Screening for haemoglobinopathies in pregnancy

Policy Statement
All Southern Health patients will receive clinical care that reflects best practice and is based on the best available evidence.

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Purpose and Rationale
To ensure pregnant women and their male partners are adequately screened for haemoglobinopathies either pre-pregnancy or in early pregnancy.

Scope
Women planning a pregnancy and pregnant women.

Definitions
Partner: Father (or intended father) of the baby.

FBE: Full Blood Examination

MCV: Mean Corpuscular Volume

MCH: Mean Corpuscular Haemoglobin

HbEPG: Haemoglobin electrophoresis
1. **Prevalence of haemoglobinopathies**
   - The World Health Organisation (WHO) has estimated at least 5% of the world’s population are carriers of a haemoglobinopathy: approximately 2.9% for thalassaemia and 2.3% for sickle cell disease.
   - It is not always possible to assume ethnicity from country of birth or surname. More information can be obtained from asking patients where their parents, grandparents or great grandparents were born. High risk ethnic groups include:
     - Southern Europe / Mediterranean
     - Middle East
     - Africa (including the Caribbean or African American)
     - China
     - South East Asia
     - Indian subcontinent
     - Pacific Islands
     - New Zealand Maoris
     - South America
     - Some Western Australian and Northern Territory Indigenous communities.

2. **Prenatal diagnosis**
   - Prenatal diagnosis is one of the options available to couples where there is a risk of having a child affected by a haemoglobinopathy and the causative globin mutations carried by the parents are known.
   - It can be time consuming to identify causative gene mutations by DNA analysis. Thus, wherever possible, DNA studies should be performed pre-pregnancy.
   - Prenatal diagnosis is performed on a sample collected by chorionic villous sampling. This is usually performed in the first trimester but may be performed in the second trimester. Amniocentesis is also an option in the second trimester.
   - Alternatives to prenatal diagnosis may include: preimplantation genetic diagnosis (PGD), donor egg or sperm, adoption.

3. **Genetics**
   - Haemoglobin A (HbA) contains two α-globin chains and two β-globin chains (α₂β₂).
   - HbA₂ is a normal minor adult type of haemoglobin and is composed of two α-globin and two δ-globin chains (α₂δ₂). It normally represents 2 to 3.5% of normal total adult haemoglobin.
   - HbF is fetal haemoglobin, a normal variant in fetal development that persists in small amounts post birth. It is composed of two α-globin and two γ-globin chains (α₂γ₂) and usually represents less than 1% of normal total adult haemoglobin.
   - The β-globin gene encodes the β-globin chain. Each individual has two copies of this gene, one from each parent.
     - Two identical α-globin genes encode the α-globin chains. Each individual therefore has four α-globin gene copies: two gene copies inherited from each parent.
4. \(\beta\)-Thalassaemia\(^1\)

**Clinical features:**
- Usually manifest within 6-12 months or birth and include pallor, lethargy, poor appetite, developmental delay, failure to thrive, irritability, splenomegaly and haemolytic anaemia. It is a severe medical condition requiring frequent blood transfusions and iron chelation therapy.
- Carriers are usually asymptomatic. It manifests as reduced red cell indices and elevated concentrations of HbA\(_2\) and can be mistaken for iron deficiency.

**Genetics:**
- Caused by reduced or absent production of the \(\beta\)-globin chain of the haemoglobin molecule.
- \(\beta\) -thalassaemia major is caused by mutations in both copies of the \(\beta\)-globin gene, resulting in virtually no functional \(\beta\)-globin chains being produced.
- \(\beta\) -thalassaemia major is inherited in an autosomal recessive manner. Carriers have a 50% chance of passing the mutated \(\beta\)-globin gene to their children. Couples who are both carriers have a 25% chance of having an affected child.
- \(\beta\)-thalassaemia minor (or trait) is the carrier state and is caused by a mutation in only one copy of the \(\beta\)-globin gene.
- Co-inheritance of \(\beta\)–thalassaemia minor and a haemoglobin variant (eg Hb Lepore, HbC or HbE) may result in a form of \(\beta\)-thalassaemia major.
- Couples where one partner is a carrier of \(\beta\)–thalassaemia and the other is a carrier of \(\alpha\)-thalassaemia are not at risk of having children with thalassaemia major.

**Investigation results:**
- FBE usually shows significant anaemia, microcytosis, hypochromia and abnormal red cell morphology including target cells. Nucleated red blood cells are usually present in individuals with thalassaemia major.
- HbEPG testing to determine HbF and HbA\(_2\) levels is usually diagnostic of \(\beta\)-thalassaemia. Affected children over the age of six months usually have elevated levels of HbF.

**Management considerations in pregnancy:**
- Carriers for \(\beta\)-thalassaemia, should have folic acid (5mg) daily 3 months preconception and throughout pregnancy
- Carriers for \(\beta\)-thalassaemia must not have long term iron treatment to attempt to cure microcytosis unless they are also iron deficient.

5. \(\alpha\)-Thalassaemia\(^1\)

**Clinical features:**
- Hydrops fetalis, resulting from deletions of all four \(\alpha\)-globin genes, is fatal in the fetus or neonate. The mother of an affected fetus is at risk of severe early pre-eclampsia, antepartum haemorrhage, post partum haemorrhage and preterm delivery.
- Haemoglobin H (HbH) disease is an intermediate form of \(\alpha\)-thalassaemia caused either by deletions or other mutations of three copies of the \(\alpha\)-globin genes. It results in the presence of HbH (\(\beta\_4\)) an
abnormal form of haemoglobin caused by excessive β-globin chains. It causes life-long anaemia of mild to moderate degree which depending on the severity may require transfusion support.

- Carriers for α-thalassaemia (α-thalassaemia minor) have one or two copies of the α-globin genes deleted. They are usually asymptomatic but may have a mild hypochromic or microcytic anaemia.

**Genetics**

- Caused by reduced or absent production of the α-globin chains of the haemoglobin molecule.
- In general α-thalassaemia major follows an autosomal recessive pattern of inheritance but the genetics is complex.

**Investigation results:**

- FBE usually shows significant anaemia, microcytosis, hypochromia and abnormal red cell morphology including target cells and fragmented cells
- Haemoglobinopathy testing demonstrates normal HbEPG
- Individuals with a two or three gene deletion may be identified by HbH bodies on HbH preparation.
- However, a normal HbH preparation does not exclude an α-thalassaemia carrier state.
- In one gene deletions the haemoglobin, MCV, MCH and haemoglobin electrophoresis are usually normal.
- Definitive identification of α-thalassaemia with one and two gene deletions requires DNA testing.

**Management considerations in pregnancy:**

- Carriers for α-thalassaemia, like with all women, should have folic acid (5mg) daily 3 months preconception and throughout pregnancy
- Carriers for α-thalassaemia must not have long term iron treatment to attempt to cure microcytosis unless they are also iron deficient.

6. **Sickle Cell Disease**¹

**Clinical features:**

- Includes anaemia due to red cell destruction, failure to thrive, repeated infections, painful swelling of the hands or feet, infarction, asplenia, abdominal pain and chest pain.

**Genetics:**

- Sickle cell disease is caused by a mutation in both copies of the β-globin genes resulting in changes to the structure of the β-globin chain of haemoglobin, ie. a haemoglobin variant. This results in red blood cells that form an irreversible sickle cell shape after repeated cycles of deoxygenation. Affected individuals may experience a sickle cell crisis due to blockage of blood vessels by the abnormal red cells causing bone and chest pain and damage to other organs.
- Sickle cell trait (or carrier state) is caused by a mutation in one copy of the β-globin gene. Carriers are usually healthy. In some very rare instances, eg. anaesthesia or long distance air travel, the red blood cells of a carrier can undergo partial sickling.
- Sickle cell disease is an autosomal recessive condition. Carriers have a 50% chance of passing the mutated gene to their children. Couples who are both carriers have a 25% chance of having an affected child.
- Co-inheritance of sickle cell trait and β-thalassaemia minor (or another haemoglobinopathy variant)
may result in a form of sickle cell disease.

Investigations:
- FBE and ferritin tests are usually normal in a carrier of HbS
- HbEPG results are abnormal in individuals with sickle cell disease. HbEPG will show sickle cell trait.

Management considerations in pregnancy:
- Same as B-thal above for carriers of HbS
- All patients with sickle cell disease should be considered for blood transfusions in pregnancy.

7. Other haemoglobinopathies

In addition to α-thalassaemia and β-thalassaemia other globin gene mutations can cause a structural variant.

- Only a small number of variants capable of causing a severe condition in the homozygote or in compound heterozygotes are encountered in Australia. These include HbS (sickle cell disease), HbC, HbD, HbE, HbO, and Hb Lepore.
- These structural variants can be identified on HbEPG testing.

Examples of combinations of mutations causing disease

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<td>Hb Lepore / HbS</td>
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References
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Background

Southern Health

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