2) A couple comes to you because they want to start a family. There is a vague history of thalassaemia in both families. Which one of the following would cause the least concern to this couple?

	The woman is carrier for	The man is carrier for
A	β thalassaemia	β thalassaemia
B	α^0 thalassaemia	α^0 thalassaemia
C	α^+ thalassaemia	α^0 thalassaemia
D	Haemoglobin E	β thalassaemia
E	α^0 thalassaemia	β thalassaemia

Legend:
β = beta
$\alpha^=$ = decreased alpha chain production
α^0 = absent alpha chain production

Answer:

Haemaglobinopathies

- Disorders affecting structure, function or production of Hb
- Common and selective advantage in endemic malaria areas
- Different Hb are produced during embryonic, foetal and adult life
- Each Hb is a tetramer comprising 4 globin chains
    - Major adult Hb (Hb A): $\alpha_2\beta_2$
    - Minor adult Hb (HbA2): $\alpha_2\delta_2$
    - Foetal Hb (Hb F): $\alpha_2\gamma_2$ (dominates from 10 weeks gestation to 6/12 old)

- Each globin chain consists of protophyrin IX ring complexed with iron atom Fe^{2+}
- Each binds one oxygen molecule; every molecule of Hb binds 4 oxygen molecule

- Oxygen binding to Hb ⇑ in affinity with ⇑ oxygen tension -> Oxygen dissociation curve
- Hb has ⇓ affinity in ⇓pH and ⇑2,3 bisphosphoglycerate -> oxygen transport to tissues
- When one molecule of oxygen binds, it is easier for the next to bind -> Cooperativity

- Inheritance: Autosomal co-dominant traits
    - Compound heterozygotes who inherit a different abnormal allele exhibit features of both

- Detection: **Electrophoresis**
    - Some Hb variants are electrophoretically silent
        - High pressure liquid chromatography (HPLC)
        - Isoelectric focusing
        - PCR to identify globin chain mutation
    - Functional tests: sickling test; solubility, oxygen affinity tests
    - Antenatal dx: PCR amplification of foetal DNA (amniocentesis/ chorionic villus sampling)

Types of Haemaglobinopathies

Type	Defect	Examples
Structural	Mutations affect amino acid sequence of globin chain	Sickle cell anaemia
Thalassaemias	Mutations that impair production or translation of globin mRNA -> deficient globin chain synthesis	β thalassaemia

	⇓ globin supply -> ⇓ Hb tetramers Unbalanced chain synthesis Hypochromia and microcytosis Clincal phenotype depends on which globin affected, degree of impairment, altered synthesis of other globins + coninheritence of other abnormal globin alleles	
Thalassaemia haemoglobin variants	Combined deficient globin chain synthesis with structural haemaglobinopathies *Importance is that compound heterozygotes with β thalassaemia can have intermedia or major, rather than the homozygotes who usually have mild disease*	Hb Lepore Hb E Hb Constant Spring
Hereditary persistence of HbF	⇑ levels of HbF in adult life with no deletrious effect	
Acquired Haemaglobinopathies	Modification of Hb molecule by toxins and abnormal Hb synthesis	CO poisoning Methamoglobinaemia ⇑ HbF in preleukaemia

α Thalassaemia Syndromes

- α thalassemias are symptomatic in utero and after birth because α globin needed for synthesis for foetal Hb too
- Non deletion alleles are also common -> ⇑ unstable α globin variants that are functionally useless

Silent	-α/αα	
α thal 2 (α thal minima)	One allele of one chromosome deleted -α/-α	Asymptomatic silent carrier
α thal 1 (α thal minor)	Both alleles on one chromosome deleted - -/αα	Clinically resembles β thalassemia minor
Hb H disease (Heterozygous α thal1 αthal2)	--/-α	HbA production only 25% normal Accumulate unpaired β chains Can form β4 tetramers (HbH) Clinically β thalassaemia intermedia - Moderate haemolytic anaemia - Mildly ineffective erythropoiesis - Can survive into mid adulthood w/o transfusions

Hydrops fetalis (Homozygous α thal 1)	--/--	Total absence of α globin synthesis Excess γ chains form Hb Barts (γ4 tetramers): $\Uparrow\Uparrow$ oxygen affinity thus delivers almost no oxygen to foetus ➔ death in utero ($\Uparrow$ output cardiac failure)

A. Risks β thalassaemia major

B. Disaster – risks complete absence of α globin synthesis ie hydrops fetalis

C. Risks Hb H

D. Hb E ($\alpha 2\beta 2^{26Glu->Lys}$) mildly unstable Hb variant. Interaction of HbE and β thalassaemia can lead to compound heterozygotes with β thal intermedia/ major

E. Correct. In fact may lead to comparatively less excess α globin chains. α globin chains are highly insoluble and tend to accumulate -> form toxic inclusion bodies -> kill developing erythroblasts in marrow.