WOMEN AND ANAEMIA

In this article the author considers the causes of anaemia in women

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The energy our body needs for processes such as digestion, locomotion, heartbeat and thought is provided from a dietary source, such as glucose, and from oxygen. Glucose and other nutrients find their way around the body in the plasma, while oxygen is carried within red blood cells. Anaemia is caused by the inability of haemoglobin and/or red blood cells to provide enough oxygen to the tissues, resulting in loss of energy.

The consequences of this insufficient oxygen (hypoxia) are a group of common signs and symptoms, outlined in Table 1, and are often used to diagnose anaemia. Unfortunately, many of these are present in a host of other conditions, such as lung disease, and so to truly define anaemia a blood test is required.

The full blood count (FBC)

This blood test provides information on platelets and white blood cells, in addition to red blood cells. Of these, the most important are:

- Haemoglobin (the protein to which oxygen binds)
- The red cell count (the number of cells in a given volume of blood), and
- The mean cell volume (a measure of the size of the red cell).

A diagnosis of anaemia is made if the subject is symptomatic (as in table 1) and has abnormalities in their red blood cells – typically a low haemoglobin and/or a low red cell count. An allied test is the erythrocyte sedimentation rate (ESR), which is abnormal in anaemia, but is also abnormal in many other diseases such as cancer and inflammatory disease such as arthritis, and so is not specific for anaemia.

TABLE 1: SIGNS AND SYMPTOMS OF ANAEMIA

Signs:
- Dark urine (a sign of red cell destruction)
- Pallor (especially of the conjunctiva)
- Tachycardia (pulse rate over 100 beats per minute)
- Glossitis (swollen and painful tongue)
- Koilonychia (spoon nails)

Symptoms:
- Dizziness and weakness
- Heart flutter and palpitations
- Lethargy, 'tired all the time', fatigue
- Shortness of breath (especially on exertion)
- Decreased exercise capacity and/or work

More serious signs and symptoms:
- Fever
- Heart problems such as angina and cardiac failure
- Enlarged liver and spleen
- Cognitive changes (loss of memory etc.)
- Jaundice (inevitable with dark urine)

NB: these are all found in other clinical situations.

The investigation of anaemia

Anaemia may arise from a number of different processes, and treatment cannot start before the reason for the anaemia has been identified. These reasons include:

- Damage to the bone marrow (where red cells are produced). The leading causes for damage include drugs, viruses and infiltration by cancers from other tissues (such as the breast or prostate), or cancer of the bone marrow itself (such as leukaemia and myelodysplasia)
- Lack of nutrients, mostly iron and vitamin B12, which may be due to malnutrition or, more likely, to malabsorption
- Disease in other organs, such as the liver, kidney and reproductive organs
- Haemolysis – the bursting, destruction or inappropriate break-up of red cells. This may be caused by drugs, infections (notably malaria) and autoantibodies, in which case the disease is called auto-immune haemolytic anaemia
- Loss through an acute or chronic bleed (that is, haemorrhage), such as after surgery, due to over-use of anticoagulants, or from a ruptured blood vessel or ulcer that may leak into the intestines
- A haemoglobinopathy, the most common being sickle cell disease and thalassaemia.

The size of the red cell

To further investigate the cause of the anaemia, knowledge of the mean cell volume (MCV) is essential. The MCV is the size of the 'average' red cell, and is recognised in three categories:

- When the MCV is small, the cell is microcytic, so there is a microcytic anaemia. There are two principle reasons for red cells becoming microcytic: lack of iron and haemoglobinopathy
- When the MCV is normal, the cell is normocytic, so there is a normocytic anaemia. This type of anaemia is present in cancer, and when there is loss of blood by haemorrhage

CASE STUDY 1

A 75 year old woman presents with slowly developing tiredness and weakness – she can't carry as much shopping home. Over the last six months she has lost nearly a stone, and complains of intermittent diarrhoea and constipation. A full blood count and ESR reveals the following:

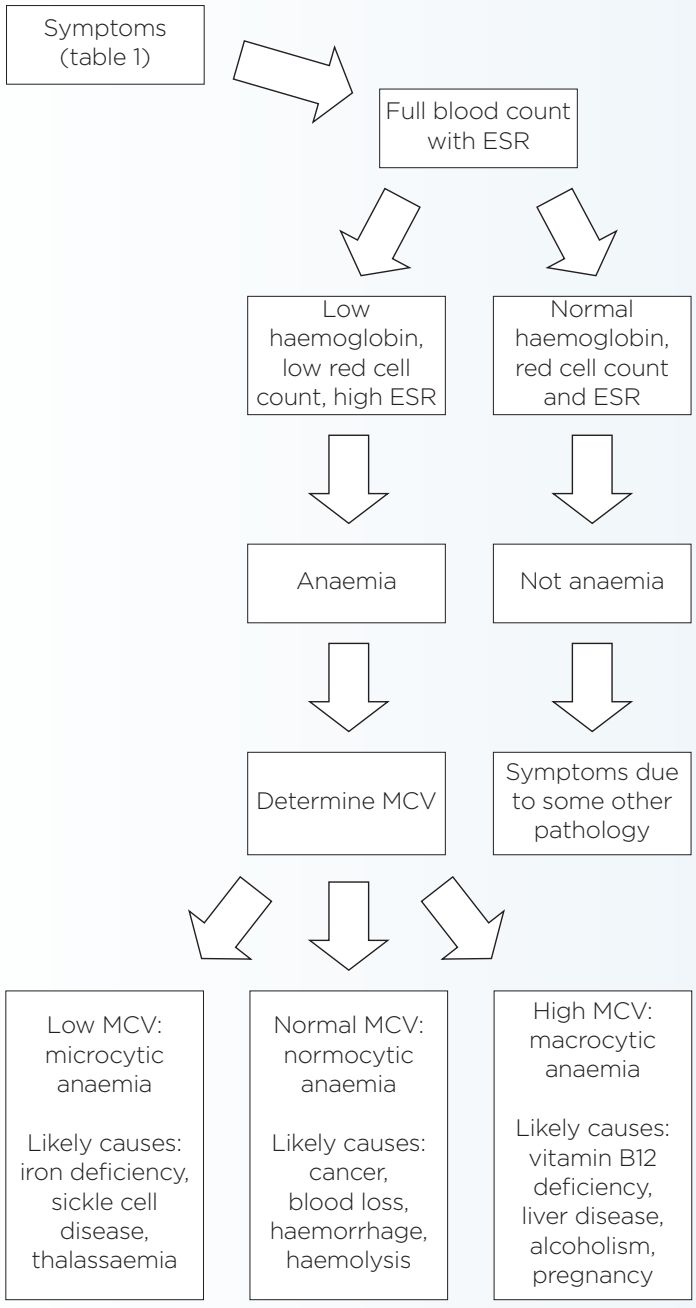
	Result (unit)	Reference range
Haemoglobin	98g/L	118-148
Red blood cells	3.4 x 1012/L	3.9-5.0
MCV	75fL	77-98
ESR	26mm/hour	<10

Interpretation

There is low haemoglobin, MCV and haematocrit, with a raised ESR. So with the symptoms, the woman has microcytic anaemia. The ESR does not add a great deal as it may be a consequence of anaemia. Although there is an initial diagnosis, aetiology must be considered. The microcytic nature points to haemoglobinopathy or iron deficiency, so the next step is for formal tests of iron status, such as serum ferritin. Should iron studies confirm the preliminary diagnosis of iron deficiency, then treatment is probably warranted. After discussion with the patient, this is likely to be oral or intravenous infusions of iron. The success of this strategy will be tested perhaps two or three months later with additional blood tests.

However, the ultimate cause of anaemia must still be determined. There is a history of weight loss and problems with defecation. These point to a bowel problem, the most serious being colo-rectal cancer. Indeed, altered bowel habits for six months alone would prompt a two-week cancer exclusion referral, regardless of haematological abnormalities. Blood loss in stools can be checked with faecal occult blood, which, if present, could account for the iron deficiency. So, although cancer in itself is linked to a normocytic anaemia, in this case the blood loss seems to have been so prolonged that it has developed into a microcytic anaemia.

FIGURE 1: INVESTIGATION OF ANAEMIA



Simplified pathway for the diagnosis and management of different forms of anaemia.
MCV = mean cell volume, ESR = erythrocyte sedimentation rate.

When the MCV is large, the cell is said to be macrocytic, and there is macrocytic anemia. Causes of this type of anaemia include lack of vitamin B12, alcoholism, liver disease and pregnancy.

Figure 1 summarises this process. For complete proof of the causes of microcytic and macrocytic anaemia, additional tests are required. These will be 'iron studies' and serum vitamin B12 and folate respectively.

Treatment of anaemia

Once a diagnosis of anaemia has been made (according to the presence of symptoms and abnormal red cell indices), the cause (such as a malignancy) must be determined, and, if possible, treated.

The MCV, followed by other blood tests, narrows down the potential causes of the anaemia, and so can direct treatment. For example, if the iron studies indicate a lack of this micronutrient, it may be supplemented orally or by parenteral routes.

Macrocytic anaemia, due to lack of vitamin B12 or folate, can be treated with injected or oral supplements respectively. As the spleen is one of the sites of the removal of abnormal red cells, splenectomy is often used to help treat haemolytic anaemia as it may be found in autoimmune haemolytic anaemic, sickle cell disease and thalassaemia. However, this surgical option would be considered after other treatments have been shown to be inadequate. Those whose anaemia is a consequence of chronic kidney disease may benefit from injection of the hormone erythropoietin. In the most severe and life-threatening situations, blood transfusion may be the only option.

CASE STUDY 2

A 17-year-old is brought to her GP by her mother with a history of increasingly heavy and prolonged periods. The young woman also complains of intense pain during her period and tiredness throughout the whole month. A full blood count brings the following results:

	Result (unit)	Reference range
Haemoglobin	109g/L	118-148
Red blood cells	3.7 x 1012/L	3.9-5.0
MCV	90fL	77-98
ESR	15mm/hour	<10

Interpretation

The blood result and symptoms point to a normocytic anaemia, the cause very likely being the blood loss from heavy periods. Iron studies are generally not called for at this stage, and treatment focuses on reducing the blood loss. A referral to a gynaecologist may be needed, although common treatments for 'teenage' menorrhagia include the oral contraceptive pill and tranexamic acid.

Once the pathology has been addressed, the red cell indices should return to the reference range.

Anaemia in women

Heavy menstrual bleeding

From the haematologist's perspective, menorrhagia exceeding 80ml of blood per cycle (although difficult to measure) can lead to a normocytic anaemia. However, if prolonged, iron stores become depleted, then the anaemia will become microcytic. Consequently, iron studies are essential, especially if the bleeding has been prolonged, and supplements may be necessary. But, of course, it is preferable to determine and treat the blood loss itself.

Iron deficiency anaemia

Globally, this is the most common form of anaemia, and is inevitably microcytic. It can only be diagnosed with other blood tests such as serum iron and ferritin. In the developed world the most likely cause is malabsorption, caused by diseases of the stomach and intestines. Abnormal absorption of iron (and other foodstuffs) is often the consequence of cancer, ulcers, and inflammation of these organs, examples of the latter including chronic gastritis and inflammatory bowel diseases such as Crohn's disease and coeliac disease. Women are more likely than men to suffer inflammatory and auto-immune diseases such as rheumatoid arthritis and lupus. These can lead to the development of 'the anaemia of chronic diseases' (ACD).

A common treatment is oral ferrous sulfate tablets, to be given as long as the symptoms of anaemia and abnormal laboratory results persist. However, this may need to be even longer if iron stores in the liver and elsewhere need to be replenished. Dependent on the degree to which iron stores have been depleted, this is likely to be at least six months. An alternative, which gets round the malabsorption problem, is slow subcutaneous injection or intravenous infusion. Although the response to parenteral iron is often no quicker than by the oral route, stores in the liver and elsewhere are likely replenished more rapidly. Side effects include hypersensitivity, nausea and vomiting. New treatments are emerging, including ferric carboxymaltose, which is administered as an injection/ infuion and can be used when tablets are ineffective.

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Anaemia and pregnancy

Normally-menstruating women need more iron than men and post-menopausal women, but this requirement for 1-2mg daily should be increased to 1.5-3mg daily if pregnant. This is because her baby will demand 300mg of iron, and other changes (uterus, red cells, placenta) another 600mg. Anaemia may be a problem because, although the pregnant woman increases her red cell mass by about a quarter, this is exceeded by an increase of a third or more in her blood volume. If the haemoglobin is as low as 100 g/L, then there may be an additional cause, and a low MCV should be investigated as the size of the red cells should stay the same or increase, not get smaller.

It is also important that pregnant women have plenty of folate, as babies need this essential micronutrient for the development of the spinal cord and central nervous system. Insufficient folate causes spina bifida, aneucephaly and neural tube defects. The pregnant woman also needs folate for her own red blood cell development. Accordingly, in the UK, NICE recommends 400 micrograms daily before pregnancy and throughout the first trimester, even if the woman is already eating foods fortified with folic acid or rich in folate. However, this should be 5mg daily throughout the pregnancy if there has been a previous neural tube defect.

CASE STUDY 3

A middle-aged South Asian woman, diagnosed with beta thalassaemia trait 20 years ago, comes to her GP with a history of increasing tiredness. In the past she has been able to adapt to her disease, but this is becoming harder to achieve. She has heard about drug treatment and transfusions, and although unwilling to undertake these, she appreciates this may be the time to start. A blood test reveals the following:

	Result (unit)	Reference range
Haemoglobin	108g/L	118-148
Red blood cells	5.5 x 1012/L	3.9-5.0
MCV	75fL	77-98
ESR	16mm/hour	<10

Because she is known to have haemoglobinopathy, the different haemoglobin species are determined by HPLC. This finds a levels of HbA2 of 3.8% (reference range <2%) and HbF of 4.5% (reference range <1%).

Interpretation

The blood tests confirming the microcytic anaemia are as expected, the high red cell count being the response of the bone marrow to a presumed tissue hypoxia. Incidentally, the low MCV and raised red cell count combine to give a haematocrit of 0.41 (reference range 0.33 – 0.47). Beta thalassaemia trait, or thalassaemia minor, can, from the clinical perspective, be mild or even asymptomatic as the one normal beta globin molecule may be able to compensate for the mutated and so dysfunctional beta globin molecule. Accordingly, there must be clinically-led decision as to whether or not to try a transfusion.

However, her haemoglobin is not that low, and transfusion is generally reserved for more severe clinical disease and a much lower haemoglobin. Although there is a place for hydroxyurea in sickle cell disease, its value in thalassaemia is unclear, as is the place of other inducers of HbF, although some are in development. However, folic acid (e.g. 5mg/day) may help. Her increasing tiredness could be due to other factors.

New treatments are emerging, including ferric carboxymaltose

SUMMARY OF KEY POINTS

1. The major disease of red blood cells, anaemia, is more often found in women than in men
2. Anaemia leads to symptoms such as tiredness and lethargy
3. The causes of anaemia include cancer, blood loss and haemorrhage, and lack of iron, vitamin B12 and folic acid.
4. From a full blood count, the laboratory provides haemoglobin, the red cell count, and mean cell volume
5. The mean cell volume is important as may point to the cause of anaemia, and so how it can be treated

RECOMMENDED WEBSITES

www.nhs.uk/conditions/Anaemia-iron-deficiency-/

FURTHER READING

Routine blood tests explained (3rd Edition). AD Blann, M&K Updates, 2014.

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