



High expectations

DR KATHY KRAMER LOOKS AT THE ROLE OF GENETIC TESTING IN PRENATAL SCREENING FOR FETAL ABNORMALITIES - ITS BENEFITS, LIMITATIONS AND POTENTIAL.

Many pregnant women worry about whether the baby is okay, and now doctors can offer so much more than soothing words.

There aren't tests for all the potential problems, but general screening for some serious conditions - and special testing for families with particular risks - have become a routine part of Australian prenatal care. In fact, the Human Genetics Society of Australia and the Royal College of Obstetricians and Gynaecologists both recommend that screening be offered to every woman.

Professor Eric Haan is a clinical geneticist at the Women's and Children's Hospital in Adelaide and an expert on prenatal genetic testing. "There are basically two time points when screening is offered for Down syndrome, and the screening picks up some other abnormalities, such as trisomy 18."

"First trimester screening involves an ultrasound at 11 to 13 weeks looking at nuchal translucency (the width of a fluid-filled space at the back of the fetal neck) plus a blood test at nine to 13 weeks."

It picks up about 90% of Down syndrome pregnancies but falsely suggests one in twenty pregnancies is affected when really it is fine.

The screening calls for a skilled ultrasonographer but also relies on the expertise of biochemists, like Dr Michael Sinosich, Scientific Director of Prenatal Testing at Sydney's Sonic Health Care.

"We really need both diagnostic modalities, biochemistry and ultrasound, monitoring different parameters to get an optimal performance in assessment of feto-placental wellbeing," he says.

In the laboratory, pathologists look at a range of different chemicals - known as markers - which are produced by the placenta or fetus, and are detectable in the mother's blood. Marker levels can change when there is an abnormality such as Down syndrome. The results are used to build a picture of how likely it is that a pregnancy is affected by the condition for which it is being screened.

There's nothing magic about the number produced by screening, he says, and different labs can produce slightly different numbers depending on how many biochemical markers they test for, what machines they use and the software they employ. "For example, we use four markers but other units may use two," he says.

Second trimester screening involves a blood test at 14 to 20 weeks (ideally 15 to 17 weeks). It picks up only about 75% of Down syndrome pregnancies and wrongly identifies about 7% of normal pregnancies as being at increased risk.

"Being told about an increased risk often causes anxiety in women at the time and during the pregnancy and even after the birth, and they often remember it very vividly as something that had a big emotional impact," Professor Haan says.

About 80% of women found to have an increased risk choose to go on to invasive diagnostic testing, he says, and most decide not to continue with the pregnancy if the baby is affected.

An ultrasound is also recommended for all women at 19 to 20 weeks. This is not part of Down syndrome screening; it checks the well-being of the pregnancy and can detect physical malformations in the baby, some of which may be due to underlying genetic problems.

"Once you know your risk is high, you have to decide, 'am I going to sort this out or not?' And the main way to sort out whether the baby does or does not have the condition after first

Another side of the story

Fetal genetic testing can also help women who have recurrent early miscarriages or a late miscarriage or stillbirth.

Fetal pathologists have a particular role in diagnosing lethal inherited disorders. In these conditions, there is a 1-in-2 to 1-in-4 chance of future pregnancies being affected. It's important to distinguish these from chromosomal disorders, where the recurrence rate varies from 1-in-3 to 1-in-100, and environmental, sporadic and uterine disorders which don't tend to recur.

Dr Adrian Charles is a perinatal and paediatric pathologist at the King Edward Memorial Hospital in Perth. There are two scenarios that typically call for his services.

The first is where an apparently normal pregnancy ends in miscarriage or stillbirth and the parents consent to an autopsy. "We say, this fetus has a range of abnormalities that amount to this type of syndrome and then we ask for that test to confirm the diagnosis. Sometimes the parents are tested and/or future pregnancies are tested early in the pregnancy with possibility of interrupting the pregnancy if it's abnormal," Dr Charles says.

A question arises over whether chromosomal testing should be offered after all pregnancy losses. "A large number of the first and early second trimester miscarriages are due to chromosomal abnormalities, so we could check for these but the test costs a few hundred dollars and most of these will not recur, so is not indicated on every case," he says.

"There is growing pressure from parents to try to find an answer: you have to be thoughtful of the health dollar but it does ease the parents' minds to identify a cause."

The second scenario is where prenatal screening has identified an abnormality and the pregnancy has been

terminated. Often there is little doubt about the diagnosis, and a post-mortem examination merely confirms, for example, that the fetus has features consistent with Down syndrome.

However, anatomical pathology comes into its own when the diagnosis can only be made by examining specific tissues. For example, an ultrasound may identify cystic kidney disease but only a pathologist can determine which of the many disease types is involved. "We look at the fetal tissues under the microscope and this can give us a very clear idea, even though we don't have a specific genetic test, about what the recurrence rate is, whether it's 1-in-4 or 1-in-2 or pretty low."

"We try to get the abnormality clearly determined so the parents can be counselled."

Dr Diane Payton, an anatomical pathologist, does similar work at the Royal Brisbane Hospital.

"If we can recognise an intact fetus, we do an autopsy," says. "If it is very tiny, we look at the external appearance and may attempt an internal examination and certainly examine the cells. From around ten to twelve weeks, we can do an excision and check the internal organs."

She takes tissue for basic genetic testing in most cases. When she has a specific diagnosis in mind - for example, such as cystic fibrosis - she may take additional cells from relevant organs. However, careful thought is required, because there isn't a screening test for all the potential different genetic problems. "Unless I can suggest what I want them tested for, there's not much we can do."

"This is a specialised area in which I usually seek advice from clinical geneticists," she says. "Many of the investigations are highly specialised and are only performed in selected laboratories in the country."

trimester screening is chorionic villous sampling [CVS] at the end of the first trimester or amniocentesis at the beginning of the second trimester, or amniocentesis after screening in the second trimester.”

If there is an increased risk of a chromosome problem - say, because the woman is more than 35 years old or because a previous pregnancy has had a chromosome abnormality - women can skip screening and go straight to a definitive (rather than screening) chromosome test. This is either CVS from 10 to 11 weeks or amniocentesis at 15 to 16 weeks. Many couples choose CVS because the result is available at a much earlier stage in the pregnancy.

The most commonly performed genetic test is a chromosome test using cells taken from the placenta (via CVS) or shed from the baby and floating in the amniotic fluid (via amniocentesis). “The chromosomes can be seen and counted, so it is a very reliable test for Down syndrome because they can see the extra chromosome,” Professor Haan explains.

DNA tests for literally hundreds of different heritable genetic conditions can also be done. The first such test was performed in 1978 for sickle cell anaemia, Professor Haan says.

The most common tests these days are for thalassaemia, fragile X syndrome, cystic fibrosis, Duchenne muscular dystrophy and infantile spinal muscular dystrophy. If doctors don't know which gene is causing a problem, there may be other ways to test for the disease; for example, if the disease involved a specific enzyme, a chemical pathologist may be able to measure enzyme levels.

However, prenatal genetic testing is not without risk. CVS and amniocentesis can trigger a miscarriage, although the risk is small.

An occasional problem with CVS occurs when some, but not all, of the placental cells contain a genetic mutation. This is called ‘mosaicism’. It usually affects only the placenta, not the baby, so amniocentesis is recommended to check the baby's cells. However, even a normal amniocentesis does not definitely exclude mosaicism.

“Also, some abnormalities may not be detected because they are too small to be seen reliably with a light microscope,” Professor Haan points out.

So, women and their partners need to know that chromosomal testing is not foolproof. 🔥

Goodbye to invasive testing?

Both chorionic villous sample and amniocentesis can trigger a miscarriage, albeit very rarely, so researchers are looking for safer ways to perform fetal genetic testing.

“It is known that there are a small number of fetal cells, shed by the placenta, that circulate in the mother's blood,” geneticist Professor Eric Haan says. “And for many years attempts have been made to isolate these cells for genetic testing. It is clearly possible to do so, but so far reliable, universally applicable and cost-effective testing in early pregnancy has not been developed.”

Preimplantation genetic testing, performed on cells removed three day after fertilisation, is an evolving field which may allow couples to implant only embryos free of a particular gene.

IVF Australia, on its website, points out that this is really only appropriate for couples where there are already family members with serious inherited genetic disorders. “Worldwide researchers are questioning whether the same technology will allow improved embryo selection prior to embryo transfer, and hence improve pregnancy rates per cycle for all couples having IVF treatment. The small studies performed so far have not been of a large enough size or been designed to answer this question accurately.”

MIRAX LIVE RT

Combine the advantages of conventional microscopy with the power of Live Robotic Telepathology

Full remote slide access and microscope control.



Carl Zeiss Pty Ltd
Unit 13, 2 Eden Park Drive
North Ryde NSW 2113 Australia
Nationwide: 1300 365 470
Email: micro@zeiss.com.au
http: www.zeiss.com.au



We make it visible.