

Advances in non-invasive prenatal diagnosis and care: free fetal DNA



Fetal genetic diagnosis

To perform a definitive diagnosis of genetic or chromosomal disease in the fetus during pregnancy, doctors must use an invasive technique to sample fetal DNA directly, either from the placenta (chorionic villus sampling, or CVS) or the amniotic fluid around the fetus (amniocentesis). Unfortunately these procedures carry a risk of miscarriage of around 1%. Several hundred healthy pregnancies are lost in the UK each year due to invasive testing; many women decide against testing for this reason, but then have to go through the whole pregnancy without knowing whether or not their child is affected. A non-invasive means of testing would therefore be hugely preferable.

Earlier diagnostic testing would also reduce the period of uncertainty for mothers, and provide more time for them to make a suitably informed choice about an affected pregnancy, whether choosing termination or preparing for the birth of a child with a disease or abnormality.



Non-invasive prenatal diagnosis

In the last ten years an exciting new technique has emerged to extract and analyse small amounts of cell-free fetal DNA

or RNA originating from the placenta directly from maternal blood, potentially allowing non-invasive prenatal diagnosis for a range of genetic diseases and chromosomal conditions, as well as identification of fetal sex and blood group status.

Not only is this approach safer than current invasive approaches, but it can also be performed much earlier in pregnancy, from as little as 6-7 weeks in the first trimester (compared with second trimester for CVS and amniocentesis), making it a highly desirable tool for clinical genetics and other antenatal-related services.

Current and future applications

In the UK, the technique has been developed by scientists and clinicians from NHS genetics

laboratories and blood services, with the most advanced applications the determination of fetal gender or Rhesus status. The approach could also be used for the diagnosis of many different genetic diseases in the fetus, or for chromosomal abnormalities.

Private providers have already begun to offer fetal sex determination using this technique, and there are plans to develop commercial testing for Down Syndrome.



Technical barriers

A number of technical difficulties remain. The major problem is in accurately distinguishing between the maternal and fetal DNA; the latter represents only a very tiny proportion of the DNA

present in the maternal blood, and so a unique fetal characteristic (or marker) must be used to selectively detect the few fetal molecules from the large number of maternal ones.

The most obvious of these characteristics is sex; if the fetus is male, then fetal DNA can be recognized by male-specific (Y-chromosome) sequences. For sex-linked genetic diseases, reliable determination of fetal sex can indicate whether or not the fetus is at risk; for example, in families affected by Duchenne Muscular Dystrophy, male fetuses may develop the disease, but female fetuses will not. In rare cases, identification of an affected fetus can even direct treatment to prevent or limit the disease.

Similarly, it has proved possible to identify fetuses with Rhesus-positive blood group in Rhesus-negative mothers via detection of fetal *RhD* gene sequences. However, the main requirement is for a sex-independent, fetal specific marker that can distinguish the DNA of male or female fetuses from that of the mother; for example, genes that are only active in the placenta.

A different approach (currently in development) is required to detect differences in chromosomal dosage between the mother and fetus, to identify large-scale, chromosomal abnormalities such as Down Syndrome and other aneuploidies.



Limitations and prospects

Even when these requirements have been successfully addressed, there remain limitations to free fetal DNA or RNA analysis. The fetal DNA is fragmented, so that complete fetal genotyping would not be possible, and genetic diseases that involve large expansions of DNA would not be amenable to diagnosis using free fetal DNA.

Ultimately though, this new non-invasive technique could allow improved (safer, earlier and cheaper) antenatal screening for many serious genetic diseases. It is also hoped that it may one day enable doctors to monitor pregnancies much more effectively for serious complications that can affect the health or survival of both the fetus and the mother, such as pre-eclampsia, intrauterine growth restriction or premature labour. Detecting changes in the levels of fetal DNA or RNA in the maternal blood could provide early warning of such conditions well in advance of the appearance of clinical symptoms in the mother.



Ethical, social and other associated issues

Besides addressing the clinical justification and context for different applications, this new approach to antenatal screening and diagnosis inevitably raises some associated issues for consideration. For example, whether testing earlier in pregnancy or for more conditions might place women under pressure to opt for termination, or how the availability of fetal sex determination early in pregnancy via commercial providers for social (as opposed to medical) reasons might impact on society.

Another concern is the feasibility of ensuring that pregnant women who were routinely offered diagnosis (as opposed to initial risk assessment and the option for diagnostic testing) for conditions such as Down Syndrome would be able to give properly informed consent. Addressing this might include ensuring that sufficient time and resources are devoted to the process of seeking consent, and to fulfilling the relevant educational needs of health professionals as well as patients.

PHG Foundation work on free fetal DNA

The PHG Foundation is working with different experts in this field (including stakeholders from the medical, scientific, patient and policy communities) on a project to assess the current status of free fetal DNA analysis for non-invasive prenatal diagnosis, and to make recommendations on actions that will be required for prompt and effective policy and service development in this area. This is to ensure that technical innovation is effectively transferred into clinical practice in a swift but appropriate manner. The findings will be presented to the Joint Committee on Medical Genetics of the British Society of Human Genetics, as well as to all other relevant professional and health service bodies.

The PHG Foundation is an independent multidisciplinary policy research organisation working to achieve better health via the responsible and effective application of genome-based science and technology in health services.