Assisted Reproductive Technologies: A Primer

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We will survey the major methods of assisted reproductive technologies (ARTs). We will then note how *in vitro* fertilization (IVF) techniques permit gene selection if embryos. These notes make extensive use of Gilbert and Pinto-Correia (2017, pp. 207 -220).

ARTs:

Hormone Therapy (HT)

Infertility in both sexes can be treated by hormone. In women, the two common classes of hormone that are used are estrogen and progesterone. While some to the hormones used for therapy have a desirable site effect of reducing susceptibility to some types of cancer, using these hormones can sometimes increase premenstrual symptoms like bloating, mood swings, cravings, and irritability.

Artificial insemination (AI)

This is the simplest ART and consists of physically introducing sperm into the female reproductive track. This is a standard response to male infertility due to impaired production of sperm, or of motile sperm, or erectile dysfunction. It is also a response to blockage in the female reproductive track due to which sperm must be placed beyond the blockage. The procedure consists of using a catheter (a tubular instrument) to place the sperm in the appropriate place in the female reproductive tract after detecting that the female is ovulating (using temperature, hormone levels, or ultrasound techniques. The sperm can be from any donor.

***In vitro* fertilization (IVF)**

Eggs and sperm are retrieved from the male and the female and placed together in a Petri dish for fertilization. After the fertilized eggs have begun cell division, the embryos are transferred to the female's uterus for implantation and embryonic development as in a natural pregnancy. The IVF procedure has four stages:

1. *Ovarian stimulation and monitoring*: IVF typically begins by producing several mature eggs so as to increase the likelihod that at least one of them will result in a pregnancy. Gonadotropins or antiestrogens are used to hyperstimulate ovaries to produce multiple mature oocytes.
2. *Egg retrieval*: Once the follicle has matured, but before it has been released from the ovary, an attempt is made to extract as many "eggs" as possible. The female gametes about to be ovulated are oocytes that have reinitiated cell division because of the hormones. The oocytes are retrived by guiding an aspiration pipette to each mature follicle to make punctures in the ovary. This is now commonly done by guiding the pipette through the upper vagina. Mature and healthy extracted oocytes are transferred to a sterile container for subsequent fertilization in the laboratory.
3. *Fertilization*: Semen is collected from the male roughly two hours before oocyte extraction. Sperm processing (called "sperm washing") occurs using a medium that artifically capacitates the sperm. The "best" sperm (that is, those that look least damaged and are the most active) are transferred to a Petri dish with the oocytes. The dish is incubated at body temperature for 12 -18 hours with a ratio of 50 000 -100 000 sperm per oocyte. The success rate of fertilization is 50 -70 %. Successful fertilization results in egg cell division producing embryos for transfer to the uterus.
4. *Embryo transfer*: Three days after fertilization, healthy embryos with six to eight cells are transferred from the Petri dish to the uterus through the vagina using a catheter. Multiple embryos are thus transferred; pregnancy results if at least one of them undergoes normal implantation and maturation.

- Variations:
  - **Intracytoplasmic sperm injection** (ICSI): This is used when sperm count is too low to make fertilization in a Petri dish likely. As the name indicates, a single sperm is injected into the cytoplasm of the egg. Low sperm count can be due to genetic factors or disease or damage in the male reproductive organs. In many cases, when ICSI is used, male offspring also have low sperm count (less that 15 million sperm/ml. of semen).
  - **Gamete intrafallopian transfer** (GIFT): Sperm is injected into the oviduct when the oocytes have matured. This is used when the reasons for a couple's infertility remain obscure.
  - **Zygote intrafallopian transfer** (ZIFT): This technique is also called **tubal embryo transfer**. Fertilization takes place in a Petri dish, as in IVF, and the zygote is then transferred into the fallopian tubes.
  - **Mitochondrial replacement therapy** (MRT): This is used when the maternal mitochondria have genetic defects. First, IVF on a Petri dish occurs using sperm and oocyte from the intended parent. Then sperm is used to fertilize the oocyte of a mitochondrial donor. However, the sperm and oocyte nuclei are then removed from the cell using a pipette. These are replaced by the nuclei from the fertilized egg of the intended parents. (In this procedure, the mitocondria are inherited from a third "parent.") Alternatively, the nucleus of the donor's oocyte could be replaced by that of the intended mother. What is important to note is that this therapy is much more radical than the others mentioned here because they involve the transfer of genes, albeit mitochondrial genes from an external individual to the reproductive couple. Hence, it has been a source of persistent controversy.

Preimplanatation Genetics:

IVF allows the detection of alleles in an embryo before implantation in the uterus. If an embryo carries an allele for a disease, it can be discarded in favor of another that does not prior to transfer to the uterus. (Recall theat IVF leads to the creation of multiple embryos.) While the embryo is still in the Petri dish at the six-to-eight cell stage, a sall whole is made in the zona pellucida to remove two cells from the embryo. Removal of these two cells makes no difference to the future development of the embryo. These two cells can have their DNA sequenced to identify all alleles. Thus, the presence of disease-related alleles can be detected. The six cells in the embryo can also have genes edited using CRISPR technology.

The same procedure can also be used to determine the sex of the embryo. Parents can choose only to have embryos of the desired sex transferred to the uterus. In cultures where women are values less than men, parents use this method to prevent having daughters. Needless to say, this process raises serious ethical concerns and different countries (and sometimes hospitals) have different rules governing sex selection. In the United States, sex selection is legally permitted. In India, both sex detection and selection are illegal but widely practiced.

References:

Gilbert, S. and Pinto-Correia, C. 2017. Fear, Wonder, and Science: In the New Age of Reproductive Biotechnology. New York: Columbia University Press.