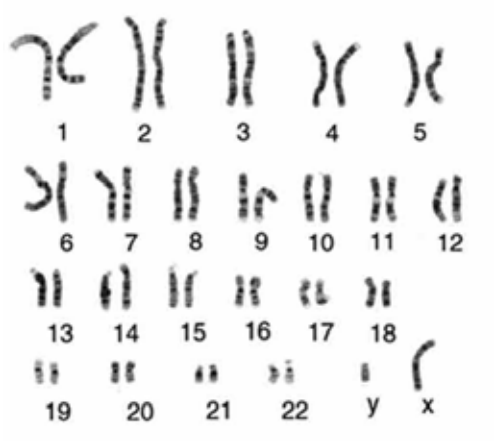
City Fertility Centre
your partners in life

ADVANCED EMBRYO SELECTION using array CGH

Advanced Embryo Selection (AES) is a term used to describe a genetic test carried out on IVF embryos prior to transfer. AES does not diagnose any specific diseases but looks more generally at the genetic makeup of the embryo.

In order to understand genetic testing of embryos we have to first grasp some basic cell biology; each cell in the body has 46 CHROMOSOMES, except eggs and sperm which have 23 each. The egg and sperm combine to give the offspring a total of 46 chromosomes - half from the egg and half from the sperm. Each chromosome has many genes, or instructions, along its length. The genes control characteristics like the hair or eye colour of your baby.

Below is a diagram of normal male chromosomes, notice that the chromosomes are made up of pairs, two of each plus an XY for males and an XX for females (making a total of 46).



When an egg and sperm combine to form an embryo, there is sometimes an extra chromosome present; we see this with disorders such as Down's Syndrome where there are 3 copies of chromosome 21. The extra chromosome can come from either the egg or the sperm and this aberration can happen in natural conception. In addition to there being extra chromosomes, there may be chromosomes missing from the embryo. In most cases, either a loss or gain in chromosomes will result in an embryo that will not implant or grow normally.

If an embryo contains the wrong number of chromosomes, let's say for example one is missing, then the cells in that embryo are missing a whole set of instructions. If there is an extra chromosome the cells will malfunction by following those instructions twice as often as they should.

ANEUPLOIDY (or CGH) testing is the name used to describe counting the number of chromosomes present in a cell. If a cell does not have exactly 46 chromosomes, it is "aneuploid". CGH testing of embryos allows us to determine the number of chromosomes in each embryo before they are transferred into the mother's uterus or frozen for future use.

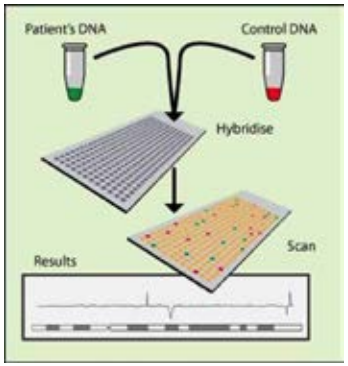
It is possible to test each individual embryo created through IVF and count the number of chromosomes present. This is done by taking cells from the embryo on either day 3 or day 5 of development and carrying out tests on those cells to analyze their genetic makeup. The embryo can easily compensate for the removal of cells with a few cell divisions. In good hands, the biopsy of an embryo has little effect on its growth, although it may slow its growth down slightly.

A photograph of an embryo biopsy on day 5 of development can be seen below:

COMPARATIVE GENOMIC HYBRIDISATION (CGH)

CGH is a genetic test of eggs and embryos. It offers much more precise information than standard genetic testing has in the past.

During CGH testing all chromosomes including X and Y are analysed and compared to a sample of "normal" DNA. The embryonic DNA is labeled green and the normal DNA is labeled red. If the embryo has a normal number of chromosomes, then there will be an equal amount of embryo (green) DNA and "normal" (red) DNA and the result should appear yellow.



If the embryo is missing a chromosome, that area appears more red (ie extra "normal" DNA). If the embryo has an extra chromosome that area appears more green.

A computerised scanner interprets the results of the slides which are then verified by a trained scientist.

The advantage of doing CGH testing over traditional testing is that all 23 pairs of chromosomes can be tested and the results are more accurate when testing for aneuploidy.

BENEFITS OF CGH TESTING

CGH may increase IVF pregnancy rates by helping to identify the embryos most likely to produce a pregnancy, allowing them to be prioritised for transfer.

In most cases, chromosomally normal and abnormal embryos look identical down the microscope. Without genetic selection an embryologist cannot differentiate between them and it is possible that chromosomally abnormal embryos could be inadvertently transferred to the uterus.

Most chromosomally abnormal embryos do not implant, or will miscarry shortly after implantation. By ensuring that embryos with a normal number of chromosomes are identified and given maximum

priority for transfer to the uterus, the probability of conceiving a healthy child should increase after CGH testing.

CGH for aneuploidy has been reported to double implantation rates in some studies, although this has yet to be confirmed in randomized controlled trials. CGH testing of embryos is likely to reduce miscarriage and it is widely accepted that genetic selection significantly reduces the chance of having a pregnancy affected by genetic disorders.

RISKS INVOLVED WITH CGH

•EMBRYO BIOPSY Advanced Embryo Selection (AES) does not guarantee the birth of a normal baby. It is unknown whether biopsied embryos have the same likelihood of implanting as embryos without biopsy. It is possible that for these embryos, biopsy may slightly lower implantation rates. However, for embryos with an AES result, selection of chromosomally normal embryos may more than compensate for any negative effect of biopsy, increasing the probability that the embryos transferred will implant.

If an embryo is damaged by the procedure, it may not produce an embryo suitable for transfer into the uterus. The risk of damaging an embryo during removal of the cells is less than 1%.

•THE PREPARATION OF BIOPSIED CELLS After biopsy, the removed cells are placed in a small test tube and their DNA is amplified. The cells are no longer viable in any way after this process and can only be used for CGH. Some biopsied cells (less than 2% per cycle) may not yield a test result: some may contain degraded DNA, which cannot be amplified; or the cells may be lost during the transfer to the test tube. Embryos without a result from the analysis may still be transferred, but the advantages of AES will not apply.

•MISDIAGNOSIS The risk of a clinical misdiagnosis resulting in a fetus or baby with chromosome abnormalities after AES is less than 2%. This is still lower that the risk of having a fetus or baby with chromosome abnormalities without AES. Due to the chance of misdiagnosis, as well as the presence of types of chromosome abnormalities which are not tested for, we strongly recommend prenatal testing by Chorionic Villus Sampling (CVS) or an amniocentesis.

•NO NORMAL EMBRYOS The test may find that none of the embryos are normal, in which case there will be no embryo transfer procedure. The likelihood that this will happen is influenced by a variety of factors, the most important of which are the patients age and the number of eggs retrieved. For female patients over 40 years of age around 10-15% of cycles do not have any embryos transferred due to all embryos being abnormal. For younger patients the risk of all embryos being abnormal is less.

•NO DIAGNOSIS OR PARTIAL DIAGNOSIS Some embryos will have no diagnosis, due to the loss of the biopsied cells, or poor DNA quality (often found in damaged or dying cells). Embryos without a result can still be transferred, but the benefits of AES will not apply in such cases. Because of the possibility of misdiagnosis, your pregnancy should be carefully monitored. Between 10 to 18 weeks, we strongly recommend prenatal testing by CVS or an amniocentesis. The fetus should also be monitored with ultrasound examination to check its growth and development.

ALTERNATIVES

The alternative to AES is to undergo an IVF cycle with no genetic testing of the embryos. In this case standard prenatal testing for abnormalities (chorionic villous sampling, amniocentesis and ultrasound examination) would be carried out if a pregnancy resulted from fertility treatment. These methods will identify pregnancies affected by problems such as Down's Syndrome, but do not increase the chances of a successful IVF cycle.

You are not obliged to undergo AES even if your doctor recommends it. The risks, benefits and alternatives of this testing should be discussed thoroughly with your genetic counsellor, fertility specialist or the person performing/ordering the tests.

COSTS

Fees for AES are in addition to the cost of the IVF cycle.
The finance department of City Fertility Centre will advise you of the fees.

WHO IS AES RECOMMENDED FOR?

Patients with:

- Recurrent miscarriage
- Previous unsuccessful IVF cycles
- A family history of chromosomal disorders
- Advanced maternal age
- Any IVF patients wishing to increase their chance of a successful cycle.

Benefits include:

- Improving IVF rates by prioritising chromosomally "normal" embryos for transfer
- Supporting elective single embryo transfer to reduce multiple pregnancies
- Reducing incidence of miscarriage
- Reducing the risk of a liveborn child with a chromosomal abnormality.
- Reducing the number of IVF cycles necessary to achieve a successful outcome.

MFS30

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