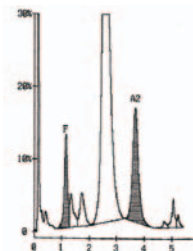


Hb disorders: Preconceptional and antenatal screening recommendations

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The haemoglobinopathies can be broadly classified into thalassaemias (α , β and $\delta\beta$) and abnormal structural variants such as HbS (sickle cell haemoglobin) and HbE. In general terms, the haemoglobinopathies are autosomal recessive disorders and the subjects who are homozygous or compound heterozygous for mutations or deletions can have clinically significant phenotypes of varying severity. These include thalassaemia major, thalassaemia intermedia, HbH disease, sickle cell disease and HbE syndromes. Those who are heterozygotes for a gene variant are usually symptom free but may show abnormalities on the blood count.



HPLC for haemoglobin separation

The reasons for screening

The aim of screening (or carrier testing) is to identify carriers of haemoglobin disorders in order to assess the risk of a couple having a severely affected child and to provide information on the options available to manage their risk.

Important lessons can be learnt from the UK, which is similar to Australia in that thalassaemia and sickle cell disease are rare disorders affecting a diverse minority of ethnic groups scattered among a majority population of Northern European ancestry that is not at risk. Prior to the implementation of a national screening program in 2001, there were significant differences in practice, with the result that in some areas only 50% of at risk couples were identified and informed of their risk in time for the offer of prenatal diagnosis.

Clinically significant haemoglobinopathies that should be detected are shown in Table 1.

Testing methods

Screening for Haemoglobin disorders usually involves a combined assessment of the blood count parameters, iron status and the results of tests used to separate the different haemoglobin fractions. In the interpretation of these results, two pieces of information are vital on the request form: the ethnic origin of the patient; and indication of recent blood transfusion (which can affect haemoglobin interpretation).

A variety of techniques are used to identify mutations and/or deletions in the α and β globin genes. Since pre-natal diagnosis is based on molecular techniques, the molecular diagnosis for each of the parents is critical. In cases where the availability of the result is urgent, the laboratory should be informed so that testing can be expedited.

When to test

Ideally, individuals from high risk groups (see Table 2) are offered pre-conceptional testing. This usually falls to the general practitioner, but any doctor can use the opportunity presented by seeing a patient of reproductive age who is from a relevant risk group. Both partners should be tested and if both partners are carriers, a referral for genetic counselling made.

In the antenatal setting, time is important. Early screening is recommended since it can be difficult to achieve antenatal screening and fetal diagnosis within a suitable timeline if the couple is unaware of the risk. Where a woman is pregnant and a carrier, organise

Table 1. Conditions to be detected as part of preconceptional or antenatal screening

Significant Maternal Haemoglobinopathies – important for antenatal care.

Sickle Cell Disease	Hb SS, Hb SC, Hb S/ β Thalassaemia, etc
β Thalassaemia major	
β Thalassaemia intermedia	
Hb H Disease	α -/--
Maternal Conditions requiring partner testing	
Carrier States in mother:	Possible significant fetal disorders
Hb AS	Hb SS, Hb SC, Hb S/ β Thalassaemia
Hb AC	Hb SC
Hb AD ^{Punjab}	Hb SD ^{Punjab}
Hb AO ^{Arab}	Hb SO ^{Arab}
β Thalassaemia Trait	β Thalassaemia major, Hb S/ β Thalassaemia
Hb AE	Hb E/ β Thalassaemia
Hb A Lepore	Hb Lepore/ β Thalassaemia, Hb S/Lepore
$\delta\beta$ Thalassaemia Trait	β Thalassaemia major, HbS/ $\delta\beta$ Thalassaemia
α^0 Thalassaemia Trait ($\alpha\alpha$ -/-)	Hb Barts hydrops fetalis (α^0/α^0 or -/-)
Any compound heterozygous state including one or more of the above conditions	
Any homozygous state of the above conditions	

Table 2. Ethnic groups with a clinically significant prevalence of Haemoglobin disorders:

Beta Thalassaemia	All ethnic groups other than Northern European
Alpha ⁰ Thalassaemia ($\alpha\alpha$ -/-)	Chinese, South East Asian, Mediterranean
Haemoglobin E	South East Asian
Haemoglobin S	African (including African-American and African-Caribbean), Greek, Southern Italian, Turkish, Arab, Indian.

partner testing and while this is underway, an expeditious referral for genetic counselling.

Timely genetic counselling important

Central to genetic counselling is the clear, timely, non-judgmental and non-directional provision of information to facilitate autonomous decisions.

Most women in the general population have positive attitudes toward antenatal screening for a range of conditions and believe prenatal testing can empower them to make informed choices. In the mid 90s, an audit of prenatal diagnosis (PND) of thalassaemia in the UK found that the main reason for a comparatively lower use of PND amongst parents of Pakistani origin, compared to other parents, was inequality of service delivery and not Muslim objection to pregnancy termination; screening was not provided and appropriately prompt

choices and options were not available.

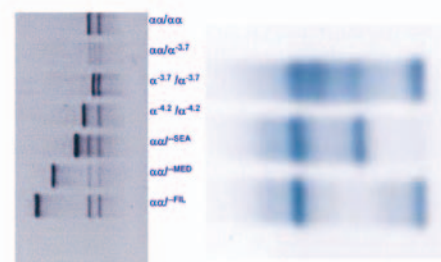
Earlier diagnosis, such as by chorionic villus sampling, as compared to amniocentesis, is likely to make PND more popular across all communities.

Pre-implantation genetic diagnosis (PGD) is an IVF based technique for testing of cells from preimplantation embryos for the detection of a specific genetic disorder before embryo transfer. PGD, by avoiding the risk of miscarriage and potential for termination of pregnancy associated with PND, may also be an acceptable option for some. It should be noted, however, that the preparation for this procedure can take a number of months and can only occur in the setting of preconceptional molecular identification of carrier status.

References available on request.



Globin gene sequencing



PCR for alpha globin deletions

Haemoglobin electrophoresis