Elevated fetal haemoglobin: a cause for concern?

At the Sickle Cell and Thalassaemia screening support service we frequently receive queries regarding antenatal screening results involving a raised level of Hb F, the fetal version of haemoglobin. Hb F is the main haemoglobin found in the baby while in the womb, but levels drop sharply after birth as Hb F is replaced by Hb A, the adult form of haemoglobin. Most adults still make some fetal haemoglobin, but this typically accounts for less than 1% of their total haemoglobin. However, some people keep making higher levels of Hb F expression throughout life (this is often termed hereditary persistence of fetal haemoglobin or HPFH). This "persistence" of fetal haemoglobin can range from 1-100% Hb F in different people.

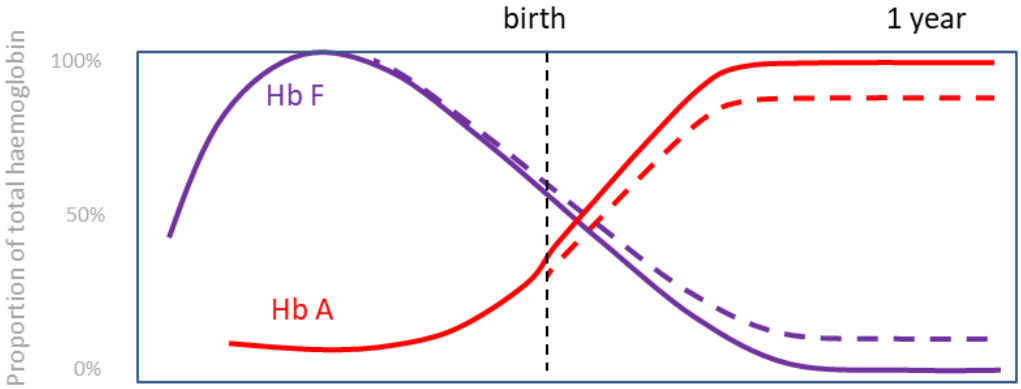

Figure 1: Haemoglobin gradually changes from the fetal form to the adult form. In most individuals (solid lines) the fetal form makes up less than 1% of the total by the time they are one year old. Individuals with HPFH (dashed lines) maintain higher levels of the fetal form of haemoglobin.

Hb F is a lot like Hb A. In fact, adults that have no Hb A but that can make enough Hb F are generally physically well and are not at increased risk of having children with health problems. In fact, Hb F can be beneficial in many circumstances and is often found at higher levels when the body needs to make more red blood cells, for example during pregnancy or after an injury resulting in a lot of blood loss. So why would an increase in Hb F during antenatal screening be anything to worry about?

Well, although an increased level of fetal haemoglobin is not a problem in itself, it is often an indication that there is a mutation in the beta globin gene region that changes the amount of the different haemoglobins being made. Some of these mutations are associated with significant health issues whereas others are not.

So, when raised Hb F is identified during antenatal screening, what should happen next? Well, there are four scenarios to consider:

1. **If the level of Hb F is under 5%, the results can be reported as normal.**
2. **If the level of Hb F is between 5 and 10% and the rest of the lady's haemoglobinopathy screening results are normal, the results can again be reported as normal. As mentioned above, a small rise in Hb F is often seen in pregnant ladies - this is of little concern if there are no other issues.**
3. **If the level of Hb F is between 5 and 10% AND the lady's red blood cells are paler than usual due to less haemoglobin being made (indicated by a mean cell haemoglobin or MCH value of less than 27 on the full blood count results) then follow up is required.**
4. **If the level of Hb F is over 10% this is more unusual and so requires follow up even if everything else is normal.**

The ladies in scenarios 3 and 4 require follow up because a small but significant minority of them could have a type of haemoglobin mutation known as delta beta thalassaemia. This does not affect the health of the lady (assuming that she has no other mutations present in this region of her haemoglobinopathy genes). However, if the biological father of her baby also has a similar type of mutation and the baby inherits the mutations from both parents, then it could develop a severe form of anaemia. Therefore, the father should be offered haemoglobinopathy screening. If his results are normal the couple can be reassured that their baby is not at significant risk of being affected by a haemoglobinopathy. If the father's results suggest that he may have a mutation affecting the beta globin gene, then DNA testing should be offered to the couple to determine whether they have mutations that could put them at higher risk of having an affected child. If they both do, they may choose to have the unborn child tested to see whether it is predicted to develop a severe haemoglobinopathy disorder. If the father is not available for testing, the mother can be offered DNA testing to help establish whether she has a mutation that might put the child at increased risk.

In some ladies, DNA testing may establish that the increased level of fetal haemoglobin is not caused by a delta beta thalassaemia but instead stems from a benign HPFH mutation that does not confer any significant health risks to her or her baby. However it is important that this information is noted and passed on to the team organising neonatal screening of the baby after birth, because if the baby inherits an HPFH mutation from one parent and a haemoglobinopathy mutation from the second

parent the newborn screening results may be misleading which could cause unnecessary alarm and confusion.

Finally, if the lady's full blood count is abnormal, don't forget to consider whether the raised Hb F is a sign that the lady is suffering from a clinical condition which may require more care during her pregnancy.

For a slightly more detailed version of this article containing further information regarding the different types of mutations associated with high Hb F (as in the diagram below) see …