Test for chromosome abnormalities sheds light on genetic origins of faulty eggs

July 5 2011

Researchers are developing a new way to test a woman's egg for chromosome abnormalities that avoids the need to manipulate and biopsy the egg itself. The research may also shed light on the crucial role played by certain genes in the development of chromosome abnormalities that are a major cause of miscarriages and conditions such as Down's syndrome.

At present, when a woman undergoes preimplantation genetic screening (PGS) in a fertility clinic, doctors are trying to select an egg or an embryo that is healthy and doesn't have a chromosome abnormality such as an extra copy of chromosome 21, which causes Down's syndrome. In order to establish this, they either have to biopsy a part of the egg called the polar body or remove a cell from the embryo for screening. Both procedures are expensive, invasive and can damage the egg or embryo.

Dr Elpida Fragouli, a research scientist at the University of Oxford and director of cytogenetics at Reprogenetics UK, will tell the annual meeting of the European Society of Human Reproduction and Embryology today (Wednesday) that she and her colleagues have discovered that cells surrounding the egg can provide information about the genetic and chromosomal status of the egg.

She explained: "In the ovary, human eggs are surrounded by a cloud of tiny cells, known as cumulus cells. The egg and the cumulus cells are in constant communication and depend upon each other for continued viability. We wondered whether the presence of chromosome

abnormalities, which are extremely common in human eggs and are incompatible with the formation of healthy embryos, would have an effect on the surrounding cumulus cells. This is important for two reasons. Firstly, an increase in the understanding of how chromosome abnormalities arise in eggs is desperately needed. For several decades we have been aware that chromosome problems are common in human eggs, that they are the major cause of miscarriage, and that they are responsible for conditions such as Down syndrome. Yet the origins of chromosome abnormalities remain poorly understood. A better understanding of the factors that lead to chromosome abnormality may help us think of ways to reduce their frequency.

"Secondly, if chromosome abnormalities in the egg result in changes in the surrounding cumulus cells, it is possible that this could lead to a new way of testing eggs, before they are fertilised, revealing those with the correct number of chromosomes as well as those that are abnormal. This could help patients undergoing IVF, by identifying the eggs most likely to make a baby without having to use an invasive and expensive procedure. Cumulus cells are routinely stripped off eggs during IVF treatments and are usually discarded, so it should be straightforward to obtain them for analysis."

Dr Fragouli and her colleagues examined the polar bodies and cumulus cells from 26 eggs donated by women undergoing PGS. Polar bodies are by-products of egg formation. They contain the chromosomes discarded by the egg as it moves from having the same number of chromosomes as all the other cells of the body (46) to the number that eggs and sperm have (23). The unfertilised egg needs to discard half of its chromosomes in order to make way for those that will be delivered by the sperm. If things go wrong and a chromosome abnormality arises in the first polar body (e.g. an extra copy of chromosome 21), then the corresponding egg will have the reciprocal abnormality (e.g. a loss of chromosome 21). The researchers identified a total of 13 normal and 13 abnormal eggs by

testing the polar bodies.

"We then looked to see how active individual genes were in the cumulus cells that had surrounded each egg. This was done using two different methods. First we used a microarray, a powerful genetic technology that allows the activity of thousands of genes to be simultaneously tested. We found that 729 genes were expressed differently in cumulus cells that had surrounded eggs that contained an incorrect number of chromosomes. In other words, these genes were either more or less active than we would usually expect. In particular, 14 genes appeared to have highly significant differences in activity when their corresponding egg was abnormal," said Dr Fragouli.

"We then used a second technique to confirm the initial findings. For this purpose we focused on 95 of the 729 genes that had been originally identified, including the 14 very significant genes. The method we used is known as real-time polymerase chain reaction (PCR). Real-time PCR is considered to be the most accurate way of quantifying the activity of genes, but is difficult to apply to large numbers of genes, which is why we used the microarray for the initial round of screening. The real-time PCR confirmed that most of the genes highlighted by the microarray do indeed show altered activity in cumulus cells associated with abnormal eggs.

"We are still in the process of establishing the usefulness of these genes as non-invasive markers of egg chromosome status and quality. However, it is interesting that several of these genes are involved in vital cellular functions of the cumulus cells and egg they enclose, such as cell signalling and regulation, hormonal response and cell death, and so they may shed light on the genetic origins of chromosome abnormality."

The researchers are running further tests to see how well results from the expression of genes in cumulus cells compare with the more established

PGS method for identifying faulty eggs. If there is a good correlation, then they plan to run a clinical trial in about a year's time.

"The general idea is that instead of manipulating and biopsying the oocyte, a test examining the corresponding cumulus cells, which are currently discarded during regular IVF treatment, is developed. At the moment, as we are still working on this, I would envisage that results would potentially be obtained between three and five hours after egg retrieval. Theoretically, it would be possible to avoid fertilisation of abnormal eggs, which might have some ethical advantages over the current invasive methods that generally take longer. In addition, current diagnostic methods available for preimplantation genetic screening only provide information on the chromosome status of an egg. While this is a very important aspect of egg quality, it is not the only factor influencing the ability of the egg to lead to a successful pregnancy. The extra genetic information that we may be able to derive from examining the cumulus cells may give us a more detailed evaluation of an egg's potential to lead to a successful pregnancy and a healthy live birth," concluded Dr Fragouli.

Provided by European Society of Human Reproduction and Embryology