ASSISTED REPRODUCTIVE TECHNOLOGY

Art

The range of medical treatments methods designed to result in pregnancy.

About Assisted reproductive technology

Assisted reproductive technology (ART) is the technology used to achieve pregnancy in procedures such as fertility medication, artificial insemination, in vitro fertilization and surrogacy. It is reproductive technology used primarily for infertility treatments, and is also known as fertility treatment. It mainly belongs to the field of reproductive endocrinology and infertility, and may also include intracytoplasmic sperm injection (ICSI) and cryopreservation. Some forms of ART are also used with regard to fertile couples for genetic reasons (preimplantation genetic diagnosis). ART is also used for couples who are discordant for certain communicable diseases; for example, HIV to reduce the risk of infection when a pregnancy is desired.

If conservative medical treatments fail to achieve a full term pregnancy, the physician may suggest the patient undergo in vitro fertilization (IVF). IVF and ART generally start with stimulating the ovaries to increase egg production. Most fertility medications are agents that stimulate the development of follicles in the ovary. Examples are gonadotropins and gonadotropin releasing hormone. After stimulation, the physician surgically extracts one or more eggs from the ovary, and unites them with sperm in a laboratory setting, with the intent of producing one or more embryos. Fertilization takes place outside the body, and the fertilized egg is reinserted into the woman's reproductive tract, in a procedure called embryo transfer.

Intracytoplasmic sperm injection (ICSI) is beneficial in the case of male factor infertility where sperm counts are very low or failed fertilization occurred with previous IVF attempt(s). The ICSI procedure involves a single sperm carefully injected into the center of an egg using a microneedle. With ICSI, only one sperm per egg is needed. Without ICSI, you need between 50,000 and 100,000.

Two techniques that enable to some extent the selection of physiologically normal spermatozoa have recently been developed. One of these is termed intracytoplasmic morphology-selected sperm injection (IMSI). Here, spermatozoa are selected for ICSI and analysed digitally prior to the microinjection procedure in order to deselect morphologically abnormal spermatozoa. With this technique, abnormalities not visible in standard ICSI procedures have been observed. IMSI increases the pregnancy rate during ICSI cycles, and some data suggests that the level of pregnancy termination is also decreased. A second technique recently introduced to assisted reproduction is that of sperm selection with hyaluronic acid (HA), e.g. PICSI. In this technique, mature sperm with HA receptors are distinguished from immature and abnormal sperm since these do not express such receptors.

Men who ejaculate no sperm, because of blocked tubes in their testes, or because of a genetic condition that prevents their sperm being released, require some form of surgical sperm retrieval to enable ICSI to take place. Epididymal sperm obtained by microsurgical aspiration (MESA) or percutaneous sperm aspiration (PESA) and testicular sperm obtained by surgical excision (TESE) or percutaneous aspiration (TESA) are used in ICSI treatment. Alternatively, the retrieved sperm can be cryopreserved for use in future sperm injection attempts. If all efforts to extract vital sperm cells fails, then donated ones may be recommended.

Infertile couples may also resort to egg donation or embryo donation when the female partner cannot have genetic children because her own eggs cannot generate a viable pregnancy. Surrogacy via a gestational carrier is also an option when a patient’s medical condition prevents a safe pregnancy, when a patient has ovaries but no uterus due to congenital absence or previous surgical removal, and where a patient has no ovaries and is also unable to carry a pregnancy to full term.
Among women with older reproductive age, with history of repetitive abortions or genetic disorders, genetic analysis is highly recommended. The PGS/PGD allows studying the DNA of eggs or embryos to select those that carry certain damaging characteristics. It is useful when there are previous chromosomal or genetic disorders in the family, within the context of in vitro fertilization programs.

The fertilized eggs (embryos) are cultivated under very stringent conditions and examined every day by the embryologist to evaluate their progress. The embryos are usually cultured for 3 to 5 days, before the best one(s) are selected to be put (transferred) in to the womb.

Morphological assessment of embryo appearance at the proper, distinct time points during development is a routine procedure in embryo selection. Moreover, time-lapse technology improvements has been evaluated as an aid to identify the embryo(s) with the highest implantation potential that enable to objectively select the embryo(s) for transfer. Time-lapse embryo monitoring allows continuous, non-invasive embryo observation without the need to remove the embryo from optimal culturing conditions.

The technique of selecting only one embryo to transfer to the woman is called elective-Single Embryo Transfer (e-SET) or, when embryos are at the blastocyst stage, it can also be called elective single blastocyst transfer (eSBT). It significantly lowers the risk of multiple pregnancies, compared with e.g. Double Embryo Transfer (DET) or double blastocyst transfer (2BT).

In a natural cycle the embryo transfer takes place in the luteal phase at a time where the lining is appropriately undeveloped in relation to the status of the present Luteinizing Hormone. In a stimulated or a cycle where a "frozen" embryo is transferred, the recipient woman could be given first estrogen preparations (about 2 weeks), then a combination of oestrogen and progesterone so that the lining becomes receptive for the embryo.

Prior to the implantation, the embryo has to escape from the ZP (Zona pellucida), a process known as hatching at the blastocyst. Some embryo implantation problems in patients with recurrent implantation failure may be explained by the inability of the embryo to hatch out of its zona pellucida. In such cases, zona pellucida can be thinned in one part using the laser technique (LAZT - laser-assisted zona thinning) to improve the pregnancy and implantation rate. Media supporting implantation may also improve implantation process. The environment created for the embryos by the cytokine contained in the medium culture "in vitro" very closely resembles the "in vivo" environment (in natural conditions) and thereby improvements their ability to implant and keep itself in mucous membrane, and grow further.

Approximately 14 days after the embryo transfer the woman should have a quantitative beta hCG (Human chorionic gonadotropin). This is the first measurable indication of embryo implantation.

The rate of success for IVF is correlated with a woman's age. More than 40 percent of women under 35 succeed in giving birth following IVF, but the rate drops to a little over 10 percent in women over 40.

**Success or failure factors**

A woman who has already had a live birth is more likely to have a successful ART procedure than a woman who hasn’t given birth before. This history of “previous birth” is counted as an advantage that gradually narrows as women age advances. Many infertile women also believe that emotional distress (for example, tension or worry) is a contributing factor to their lack of natural fertility and lack of success with fertility treatment.

Age of the women and smoking habits of pregnant woman under treatment are found to be linked with the success of the procedure. Delayed childbearing has resulted in an increase in the number of women having children later in life. Thus more women face the problem of age-related infertility and cannot achieve their desired number of children. Childbearing postponement is one of the main reasons for the increasing use of assisted reproductive technology (ART).

**Complications**

Assisted reproduction techniques are associated with obstetric and neonatal risks as well, such as: maternal age, previous sterility and an unfavorable obstetrical past. Such risk factors can be aggravated according to the number of fetuses, increasing significantly with the gestation of three or more fetuses. Multiple pregnancy is the
most frequent and serious iatrogenic complication of the assisted reproduction techniques. In cases of preterm delivery, preeclampsia or early detachment of the placenta, the neonatal morbidity rate is higher in the short and long terms. Low birth weight and preterm birth are strongly associated with many health problems, such as visual impairment and cerebral palsy, and children born after IVF are roughly twice as likely to have cerebral palsy.

ART also increases the risk of adverse maternal complications such as GDM (Gestational Diabetes Mellitus), PE (Pulmonary embolism) and ICP (Increased Intracranial Pressure). The exogenous sex hormones, GnRH-a (Gonadotropin-releasing hormone agonist) and Gn (Gonadotropin) may affect the sex hormones secretion through hypothalamic-pituitary-gonadal axis and other mechanisms. So the hormone-related complications like GDM, PE and ICP may occur.

Many studies have reported that the incidence of pregnancy complications including GDM, PE, ICP, placenta previa and preterm labor in infertility patients who get ART treatment is higher than pregnant women with natural conception.

### Prognosis

ART is currently a commonplace technology that has successfully treated millions of infertile couples the world over. According to the results of a study published in the New England Journal of Medicine recently, live birth rates from ART can approach those of natural fecundity in the general population, as long as the couple and embryo criteria are favorable and there are no contraindications for treatment continuation. However, financial limitations, environmental stresses and repeated implantation failures in the first two or three cycles or implication of other factors reduce live birth rates from ART dramatically.

The long-term evaluation of the offspring of couples who underwent ART compared to offspring conceived naturally, do not show an increase of congenital anomalies and physical growth is similar, as well as the rate of cerebral palsy, however mild neurological disorders are higher in the ART group.

### Find more about related issues

#### Diagnoses

- **Sertoli cell-only syndrome**
  The absence of any developmental stage of sperm cell in the testes.
  Learn more at: [www.fertilitypedia.org/therapy/diag/sertoli-cell-only-syndrome](http://www.fertilitypedia.org/therapy/diag/sertoli-cell-only-syndrome)

- **Testicular failure**
  The inability of the testicles to produce sperm or testosterone.
  Learn more at: [www.fertilitypedia.org/therapy/diag/testicular-failure](http://www.fertilitypedia.org/therapy/diag/testicular-failure)
In vivo and in vitro steps of fertilization

I. In vitro maturation (IVM) of gametes.
II. Fertilization technique: ICSI vs IVF.
III. Embryo culture.
IV. Embryo manipulation: pre-implantation genetic diagnosis and embryo transfer.
V. Maternal-embryo signaling during the pre-implantation period.

Percentage of fertility specialists reporting use of fertility management treatments

<table>
<thead>
<tr>
<th>Fertility management type</th>
<th>Denmark</th>
<th>Germany</th>
<th>Italy</th>
<th>Norway</th>
<th>Sweden</th>
<th>UK</th>
<th>USA</th>
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<tbody>
<tr>
<td>IVF</td>
<td>25%</td>
<td>16%</td>
<td>25%</td>
<td>11%</td>
<td>35%</td>
<td>14%</td>
<td>27%</td>
</tr>
<tr>
<td>ART</td>
<td>48%</td>
<td>48%</td>
<td>31%</td>
<td>34%</td>
<td>49%</td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td>Clomiphene</td>
<td>1%</td>
<td>5%</td>
<td>2%</td>
<td>2%</td>
<td>7%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Gonadotropins</td>
<td>1%</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Percentage of patients who received type of ART treatment by patient age group

<table>
<thead>
<tr>
<th>Proportion of ART cycles (By patient age group)</th>
<th>Proportion of live births (By patient age group)</th>
</tr>
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<tbody>
<tr>
<td>&lt;25</td>
<td>25-35</td>
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<tr>
<td>36-40</td>
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<tr>
<td>&gt;95</td>
<td>100</td>
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</table>

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