

# Assisted Reproductive Technologies

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Humans are naturally reproductive beings with strong reproductive instincts developed through generations of evolutionary selection. Without the use of contraceptives, we are normally an extremely fertile species. Any given month, there is a 50% chance of fertilizing a mature oocyte (egg). However, with the prevalence of spontaneous abortions (miscarriages), the chance that one month's intercourse will produce a term pregnancy (pregnancy which goes full-term and results in a live birth) is reduced to 25%.

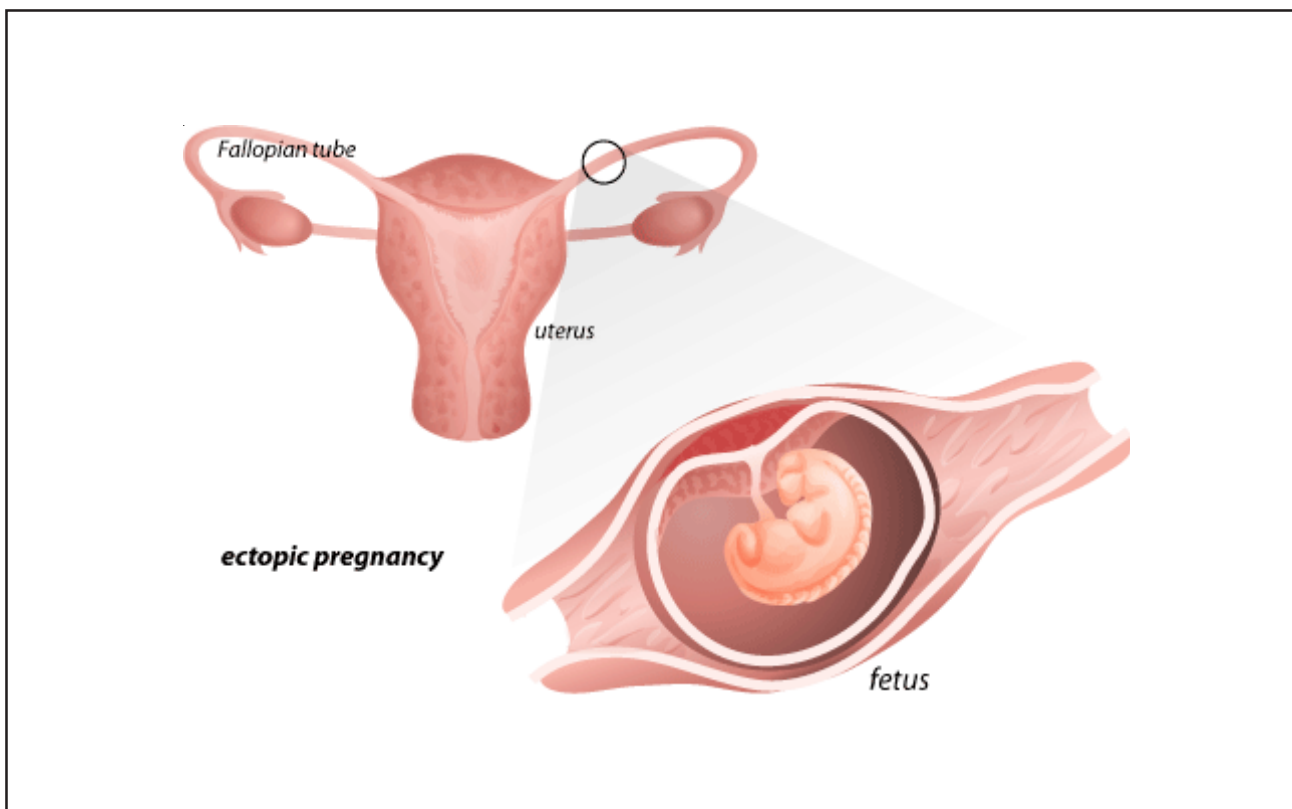
The largest recorded number of live births dates back to the eighteenth century when a Russian woman had 69 children. More recently, the Guinness Book of World Records cites a living Argentinean woman who has given birth to 32 living children<sup>1</sup>. The conception of a child relies heavily on the status of the woman's fertility cycle. Men are generally always fertile whereas women undergo a cycle where the levels of specific hormones present in the body regulate the timed release of one oocyte per month. During embryonic development, the female fetus produces all of the primary oocytes the individual will ever possess throughout her lifetime. These oocytes are stalled in meiosis and stored in immature follicles in the ovaries until puberty. With the onset of puberty, the woman begins to produce significant amounts of the hormones responsible for ovulation. Recent research has suggested that the link between hormone levels and ovulation may be more complicated than previously thought, and that ovulation may occur at more than one point during a monthly cycle<sup>2</sup>.

The gradual increase of follicle stimulating hormone (FSH) stimulates the maturation of a few follicles that secrete estrogen. Heightened estrogen levels combined with a surge of luteinizing hormone (LH) trigger the rupture of one of the follicles to release the primary oocyte into the oviduct<sup>3</sup>. This ovulation occurs predictably fourteen days prior to the beginning of the

next cycle. There is a window of a few days during which fertilization may occur within the oviduct as the oocyte (also known as the ovum) is only viable for about 18 to 24 hours<sup>4</sup>. If not fertilized, the ovum dies and is sloughed off with the uterine lining in response to decreasing estrogen and progesterone levels. However, if fertilized, the oocyte completes meiosis within the oviduct. The resultant diploid zygote continues its journey down the fallopian tube making its way into the woman's uterus where its differentiating trophoblast cells enable it to implant in the wall of the woman's uterus and proceed with fetal development. However complicated the woman's fertility cycle appears, the tight regulation of hormone levels is responsible for the scheduled rupture of the mature follicle and ensuing ovulation. The predictable nature of the woman's fertility cycle has enabled scientific researchers to develop many technologies both to promote and prevent the fertilization event.

## Infertility

There are a small number of couples who have difficulty conceiving a child. A couple is considered infertile when they fail to conceive after a full year of unprotected intercourse. The term 'infertile' describes a state of reduced fertility whereas the complete inability to reproduce is defined as sterility<sup>5</sup>. In Canada, one in six couples has difficulty achieving a pregnancy. Over 250,000 Canadians are considered infertile<sup>5</sup>. With the accumulation of novel medical achievements and cutting edge research developments, many of these naturally infertile people have been given the opportunity to reproduce offspring of their own biological lineage. Assisted reproductive technologies include intrauterine insemination, ovulation-stimulating hormone therapies, tubal surgery, *in vitro* fertilization, and surrogacy. While exploring how infertile couples



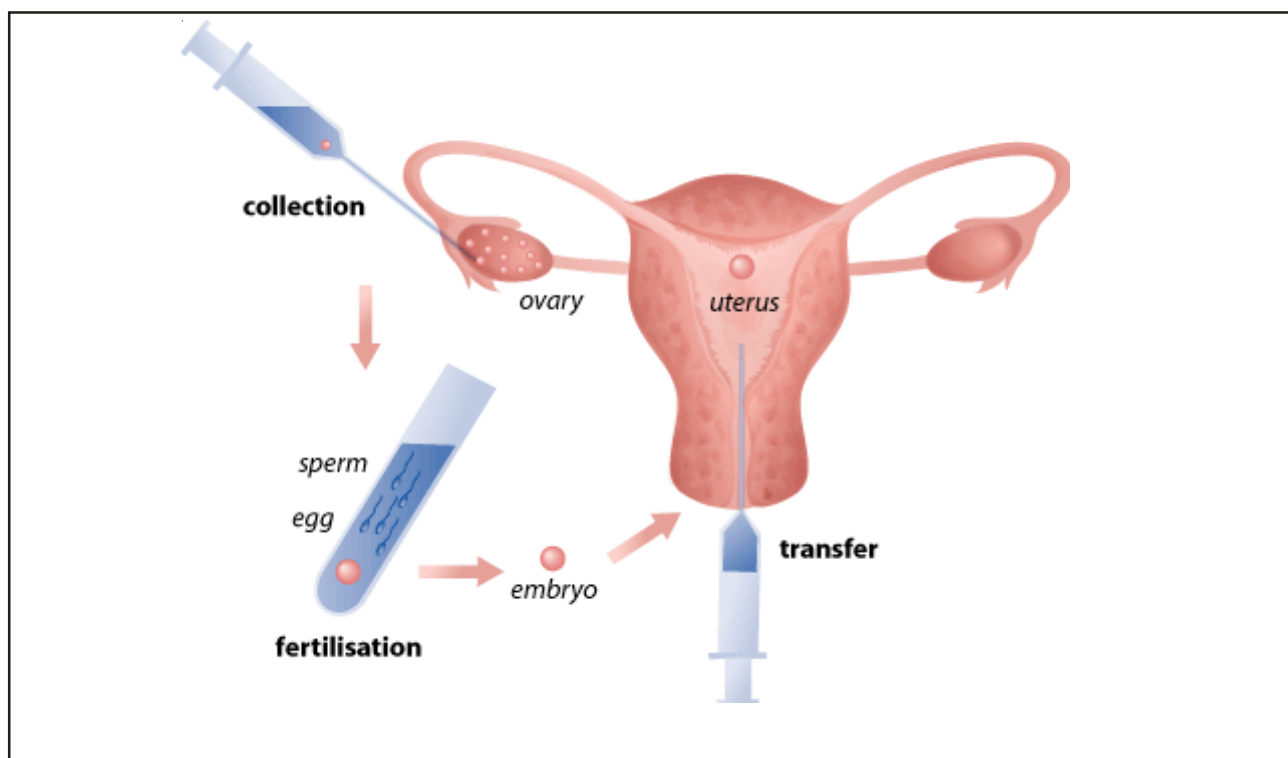
**Figure 1.** An ectopic pregnancy occurs when the fertilized egg becomes implanted in the wall of the fallopian tube.

are enabled to procreate, it is important to investigate some of the causes of infertility entailing the use of such technologies and the adjunct costs involved.

Infertility is becoming more and more prevalent. With the higher incidence of chemical pollution changing the components of our environment and the increased usage of pharmaceutical compounds detrimental to our reproductive systems, fertility in general has been seen to decrease over the years. The immediate, self-imposed environment has an even more direct effect on an individual's ability to produce healthy gametes. It has been suggested that our diets and smoking habits can be detrimental to the health of our gametes. Men who smoke risk becoming impotent while women who smoke tend to develop unhealthy eggs. Further, anabolic steroid users suffer from inadequate levels of testosterone which ultimately affects their sperm counts. Other causes of self-imposed infertility include undergoing tubal ligation or vasectomy operations. To reverse such surgeries is taxing and does not guarantee restored fertility.

In terms of involuntary infertility, many common and not so common influential sources exist. It has recently been suggested that a rare occurrence of immunological problems can be associated with the inability of the sperm to reach the egg's vicinity. This autoimmunity in men leads to the destruction of the gametes prior to ejaculation. Likewise, women who develop an immune response to their partner's sperm will often destroy the male gametes prior to successful fertilization. Limited information is available with respect to this cause of infertility and many individuals in the scientific community disagree on the validity of such a proposal. Another uncommon form of infertility results from uterine problems where the woman's uterus is unable to support a pregnancy. In such a case, the couple would have to resort to adoption or the use of a surrogate mother to carry their biological offspring to term.

The most common sources of infertility include ovulation problems, egg quality problems, tubal infertility, age-related factors, and sperm issues. While most of these causes impose themselves on women,



**Figure 2.** In vitro fertilization is one of the technologies available to help infertile couples become pregnant.

40-50% of all infertility cases are attributed to male infertility<sup>5</sup>.

When it comes to male infertility, it is not the number or motility of the sperm that accounts for a successful fertilization event. The actual event of conception involves an intricate combination of preliminary activities on behalf of both the sperm and egg. The egg emits chemicals to help guide the approaching sperm. The sperm use flagella, powered by mitochondria, to propel them up the fallopian tube. Sperm that reach the fallopian tube ampulla (the middle, one-third region in which fertilization usually occurs) meet the cumulus cell mass surrounding the oocyte and penetrate it by chemical and mechanical means. The cumulus cells themselves stimulate the head of the sperm to release enzymes required to break through the egg's outer layers. Once through the layer of supportive cells, the sperm reach the zona pellucida - a protein coat surrounding the egg that acts as a species-specific barrier to keep out foreign sperm<sup>6</sup>. One sperm binds to receptors on the oocyte and penetrates the zona pellucida which rearranges its structure to prevent further sperm entry. Due to the

complexity and integral involvement of sperm and egg in the fertilization event, many sperm malfunctions along a variety of lines can result in reduced fertility. It would be misleading to limit male infertility to either sperm count or sperm motility. An individual's sperm, though low in number, can still successfully penetrate the egg despite its decreased probability of occurrence. Likewise, an individual with slower moving sperm can still fertilize an oocyte. Sperm will remain viable in the female reproductive tract for about 48 hours, although this can vary<sup>6</sup>. What matters is not really how many there are or how fast they swim, but whether the sperm are biochemically capable of fertilizing an egg.

### Solutions to infertility

When the sperm has difficulties reaching the egg, whether due to male infertility or tubal infertility, intra-uterine insemination is a suitable technology to enable the fertilization event. In this procedure, sperm is placed either in the cervix or high in the uterine cavity using a very thin, soft catheter. This by-passes the

Type of Surgery	Pregnany rate	Tubal pregnancy rate
Reconstruct damaged end of tube	50% over 1-2 years	12% of pregnancies
Cut away scar tissue on tubes or on ovary	45% over 1-2 years	6% of pregnancies
Make opening in blocked tube	25% over 1-2 years	25% of pregnancies
Reconnect tubes after tubal ligation	50-70% over 1-2 years	4-15% of pregnancies
In vitro fertilization (for comparison)	50-60% (age >35, blocked tubes)	1-5% of pregnancies (women with blocked tubes)

**Table 1.** Pregnancy rates after tubal surgery and in vitro fertilization<sup>4</sup>.

blocked tubes and gives the sperm a ‘head start’ in their quest.

While intra-uterine insemination is an inexpensive option for prospective parents unable to naturally fertilize gametes, it also serves the needs of single women wishing to bear children. Many sperm banks offer intra-uterine insemination for between \$500.00 and \$1000.00 CAD to both couples and single women<sup>4</sup>. All donors are thoroughly screened by the sperm bank for infectious diseases such as HIV, hepatitis, and gonorrhea. The woman can choose the sperm she wants to be inseminated with based on the donor’s ethnic background, eye color, hair color, height, weight, blood type, and other desired attributes. Often in cases where healthy donor sperm is used, the sperm is placed high up in the recipient’s cervix with a syringe rather than being injected into the uterus. This means of insemination is cheaper and more comfortable than injection via a catheter.

On the female end of infertility, many factors may be involved. Ovulation problems may contribute to a woman’s infertility. Anovulation is characterized by

unpredictable ovulation, that is, the woman may not ovulate every month. Polycystic ovarian syndrome, where the ovaries contain multiple small cystic structures, often causes anovulation in women<sup>6</sup>.

More extreme cases like amenorrhea result in the absence of ovulation for years at a time. Many female athletes develop amenorrhea due to high levels of testosterone present in the body in response to intense physical exertion. These higher than normal levels of testosterone interfere with the homeostasis of the steroids involved in the reproductive cycle.

In order to artificially stimulate ovulation when it may not occur naturally, many hormone and drug therapies can be used. There are four widely accepted therapies that range in cost from \$800 to over \$3000 in Canadian funds. Some of the unwanted side-effects associated with the use of hormone therapies to induce ovulation include: over-stimulation of the ovaries, resulting in enlarged ovaries, abdominal pain, fluid build-up within the abdomen and potential strokes. Multiple pregnancies are also common, resulting from the release of several eggs in one cycle. Despite the

relatively lower expense of this therapeutic development, drug therapy may bring with it many undesirable side-effects. However, it is also commonly used concomitantly with other therapies such as *in vitro* fertilization and intra-uterine insemination, in order to time the fertilization event with the determined presence of the egg. Ovulation-stimulating pharmaceutical intervention is useful in many situations but it cannot ensure that the eggs released are useful or of high quality.

In the event that the ovulated eggs are of poor quality, fertilization may proceed but a successful pregnancy may not occur. Abnormally shaped eggs may not divide properly or undergo normal chromosome segregation<sup>5</sup>.

Despite the higher occurrence of abnormal oocytes in older women, younger women may also produce abnormal ova. In the event of such misfortune, many couples pursue *in vitro* fertilization with the use of donor oocytes. The children produced are not biologically related to the mother. However, more research into nuclear transplant from an adult cell to an enucleated donor oocyte could restore the parental inheritance. Nuclear transfer for reproductive purposes is currently prohibited globally.

Tubal infertility is another form of female infertility associated with 20-25% of all cases of infertility. It is characterized by completely blocked fallopian tubes or by scar tissue and adhesions formed in the reproductive region which prevent the passage of the sperm to the ovum and subsequent transport to the uterus.

Tubal infertility is often elicited by endometriosis or pelvic inflammatory disease. Present in 5-10% of all women, endometriosis is a natural condition of uterine wall thickening which prevents zygote implantation. Alternatively, pelvic inflammatory disease can result from chlamydia or gonorrhea infections traveling up the fallopian tubes, or from the use of the intra-uterine contraceptive device<sup>5</sup>. Both elicit an inflammatory immune response which may lead to tubal blockage. Tubal infertility can surgically be repaired by scoping out the blocked tissues. However, the risk of attaining an ectopic pregnancy (embryo developing in fallopian tube) remains high. Greater pregnancy success in the presence of partially blocked fallopian tubes is achieved with the use of *in vitro* fertilization.

Table 1 clearly distinguishes pregnancy rates after tubal surgeries compared to those achieved by *in vitro* fertilization according to the Advanced Fertility Center of Chicago.

The first test tube baby was born in July of 1978. Since then, *in vitro* fertilization clinics have become more common globally, due to their wide acceptance by many communities. This procedure can be used in many situations to combat infertility and is often combined with other techniques such as hormone therapy and surrogacy. A number of mature ova are extracted from the woman's body after stimulating multiple egg development. Such oocytes are fertilized in the laboratory with the partner's sperm. In the event of male infertility, the sperm is injected into the egg manually. This will allow the use of the husband's sperm despite his inability to fertilize the egg naturally.

After fertilization, the resulting zygotes are cultured *in vitro* for two to six days to ensure they are dividing properly. Subsequently, three or so of the healthiest embryos are selected and re-implanted into the woman's uterus. Some countries permit the genetic screening of embryos prior to implantation to prevent the gestation of an abnormal embryo. There are currently screens available to detect Huntington's disease, Cystic Fibrosis, Down's syndrome and Spina Bifida<sup>5</sup>. Many ethical questions arise with the use of pre-implantation diagnosis technologies. Many fear the onset of pre-natal eugenics which would ultimately rid our civilization of much of the diversity we are currently familiar with. Furthermore, in the process of fertilizing embryos outside of the woman's body, several oocytes are fertilized but not all are implanted in the woman's uterus. The remaining embryos are frozen for future IVF trials, donated to other infertile couples, or subjected to the harvesting of their stem cells for embryonic stem cell research. Many ethicists, fetalists in particular, argue that IVF procedures dance on a thin line of morality where the status of the embryo is reduced from a potential person to simply a cluster of cells. However, when infertile couples seek assisted reproductive technology, *in vitro* fertilization has been proven to be the most effective method of enabling two people to procreate an individual from their own biological lineage. Pregnancy rates with *in vitro* fertilization exceed 30% per cycle. Despite the high costs associated with this method (\$11 000 - \$13 000 CAD), a "test-tube" baby is born every day.



*In vitro* fertilization is not always a feasible method of assisted reproductive technology as is the case for women with uterine problems. Such an individual is likely unable to support a pregnancy to full term as a consequence of an abnormal or weakened uterus. In this situation, the couple involved can pursue considering surrogacy as an option for reproductive assistance. Surrogacy involves *in vitro* fertilization with the biological parents' gametes. The embryos are subsequently implanted into a surrogate mother's uterus. This method of assisted reproduction has resulted in many legal court battles due to terminated contracts and the like. The cost of surrogate gestation ranges up from \$20 000.00 US. Surrogacy is also a relevant option for mature couples wishing to conceive<sup>7</sup>.

Age-related infertility factors are more prevalent in women than men and most commonly manifest as poor egg quality, unequal chromosome distribution, and increased miscarriage rates. With age, women experience abnormal hormone levels that are reflected in the quality of the ova released. The shape of the eggs often reflects whether or not a successful pregnancy will occur. The meiotic spindle is a critical component of the egg's viability. It is involved in organizing the chromosome pairs so that a proper division of the pairs can occur as the egg is developing. A study published in the medical journal "Human Reproduction", in October of 1996, investigated the influence of maternal age on meiotic spindle assembly in human eggs. This study illustrated how chromosomally abnormal eggs (and therefore abnormal embryos) are produced more often in older women. When the chromosomes line up properly in a straight line on the spindle apparatus in the egg, the division process would be expected to proceed normally so that the egg would end up with its proper complement of 23 chromosomes. However, with a disordered arrangement on an abnormal spindle, the division could easily be uneven - resulting in an unbalanced chromosomal situation in the egg<sup>8</sup>. The increasing incidence of poor egg quality and chromosomal abnormality in older women is responsible for the increased number of miscarriages with augmenting maternal age. Meanwhile, the sperm of men is not largely affected by increasing age. However, the decline in testosterone and other steroid

hormone production is a contributing factor to decreased male sex drive, resulting in less frequent intercourse in older couples.

When a couple is considering a form of assisted reproductive technology, there are many factors they should take into account. The source of infertility strongly influences the appropriate action to take in the quest for conception. While male infertility is often evaded with intra-uterine insemination, female infertility is addressed by a variety of options that differ extensively in cost and comfort. Women with ovulation difficulties can attempt to induce egg development with hormone therapies, while those with more severe problems like fallopian tube blockage can undergo invasive surgery, insemination, or *in vitro* techniques. Surrogacy is considered the best option for ageing women who wish to conceive as well as for women with uterine problems. Surrogate mothers can also be considered for women who produce abnormal eggs. However, other options including *in vitro* techniques using donor oocytes, may be more cost-effective and practical. The *in utero* bonding a woman experiences with her unborn child is a developmental foundation upon which parental relationships are built. While natural conception is the optimal means of passing on heritable traits, recent advances in reproductive technology have enabled infertile couples to become parents as well.

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