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AN INTRODUCTION TO ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

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Abstract: Assisted reproductive technologies (ART) have enabled millions of people in the world to have biological children who otherwise would not have been able to do so. The new technologies have transformed the way we view reproduction. While they have created new hopeful possibilities, they also require that we pay attention to issues of health, ethics, law, and policy. This article reviews techniques of ART.

I. INTRODUCTION

ASSISTED reproductive technology (ART) according to the WHO definition refers to infertility treatments where both eggs (oocytes) and sperm are handled to achieve a live birth. In conventional ART procedures the oocytes and sperm are combined in a laboratory (in vitro) and the resulting embryo is transferred to a woman. It is estimated that about 8%–10% of couples experience some sort of infertility in their reproductive lives (1). In India, primary and secondary infertility figures, as given in WHO studies, are 3% and 8%, respectively (2,3). Evidence from a village-level study in the state of Maharashtra in India puts the level of infertility at 6%–7% (4). According to the recent

National Family Health Survey in India, 3.8% of women between the ages of 40 and 44 years have not had any children and 3.5% of currently married women are declared infecund(5).

ARTs include in-vitro fertilisation (IVF) with or without injection of a sperm into the oocyte (intracytoplasmic sperm injection, ICSI). Using this definition, some treatments for infertility such as ovulation induction with timed intercourse and artificial insemination, while being a treatment for infertility, are not therefore classified as an ART. However, in this report, the terminology 'assisted reproductive technologies' will be used to refer to ARTs as defined by the WHO, ovulation induction, and artificial insemination inclusively.

ART involves a series of interventions usually commencing with the use of hormones in the female partner to stimulate the ovaries to produce mature oocytes. In ICSI and IVF these oocytes are collected by needle aspiration and combined with sperm from the male partner in vitro. IVF/ICSI conventionally involves transfer of the embryo to the women's uterus at the cleavage stage of embryo development (usually day 2 or 3). Embryo transfer may be performed with fresh embryos, or embryos may be frozen (cryopreserved) for thawing and transfer at a later time.

ART includes:

- IVF
- Gamete Intrafallopian Transfer (GIFT)
- Zygote Intrafallopian Transfer (ZIFT)
- Embryo Transfer (ET)
- Intracytoplasmic Sperm Injection (ICSI)
- Assisted Hatching (AH)
- Testicular Sperm Aspiration (TESA)
- Microsurgical Epididymal Sperm Aspiration (MESA)

II. OVERVIEW OF CURRENT TECHNOLOGIES

ART encompasses a variety of technologies,18 some used to initiate pregnancy, and others more specifically used to increase likelihood of pregnancy and/or to test for the presence of certain genes so prospective parents can choose which embryos to implant after in vitro fertilization. There are three primary means of initiating pregnancy: alternative insemination (AI), prescription fertility-enhancing drugs, and in vitro fertilization (IVF). Some commonly used techniques definitions, are discussed below

Infertility: when a male or female is unable to conceive or produce conception after ≥ 12 months of frequent, unprotected heterosexual sexual intercourse or ≥ 6 months of frequent unprotected heterosexual sexual intercourse if the female partner is > age 35 years. (Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months)

Artificial insemination (AI): AI (IUI, ICI and IFI) may be utilized as follows

- *Unstimulated AI* — for infertile couples with mild male-factor infertility, unexplained infertility, minimal to mild endometriosis
- *Clomiphene*-citrate-stimulated AI — for infertile women with WHO Group II ovulation disorders (i.e., polycystic ovarian syndrome) who ovulate with clomiphene citrate, but who have not achieved pregnancy post ovulation induction with clomiphene. (Stimulated AI is not offered in management of male-factor infertility because it is not more effective than unstimulated AI)
- *Human gonadotropin and IUI* — often used when the member fails to become pregnant by other means

Donor insemination — for the following conditions:

- Obstructive azoospermia
- Nonobstructive azoospermia
- Infectious disease in the male partner (i.e., HIV)
- Severe rhesus isoimmunization
- Severe semen quality deficits in couples who do not wish to undergo intracytoplasmic sperm injection
- Where there is a high risk of transmitting a genetic

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disorder in the male partner to the offspring
- When there is no male partner

Electroejaculation— used for total anejaculation secondary to neurologic impairment, e.g. spinal injury, retroperineal surgery (e.g., retroperineal lymphadenectomy) or diabetic neuropathy. (Insufficient evidence of therapeutic value for > 1 AI within a 30-day period)

Assisted hatching (AH) — implantation (for some IVF patients; including those that have embryos with thick zona) is precluded because of the inability of the embryo to hatch out of the zona. A 30-micron-size hole made in the zona at the time of transfer improves implantation. The embryo is then transferred to fresh medium and transferred into the uterus. (AH is not recommended because it has not been shown to improve pregnancy rates)

Assisted oocyte fertilization microtechnique— IVF involves the retrieval of female oocytes and the insemination of these oocytes with male-donor sperm; fertilization occurs in a test tube or petri dish. A number of micromanipulation techniques have been developed to help in cases when sperm cannot penetrate the outer envelope of the oocyte (zonapellucida). Penetration difficulties typically occur when semen quality is poor or when there is insufficient motile sperm.

Assisted reproductive technologies (ART) — consists of procedures that directly unite sperm and eggs in order to overcome some infertility factors. Various fertility drugs are used in to stimulate the growth of multiple oocytes; increasing the chance of fertilization and therefore pregnancy. ART includes:
- IVF
- Gamete Intrafallopian Transfer (GIFT)
- Zygote Intrafallopian Transfer (ZIFT)
- Embryo Transfer (ET)
- Intracytoplasmic Sperm Injection (ICSI)
- Assisted Hatching (AH)
- Testicular Sperm Aspiration (TESA)
- Microsurgical Epididymal Sperm Aspiration (MESA)

In vitro fertilization (IVF) — the most commonly used form of ART; especially helpful in the presence of tubal problems, consists of the following 4 stages:
- Gonadotropins are used to recruit follicles and to mature oocytes.
- The oocytes retrieval from the ovaries
- The oocytes lab-fertilization in dish by sperm collected from the male partner.
- Embryos are transferred to the uterus. A cycle is defined as 1 egg-retrieval and 1 transfer. (Note: Incomplete transfer counts towards cycle)

Gamete intrafallopian transfer (GIFT) — a mixture of sperm and egg placed directly into the woman's fallopian tubes during surgical laparoscopy.

Zygote intrafallopian transfer (ZIFT) — a form of IVF; eggs are harvested and fertilized in a dish in the laboratory, approximately a day later the fertilized egg is placed inside the fallopian tube.

Embryo transfer (ET) — done after approximately 3–5 days of laboratory culture; the physician places the embryos (fertilized eggs) in the uterus. The embryos are aspirated into a small catheter, which is passed through the cervix and implanted into the uterus.

Intra cytoplasmic sperm injection (ICSI) — a technique whereby a single sperm is picked up in a micropipette and injected directly into the oocyte cytoplasm. ICSI may be utilized for severe deficits in semen quality or quantity or for couples where a previous in vitro fertilization treatment cycle has resulted in failed or poor fertilization.

Assisted hatching (AH) — implantation (for some IVF patients; including those that have embryos with thick zona) is precluded because of the inability of the embryo to hatch out of the zona. A 30-micron-size hole made in the zona at the time of transfer improves implantation. The embryo is then transferred to fresh medium and transferred into the uterus.

Testicular sperm aspiration (TESA) — minor outpatient procedure where sperm is aspirated directly from the testicles where it is produced. If successful, the sperm can then be used with IVF/ICSI.

Microsurgical epididymal sperm aspiration (MESA) — specialized sperm retrieval technique

III. CLINICAL CRITERIA

A. Precertification Requirements
- 12 months of frequent unprotected heterosexual intercourse or 6 months if the female partner is > 35 years of age
- Women < 35, including single female patients and same sex couples — member must have undergone a total of 6 IUI cycles (with at least 2–4 cycles of ovulation induction)
- Women > 35, including single female patients and same sex couples — member must have undergone a total of 3 (physician-supervised) IUI cycles (with at least 2–3 cycles of ovulation induction)
- Men with azoospermia or severe deficits in semen quality or quantity (and the couple accepts donor insemination) — number of AI attempts depends on the woman's age
- FSH — value should be < 15 on day 3 of menstrual cycle
- FSH test result valid for 12 months in women < 35 years of age; result valid for 6 months in women > 35. Clomiphene challenge test or other ovarian reserve test should be done every 12 months in women > 40
- Estradiol — value should be < 100; an elevated estradiol with a low FSH is still consistent with decreased ovarian reserve
- Reversal of elective tubal ligation or vasectomy — If an elective tubal ligation or vasectomy is reversed

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and the reversal is successful (as shown by patent tubes or normal semen analysis) and the member is unable to conceive after meeting the clinical definition of infertility, then the member may be ART-eligible; however, the reversal of the tubal ligation or vasectomy is not a covered benefit

IV. ART INDICATIONS

Members who do not achieve conception through less invasive treatments (i.e., medical, hormonal therapy or surgical) may be treated with an ART procedure when either of the following is met:

Failure of artificial insemination with gonadotropin (FSH) or clomiphene citrate ovarian hyperstimulation as noted above

OR

Couples for whom natural or artificial insemination would not be expected to be effective including:

- Men with azoospermia or severe deficits in semen quantity (< 10M) and quality (< 4% normal forms), and the couple declines donor insemination (Note: It is expected that the male have at least 2 unprocessed semen analyses with 1 week or more in between the tests)
- Women with tubal factor infertility:
    - Bilateral tubal disease (e.g., tubal obstruction, absence or hydrosalpinges)
    - Endometriosis stage 3 or 4
    - Failure to conceive post pelvic surgery with restoration of normal pelvic anatomy after:
        - Attempts to conceive for 6 months if < age 35
        - Attempts to conceive for 3 months if ≥ age 35
- Infertility resulting from ectopic pregnancy
- Ectopic pregnancy occurring during infertility treatment
- Unilateral tubal disease with failure to conceive after:
    - Attempts to conceive for ≥ 6 months if < age 35
    - Attempts to conceive for 3 months if ≥ age 35

Inadvertent ovarian hyperstimulation (estradiol level > 1500–2000 pg/mL and > 6 follicles > 16 mm, or 6–10 follicles > 14 mm, or a larger number of smaller follicles) during preparation for a planned stimulated IUI cycle in women < age 40 with a diagnosis other than polycystic ovarian syndrome.

(In women ≥ 40, it is typically not medically necessary to convert an AI cycle to IVF due to ovarian hyperstimulation)

V. ART UTILIZATION

An ART cycle consists of any of the following: IVF with embryo transfer, GIFT or ZIFT:

- IVF with fresh embryo transfer.5
  ET — it may be considered medically necessary to freeze embryos not transferred during a stimulated IVF cycle and to transfer them prior to the next stimulated treatment cycle because this will minimize ovulation induction and egg collection, both of which carry risks for the woman. Prior to proceeding to the next fresh ART cycle, ET using cryopreserved embryos must be used if ≥ 3 cryopreserved embryos of a similar developmental stage are available (for women ≥ age 35); however, embryo storage is not covered.
- ICSI is medically necessary where there is azoospermia or oligospermia (obstructive or nonobstructive), severe semen quality or quantity deficits, or for couples where a previous IVF treatment cycle has resulted in failed or poor fertilization. ICSI is covered for severe male factor when at least 2 unprocessed semen analyses show < 10 million total motile sperm or 4% strict Krueger normal forms or post processing semen analyses show < 3 million total motile sperm. It is expected that at least 50% of oocytes should fertilize with insemination; anything less than 40% is abnormal and is considered reduced or poor fertilization.
- GIFT is considered a medically necessary IVF alternative for women with female-factor infertility6 (male factor excluded); it includes the following:
    - Laparoscope oocyte (egg) retrieval
    - Immediate oocyte loading with sperm into a transfer catheter and insertion into the member's fallopian tube via the same laparoscope (there must have at least one patent fallopian tube for this method to be an effective infertility treatment)

ZIFT, tubal embryo transfers (TET) or pronuclear stage tubal embryo transfers (PROUST) are considered medically necessary IVF alternatives for women with female-factor infertility (male factor excluded)

- Specialized sperm retrieval techniques — considered medically necessary to overcome anejaculation (e.g., vasal sperm aspiration, MESA, percutaneous epididymal sperm aspiration [PESA], electroejaculation, TESA, seminal vesicle sperm aspiration and sperm recovery from bladder or urine for retrograde ejaculation)
- Oocyte donation — considered medically necessary in women for the management of infertility associated with the following conditions when the infertile member is the intended recipient of the resulting embryos:
    - Premature ovarian failure
    - Gonadal dysgenesis including Turner syndrome
    - Bilateral oophorectomy
    - Ovarian failure following chemotherapy or radiotherapy
    - IVF treatment failure
    - High risk of transmitting a genetic disorder from the female partner to the offspring

Assisted hatching — not recommended because it does not improve pregnancy rates; however, it may be indicated for

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women > age 38 and when any of the following are applicable:

- ≥ 3 failed IVF attempts (failure to detect rise in HcG)
- Thickened zonapellucida
- Documented previous pregnancy after IVF with AH

VI. PRE-IMPLANTATION GENETIC DIAGNOSIS (PGD)

PGD is considered medically necessary when the member meets ART criteria and any of the following is applicable:

- The test is used to improve the implantation rate of in vitro fertilization (IVF) in infertile couples who have had three prior failed attempts at IVF
- One partner is known to have a balanced translocation
- To determine the sex of an embryo when there is a documented history of an x-linked disorder and deselection of an affected embryo can be made on the basis of sex alone
- Deselection of embryos with genetic mutation when partners meet at least one of Criteria A and all of Criteria B

A. ≥ 1:

- Both partners are carriers of the same autosomal recessive disorder
- One partner is a carrier of an autosomal recessive disorder, and the couple produced an offspring affected by that disorder
- One partner is a carrier of a single gene autosomal dominant disorder
- One partner is a known carrier of a single gene X-linked disorder

B. All:

- The genetic disorder is identified with high degree of reliability through specific mutations
- The genetic disorder is associated with severe disability or has a lethal natural history
- Testing is accompanied by genetic counseling

Pre/post-test genetic counseling is required to inform decision-making

VII. OUTCOMES ASSOCIATED WITH UNTREATED INFERTILITY

Infertility, generally considered to be the inability to conceive after one year of attempting pregnancy, has been identified as a significant independent predictor of adverse obstetrical and perinatal outcomes. Unadjusted analyses suggest a 2-fold increased risk of preeclampsia, placental abruption, Caesarean section, and vacuum extraction, and a 5-fold increased risk of placenta previa in spontaneous singleton pregnancies in women with a history of infertility compared with women in the general population. Summarizes a number of studies documenting adjusted obstetrical, perinatal, and neonatal risks in populations of women with infertility or subfertility compared with control women. Some of these studies compared women with various delays in time to pregnancy that eventually conceived spontaneously to populations of women with short TTP, and found significant differences in a number of adverse outcomes, including preterm birth, LBW, and perinatal mortality. Other studies compared populations of women with delays in TTP with and without ART and found insignificant differences between these 2 groups, but increases in adverse outcomes between these 2 groups and a control group of women with no delay in TTP.

Maternal factors related to an increased risk of infertility also have an independently associated risk of adverse obstetrical outcomes. Advancing maternal age is associated with both declining fertility and multiple adverse outcomes of ongoing pregnancy, as noted recently in an SOGC committee opinion on delayed childbearing. Research shows obesity impairs fertility, although whether this effect is primarily ovarian or endometrial is controversial. Obesity is also independently related to adverse obstetrical outcomes, many of them similar to those associated with advancing maternal age38 and overlapping with those associated with AHR.

Although there is little remaining debate about the association of infertility or subfertility with adverse obstetrical outcomes following AHR, more specific associations between ovarian/ovum or testicular/sperm factors, endometrial factors, or other factors and adverse outcomes are not well understood.

VIII. OUTCOMES ASSOCIATED WITH FEMALE FACTOR INFERTILITY

Infertility is exclusively due to a female factor in 35 to 40% of couples. Approximately 21% to 45% of female infertility (15% of all infertility in couples) is due to ovulatory disorders. Ovulatory disorders may be caused by various factors, including aging or premature ovarian failure, endocrine dysfunction, stress, excessive exercise or weight loss, or tobacco use.

The WHO classifies ovulatory disorders into 3 categories:

1. WHO Group 1 – Hypogonadotropichypogonadal an ovulation. These women usually have amenorrhea and an ovulation due to estrogen deficiencies caused by decreased secretion of gonadotrop in releasing hormone (GnRH) by the hypothalamus, or lack of responsiveness to GnRH by the pituitary gland. They may also have low levels of follicle stimulating hormone (FSH) or prolactin (approximately 5% to 10% of an ovulatory women are in this category).

2. WHO Group 2 –Normogonadotropicnormoestrogenic an ovulation. These women are not deficient in estrogen, and may have normal FSH and prolactin levels, but luteinizing hormone (LH) levels may be normal or elevated. Most of the women in this group (over 90%) have polycystic ovarian syndrome (PCOS).Group 2 is the most common type of ovulation disorder (approximately 70 to 85% of anovulatory women fall within this category).

3. WHO Group 3 –Hypergonadotropichypoestrogenic anovulation. This category includes women with ovarian insufficiency (lack of ovarian follicles due to early menopause) or diminished ovarian reserve (approximately 10% to 30% of anovulatory women are in this category).

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Other causes of female infertility include tubal obstruction, endometriosis, uterine polyps or fibroids, and abnormal cervical mucus. Approximately 14% to 30% of infertile women have damaged fallopian tubes, sometimes due to blockage or scar tissue caused by pelvic inflammatory disease (PID).Endometriosis affects approximately 10% to 15% of infertile women. For about 3% to 10% of infertile women, other conditions of the uterus or peritoneum, such as uterine polyps or fibroids, are the cause.

IX. OUTCOMES ASSOCIATED WITH MALE FACTOR INFERTILITY

Infertility is associated with male factor or abnormal perm parameters in approximately 50% of cases. Studies have shown that 4.6% of oligozoospermic men and 13.7%of a zoospermic men have constitutional chromosomalabnormalities, the most common being sex chromosomalabnormalities and autosomal translocations. Karyotype analysis of men with fewer than 5 million spermatozoa per milliliter of semen has been recommended as routine by the World Health Organization since 2000.As expected, infertile men with chromosomal abnormalities are more likely to have genetically abnormal spermatozoa and to father chromosomally abnormal pregnancies. Azoospermia can be classified as non-obstructive or obstructive. The most common cause of obstructive azoospermia is a congenital bilateral absence of vas deferens, a feature associated strongly with mutations in the cystic Fibrosis transmembrane conductance regulator genes. In either presentation, a consultation with a urologist may lead to surgical extraction of sperm for use with IVF/ICSI. Microsurgical testis sperm extraction is estimated to be successful in 50% of attempts in non-obstructive azoospermia. Success with extracted sperm used in IVF/ICSI procedures has been documented with a pregnancy rate approaching 40%.A recently published systematic review summarized the potential reproductive Outcomes of various male reproductive genetic abnormalities associated with azoospermia.

X. UNEXPLAINED INFERTILITY

Approximately 25% to 30% of couples with infertility have both female and male fertility, or have unexplained infertility (where the cause is unknown). One study of couples on a Dutch waiting list to receive IVF found a cumulative pregnancy rate of 9.1%. Pregnancy rates were highest amongst couples with unexplained infertility and lowest in those with infertility due to tubal factors or endometriosis. The cause and the duration of infertility also affected pregnancy rates.

XI. LIMITATIONS/EXCLUSIONS

1. Coverage exclusions:

- Less than 12 months of frequent unprotected heterosexual intercourse or 6 months if the female partner is > age 35 years
- Cryopreservation and storage procedures of the egg or sperm
- Embryo storage
- All donor services and fees including sperm, egg and surrogacy
- Reversal of elective sterilization procedures (i.e., tubal ligation, vasectomy)
- Cloning
- Ovulation predictor kits or devices
- Frozen embryo transportation
- Sex preselection

2. Pre-implantation genetic screening is not considered medically necessary when any of the following is applicable:

- The selection of embryos with specific HLA typing to provide a match for an individual in need of an allogenic transplant
- The selection of embryos with the sole purpose of determining the gender of the resultant offspring.
- When ART criteria are not met

3. Mock embryo transfer is not a covered procedure, as such planning, performed in anticipation of embryo transfer, is considered to be inclusive to the evaluation and management service provided

4. Infertility services are not considered medically necessary once pregnancy is established. (Member will have to re-qualify for ART services)

5. Requests for fertility preservation services (e.g., embryo, egg or ovarian tissue cryopreservation) for iatrogenic infertility (i.e., secondary to chemotherapy, etc.), as well as storage procedures, will not be considered, as these services are excluded from coverage.

6. The following laboratory services/treatments are not considered medically necessary because they are ineffective or investigational:

- Aromatase inhibitors (testolactone) for idiopathic male infertility (i.e., for men without documented hypogonadotropichypogonadism)
- GIFT for male factor infertility or unexplained infertility problems
- Leukocyte immunization (immunizing female partner with male partner leukocytes)
- FSH manipulation of women with elevated FSH levels as an effort to reduce FSH level
- Growth hormone administration during ovulation
- Intravenous immunoglobulins administration
- Fine needle aspiration (mapping) of testes
- For male infertility evaluation, the following laboratory services: Seminal alpha-glucosidase, zinc, citric acid and acid phosphatase
- ZIFT for male factor infertility or unexplained infertility problems

The following sperm function tests:

- Sperm chromatin assay
- Sperm DNA fragmentation assay
- Hemizona assay
- In vitro testing of sperm penetration

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- Hypoosmotic swelling test
- Sperm nucleus maturation
- Hyaluronan binding assay

XII. CONCLUSION

This review has attempted to address the current state of several assisted reproductive technology interventions, with a particular focus on the clinical benefit provided to patients in addition to their safety. Not all established or developing techniques have been discussed as they are beyond the scope of this review, but the considerations raised will none the less be relevant for other technologies such as in vitro maturation, artificial oocyteactivation, sperm selection by hyaluronic acid-binding assays and pronuclear transfer for overcoming mitochondrial disease. ARTs is associated with increased complications during pregnancy and delivery, and increased rates of multiple births, preterm delivery, low birth weight infants, birth defects and malformations, and cerebral palsy compared to naturally conceived pregnancies. The underlying causes of infertility, rather than ARTs procedures, may be responsible for some of these complications.

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