Pre-Implantation Genetic Testing of Embryos

A Guide for Couples

Professor Steve Robson

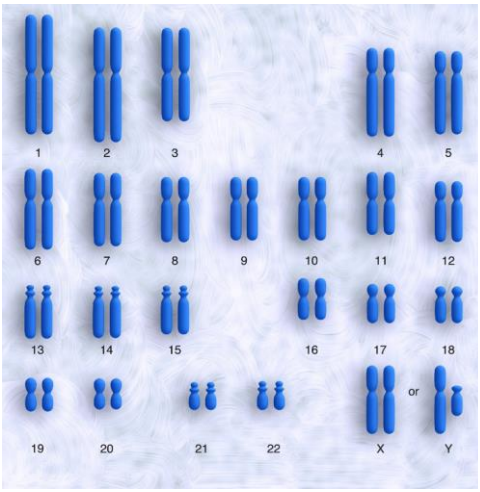
Modern IVF techniques mean the pregnancy is common with fertility treatment. However, even when a healthy-appearing embryo is placed, in many cases pregnancy does not occur. This is obviously disappointing, and has led to a search for the reasons that some embryos do not implant and grow into ongoing pregnancies.

Advances in genetic science and technology now allow for rapid and accurate assessment of the chromosomes in IVF embryos. There is clear evidence that embryos that have a normal number and arrangement of chromosomes are more likely to lead to a healthy ongoing pregnancy.

This eGuide is designed to help you understand the science and technology of genetic testing for embryos. It will also summarise what we know about where the testing is appropriate, and the circumstances when it is likely to benefit.

Chromosomes and Embryos

When an egg is fertilized, a healthy embryo is created with equal numbers of chromosomes from the mother and the father. Each of us has a total of 46 chromosomes, arranged in 23 pairs. Sometimes, however, during fertilization or early in the development of the embryo the number of embryos can change. When an extra chromosome is present in addition to the usual pair, this is called a ***tri***somy. Sometimes one of the pair of chromosomes is missing – this is called a ***mono***somy.



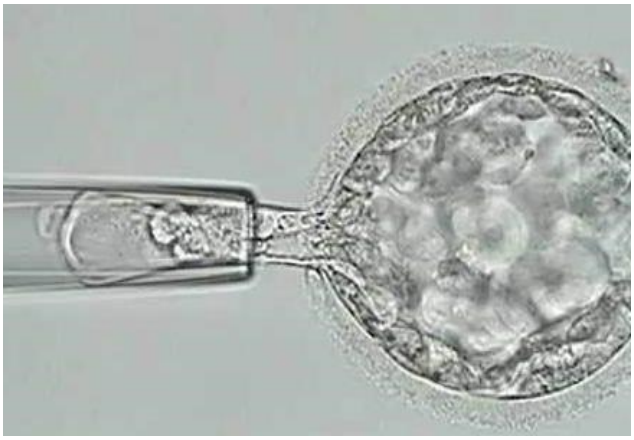
As new genetic testing technologies have become available, they have been used to test the cells within an embryo. Studies and clinical experience with this testing show that many embryos that appear to be healthy and developing normally actually have a different number or arrangement of chromosomes.

When embryos with a number of chromosomes that is different to the typical 23 pairs are used in IVF, pregnancy is much less likely to happen and, if pregnancy does occur, miscarriage is more likely to be the outcome.

For this reason, there has been a great deal of interest in whether performing genetic testing on embryos during IVF is beneficial. However, genetic testing is expensive and there has been a great deal of controversy about the correct role of genetic testing, and which women and couples are most likely to benefit from the testing.

The Testing Process

Testing the chromosomes of an embryo requires a small biopsy to be taken. This is usually performed on the fifth day of embryo development, at the 'blastocyst' stage. The embryo often is beginning to 'hatch' from its shell, and a microscopic glass suction instrument is used to remove a small number of cells.



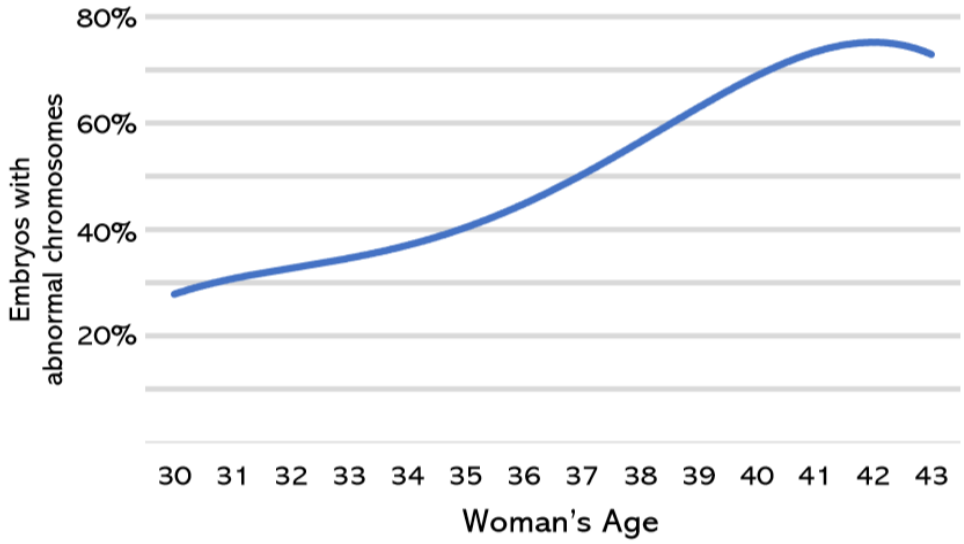
The cells are then prepared for the testing process, and this can take a week or more. During this time, the embryo is frozen (cryopreserved) awaiting the results of genetic test.

The testing process involves isolating the chromosomes and then breaking the DNA that they are made of into small pieces. Using a highly-computerized process called 'comparative genomic hybridization (CGH),' it is possible to determine whether the embryo contains 23 chromosome pairs.

There are four possible outcomes of the testing process. The testing might determine that the embryo has 23 chromosome pairs and is suitable for transfer. Alternatively, it might show that there is a different number or arrangement of chromosomes meaning that the embryo is very unlikely to lead to a healthy ongoing pregnancy. Sometimes, there may be different numbers of chromosomes in each of the cells in the sample – this is known as a 'mosaic' embryo. Lastly, it is possible that the test will not provide a result and the number of chromosomes in an embryo remains unknown.

When is Testing of Value?

The first group who are likely to benefit from testing of embryos is women in an **older age group**. This is because that increasing age of the woman is closely associated with abnormal numbers of chromosomes in the embryo. The graph below shows the typical proportion of embryos created in IVF that have an abnormal number of chromosomes on testing, according to age.



While embryo genetic testing seems, on the surface, to be a very useful option large studies of the technique have not been quite so reassuring.* Scott's study revealed the about 10% of embryos diagnosed as abnormal on testing actually were normal, and that about 7% of embryos that on testing would have been discarded actually led to pregnancy. There is also evidence that the biopsy process itself might cause trauma to the embryo. Another large clinical trial – the 'STAR' trial – found that for women aged less than 35 years, as many as 40% of embryos that would have implanted and grown into pregnancy might have been lost as a result of the testing process and its results.

Overall, it is likely that embryo genetic testing does not increase the chance of pregnancy in women under the age of 35 years and, for these women, is probably expensive and unnecessary. For women aged 36 and older, testing probably increases the chance of pregnancy IF there are a large number of embryos to choose from and test.

*Scott. Comprehensive chromosome screening… *Fertility and Sterility* 2012; **97**: page 870

Recurrent Pregnancy loss

It seems likely that women who have had recurrent pregnancy loss (recurrent miscarriage) also are likely to benefit from IVF and genetic testing of embryos. This is because the most common cause of early pregnancy loss is an abnormal number or arrangements of chromosomes in the embryo.

Diagnosis of Genetic Conditions

Embryo testing is a very effective technology to help women and couples who carry genes for diseases such as spinal muscular atrophy. Embryos can be tested for the abnormal gene (mutation), and only embryos that do not carry the gene and that have a normal number of chromosomes are transferred to ensure a healthy pregnancy.

Summary

Embryo Genetic Testing in a Nutshell

Advances in the science of genetic testing now allow very accurate testing of embryos in IVF. This testing is particularly useful for two things:

- Testing the number of chromosomes in an embryo, and
- Testing whether a genetic change (mutation) associated with a disease or condition is present in an embryo.

As women become older, the more likely it is that embryos will have an abnormal number or arrangement of chromosomes. Embryos with these changes are less likely to lead to pregnancy, and have a greater risk of miscarriage. However, it is likely that the testing process – taking a biopsy from an embryo – might cause damage the reduces the chance of pregnancy. The genetic testing also is potentially expensive.

Large studies suggest that routine testing of embryos in otherwise healthy young women (women in their early to mid-30s) does little to increase the chance of becoming pregnant. However, women in their late 30s and early 40s are more likely to benefit.

There are two situations were genetic testing of embryos is likely to be of benefit to women and couples:

- Where there is a history of **recurrent early pregnancy loss** – where women become pregnant but have repeated distressing miscarriages, and
- Where women have had three or more healthy embryos transferred in IVF but there has been no ongoing pregnancy.

When women or couples are known to carry a genetic change – a mutation – and wish to have a pregnancy where the baby does not carry the mutation. In this process, IVF is undertaken and embryos are tested. Embryos that do not carry the mutation and that have the normal number of chromosomes can be identified, allowing a choice for couples.

About Professor Steve Robson MD PhD

Steve Robson is internationally recognised as one of the world's foremost specialists. In 2019, Steve was the recipient of the American College of Obstetricians and Gynaecologists highest honour - the **Distinguished Service Award**.

Steve undertook his specialist training in Australia, England, and Canada. In his first year of formal training in IVF and reproductive medicine in 1998 he won the **Young Clinician's Prize** of the Fertility Society of Australasia (FSA).

Steve Robson is the immediate past-President of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), and is Professor in Obstetrics and Gynaecology at the Australian National University. He holds two doctorates, both a Doctor of Medicine (MD) and PhD, as well as Fellowships of the Australian, British, and American Colleges of Obstetricians and Gynaecologists.

Steve was appointed by the Health Minister to the National Health and Medical Research Council (NHMRC), as well as to the National Endometriosis Advisory Group – part of the National Action Plan for Endometriosis.

Professor Robson is one of the authors of the *Oxford Textbook of Obstetrics and Gynaecology*, and as a researcher is the author of hundreds of research articles, editorials, reviews, and book chapters. His research has been published in the most prestigious international IVF journals – *Fertility and Sterility*, and *Human Reproduction*.

He has published research papers not only on IVF and assisted reproduction, but also on reproductive surgery and endometriosis surgery.

In addition, Professor Robson is Chair of the organising committee for the International FIGO meeting in 2021, and is a member of the internationally ground-breaking *Mackenzie's Mission* project.