E2. Assisted Reproduction

Chapter objectives

There are many ways that we use medicine to improve our health. Reproduction is also part of human health, and there are ways to assist persons who are infertile. More and more technologies are being developed which change the roles of different persons involved in reproduction, including genetic and social parents.

This chapter aims to:

1. Describe some assisted reproductive technologies.

2. Highlight major bioethical concerns.

3. Consider which technologies each person may choose.

Q1. Look at the names of assisted reproductive technologies (ART) in Box 1, and list the ones you have heard of before. In this chapter most but not all of these techniques will be introduced and discussed.

Box 1: Major Assisted Reproductive Technologies (ART)

- ☐ Artificial insemination by donor or by husband (AID; AIH)
- ☐ In vitro fertilization and embryo transfer (IVF-ET)
- ☐ Direct intra-peritoneal insemination (DIPI)
- ☐ Gamete intra-fallopian transfer (GIFT)
- ☐ Zygote intra-fallopian transfer (ZIFT)
- ☐ Intracytoplasmic sperm injection (ICSI)
- ☐ Sperm collection by way of microsurgery
- ☐ Embryo and sperm cryopreservation and storage
- ☐ Cytoplasmic transfer
- ☐ Preimplantation genetic diagnosis (PGD)
- ☐ Karyotyping and genetic manipulation
- ☐ Tissue banking
- ☐ Ovulation induction
- ☐ Laparoscopy and hysteroscopy
- ☐ Laser laparoscopy
- ☐ Hystero-sonography
- ☐ Ultrasound scanning
- ☐ Egg and embryo donation; posthumous gamete donation
- ☐ Flow cytometry
- ☐ Surrogacy
- ☐ Cloning technology

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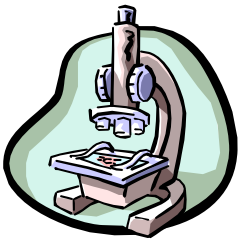
E2.1. Assisted Reproductive Technology (ART)

Since the first 'test-tube baby' Louise Brown was born in Britain in 1978, more than a million children have been born through assisted reproductive technology (ART). The original IVF technology involved mixing eggs and sperm in a laboratory dish (*in vitro* fertilization or IVF) and then implanting the resulting embryos (embryo transfer or ET) into the womb or uterus. The technique was developed to help women with blocked fallopian tubes and apart from their blocked tubes there were no additional fertility problems. Since early studies suggested that the new technology was without additional risk to mother and baby, IVF soon became widely accepted and modified developments for the treatment of complex types of infertility became available.



E2.2. Male-Factor Infertility

In this section some factors that affect male fertility are discussed.

(i) Standard Semen Parameters

A variety of factors (**parameters** = a factor we can measure) can indicate poor quality semen that reduces male fertility. These are **sperm count** (number), **sperm motility** (movement), **sperm morphology** (shape) and **sperm fertilizability** (joining of sperm with the egg). Sperm counts are easy to perform, so it is often used to assess fertility. Sperm morphology is one of the best indicators of fertility; however, examination with the light microscope can provide only limited information on their internal structure.

The most common group of conditions affecting fertility is characterized by insufficient or poor-quality sperm in the man's semen (see the Chapter on infertility for lifestyle/social factors). The usual **rule of thumb** is that a man is likely to be subfertile if there are fewer than 20 million sperm per milliliter of semen or if the fraction of the sperm that has normal motility is less than 50%.

Q2. Do you know where in your city there are frozen sperm collections?

(ii) Artificial insemination

If sperm numbers are too low, semen can be collected over a period of time and frozen. Then the entire collected amount can be placed in the woman's vagina or directly into her uterus at a time coinciding with ovulation.

Partner insemination is usually called artificial insemination by the husband (AIH). It has been also used in cases of forced separation of couples (e.g., prisoners on long-term sentences). The procedure can also be done **proactively** where men with normal sperm counts may store their own sperm in advance of medical procedures that could affect their fertility; such as **chemotherapy**, radiation treatment and surgery on the testes or reproductive tract including sterilization.

If the male partner is completely sterile or the couple does not want to use his sperm as, for example, when he carries a gene for a serious genetic disease, women can use **artificial insemination by donor** or AID. **Donor insemination** (DI) is also employed for single women who want to become pregnant, or for women who are partnered by other women.

Internationally recognized insemination centers restrict donor recruitment to men who are healthy, free from transmissible genetic disorders and sexually-transmitted disease and have semen with a high fertilization potential. Information about potential donors' physical appearance, profession and other interests is usually available to potential recipients.

Donor insemination is more successful than partner insemination, does not carry an increased risk of spontaneous abortion or congenital anomalies, and has advantages over adoption in that the child is genetically related to the mother and the couple can experience conception, pregnancy and delivery. It is, therefore, one of the major treatments for male infertility (see also the section on 'Sperm, Egg and Embryo Donation).

Q3. Do you think there should be restrictions on who can use donor insemination? What sorts of restrictions?

(iii) Intracytoplasmic sperm injection (ICSI)

Intracytoplasmic sperm injection or ICSI, in conjunction with IVF technology, has given hope to men with severe infertility problems. This technique involves the injection, via a micropipette, of a single sperm directly into the cytoplasm of the oocyte (egg) and can be used for non-motile or otherwise damaged sperm. Even a man who produces no mature sperm at all may be able to father a child. Immature spermatids (sperm precursor cells) can be harvested by needle aspiration of the man's testis and used to fertilize the egg.

Soon after the development of the ICSI technology it became the standard treatment for severe male-factor infertility but there remain unanswered questions relating to unidentified risks in the children conceived by this procedure. Debate is also continuing as to its use when the male has normal semen parameters. In the presence of normal semen parameters, fertilization by ICSI does not show an advantage over conventional IVF treatment, however, some centers use ICSI for all cases of IVF in order to protect against the possibility of fertilization failure.

E2.3. Female-Factor Infertility

About 20% of female infertility is caused by abnormalities of the reproductive tract with the commonest being abnormal fallopian tubes. They can become scarred, obstructed, or denuded of cilia as a consequence of pelvic inflammatory disease – a general term for infections of the uterus or oviducts, usually caused by sexually transmitted organisms such as chlamydia or gonorrhea. Another condition that can interfere with fertility is endometriosis, a condition where endometrial (uterine) tissue grows at unusual locations such as on the ovaries or oviducts. Although surgery can sometimes restore fertility in such conditions, it often fails to do so. In such cases it is possible to bypass the fallopian tubes by performing IVF and placing the resulting embryos directly into the uterus.

Another 20% or so of infertility cases are caused by failure to ovulate. These conditions can be caused by a variety of physical and psychological stresses (see the Chapter on Fertility). Menstrual irregularity may be caused by, for example, excessive weight loss, strenuous athletic training, anxiety, grief, depression and certain drugs.

Q4. Do you think the government should fund ways to help people have children if their infertility was the result of their unhealthy lifestyle during their younger days?

E2.4. *In Vitro* Fertilization (IVF) Technology

In vitro fertilization can circumvent many sperm problems. '*In vitro*' means 'in glass' – short for in a petri dish. In the standard IVF procedure the woman is given hormones to promote the development of a batch of follicles on a precisely timed schedule. When the follicles are nearly ready to ovulate, a fine needle is passed into each one under ultrasound control, and the oocyte is flushed out. As many as twenty oocytes can be harvested in a single procedure. The collected oocytes are placed in a Petri dish, and the partner's sperm are then added.

Regardless of the exact IVF procedure used, the artificially fertilized oocytes – now embryos - are kept in tissue culture for several days, during which time they divide several times. It is possible at this stage to remove a cell or two from the conceptuses without harming them; the sex and genetic makeup of the removed cells can then be determined. This **preimplantation genetic screening** procedure is useful if one of the parents carries a disease-causing gene and the couple wants to ensure that their child does not inherit it (as discussed in section E2.5).

One or two embryos are placed in the woman's uterus at the same time in order to maximize the chances that at least one will implant. If several embryos are transferred and all implant, the woman may be offered the opportunity to have the number reduced by a fetal reduction abortion. This practice presents ethical problems. High-number or multiple pregnancies such as triplets or quadruplets are associated with all kinds of serious risks to the fetuses and to the mother. Serious outcomes are still births, birth defects and other disabilities, including intellectual, evident by the age of 2 years.

A more common problem, however, is not multiple fetuses, but having no fetuses. About a quarter of the attempts achieve pregnancy and birth. The prospects are particularly poor for women over 40 years of age where only about 8% will achieve a successful pregnancy after a single IVF attempt.

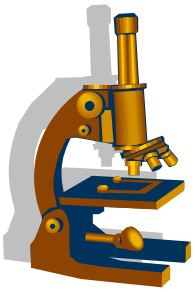
Q5. How many times would you try IVF in order to have a child?

E2.5. Preimplantation Genetic Diagnosis (PGD)

The risk of genetic disorders is a major problem for many couples when thinking about pregnancy. Special tests can detect fetal abnormalities and congenital disorders. These tests include **ultrasound** scans, **amniocentesis**, **chorionic villus sampling** and preimplantation genetic diagnosis. These procedures can also be used to determine the fetus's sex.

Preimplantation genetic diagnosis is now considered a valuable approach, which in combination with *IVF* techniques, enables the screening for genetic disorders before the corresponding embryo is transferred to the expectant mother. Reasons for preimplantation genetic diagnosis include: for carriers of single gene diseases such as cystic fibrosis that is especially frequent in infertile male populations; for carriers of **thalassemias** that are endemic in the Mediterranean area; for sex-linked diseases; to prevent the transfer of chromosomally abnormal embryos obtained from 'at risk' groups such as older women.





E2.6. Sperm, Egg and Embryo Donation

Please read the section on Artificial Insemination before this one.

There may be surplus embryos generated during IVF treatment that are not transferred into the uterus. Before treatment begins, the couple is required to write their wish regarding the fate of surplus IVF embryos, should there be any. Spare embryos may be discarded, stored frozen for later use, donated to infertile couples or donated to research.

If a woman's oocytes cannot be used, oocytes can also be obtained from donors. Obtaining oocytes from female donors is more complex and expensive than sperm donation because the donor must undergo hormone treatment followed by oocyte aspiration (see IVF section). There are certain risks for the donor, including the risk of injury or infection associated with the procedure itself, the risk of unwanted pregnancy (because the donor cannot use oral contraceptives during the period before the donation), the risk of psychological trauma, and a small chance of negative effect on future fertility. Still many women altruistically become donors.

Reproductive technologies such as IVF and ICSI are increasingly used by couples experiencing infertility. In many countries they have become standard procedures and the number of children born with their help is increasing annually (even in Japan alone more than 11,000 IVF babies were born in the year 2000). Many parents feel unsure about how, if at all, to communicate the method of their child's conception with their child and significant others. Sharing of information is especially significant when donor material has been used since failure to do so denies the child access to its identifying heritage. Knowing one's origins

provides emotional security in terms of identity and belonging and in terms of medical history, as genetic knowledge is sometimes indispensable. It is for this reason that access issues are a major aspect of prenatal ART counseling services. By way of protecting children's best interests, parents are now expected to tell the truth about their conception at some point, preferably before they reach the age of consent. The importance of access to information applies equally whether the child is the result of adoption, donor gametes, donor embryos, some variant of surrogacy or just technological support.

Q6. If you were born from donated eggs or sperm, or were an adopted baby, do you think your parents should tell you who your genetic parents are?

E2.7. Summary

The main difficulty in evaluating new technology for effectiveness is that we have no good way of seeing how they all work together with each other. It would be wrong to look upon assisted reproduction as the panacea for all causes of childlessness.

Instead the technologies are assessed one by one, as if they exist in isolation when what is needed is to assess the impact of ART innovation as a whole. Thus, when forced to choose among several ART possibilities, the logical clinical protocol is to integrate the best available evidence from the literature with clinical expertise and tailor it to the individual situation. Certainly there is also the responsibility for researchers to assess the risks posed by assisted reproduction. This requires epidemiological follow-up studies to determine whether the ART created children bear any cellular or molecular abnormalities beyond the expected in the population at large. Some recent studies have started to raise doubts about the safety of IVF, but for most children born they are merely grateful for the means for their creation.

For the sake of future generations of assisted reproduction children, research on human embryos should be encouraged. Finally, taking into consideration new scientific insights, we may be able to retain what is biologically relevant and adaptive, and modify what is not.