Screening brief

Antenatal screening for β thalassaemia (and its variants)

The disorder

- An autosomal recessive genetic haematological disorder resulting in a deficiency of the production of the β chains in haemoglobin and hence little or no production of adult haemoglobin.[1 2] Over 100 mutations have been described. Similar clinical pictures occur in the compound heterozygote states of β thalassaemia with, for example, HbE, Hb Lepore, and δβ thalassaemia

Prevalence

- Most common in the Mediterranean, Middle East, Indian subcontinent, and southeast Asia, with a carrier (heterozygote) rate of 2–15%.[3] Birth prevalence of homozygotes in these regions varies from 0.2 to 7 per 1000
- It is rare in people of Northern European origin (homozygote birth prevalence of about 1 in 4 million)[3]
- In the UK between 1990 and 1994 there were 85 live births and 87 terminations of pregnancy for β thalassaemia major[4]

Prognosis

- Over 90% of homozygotes have the severe form of the disorder (β thalassaemia major); the others have a milder form (β thalassaemia intermedia)
- Without treatment, those with β thalassaemia major have multiple complications, including severe anaemia and enlargement of the liver and spleen and a high childhood mortality. Treatment is by lifelong monthly blood transfusions (accompanied by iron chelation therapy) or bone marrow transplantation
- Carriers have reduced mean cell volume (MCV) and mean cell haemoglobin (MCH) and may have mild anaemia

Screening

- Mother: Determine the carrier status of the pregnant woman. Initital screening by determining ethnic origin has difficulties and is probably best avoided. Her red cell indices (MCV or MCH) are obtained and these determinations are essentially cost free because they are included in routine blood analyses. If they are below a specified cut off level (usually MCV <80 fl or MCH <27 pg) carrier status is established by measuring haemoglobin (Hb)A_2 level using quantitative electrophoresis or automated high performance liquid chromatography (HPLC).[5 6] If the HbA_2 is >3.5% she will invariably be a carrier (HbF determination can also be carried out to detect δβ thalassaemia)
- Father: If the mother is a carrier, test the father. If he too is a carrier, the fetus has a 1 in 4 chance of having β thalassaemia and prenatal diagnosis is offered to the couple
- The table shows a hypothetical screening programme for 50 000 women in whom the heterozygote prevalence is taken to be moderately high (5%)

In 50 000 pregnant women	*No of women*	*Carrier with*		*Non-carrier*	*OAPR*
		Homozygote fetus	*Unaffected fetus*		
All women	50 000	31	2469	47 500	1:1600
Number with MCH <27 pg (and offered HbA_2 testing)	13 400	31	2444	10 925	1:430
Number with HbA_2 >3.5% (and partner offered testing)	2 450	30	2420	0	1:80
Number with carrier partner (and offered prenatal diagnosis)	121	30	91	0	1:3
Number with homozygote fetus (and offered termination)	30	30	0	0	1:0

It assumes 99% of carriers and 23% of non-carriers have MCH <27 pg (personal communication, Stephens A, Letsky E) and 99% of carriers have HbA_2 >3.5%. OAPR = odds of being affected (that is, homozygote) given a positive result.

- Screening for β thalassaemia may be part of a screening programme for other haemoglobinopathies (for example, sickle cell disease)

Diagnosis

- Fetal cells are obtained by chorionic villus sampling or fetal blood sampling. β Thalassaemia is diagnosed by DNA methods such as polymerase chain reaction (PCR) to identify mutations on the β globin gene or globin biosynthesis

Intervention

- Information on disorder and its prognosis
- Advice on recurrence
- Counselling and offer of termination of pregnancy

Overall assessment

- Given the severity and prevalence, screening is worthwhile
- National screening programmes have reduced the birth prevalence of β thalassaemia major by 80–95% in several countries in the Mediterranean. In the UK the birth prevalence of β thalassaemia major has fallen by only 50%; most affected live births are the result of failure to deliver screening appropriately[7]

1 Letsky E. Prenatal diagnosis of haemoglobinopathies. In: Turnbull A, Chamberlain G, eds. *Obstetrics*. London: Churchill Livingstone, 1989.
2 Weatherall DJ, Letsky E. Genetic haematological disorders. In: Wald NJ, ed. *Antenatal and neonatal screening*. Oxford: Oxford University Press, 1984.
3 Report of a Working Party of the Standing Medical Advisory Committee on Sickle Cell, Thalassaemia and other Haemoglobinopathies. London: HMSO, 1994.
4 Thalassaemia working party of the British Committee for Standards in Haematology (BCSH). Guidelines for the investigation of the alpha and beta thalassaemia traits. *J Clin Pathol* 1994;**47**:289–95.
5 Globin gene disorder working party of BCSH. Guidelines for fetal diagnosis of globin gene disorders. *J Clin Pathol* 1994;**47**:199–204.
6 Working party for the BCSH. The laboratory diagnosis of haemoglobinopathies: Guidelines. *Br J Haematol* 1998;**101**:783–92.
7 Modell B, Petrou M, Layton M, *et al*. Audit of prenatal diagnosis for haemoglobin disorders in the United Kingdom: the first 20 years. *BMJ* 1997;**315**:779–84.