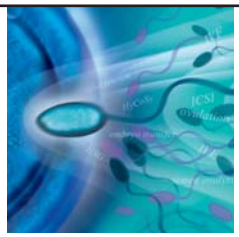

Developments in infertility therapy

Diagnosis of genetic disease in embryos

BACKGROUND The general practitioner plays a vital role in assisting couples through the difficult and emotional field of assisted reproductive techniques including in vitro fertilisation (IVF).

OBJECTIVE This article discusses the most recent developments in IVF so that GPs may better explain this ever changing field of medicine to their patients.

DISCUSSION This article begins by explaining how sperm can be brought together with oocytes for fertilisation outside the body, and then moves on to selecting the most genetically appropriate embryos for implantation. From this comes the issue of examining the fertilised oocytes to detect abnormalities, and the options available to couples with ethical concerns. The promise of regenerative medicine through the use of stem cells is also discussed.

Regular IVF

In vitro fertilisation (IVF) is established as a method to assist infertile couples to have children. The basic method involves treatment of the female partner with fertility drugs over several weeks to induce a batch of eggs to develop in the ovary instead of the single egg that is normally formed each menstrual cycle. The fertility drugs usually result in about 8–10 eggs that are recovered using ultrasound guided needle puncture through the vagina. Women are given sedation or light anaesthesia to recover the eggs.

Immature oocyte collection

Fertility drugs can produce uncomfortable side effects and in some rare cases, dangerous hyperstimulation. Immature oocytes can be recovered without fertility drugs – usually few are recovered, and they can be matured in the laboratory. Immature oocyte collection (IOC) may be preferred by women wanting to avoid treatment with fertility drugs.

ICSI and IVF

Eggs that are collected are fertilised with the partner's sperm, which is usually recovered by masturbation. The normal IVF procedure involves mixing eggs and sperm for a few hours to enable a sperm to penetrate the soft egg shell (zona pellucida). In cases of male infertility where few sperm are produced, or sperm are immotile or structurally abnormal, the sperm is injected directly into the egg (intracytoplasmic sperm injection [ICSI]) using a micromanipulator. In some cases, sperm are recovered from the testicles of infertile men who do not have any sperm in their ejaculates.

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Pre-implantation genetic diagnosis

Fertilised eggs are termed 'embryos', and the single egg cell divides into two cells, four cells, eight cells, and so on, at about 18–24 hour intervals. On the morning of the third day after mixing sperm and eggs or ICSI, the eight-cell embryos can be biopsied – a single of two cells removed using a micromanipulator. The sampled cells can be analysed for chromosomal errors (eg. Down syndrome) or inherited genetic diseases (eg. cystic fibrosis, Huntington disease, muscular dystrophies, thalassaemia). Embryos with chromosomal errors or genetic mutations for genetic diseases can be discarded, and only the apparently normal embryos transferred to the woman's uterus. This procedure is known as pre-implantation genetic diagnosis (PGD) and involves the use of sophisticated molecular biology techniques available in some major IVF clinics.

It is also possible to identify embryos with high probability of diseases such as breast cancer, diabetes and other serious diseases. Pre-implantation genetic diagnosis can be used to ensure that high probability diseases are not passed on to children. This requires genetic counselling by registered professionals to ensure patients understand the probability of diseases with and without PGD.

Pre-implantation genetic diagnosis is also used in rare situations to identify embryos that are compatible for transplantation of umbilical cord blood stem cells to seriously ill siblings with blood cell diseases such as Fanconi's anaemia, lymphoma and leukaemia. Embryos that are compatible are identified by PGD, transferred to the mother, and the cord blood cells harvested for stem cells at birth. This has been successful in the recovery of very sick children where compatible bone marrow transplants were not available.

It is also possible to sample cells from the day 5 or day 6 embryo, which is known as a 'blastocyst'. The cells are sampled from the trophoblast – the cells that attach the embryo to the uterus. Usually 5–20 cells are sampled for chromosomal and genetic analyses. At this stage, it is possible to select the most viable genetically normal embryo for transfer to the woman.

Embryo transfer

In the interests of minimising the number of multiple births, it is recommended that only one or two embryos be transferred to the woman's uterus. This is a painless procedure in which a fine catheter containing the embryo(s) is carefully threaded through the vagina and cervix to deposit them within the uterus. New biochemical and molecular methods have been devised to identify the most viable embryos for transfer. It is expected that pregnancy rates are 25–40% each cycle of treatment, so patients can expect a one in 2 or 3, to one in 5 cycles of IVF treatment to result in a healthy baby.

Egg and embryo freezing

Excess embryos can be successfully frozen at any stage. This is usually done after selection of embryos for transfer. It enables couples to have thawed embryos transferred in the event of no pregnancy from the initial transfer, or if another child is desired. The success of transferring frozen-thawed embryos is around a 25–35% pregnancy rate (one in 3, to one in 4 cycles of frozen-thawed embryo transfers) for every 1–2 embryos thawed. Patients will often have embryos remaining frozen after completing their treatment for infertility. These embryos can be donated to other infertile couples, destroyed, or donated for research, depending on the desires and consent of the couple. A licence from the National Health and Medical Research Council is required by scientists wishing to use embryos for any type of research and must be accompanied by consent from the IVF couple.

Unfertilised eggs can be frozen, but the efficiency is considerably less than for fertilised eggs or embryos. It would be expected that only 1–3% of frozen eggs develop to a healthy baby. This option may be chosen if patients have ethical concerns about freezing embryos.

Ovarian transplantation

It is possible to freeze ovarian tissue samples for patients who may be concerned about loss of fertility due to radio- or chemotherapy, or surgery for diseases such as cancer and endometriosis. At the present time, it is known that the tiny primordial follicles from which eggs are recruited to grow and develop in the ovary will survive freezing and thawing. However, there is little evidence at the present time that fertility can be regained after thawing and transplantation of frozen ovarian tissue, despite a single pregnancy recently reported in Belgium.[1]

Stem cells and regenerative medicine

Human embryonic stem cells can be produced from embryos that are leftover from IVF treatment. With consent of the couple, the excess embryos can be thawed for growth to the blastocyst stage and the nest of inner cell mass cells isolated to become embryonic

stem cells. These cells are 'immortal' (grow continuously for many years) and are pluripotential (form any cell of the body). Research is presently underway to demonstrate these cells can be used to treat severe degenerative diseases such as diabetes, Parkinson disease, motor neurone disease, multiple sclerosis, cardiovascular disease, and respiratory disease.

Umbilical cord blood cells include adult haematopoietic stem cells that are capable of regenerating bone marrow and hence, all the cells of the blood. There may also be other useful stem cells in cord blood, so it can be worthwhile considering the banking of the baby's cord blood at birth for future use by patients with serious blood diseases. The cord blood cells are completely compatible for transplantation to the baby they are obtained from, and may be used by the child or when an adult – although the probability for the baby's own use is very low.

Conclusion

General practitioners should feel empowered to discuss these new techniques with their patients and to help them understand the available options. Significant advances are occurring on a regular basis and no clinician working outside this field could be expected to remain completely informed. Nevertheless, an empathetic GP who is prepared to listen and to advocate for the best interests of their patients is an invaluable ally in the desire to have a child.

Conflict of interest: none declared.

Reference

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