Preimplantation Genetic Testing For Monogenetic Disorders (PGT-M)

Concept Fertility Centre

12.2.12

How Does Preimplantation Genetic Testing work?

Preimplantation Genetic testing requires couples or individuals to go through routine IVF egg collection and Intracytoplasmic sperm injection (ICSI; refer to information sheets 12.3.5; 12.3.8) so that their embryos can be tested before being transferred to the woman's uterus. Five or six days after fertilization when the embryos are at the expanded blastocyst stage of development around six of the embryonic cells can be removed by embryo biopsy. The embryo biopsy procedure involves making a fine hole in the zona pellucida (outside shell surrounding the embryo) and gently removing the cells which are called trophectoderm cells. The cells are then processed and tested to see if they are free from the genetic condition being tested for and and have the normal number of chromosomes.

The embryos that are identified as being normal can then be transferred to the woman's uterus in the hope of establishing a healthy pregnancy.

The embryo biopsy procedure is routinely performed in many centers around the world and does not appear to harm the developing embryo.

Chromosome Screening

Screening to see if the embryo has the correct number of chromosomes can also be done. Growing evidence suggests that a major factor in the failure to establish or maintain a pregnancy is when the cells in the embryo contain the wrong number of chromosomes, a condition termed aneuploidy. It has been known for some time that a significant number of human embryos have the wrong number of chromosomes (aneuploid). It is normal for a cell to contain 22 pairs of chromosomes plus the sex chromosomes, either XX for females or XY for males. Problems can arise when the embryo's cells contain too many or too few chromosomes (see back page for an expanded description).

Who are eligible for PGT-M?

- Where there is a known diagnosed family monogenic disorder.
- Approval for each case must be granted after application to the Reproductive Technology Council. The application requires a letter of support from a Clinical Geneticist.

Preparation for PGT-M

Appointment with Clinical Geneticist

This appointment is to discuss all the reporductive options available including PGT-M. The Clinical Genetisits will write a summary of the meeting and state their support of using PGT-M. This letter is submitted to the Reproductive Technology Councill as part of the PGT-M approval applcation.

Meeting with Concept Scientific Director

At this meeting information about the PGT-M process will be provided.

PGT-M test evaluation inquiry

Concept will submit an inquiry to the external genetics laboratory to see whether they can develop a specific test for the condition. A copy of any genetics reports is needed to send with the inquiry.

PGT-M Feasibility test

The feasibility test is necessary so that the genetic laboratory can design a test to identify the family gene in the embryos. For the feasibility test a blood sample or cheek swab from the couple is taken and sent to the genetics laboratory. It is likely that other family members will be asked to provide a blood sample or cheek swab.

Application to the Reproductive Technology Council (RTC)

In 2004 the *Human Reproductive Technology Act 1991* was amended to allow genetic testing of embryos. In accordance with this amendment each individual PGT-M case has to be approved by the RTC. Concept will submit the application which must include a letter of support from a Clinical Geneticist.

Meeting with Concept Scientific Director

Once the feasibility test has been completed and a test developed a second meeting with Scientific Director is required. At this meeting all the details of the IVF and embryo biopsy processes will be discussed. Following this meeting the IVF cycle can commence.

How is PGT-M managed at Concept?

- Egg collection and ICSI.
- Embryos are biopsied on day 5 or 6 and frozen.
- Biopsied cells are sent to a genetics laboratory for genetic analysis.
- Results received in two to three weeks.
- Frozen embryo transfer. It is recommended not to start a frozen embryo transfer cycle until the results of the testing are known.
- Once you have informed Concept that you would like to go ahead with testing please confirm your intention to start the test process by email to pgs@conceptfertility.com.au You will then be placed on the list for testing and be contacted with the test dates.

Considerations

- There is some increased risk of birth abnormalities in children born after ICSI (5% in naturally conceived children and 8% after ICSI).
- For the embryo biopsy and testing to take place the embryos need to be an expanded blastocyst on day 5 or 6. Some embryos may not be suitable for biopsy.
- It is possible that the embryo might be damaged during the biopsy procedure although this is very rare (<1%) at Concept.
- It is possible that all the embryos will have the genetic disorder or the wrong number of chromosomes and therefore no embryos would be available for transfer. Research has shown that in situations where all the embryos were affected in the first cycle, 50% of cases had an embryo suitable for transfer in their second cycle.
- Some embryos might not develop to day 5/6 and be suitable for biopsy. This is due to developmental problems present in the embryo.
- Even though an embryo is genetically normal there can be other problems that prevent the embryo from implanting and becoming a healthy pregnancy.
- There is a 6% chance an embryo may not survive the freezing process.
- If a low number of embryos (<5) are suitable for testing it might be possible to have another egg collection procedure and then test both sets of embryos. Concept will need to apply to the Reproductive Technology Council for approval to undergo an egg collection procedure if three or more embryos are in storage.
- There is a cost for PGT-M (not included in IVF cycle related fees) and this is not covered by Medicare or private health insurance. Please see fee schedule (12.4.2).

Limitations of PGT-M

- The test results are not 100% accurate. Pre-natal screening is therefore recommended.
- Mosaic embryos- it is possible that the cells of the embryo are different to the biopsied trophectoderm cells and have a different set of chromosomes. Mosaic embryos can be detected if a mixture of normal and abnormal cells are taken at the biopsy. The difficulty arises when biopsied and tested cells are normal and the cells remaining in the embryo are abnormal (eg only normal cells taken at biopsy). This is a limitation of testing only a small number of cells.
- The results might be inconclusive for some embryos, and for some embryos a result is not possible, although these occurrences are rare (<1%).
- PGT-M cannot identify other abnormalities or birth defects that are not associated with the gene disorder or the number of chromosomes and therefore doesn't guarantee a healthy pregnancy or birth.

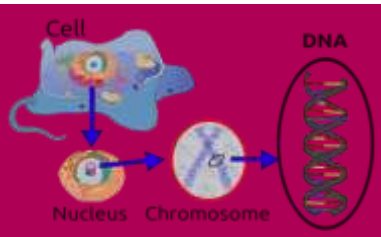
Stages Involved In PGT-M

Embryo Biopsy –
Embryo biopsy procedure is performed by careful removal of a small number of trophectoderm cells that have herniated through the zona pellucida (outside shell) of an expanded blastocyst. The biopsy sample is then placed in a tube for testing and the embryo is cryopreserved. The biopsied cells are sent interstate to an external genetics laboratory.

Genetic Analysis –
To test for the presence of a specific genetic condition, techniques such as polymerase chain reaction (PCR), SNP array, karyomapping or next generation sequencing (NGS) can be used. It might be possible to include chromosome screening with these techniques.

Frozen Embryo transfer cycle –
Unaffected embryos can be transferred on day 5 or 6 in a frozen embryo transfer cycle. Excess normal embryos can remain frozen and stored for future use.

Embryo biopsy



Biopsied cells contain a nucleus with all the genetic information that is needed.

Genetic analysis
Genetic analysis can be done using one of the tests below:

SNP array,

PCR,

Karyomapping, or

NGS

Frozen embryo transfer procedure
Frozen genetically suitable embryos can be thawed and transferred to the uterus. One embryo is transferred per procedure.

Questions and Notes

Genetics and chromosomes

Our bodies are made up of millions of cells which each contain a complete copy of our individual genetic makeup (genes). The genes are tightly packaged together in the cells in the form of chromosomes. Each cell should contain 46 chromosomes (22 pairs and the two sex chromosomes). The chromosomes are numbered from 1-22 and the sex chromosomes are called X and Y. A female will have two X chromosomes and a male one X and one Y.

Eggs and sperm contain 23 chromosomes, made up of 22 chromosomes and sex chromosomes (X or Y). When the egg and sperm join together at fertilization the embryo should have 46 chromosomes in its cells, made up of 22 pairs of chromosomes numbered 1 - 22 and the sex chromosomes; XX for female or XY for male.

A chromosomal condition occurs when an individual is affected by a change in the number, size or structure of his or her chromosomes. These changes in the cells may result in problems in growth, development and functioning of the body systems.

There are two main types of chromosome changes that can occur – structural and numerical. Structural changes include chromosome translocations which occur when chromosomal material from two or more chromosomes are rearranged. Numerical changes occur when there is missing or extra chromosomes. For example Downs Syndrome occurs when there is an extra copy of number 21 chromosome (also called trisomy 21).

Human embryos have a high rate of chromosome imbalance (aneuploidy) and this is closely related to female age. The table below shows the frequency of normal embryos (euploid) tested on day 3 and 5 of development and female age. This provides a percentage estimation of the likely chance a woman of a particular age would have a normal embryo.

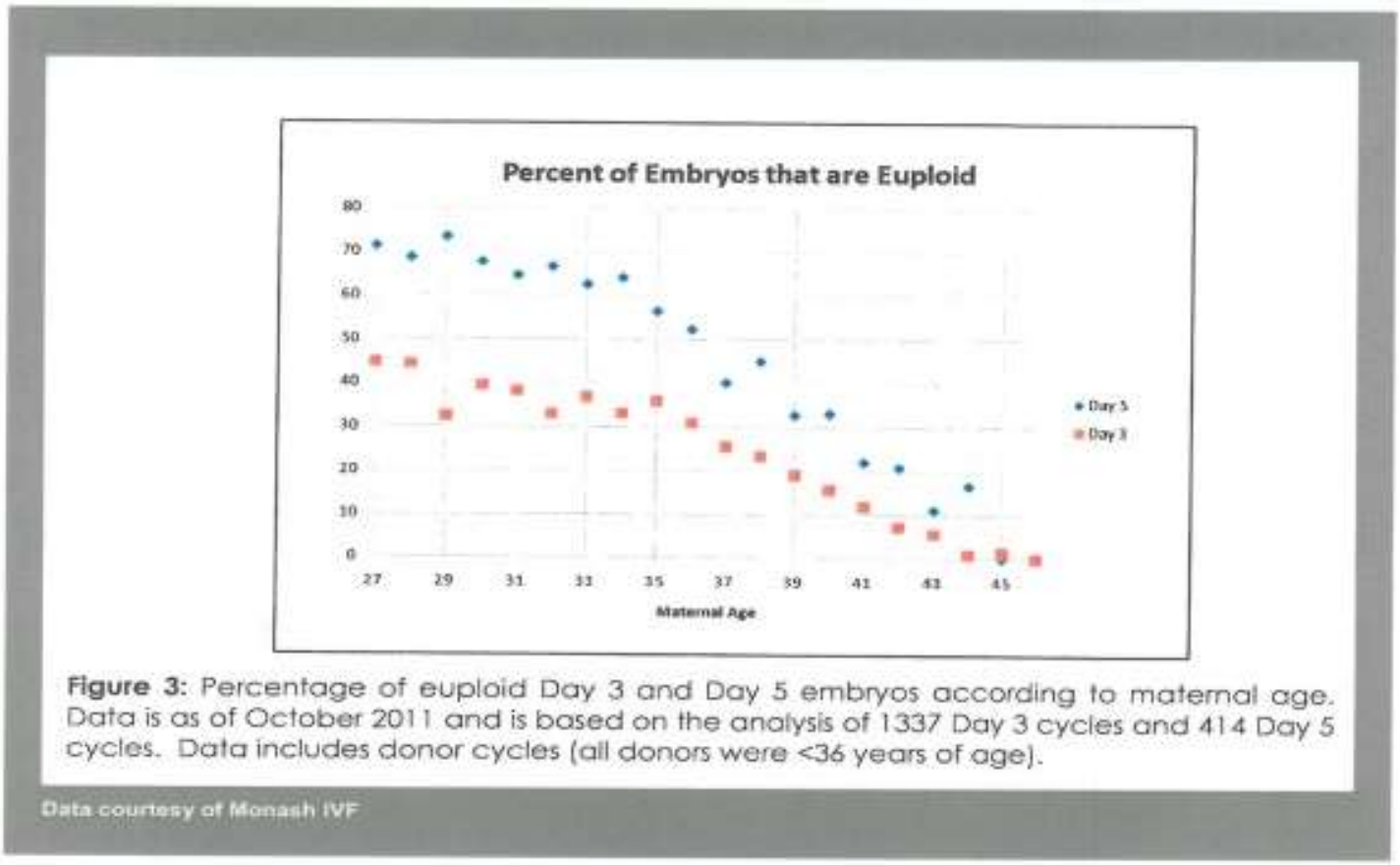


Figure 3: Percentage of euploid Day 3 and Day 5 embryos according to maternal age. Data is as of October 2011 and is based on the analysis of 1337 Day 3 cycles and 414 Day 5 cycles. Data includes donor cycles (all donors were <36 years of age).

Data courtesy of Monash IVF

Contact Us

218 Nicholson Road
Subiaco WA 6008
Telephone: (08) 9382 2388

concept@conceptfertility.com.au

www.conceptfertility.com.au