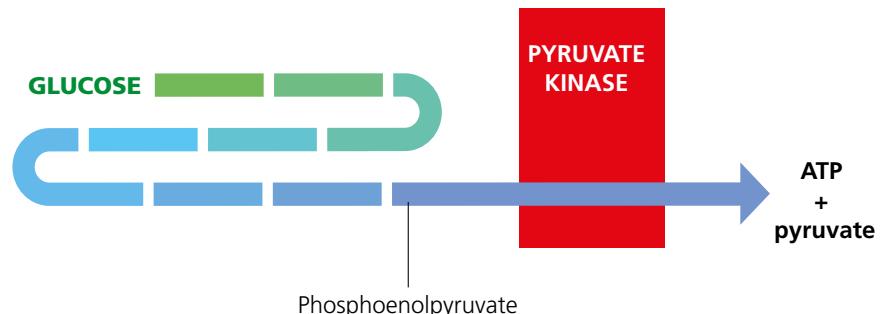


Red blood cells have a flexible shape called a biconcave disc, which looks like a flattened sphere. This flexible shape allows the cells to squeeze through narrow blood vessels (capillaries) as they deliver

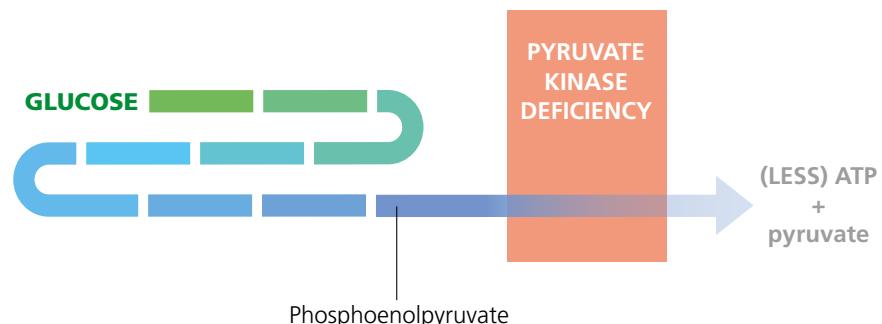
oxygen to the body. Healthy red blood cells can squeeze through the smallest capillaries.

The role of pyruvate kinase

Red blood cells make energy by converting glucose (a sugar) into pyruvate (an important molecule in metabolism) and a high-energy molecule called adenosine triphosphate (ATP) in a multistep process called glycolysis.



Pyruvate kinase is an enzyme that makes the last step in this process happen. It converts a protein called phosphoenolpyruvate into pyruvate and ATP. Less pyruvate kinase results in less ATP, so red blood cells have less energy.

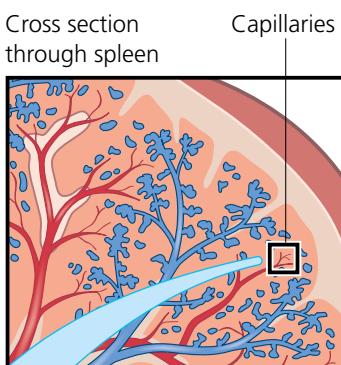
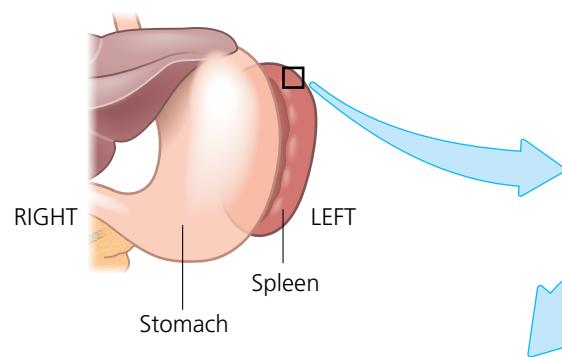


The energy generated by glycolysis helps healthy red blood cells to keep their normal shape, stay flexible and protect themselves from injury (oxidative damage). In people with a normal amount of pyruvate kinase, red blood cells can generate enough ATP to last an average of 120 days.

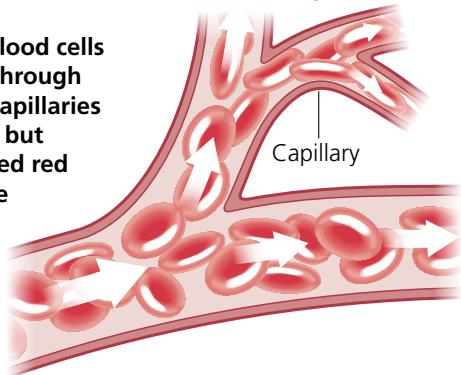
The breakdown of red blood cells

The breakdown of red blood cells is called hemolysis. Normally, after 120 days, red blood cells break down and are removed from the circulation by the spleen.

- 1 Blood is filtered through the spleen, an organ located on the left side of the abdomen



- 2 The blood is filtered through capillaries in the spleen



- 3 Healthy red blood cells can squeeze through the smallest capillaries in the spleen, but old or damaged red blood cells are removed

Red blood cells that do not have enough pyruvate kinase cannot make enough energy to hold their shape, and they break apart more easily than healthy red blood cells. Instead of lasting 120 days, PK-deficient red blood cells only last a few days to weeks.

The breakdown of red blood cells (hemolysis) causes hemolytic anemia (a low red blood cell count or low hemoglobin level) and jaundice (yellowing of the skin), which is caused by bilirubin, a substance released from red blood cells as they break down.

Replacement of red blood cells

In healthy individuals, the bone marrow makes enough young red blood cells (reticulocytes) to balance the old or damaged red blood cells that are removed from the circulation by the spleen. Reticulocytes usually make up 1–2% of all the circulating red blood cells. The bone marrow also makes more reticulocytes when PK-deficient red blood cells break down, but overall more red blood cells break apart than are made.

Reticulocytes require more energy in the form of ATP than older red blood cells but, unlike mature red blood cells, they can make energy through pathways other than glycolysis. Reticulocytes are therefore less reliant on normal levels of pyruvate kinase than mature red blood cells. However, these alternative pathways rely on the presence of oxygen. The capillaries in the spleen are low in oxygen, so when reticulocytes flow through the spleen the alternative energy pathways no longer function, and the reticulocytes become reliant on glycolysis for energy.

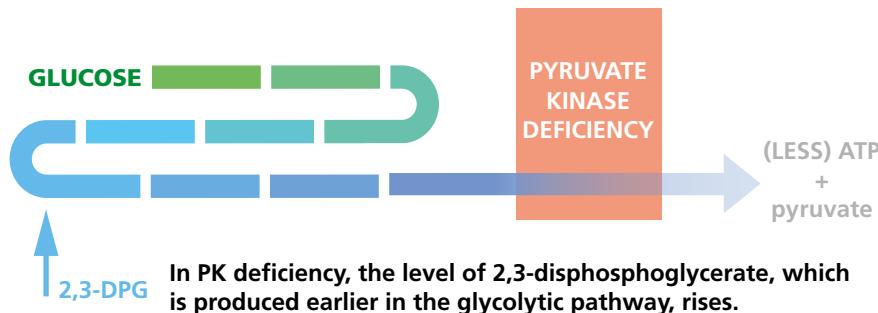
In this environment, PK-deficient reticulocytes cannot make enough ATP and become dehydrated. They are then quickly destroyed in the spleen and/or liver. If people with PK deficiency have their spleen removed surgically (splenectomy), the reticulocytes have enough oxygen to make energy through the alternative energy pathways and can last longer. This is why the reticulocyte count increases after splenectomy in patients with PK deficiency (see Splenectomy, pages 23–6).

My main concerns

Make a note here of anything you want to ask your doctor about PK deficiency ...

What else happens to glycolysis in PK deficiency?

Although the main problem in PK deficiency is the inadequate amount of ATP made at the end of glycolysis, without enough pyruvate kinase for glycolysis to work efficiently, products made earlier in the pathway build up.



2,3-DPG controls the release of oxygen from red blood cells to different parts of the body. As 2,3-DPG rises, more oxygen is released from hemoglobin into the tissues.

Normally, the amount of 2,3-DPG is tightly regulated so that the body receives the right amount of oxygen. In PK deficiency, the levels of 2,3-DPG rise and more oxygen is released from hemoglobin into the tissues. Because of this, people with PK deficiency may tolerate a lower hemoglobin level than people with other types of anemia in which 2,3-DPG is not elevated.

FAST TEST

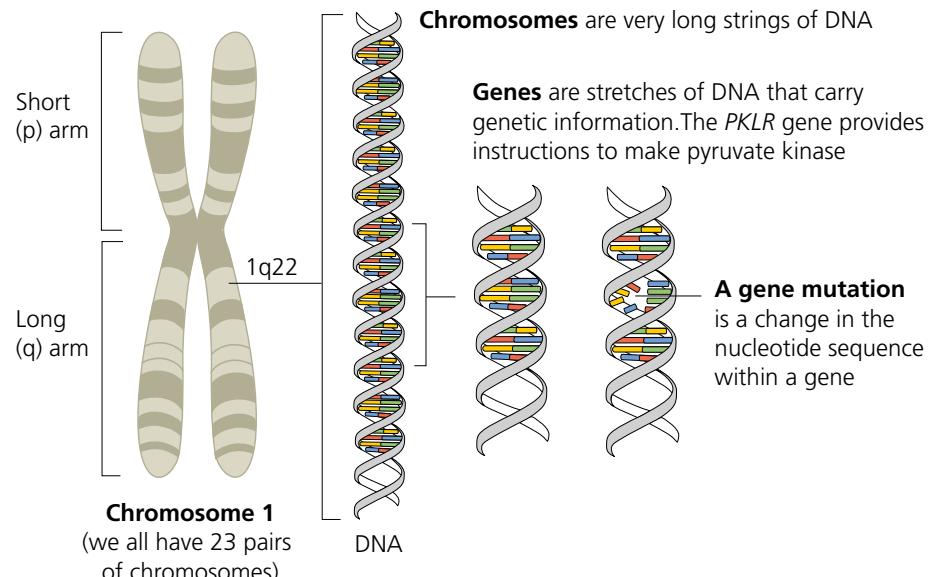
What does pyruvate kinase help red blood cells to do?

- a) Carry oxygen
- b) Make energy
- c) Break apart

Answer: b)

What causes PK deficiency?

The production of pyruvate kinase is controlled by a gene called *PKLR*, which is found on the long (q) arm of chromosome 1 at position 22 (1q22).



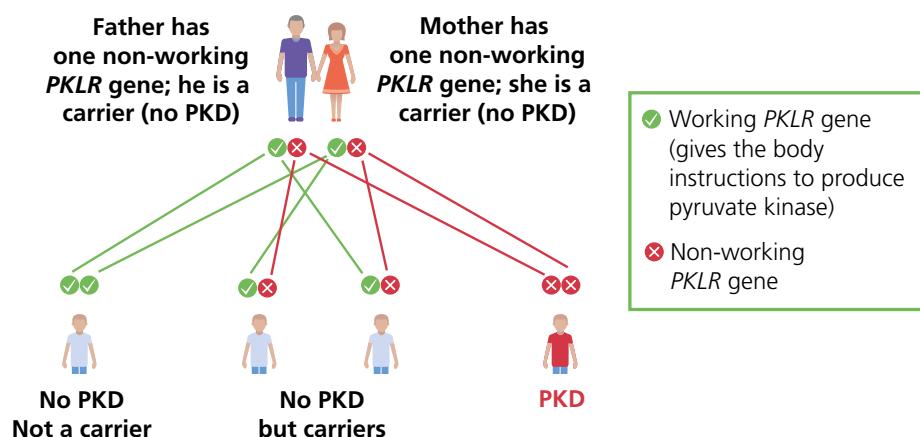
Ask your doctor

Have I had genetic testing? What did it show?

How is PK deficiency inherited?

Everyone inherits two copies of the *PKLR* gene, one from each of their parents. To inherit PK deficiency you have to receive two non-working copies of the *PKLR* gene. This is called an autosomal recessive genetic disease.

People who inherit only one non-working copy of the *PKLR* gene (from one parent) do not have symptoms of hemolysis or anemia but are known as carriers of PK deficiency.



The *PKLR* gene provides instructions to produce two types of pyruvate kinase, one found in red blood cells and one found in liver cells. The liver is able to compensate for non-working *PKLR* genes whereas the red blood cells are not.

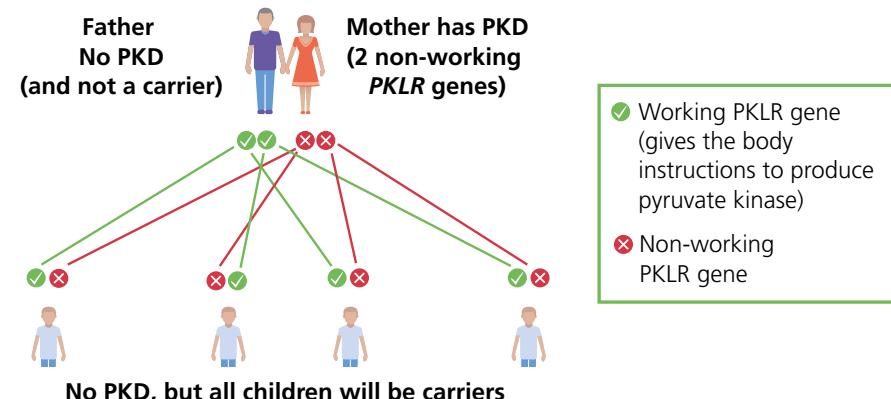
PKLR gene mutations

Over 300 different mutations of the *PKLR* gene have been identified. Most people inherit a different *PKLR* mutation from each of their parents.

Many *PKLR* gene mutations are very rare, occurring only once; approximately 25% of people diagnosed with PK deficiency have a newly described genetic mutation.

If I have PK deficiency, will my children have it too?

If your partner does not have or does not carry PK deficiency, your child will not have PK deficiency but will carry one non-working *PKLR* gene (inherited from you). So your child will be a carrier of the disease, but will not develop the disease.



PK deficiency is uncommon, so it is very unlikely that your partner will carry a non-working *PKLR* gene. However, if you have a child with someone who is from an area where PK deficiency is more common (for example, in the Amish community), then your partner could consider a genetic screening test to better understand the likelihood of having a child with PK deficiency.

FAST TEST

How many non-working copies of the *PKLR* gene do you have if you have PK deficiency?

- a) 1
- b) 2
- c) 3

Answer: b)

Who is most at risk of inheriting PK deficiency?

PK deficiency is equally common in men and women.

People with PK deficiency are from all over the world. Although most mutations are rare, some specific amino acid changes are found more commonly in particular populations such as the Amish community, the Romany population and in some Mediterranean countries. The frequency of PK deficiency is highest in the Amish community in Pennsylvania, USA, because of the founder effect. The founder effect is when a group of people has common ancestors and therefore less genetic variation. In the Amish community, PK deficiency can be traced to a single immigrant couple.

It is thought that carriers of PK deficiency may be more resistant to malaria infection and, therefore, carriers are more likely to be found in regions where malaria is common.

In studies looking at the most common *PKLR* mutations in white populations, PK deficiency has been estimated to affect 1 in 20 000 people. However, in clinical practice, PK deficiency appears to be even more rare than this estimate suggests. Doctors and researchers have been trying to understand why this is the case. It may be that PK deficiency is under-diagnosed (particularly in people with mild findings). In addition, many patients may be misdiagnosed with an alternative type of hemolytic anemia.

My questions

Is there anything you don't understand about the genetics of PK deficiency?
Write your questions here, so that you can ask your doctor ...

How is PK deficiency diagnosed?

PK deficiency is present from birth. However, some individuals are not diagnosed until late childhood or adulthood.

Signs and symptoms

As discussed, in PK deficiency red blood cells break apart more easily (hemolysis), causing hemolytic anemia. As a result, you may look pale, feel tired and/or lack energy for exercise.

You may also have yellowing of the whites of your eyes (scleral icterus), yellowing of your skin (facial jaundice) and/or dark urine.

Some people with PK deficiency have a lot of symptoms; others have none, with PK deficiency being diagnosed on routine laboratory tests.

Blood tests for hemolytic anemia

First, your doctor will take a blood sample to send for laboratory testing to see if you have hemolytic anemia.

Blood test findings of hemolytic anemia

- ⬇ Decreased hemoglobin or hematocrit (red blood cells)
- ⬆ Increased reticulocytes (young red blood cells)
- ⬆ Increased bilirubin from the breakdown of red blood cells

My test results

Make a note of your test results here ...

Tests for PK deficiency

Enzyme activity test

For the specific diagnosis of PK deficiency, you will need a further blood test to measure pyruvate kinase enzyme activity. Your doctor will take a blood sample to send to a specialized laboratory to ensure the accuracy of the test.

Most people with PK deficiency have 5–25% of the normal enzyme activity. Occasionally, even though you have PK deficiency, your test may show that you have a normal level of PK enzyme activity. If this is the case, your PK enzyme activity will be compared to that of other red blood cell enzymes (such as hexokinase or glucose-6-phosphate dehydrogenase), which will be higher in comparison.

Genetic testing

Analysis of the *PKLR* gene is also used to screen for, or confirm, PK deficiency. Genetic testing is useful:

- if you receive frequent blood transfusions, as the transfused blood will make the enzyme activity test difficult to interpret
- to confirm the diagnosis if you have low or low-normal pyruvate kinase enzyme activity and a high suspicion for PK deficiency
- to test your parents, to confirm you inherited one non-working *PKLR* gene from each parent
- before the birth of a child, if you already have a child with PK deficiency.

FAST TEST

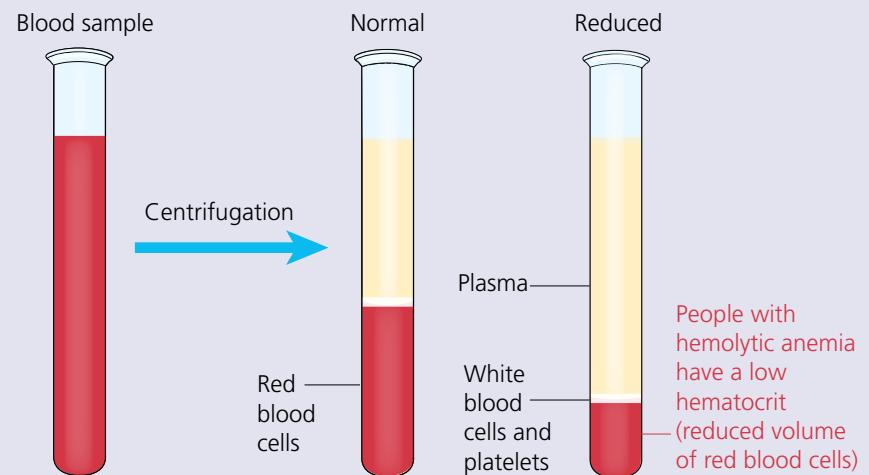
Which of the following blood test results are consistent with a diagnosis of hemolytic anemia?

- Increased levels of hemoglobin
- A low number of reticulocytes
- A reduced volume of red blood cells
- Increased levels of bilirubin

Notes: If you have hemolytic anemia you will have low hemoglobin levels and a high reticulocyte count
Answer: c and d)

TERMINOLOGY TIP

Hematocrit is the volume (as a percentage) of red blood cells in the blood

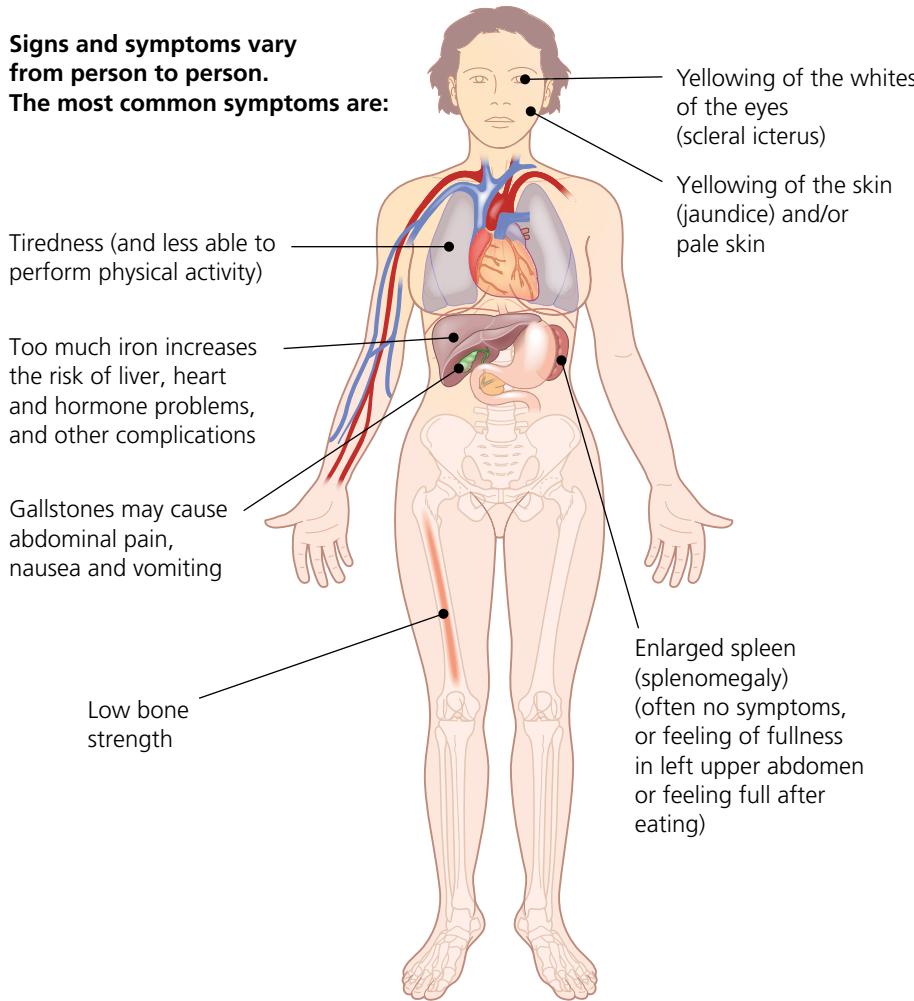


My questions

Make a note of any questions you have about your test results here ...

How will PK deficiency affect me or my child?

The symptoms and complications that you or your child experience may be very different from someone else with PK deficiency, as they vary widely between people. The hemolytic anemia caused by PK deficiency can vary from mild to severe, with a typical hemoglobin level of 6–12 g/dL. Normal hemoglobin levels in healthy individuals vary by age and sex, ranging from 10.5–16 g/dL.



My symptoms and complications

Less common signs and symptoms may occur, so make sure you discuss all your symptoms and complications with your doctor ...

Can you predict symptom severity?

Patients and doctors often wonder if there are any laboratory tests or findings early in childhood that might predict the likelihood of certain symptoms, or indicate whether transfusions or a splenectomy might be needed later in life. Researchers are currently looking at these relationships.

To date, studies have found no relationship between the level of pyruvate kinase enzyme activity and the degree of hemolysis. One reason for this is that the most enzyme-deficient red blood cells break down before pyruvate kinase enzyme activity can be measured (i.e. the results of your enzyme activity test come from your healthiest or most PK-sufficient red blood cells).

People with more disruptive *PKLR* gene mutations are more likely to have complications.

People with lower hemoglobin levels have a higher likelihood of complications. However, anyone with PK deficiency can develop the complications described on the following pages.

Jaundice/scleral icterus

You may develop yellowing of the whites of your eyes (scleral icterus) and/or yellowing of your skin (facial jaundice) as a result of your PK deficiency. These signs may be apparent all the time or just in times of illness, dehydration or stress.

Although removal of the spleen (splenectomy) improves anemia for most people with PK deficiency, it does not resolve the issue of jaundice/scleral icterus, as the hemolytic process continues after splenectomy.

Why do some people have more jaundice than others?

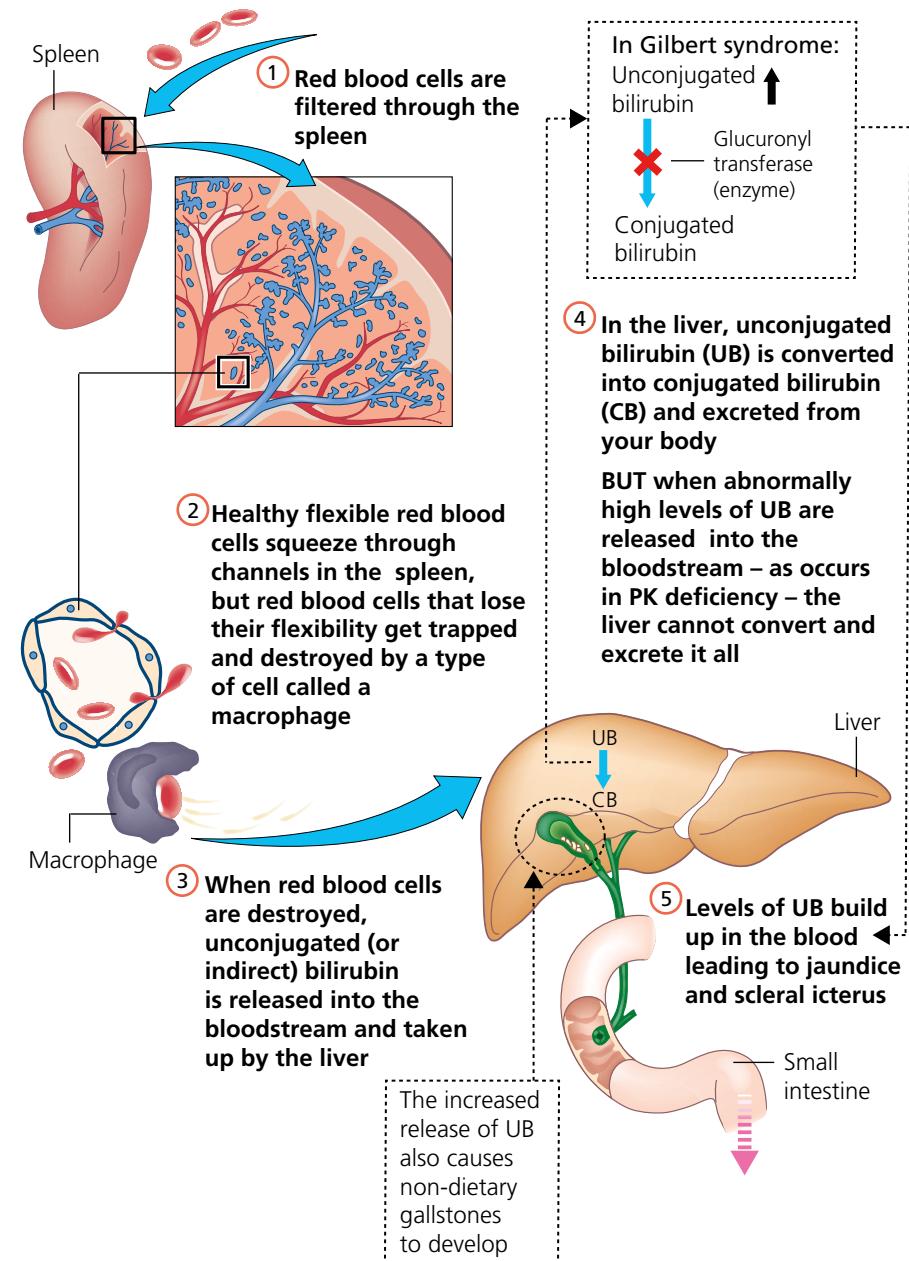
The degree of jaundice or scleral icterus is linked to your total unconjugated bilirubin level. This is determined both by the degree of hemolysis and by your ability to metabolize bilirubin, which is genetically determined.

People with Gilbert syndrome have an inherited abnormality (two copies of a non-working gene) that reduces the production of an enzyme involved in the processing of bilirubin in the liver (i.e. bilirubin is metabolized more slowly). Gilbert syndrome is common (affecting 5–15% of the population), so it is possible for someone to inherit both PK deficiency and Gilbert syndrome. People with Gilbert syndrome often have worsening of their everyday jaundice around the time of puberty.

Splenomegaly

Your spleen may become enlarged (splenomegaly) as a result of more red blood cells being broken down in the organ. The spleen can further increase in size during hemolytic episodes and/or if you have a viral infection. The spleen is typically enlarged in PK deficiency, but if you have a normal-sized spleen that does not exclude the diagnosis of PK deficiency or the likelihood of increased breakdown of red blood cells in the spleen. If you have severe anemia, removal of the spleen (see page 23) may be beneficial even if your spleen is a normal size.

Why do jaundice and scleral icterus develop?



An enlarged spleen does not typically cause pain. However, if your spleen is significantly enlarged, it may compress the stomach, making you feel full quickly when you eat. An enlarged spleen can also act as a sponge, causing transfused red blood cells and other blood cells (platelets and white blood cells) to get stuck, resulting in lower blood counts.

An enlarged spleen, when it can be felt below the rib cage, can be more at risk of injury, so your doctor is likely to recommend avoiding contact sports.

Hemolytic episodes

Hemolytic episodes or crises develop in response to stressors or triggers of hemolysis. These are most often infections and, therefore, are more frequent in childhood. Pregnancy can also be a common hemolytic trigger.

During these episodes, you may find your everyday symptoms, such as fatigue, paleness, scleral icterus, jaundice and/or dark urine, get worse. Your spleen may also increase in size. Blood tests will reveal:

- decreased hemoglobin/hematocrit
- increased reticulocyte count
- increased bilirubin
- increased lactate dehydrogenase (a marker of red blood cell breakdown in the blood vessels).

FAST TEST

Which of the following might trigger a hemolytic crisis?

- a) Pregnancy
- b) Infection
- c) Jaundice
- d) Blood transfusion

Answer: a) and b)

Aplastic crisis

An aplastic crisis is caused by parvovirus B19 infection (also known as Fifths disease). This common viral infection typically causes a high fever and facial rash.

In people with PK deficiency, parvovirus infection decreases hemoglobin and reduces or stops reticulocyte production in the bone marrow.

This infection can only occur once in your life and self-resolves like other viral infections. Testing for antibodies to parvovirus can diagnose a current or recent infection or a history of previous infection (i.e. immunity to the virus).

In PK deficiency, aplastic crises often require blood transfusions (see page 22).

Gallstones

Gallstones are a frequent complication in children and adolescents with PK deficiency due to the increased release of unconjugated bilirubin (see pages 16 and 17).

Unlike dietary-related gallstones in middle-aged adults, you can develop pigmented (bilirubin) gallstones at any age. The risk of gallstones is life-long due to ongoing hemolysis and will continue even if you have your spleen removed.

Some people with gallstones have no symptoms, or you may have nausea or abdominal pain after eating. Gallstones can also get stuck in the organs and ducts that create and store bile (the biliary system) and can cause significant worsening of baseline jaundice.

Gallstones can also be associated with other complications, such as infection of the gallbladder (cholangitis) or inflammation of the pancreas (pancreatitis). If you are diagnosed with these problems your doctor is likely to recommend surgical removal of your gallbladder (cholecystectomy) (see page 31).

Iron overload

Transfusion-related iron overload. Red blood cells contain iron, so every time you receive a blood transfusion you are putting more iron into your body. The body does not have a mechanism to remove the excess iron, so it can build up and damage your organs. The iron is most commonly deposited in the liver, but it can also be deposited in the heart and hormone-producing organs (endocrine organs).

Health problems associated with iron loading

- No symptoms (most common)
- Irregular heart beat/heart failure
- Fatigue
- Bone and joint problems
- Abdominal pain
- Liver problems
- Loss of sex drive
- Endocrine/hormone problems

Iron loading is not associated with symptoms until a significant amount of iron is deposited, so if you receive regular transfusions it is important you are closely monitored for iron loading and remain on treatment (chelation) to remove iron (see page 29).

Non-transfusion-related iron overload. Even if you do not receive transfusions as part of your treatment, you may still be at risk for iron loading. Regular iron monitoring is important. Transfusion-independent iron loading is common in people with PK deficiency; it can occur at any age and in patients with any hemoglobin level.

Although transfusion-independent iron loading is not well studied in PK deficiency, it is thought that the body responds to the anemia by absorbing more iron, even though there is no iron deficiency. It is not clear why some people with PK deficiency absorb more iron than others. Care should be taken to avoid iron supplements (including multivitamins with iron) and excessive ingestion of foods high in iron (e.g. liver and red meat).

Extramedullary hematopoiesis

When your body has to make an excessive number of red blood cells every day, blood cell production (hematopoiesis) can begin to occur outside of the bone marrow in organs such as the liver or spleen, or in other locations, such as around the spine or in the chest. This finding is usually diagnosed by a radiology scan and/or a tissue biopsy.

Extramedullary hematopoiesis is not a frequent complication in PK deficiency but is also not uncommon.

Low bone density

Low bone density is another potential complication of PK deficiency. The reason for this is not clear but it may be associated with the increased rate of red blood cell production in the bone marrow. You may find it beneficial to pay close attention to your vitamin D and calcium intake.

Infrequent complications

Pulmonary hypertension (high blood pressure in the arteries in the lungs and the right side of the heart) is an infrequent complication of PK deficiency. It can be detected on routine screening tests, or may cause symptoms including shortness of breath and fatigue. Leg ulcers related to PK deficiency occur in some people, but the cause is not well understood; leg ulcers occur in other types of hemolytic anemia as well.

Other, less common, signs and symptoms may occur so be sure to ask your doctor about any symptoms or problems that you have.

Psychological problems

The effects of chronic anemia and/or the treatments associated with PK deficiency can affect your psychological wellbeing. If you are feeling sad, or having difficulty sleeping or other mood-related symptoms, please consult your doctor.

Treating PK deficiency

At present, there are no approved drugs that directly treat PK deficiency, but it is possible to manage your symptoms. The type of supportive treatment you are given will depend on how the disease affects you.

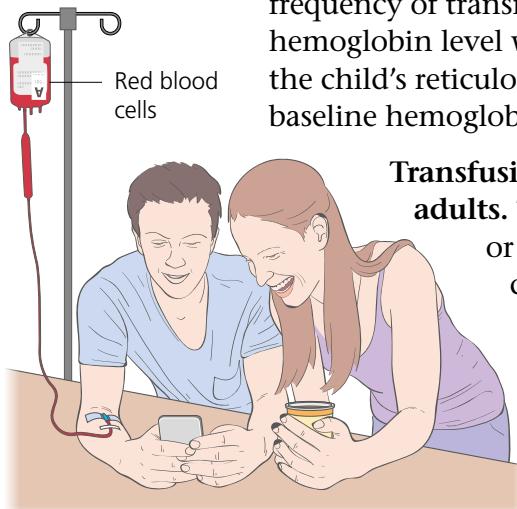
Managing the anemia

Transfusions

It is not your level of hemoglobin, but how well you tolerate the hemolytic anemia caused by PK deficiency that will determine whether you need to have blood transfusions. In PK deficiency, the increase in 2,3-DPG in red blood cells means that more oxygen is released to the body (see page 6). As a result, you may be able to tolerate moderate anemia with few symptoms.

Transfusions in newborns and young children. The goal is to avoid transfusions if possible, but during the first years of life, red blood cell transfusions may be required to manage severe anemia. The transfusions may be needed to support normal growth and development and/or to avoid symptoms of anemia, including fatigue and poor feeding. For some young children, decreasing the

frequency of transfusions to permit a lower hemoglobin level will allow the doctor to assess the child's reticulocyte response and the true baseline hemoglobin level.



Transfusions in older children and adults. There is no standard criteria or schedule when it comes to deciding whether to give an older child or adult a transfusion. The degree of anemia and the associated symptoms can vary between individuals.

You may never need a transfusion or may only have a transfusion in the setting of a hemolytic episode or aplastic crisis (see pages 18 and 19). Alternatively, you may require regular transfusion therapy and may consider opting for a splenectomy.

Splenectomy

If you receive frequent blood transfusions and/or have significant symptoms related to anemia, you may benefit from having surgery to remove your spleen.

Old or damaged red blood cells will continue to be removed in the liver, and so splenectomy is only partially effective in improving the hemolytic anemia.

Both open surgery and laparoscopic (minimally invasive or keyhole) surgery are performed under general anesthesia. The type of surgery may depend on the size of your spleen; your doctor will discuss this with you.

Most patients will spend at least a few nights in hospital after surgery

Laparoscopic surgery usually results in less pain, a faster recovery and a shorter hospital stay. Several small openings are made in the abdomen, and the surgeon will use a slender tool called a laparoscope, with a light and camera on the end, to look into the abdominal area. Other medical instruments will be passed through the other openings to disconnect the spleen from the body's blood supply before removing it. The surgical openings are closed using stitches or sutures.

Open surgery. A larger cut is made, often underneath the rib cage, to remove the spleen. The method used will depend on your overall health and the size of your spleen.

Partial splenectomy (only part of the spleen is removed) has not been reported to be beneficial in patients with PK deficiency.

Benefits and risks. Your hematologist can help you and your family weigh the potential benefits and risks to decide if splenectomy is the right option for you.

Risk of infection. The spleen is an important organ that helps your body to fight infections. Splenectomy raises the risk of infection from certain bacteria, such as pneumococcus, meningococcus and haemophilus. These infections can be very serious, even life threatening, and the risk will remain for your lifetime.

Although the absolute risk of serious infection after splenectomy is very low, it is much higher in people who have had a splenectomy than in the healthy population. For this reason, surgery in children should be delayed when possible until they are at least 5 years old.

In determining the timing of splenectomy, the risk of a serious infection must be balanced against the risks of red blood cell transfusions and iron loading. After splenectomy, other infections for which you will be at higher risk include malaria (from mosquitos) and babesiosis (from ticks) in endemic areas.

How can I protect myself from getting an infection? After a splenectomy, you are likely to be given antibiotics to protect against the possibility of a serious infection. Some doctors recommend twice daily antibiotics for a period of time after splenectomy; others advise continuing antibiotics for life. You must seek urgent medical attention for all fevers, to be assessed and treated with broad-spectrum antibiotics (see box below).

It is very important that you have the recommended vaccines before splenectomy and then stay up to date with your immunizations (vaccines) after surgery. Ask your hematologist and/or general physician whether your vaccines are up to date.

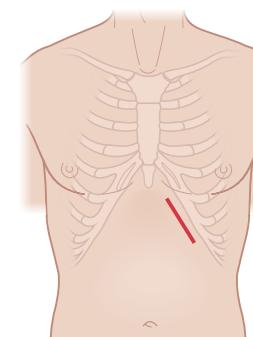
IMPORTANT

After splenectomy, you are at risk of serious infection.

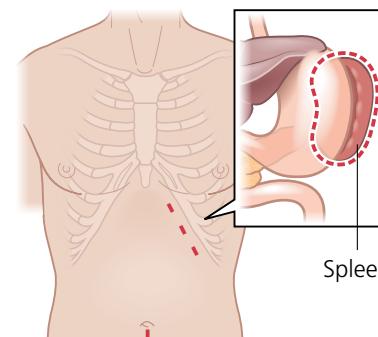
See a doctor immediately if you develop a fever over 38.5°C (101.5°F).

You must seek medical attention even if you have other infectious symptoms, such as a cough or congestion, or you have multiple family members with similar symptoms. A sample of your blood will be sent for laboratory tests (blood culture and complete blood counts) and you will be given intravenous or intramuscular broad-spectrum antibiotics.

If you are considering a splenectomy, you should have an ultrasound examination beforehand to see if you have gallstones – if so, your gallbladder can be removed at the same time as your spleen



Open splenectomy
incision site



Laparoscopic splenectomy
incision sites

Potential benefits and risks of splenectomy

Benefits

- Anemia or hemolysis improves*
- The need for transfusions ceases or decreases (in most patients)
- Hemoglobin levels rise by an average of 1.5–2 g/dL (in most patients)
- Reticulocytes survive and numbers increase (from 5–15% before splenectomy to 50–70% in some cases)
- No further risk of splenic injury or rupture (if spleen was enlarged)

Risks

- General risks associated with anesthesia and surgery (discuss these with your surgeon before the operation)
- Higher lifetime risk of serious, even life-threatening, infections
 - long-term antibiotic treatment required
 - long-term fever management protocol required
- Rarely, no significant effect on hemoglobin; transfusions still required
- 10% risk of blood clots

* **Splenectomy is almost always followed by an improvement in the anemia or hemolysis associated with PK deficiency, but hemolysis persists in nearly all cases, with a rise in in reticulocyte and bilirubin levels.**

Risk of blood clots. As a filtering organ, your spleen plays a role in protecting you from blood clots (thrombosis). Blood clots can form in the large veins of the arms or legs (deep vein thrombosis), the blood vessels around the liver (portal vein thrombosis) or other concerning locations. Clots in the arteries can also occasionally develop.

The risk of developing a blood clot after splenectomy for PK deficiency is approximately 10%. Some individuals take aspirin or other medications after splenectomy to decrease this risk. Consider speaking to your doctor about this.

My concerns and questions

Make a note here of anything you want to ask your doctor about transfusions or splenectomy ...

Stem cell transplantation

A bone marrow (stem cell) transplant can cure PK deficiency. This has been carried out successfully in studies in animals with PK deficiency, but the procedure is associated with significant risks, including the development of new chronic medical issues and the risk of dying from complications related to the transplant.

In total, 16 individuals with PK deficiency have undergone stem cell transplantation in Europe and Asia, with a range of conditioning (preparation) regimens and management strategies. These patients had a high rate of graft-versus-host disease (i.e. the donor cells attacked the host's own cells), a chronic complication that can cause issues related to the skin, gastrointestinal tract and other organs.

Most doctors think that the risk–benefit ratio is currently weighted in favor of splenectomy over stem cell transplantation. However, over time, the risks associated with transplantation may decrease and this may be an option for more patients.

Managing the complications of PK deficiency

Treating excess bilirubin in newborns

Most newborn babies with PK deficiency develop jaundice because of the breakdown of red blood cells and the inability of their immature livers to conjugate bilirubin (see page 17).

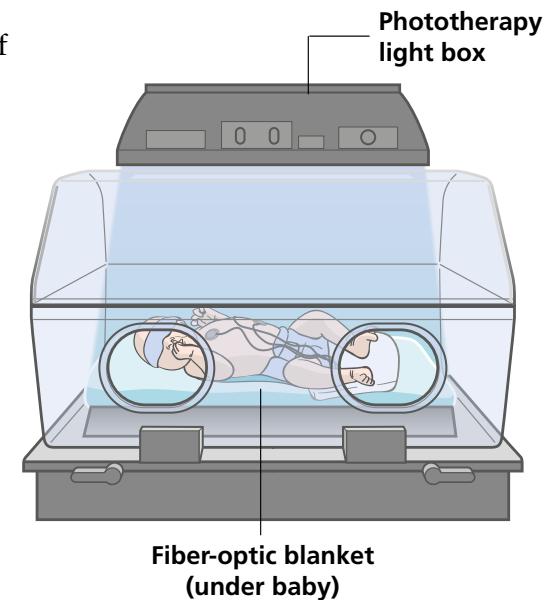
An increase in unconjugated bilirubin in a newborn can lead to significant neurological complications, including a problem called kernicterus (damage to the brain and central nervous system). Newborns with severe jaundice therefore need treatment to decrease the bilirubin levels.

Phototherapy (light therapy) exposes your baby's skin to as much light as possible. It lowers bilirubin levels through a process called photo-oxidation. Oxygen is added to the bilirubin, making it easier for the baby's liver to process the bilirubin.

There are two main types of phototherapy:

- conventional – the baby lies under a halogen or fluorescent lamp
- fiber-optic – the baby lies on a fiber-optic blanket so that light shines on the baby's back.

Continuous multiple phototherapy may also be offered, using more than one light and a fiber-optic blanket at the same time.



Bilirubin levels will be tested every 4–6 hours after phototherapy has started, then every 6–12 hours once the levels start to decrease.

The treatment will be stopped when the bilirubin reaches a safe level, usually within 48 hours. Intravenous fluids and/or increased feeding may also help with the clearance of the bilirubin.

Exchange transfusion. When phototherapy does not adequately decrease the bilirubin level, a procedure called exchange transfusion is recommended to avoid the risk of kernicterus.

Small amounts of your baby's blood are removed and replaced with blood from a donor (i.e. a blood transfusion) through an intravenous catheter that is placed in their umbilical cord, arms or legs. A protein called albumin may be transfused as well to help decrease the bilirubin level.

The process can take several hours, with regular checks on bilirubin levels to make sure they are falling. If bilirubin levels remain high, the procedure may need to be repeated.

In addition to reducing the bilirubin level, this procedure raises the hemoglobin level and treats anemia.

My concerns and questions

Make a note here of anything you want to ask your doctor about phototherapy or exchange transfusion ...

Treatment of iron overload

If you receive regular blood transfusions for your PK deficiency, you will need treatment to remove excess iron from your body (see page 20). If you have iron overload in the absence of transfusions, you may find you need iron removal treatment for a period of time and are then able to stop the treatment, maybe restarting it again years later based on iron monitoring results.

Depending on the degree of iron burden, drugs that remove iron from the body (chelation therapy) and/or therapeutic withdrawal of blood to remove iron from the body (phlebotomy) may be prescribed. Whether phlebotomy is an effective treatment for iron removal in PK deficiency and how it compares to iron chelation therapy have not been studied. Therefore, most patients with PK deficiency are treated with chelation for iron removal, rather than with phlebotomy.

Chelation therapy. Chelation agents bind with the iron to form substances that can be excreted from the body easily. The table overleaf provides a list of chelation medicines. Even if you receive infrequent transfusions or you've never received a transfusion, you may still need iron chelation treatment.

Phlebotomy (blood draws)

Phlebotomy is an alternative treatment to remove excess iron if you do not receive transfusions. A small volume of blood is removed periodically (for example, every 4 weeks) intravenously to remove the iron. The volume of blood removed will depend on your size and your baseline hemoglobin level, but may be 50–300 mL. A sample of blood will be taken before the procedure to measure your hemoglobin. Phlebotomy is safe if you have not had a transfusion and your hemoglobin is high enough to tolerate blood removal.

TERMINOLOGY TIP

Chelation comes from the Greek word 'chele', which means 'claw', in the sense of a pincer-like claw of a lobster or crab, and suggests gripping or holding something firmly. Chelation agents bind with metals such as iron to form substances that can be easily excreted from the body.

Chelation therapy

Chelating agent	Route of administration	Monitoring*	Considerations
Deferoxamine	Infusion under the skin (subcutaneous) or into a vein	<ul style="list-style-type: none"> Kidney and liver function tests Complete blood counts Hearing and eye tests 	Generally few side effects, but long infusions every day can make sticking to the treatment challenging
Deferasirox	Oral – tablets, a tablet to mix in water, or sprinkles	<ul style="list-style-type: none"> Kidney and liver function tests Complete blood counts Measurement of creatinine and creatinine clearance Monitoring for signs of gastrointestinal ulcers and/or bleeding 	Easy to swallow; often the best tolerated of the chelators
Deferiprone	Oral – tablets	<ul style="list-style-type: none"> Hearing and eye tests Absolute neutrophil count (at baseline and weekly)** Liver function tests Measurement of zinc levels 	Risk of low white blood cell count, so usually only considered when other chelation therapy does not work or in patients with severe iron loading in the heart

* In addition to regular ferritin monitoring and/or magnetic resonance imaging (a type of body scan).

** Neutrophils are a type of white blood cell that fights against infection.

Note: These drugs have other potential side effects, which should be discussed in detail with your healthcare provider before starting treatment. Monitoring may vary by center.

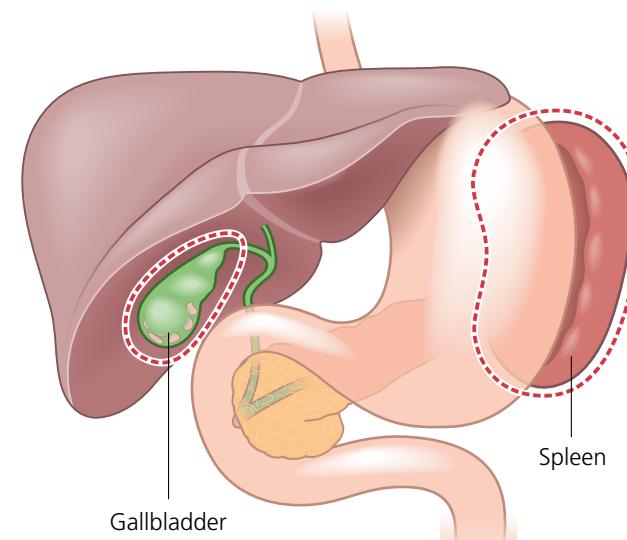
My concerns and questions

Make a note here of anything you want to ask your doctor about treatment of iron overload ...

Gallbladder removal (cholecystectomy)

Gallstones can be associated with nausea or abdominal pain after eating and/or complications if they become stuck in the biliary tract.

You will have an ongoing risk of developing gallstones because of continued hemolysis. Given this, surgical removal of the gallbladder is recommended in PK deficiency if you have gallstones.



If you are considering a splenectomy, you should have an ultrasound before the procedure to see if you have gallstones. Even if you do not, you could consider having a cholecystectomy at the same time as your splenectomy, given the likelihood that you will develop gallstones in future.

Vitamin supplements

Folic acid is needed to make red blood cells. If you have an elevated reticulocyte count, you will need to ensure you have sufficient folic acid. Depending on the amount of folic acid in your diet, you may need to take folic acid supplements.

Vitamin D/calcium. Given the risk for low bone density in people with PK deficiency, you may find it beneficial to take vitamin D and calcium supplements for bone health. This will depend on how much vitamin D and calcium you have in your diet.

Exercise can also help to strengthen your bones. If your bone density is very low, your doctor may recommend other treatments.

A NOTE OF CAUTION

People with PK deficiency tend to overload with iron, so you must **avoid** taking additional iron supplements in the form of multivitamins or prenatal vitamins.

TRUE OR FALSE?

If you do not receive blood transfusions as part of your treatment for PK deficiency, you will not need chelation therapy.

Notes: Even if you have never had a blood transfusion you may still be at risk of iron loading. Transfusion-independent iron overload is common in people with PK deficiency. (see page 20).

Answer: False

What sort of monitoring might I need?

The types and frequency of tests for monitoring people with PK deficiency will differ from person to person. For example, if you are receiving iron chelation treatment (see page 30) you will need additional types of regular monitoring depending on the type of chelation you are using.

Blood test monitoring

For these tests your doctor will send a blood sample to a laboratory.

Blood test	Description
Blood counts, reticulocyte count	Performed annually and as needed for symptoms of worsening anemia
Bilirubin	Performed annually and as needed for symptoms of worsening anemia and/or worsening jaundice
Ferritin	Performed annually for iron monitoring or more frequently if you are receiving chelation or phlebotomy treatment for iron removal
Vitamin D	Performed annually to optimize bone health
Viral screening (HIV, hepatitis A, B, C)	Performed annually to screen for viruses in patients who have received transfusions
Hormone evaluation	Individuals with iron loading should be screened for hormone changes, including thyroid and sex hormones, and for signs of diabetes

Note: The hemoglobin A1c (HbA1c) test that is used for diabetes screening cannot be used in patients with hemolysis. A different test (e.g. a fructosamine level) will need to be carried out instead to test for diabetes.

Imaging tests

For these types of test a doctor will use different types of radiology machine to examine your organs and bones.

Imaging test	Description
MRI (magnetic resonance imaging)	Performed annually to look for iron overload in the liver and heart. An MRI does not involve any radiation exposure. MRI requires a period of time lying still, so it is often deferred until a child can lie still for long enough without sedation. Some doctors will recommend this test in all individuals with PK deficiency and others will recommend it only in those whose ferritin levels exceed a certain threshold (for example, ferritin > 500 ng/mL)
DEXA scan (dual-energy X-ray absorptiometry)	Performed annually to assess bone strength. A DEXA scan involves a similar amount of radiation as an X-ray. A baseline reading may be recorded in late adolescence or early adulthood from which to compare future readings
Abdominal ultrasound	Performed to look for gallstones and/or other complications of the gallbladder. An ultrasound does not involve any exposure to radiation. It may be performed routinely for screening and will also be carried out before splenectomy and for new abdominal symptoms, worsening jaundice and other symptoms potentially related to gallbladder disease
Echocardiogram (echo)	Performed to assess heart function and signs of pulmonary hypertension.* An echocardiogram should be considered in individuals aged 30 years and older and at any age in individuals with symptoms that suggest poor heart function (i.e. worsening shortness of breath)

* Pulmonary hypertension is a type of high blood pressure that affects the arteries in your lungs and the right side of your heart.

My monitoring

Make a note here of the monitoring your doctor has suggested you should have ...

Special situations

PK deficiency in the fetus and newborn

Approximately one quarter of babies with PK deficiency have complications before or at the time of birth. These include:

- problems with growth (intrauterine growth retardation)
- anemia in the womb, which requires transfusions
- hydrops (fluid outside the organs due to anemia)
- preterm birth.

After birth, most newborn babies with PK deficiency develop jaundice and hemolysis, which requires phototherapy and/or simple or exchange transfusions (see pages 27–8).

Several newborns with PK deficiency have developed severe liver disease, which can lead to serious complications.

PK deficiency in pregnancy

Pregnancy in women with PK deficiency is associated with good outcomes for both mother and child. However, the degree of hemolysis may worsen during pregnancy.

Most women are given transfusions during pregnancy or after delivery, even if they did not need them before they became pregnant. At present, there is not enough information about PK deficiency during pregnancy to recommend a specific hemoglobin threshold for transfusion.

Multidisciplinary care with a hematologist and high-risk obstetrician is recommended, with close attention being paid to fetal growth to determine how often transfusions are needed.

Normally, the mother provides the fetus with a significant amount of iron during pregnancy, which helps to balance the iron loading caused by transfusions during pregnancy. However, pregnant women with PK deficiency should be careful to avoid prenatal vitamins containing iron.

My questions

Make a note of any other concerns you have about your pregnancy or the health of your newborn child here ...

When should I see my doctor?

You should visit your doctor annually (or more frequently) for routine monitoring and screening. You should also visit if you experience any of the following:

- Worsening fatigue or pallor
- Significant worsening of jaundice
- New abdominal pain
- Worsening or new shortness of breath
- Fever after splenectomy
- Any new symptoms

This is an urgent medical issue for which you should be seen by your doctor immediately

And, of course, you should contact your doctor if you have any questions about your condition.

What can I do to help myself?

- Eat a healthy diet
- Exercise if possible
- Get outdoors
- Ask your doctor questions; be an advocate for yourself/your child
- Consider joining a patient group and meeting others with PK deficiency

TALK TO OTHERS

There is a very active patient group on Facebook called 'People with pyruvate kinase deficiency'. To join you will need to be connected to Facebook; search for 'People with pyruvate kinase deficiency' and you will be able to ask to join the group. The group is only accessible to people with PK deficiency and their relatives. There is also a French patient group on Facebook called 'Déficit en Pyruvate Kinase'.

Useful resources

Pyruvate Kinase Deficiency Group

pyruvatekinasedeficiency.com

Informative website created and managed by people with PK deficiency.

National Organization for Rare Diseases (NORD)

rarediseases.org/rare-diseases/pyruvate-kinase-deficiency

A patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them

Genetic and Rare Diseases Information Center

rarediseases.info.nih.gov/diseases/7514/pyruvate-kinase-deficiency

Information about rare or genetic diseases in English and Spanish

Dutch Foundation for Rare Blood Diseases

bloedziekten.nl/pkd-en

Useful information on PK deficiency. Includes the PKD contact group:
bloedziekten.nl/pkd/pkd-contactgroep

Clinical Trials Information

clinicaltrials.gov

For a list of ongoing and recruiting clinical trials, type *pyruvate kinase deficiency* in the 'Condition or disease' box on the home page and press 'Search'. Before participating in a study, talk to your healthcare provider about the potential risks and benefits.

Ask your Doctor

Make a note here of any other questions you want to ask your doctor
(e.g. Are there any clinical trials for PK deficiency that would benefit me?
What is the latest research on PK deficiency?)

Glossary

Aplastic crisis: the production of new red blood cells temporarily stops completely

ATP: adenosine triphosphate; a high-energy molecule made by glycolysis, which red blood cells use for energy

Biliary system: the organs and ducts that create and store bile (e.g. the gallbladder)

Bilirubin: a substance released from red blood cells when they break down, which causes jaundice and scleral icterus

Capillaries: small narrow blood vessels found throughout the body

Chelation therapy: drugs that remove excess iron from the blood by binding with the iron to form substances that can be excreted from the body easily

Cholecystectomy: surgical removal of the gallbladder

Extramedullary: outside the bone marrow

Gallstones: small stones that form in the gallbladder

Gene mutation: a permanent change in the DNA sequence of a gene, altering the gene's instructions to make a protein (in this case pyruvate kinase) so that the protein stops working properly

Glycolysis: a multistep process in which glucose (a sugar) is converted into pyruvate and ATP

Hematocrit: the volume of red blood cells in the blood (expressed as a percentage)

Hematopoiesis: red blood cell production

Hemoglobin: a protein in red blood cells that transports oxygen around the body

Hemolysis: the destruction of red blood cells

Hemolytic anemia: low numbers of red blood cells or a low hemoglobin level due to destruction of red blood cells

Intramuscular: into a muscle

Intravenous: into a vein

Iron overload: an excess of iron in the body

Jaundice: yellowing of the skin

Kernicterus: damage to the brain and central nervous system in newborn babies caused by high bilirubin levels

Laparoscopic surgery: minimally invasive (or keyhole) surgery

Phlebotomy: withdrawal of blood from the body

Pyruvate: an important metabolic molecule that is the end product of glycolysis

Pyruvate kinase: an enzyme that makes the last step in glycolysis happen, converting phosphoenolpyruvate into pyruvate and ATP

Reticulocyte: young (not fully mature) red blood cell

Scleral icterus: yellowing of the whites of the eyes

Splenectomy: surgical removal of the spleen

Splenomegaly: enlargement of the spleen



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Questions for the Editor

What have you found the most useful about this book? What is missing?
Do you still have any unanswered questions? Please send your questions, or
any other comments, to feedback@fastfacts.com and help future readers of
future editions. Thank you!

“PK deficiency is a complex disease, and the information presented here
may appear a bit overwhelming at first. Stick with it, and use it to ask lots
of questions. It will become a valuable aide over time. I shared this resource
pre-publication with parents whose baby had just been diagnosed with PKD.

They found it very useful. My nurses love it too!”
Bertil Glader, Professor of Pediatrics (Hematology/Oncology) and
Director, Red Blood Cell Special Studies Laboratory,
Stanford University School of Medicine, California, USA

“This engaging book is packed with useful information and helpful
illustrations that address the important questions patients with
PK deficiency often have. Highly recommended.”

Wilma Barcellini, Associate Professor in Blood Diseases,
Oncology and Rheumatology, University of Milan, Italy

With sincere thanks to those who have reviewed this publication
for all their help and guidance

Pyruvate Kinase Deficiency

A rare genetic disease that affects red blood cells

"As a person living with pyruvate kinase deficiency, this booklet is a comprehensive godsend and will raise much needed awareness of the impacts and implications of living with this disorder. I will be taking it with me wherever I go in the hope of educating doctors with the most up-to-date information."

Patient with PK Deficiency, Australia

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