Research Article

ASSISTED REPRODUCTIVE TECHNOLOGY: A BRIEF DISCUSSION

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ABSTRACT

As many as one in six couples will encounter problems with fertility, defined as failure to achieve a clinical pregnancy after regular intercourse for 12 months. Increasingly, couples are turning to assisted reproductive technology (ART) for help with conceiving and ultimately giving birth to a healthy live baby of their own. With this in mind, it is important that each step of the ART cycle is supported by good evidence from well-designed studies. Herein, the health economics research in this area are critically appraised. The cost-effectiveness of different interventions should be considered when making decisions about treatment. The rapid advancements in sciences have revolutionized modern medicine in a number of ways; genetic engineering, Assisted Reproductive Technologies (ART), human cloning, stem cells etc. has opened up the unimagined and promise unquestionable and undreamed benefits to mankind. At the same time, they raise many questions of law and ethical issues relating to public interest, social and religious sentiments and family concern. There is a certain element of risk associated with all assisted reproductive procedures. It is, therefore, necessary to ascertain the therapeutic and research value of the AR procedure in each case. This article reviews techniques of ART along with its costs, ethical & legal issues as well as implementation in today's society.

INTRODUCTION

The special programmes by WHO on human reproduction has estimated that there are 60 to 80 million infertile couples worldwide; between 6-10% of the couple are infertile, (World Health Organization, 2009) The advent of Assisted Reproductive Technologies (ART) from the late 70s has not only enhanced the possibility of pregnancy but has also made women conceive in situations which would not have been possible decades ago. However, many of these technologies require enormous technical expertise and infrastructure, are expensive and the couple’s endurance physically, emotionally, socially and economically. (Barreiro et al., 2007) In order to ensure quality of care, it is imperative that standardised protocols and guidelines should follow for the establishment and accreditation of ART Centres. National guidelines for Accreditation, Supervision and Regulation of ART Clinics have been formulated by ICMR in 2005 (Terriou et al., 2005) to provide optimum benefit of these newer technologies by skilled team of experts, at affordable health and economic cost. Assisted reproductive technologies include any fertilization involving manipulation of gametes/embryos outside the human body and transfer of gametes/embryos into the body. (Royce et al., 1997) The new reproductive technologies give great help and offer biomedical parenthood to various infertile couples who have exhausted all other avenues to have a child of their own. The first live birth resulting from IVF worldwide occurred in England in 1978. Nowadays IVF is a well-established and accepted treatment for infertility in most developed countries. Advances in ART, including the use of donor gametes and ICSI, have led to increased numbers of infertile couples being treated with ART in recent years. ART accounts for 1 to 3% of annual births in developed countries (Semprini et al., 1992). In 2002, 2.3% of babies born in Australia were conceived following the use of ART, (Peña et al., 2003). Over the past twenty years, there has been a steady decline in the number of embryos transferred in a single cycle due to growing concerns about the risk and very serious health consequences of multiple pregnancy. (Human immunodeficiency virus and infertility treatment, 2004) In 1993, 55.3% of treatment cycles transferred three or more embryos. In 2002 this had decreased to 5.8% of cycles. Over this same period, the success of ART in increasing the number of births has not been uniformly high. In Australia and New Zealand has steadily increased. (Nicopoullos et al., 2004)

Measurement of ART Effectiveness

Estimates of ART effectiveness may vary according to the definitions of treatment success and the treated population. Live
Infertility and need for fertility assistance services is likely to delay having children until a later age, the prevalence of infertility is defined as a circumstance where there has been either an inability to conceive or carry a pregnancy to a live birth after the initial oocyte retrieval within the same treatment cycle (Chu et al., 2006).

Clinical need

In developed nations throughout the world, the total fertility rate has been declining and, in many countries, is currently below the population replacement value of 2.1 births per woman. In Australia, the total fertility rate in 2002 was 1.76, which is comparable to that in the UK, USA and Canada (Veiga, 1999). It is estimated that 12–25% of couples are affected by infertility, but the number of couples seeking medical advice is not accurately known (Savasi et al., 2007). However, there is no national data collection on infertility in Australia. A recent population-based telephone survey of Australian men (Men in Australia, Telephone Survey, MATeS) found a self-reported failure to conceive of 7.6% (Chu et al., 2006). In developed nations, as an increasing number of women delay having children until a later age, the prevalence of infertility and need for fertility assistance services is likely to increase. The median age of child-bearing in Australian women increased from 26.8 years in 1982 to 28.7 years in 1992, and to 30.2 years in 2002. (Sauer et al., 2002)

Infertility

Infertility is defined as a circumstance where there has been either an inability to conceive or carry a pregnancy to a live birth after one year of unprotected sexual intercourse; or there is a medical condition that will reduce the likelihood of either conception or carrying a pregnancy to a live birth, (Bujan et al., 2007). Observational studies conducted in couples using natural methods to conceive have indicated that approximately 80% of couples will conceive in the first six menstrual cycles, and an additional 10% will conceive spontaneously within the next six cycles. (Kowalska et al., 2005) Of the 10% of couples classified as infertile after one year of trying to conceive, approximately half will achieve a spontaneous conception over the next three years.

Overview:

Infertility affects approximately 13-14% of reproductive-aged couples. It is defined as the inability to conceive after 1 year of properly timed, unprotected intercourse. This definition is based on the cumulative probability of pregnancy.

Table 1. Cumulative Probability of Pregnancy in Couples With Normal Fertility (All Reproductive-aged Women): (Lee et al., 2001)

<table>
<thead>
<tr>
<th>Month</th>
<th>Monthly Probability</th>
<th>Cumulative Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>0.20</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>0.36</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0.49</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.59</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>0.67</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>0.74</td>
</tr>
<tr>
<td>7</td>
<td>0.2</td>
<td>0.79</td>
</tr>
<tr>
<td>8</td>
<td>0.2</td>
<td>0.83</td>
</tr>
<tr>
<td>9</td>
<td>0.2</td>
<td>0.86</td>
</tr>
<tr>
<td>10</td>
<td>0.2</td>
<td>0.89</td>
</tr>
<tr>
<td>11</td>
<td>0.2</td>
<td>0.91</td>
</tr>
<tr>
<td>12</td>
<td>0.2</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Cycle fecundability is the probability that a single menstrual cycle will result in pregnancy (see Table 1 above). Cycle fecundity is the probability that a single cycle will result in a live birth. Assuming a constant monthly probability of conceiving (fecundability) of 20%, the theoretical cumulative pregnancy rate after 12 months is 93%. However, studies show that this number is actually lower. The number and quality of a woman’s oocytes declines with age. The decline in the number of oocytes begins at 20 weeks’ gestation when the female fetus has approximately 6-7 million oogonia, (Manigart et al., 2006).

Cause of Infertility

The cause of infertility can be easily identified in some couples. In other couples the cause is much less clear, and multiple factors may contribute. The major recognized causes of infertility are listed in Table 2.

Table 2. Causes of Infertility: (Mencaglia et al., 2005)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Couples</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>35%</td>
<td>--</td>
</tr>
<tr>
<td>Ovulatory</td>
<td>15%</td>
<td>40%</td>
</tr>
<tr>
<td>Tubal</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>Other</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Unexplained</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Obtaining a thorough history and physical examination is essential in evaluating an infertile couple. The questions asked during the evaluation should include the following topics:

- Current and past medical/surgical problems and recent changes in health
- Employment and potential chemical/environmental exposures
- Family history of miscarriages
- Personal and family history of birth defects or inheritable disorders
- Updated medicine list (including any over-the-counter medicine or herbs)
Tobacco, alcohol, and drug use
Coital frequency and any sexual dysfunction
Thorough gynecologic history, including pelvic pain, discomfort with intercourse, menstrual cramps, cycle length, and duration of flow
Prior pelvic infections
Duration of infertility
Prior pregnancies from either partner
Use of prior contraception

Risk factors
The NICE review provides detailed guidelines based upon the evidence available for known risk factors for infertility. These factors are outlined briefly below.

- Female age is the major determinant of infertility. Natural female fertility falls gradually after age 30 years, with a rapid decline after age 35 years to cessation at menopause.

Other factors associated with female infertility are obesity (body mass index greater than 29) and low body weight (body mass index less than 19 and irregular or absent menstruation) and smoking, (Tay et al., 2007).

- Obesity has also been associated with male infertility. Excessive alcohol intake, smoking and elevated scrotal temperature due to sedentary work position, occupational heat exposure and wearing tight underwear has been associated with reduced semen quality in men, although the impact of this on male fertility is not known, (PubMed)

- Prescription and recreational drugs and occupational hazards such as exposure to solvents have been associated with infertility in both males and females.

Diagnostic Tests
When evaluating an infertile couple, diagnostic studies should be selected as indicated. If the history is unclear, then tests that address the above-mentioned major categories of infertility should be obtained.

Male factor testing- After a medical history and physical examination, semen analysis is the single best test for evaluating for male factor infertility

For optimum and consistent results, abstinence is required 3-5 days prior to semen collection. The World Health Organization (WHO) has established methods for semen analysis, but methods may vary among facilities. Additionally, the WHO has established normal reference values. Another commonly used method for evaluating morphology is the strict Kruger method, (Farhi et al., 2007). Sperm concentration - 20 million/mL or more Motility - At least 50% or more with forward progression Morphology - At least 30% or more normal forms (14% strict Kruger criteria) White blood cells - Fewer than 1 million/mL Round cells - Fewer than 5 million/mL More recently, other tests have been devised to evaluate sperm. The Halosperm test and the Sperm Chromatin Structure Assay (SCSA) have been devised to evaluate the DNA fragmentation of sperm.

Ovulatory function testing- Women of reproductive age who have regular menstrual cycles lasting from 21-35 days are likely ovulatory. However, for patients to become more accustomed to predicting ovulation so that they can appropriately time intercourse, they may wish to initiate basal body temperature monitoring or use luteinizing hormone (LH) detection kits. (Dovey et al., 2008)

Basal body temperature (BBT) monitoring is largely a historical method for determining the correct timing of intercourse. A 0.5–1.0°F rise in temperature is noted 2 days after the luteinizing hormone (LH) peak, which occurs after the day of ovulation. This results from progesterone production from the corpus luteum. Since most studies show that the best day to introduce sperm into the female reproductive tract is either the day of ovulation or the day before ovulation, BBT monitoring -is not useful for coital timing in a current cycle but best serves as a method to confirm the time of ovulation and helps the patient to predict future cycles based on data she has gathered over prior cycles, (Zadehmodarres et al., 2009). A deficiency in progesterone production by the corpus luteum (CL) has historically been attributed to infertility and recurrent pregnancy loss in many women with otherwise unexplained miscarriages. The significance and presence of an inadequate luteal phase (also referred to as luteal phase defect (LPD)) has been questioned throughout the literature.
Ovarian reserve testing - Several simple tests for ovarian reserve exist. Initial testing usually includes cycle day 3 laboratories including follicle stimulating hormone (FSH), estradiol (E2), and leuteinizing hormone (LH). Typically, if the FSH level is greater than 15 mIU/mL or the estradiol level is greater than 75 pg/mL, the prognosis is poor. Day 3 antral follicle scans and ovarian volume may also be used to evaluate ovarian reserve and are simple and accurate, (Nyboe Andersen et al., 2005) In patients older than 40 years or for whom poor ovarian reserve is suspected, a clomiphene citrate challenge test may be performed. Clomiphene citrate (100 mg PO qd) is administered on cycle days 5-9. FSH and estradiol levels are drawn on days 3 and 10.

Cervical disease testing - Women who have had cervical cone biopsies or trauma to the cervix are at risk for cervical abnormalities and cervical stenosis. If a cervical abnormality is found, the most logical approach is to recommend bypassing the cervix with intrauterine inseminations (IUI), (Kovacic et al., 2010) especially if the rest of the findings from the infertility evaluation are normal.

- Hirsutism or hair loss
- Abnormal weight gain
- Oily skin or acne
- Purple striae on the abdomen
- Polyuria/polydipsia
- Irregular menses
- Heat or cold intolerance

Headaches, visual problems or lactation without prior pregnancy, (Melo et al., 2008; Prisant et al., 2010).

Infertility treatments

In some couples presenting with infertility, treatment can be directed at reversing the underlying cause. As described in the aetiology section above, this may involve surgical measures to treat genital tract obstruction or endometriosis; or hormone treatment to restore ovulatory function. ART procedures are effective in cases where alternative treatments are of doubtful value; the underlying cause is not amenable to other treatments; or the infertility is unexplained. (Queiroz et al., 2008)

Indication for ART: (Egger et al., 1993)
- When husband is impotent.
- When husband is infertile.
- When husband is unable to deposit semen in female genital i.e. hypospadesis, epispadesis etc.
- When Rh incompatibility between husband and wife.
- When husband is suffering from hereditary diseases.

Oxidative stress in the ART setting

Despite the advancement of ART techniques, gametes and embryos when handled, prepared and manipulated for ART procedures, are exposed to various potential ROS-inducing factors. In vitro, the risk of oxidative stress development is greater than in vivo(Egger et al., 2001) and its negative impact may be amplified due to the lack of physiological defense mechanisms, absence of natural antioxidants and the presence of multiple potential sources of ROS (van Leeuwen et al., 2005).

These sources of ROS during ART procedures could either be endogenously from gametes or via exogenous environmental factors (Chu et al., 2005). However, unless measures are taken to curb ROS production, both the endogenous and exogenous sources of ROS will ultimately lead to the development of oxidative stress, which would then negatively impact on fertilization rates and pregnancy outcome.

ART: Step-by-Step Guide

Every cycle of ART involves multiple steps, and each occurs at a specific time during a four to six-week period. The following is an overview of the IVF procedure. The procedure begins in the month preceding the actual ART cycle. An IVF cycle typically includes the following steps or procedures: (Guttmacher et al., 1956)

- Medications to grow multiple eggs
- Retrieval of eggs from the ovary or ovaries
- Insemination of eggs with sperm
- Culture of any resulting fertilized eggs (embryos)
- Placement (“transfer”) of one or more embryo(s) into the uterus

Figure 3: Infertility Treatments (Queiroz et al., 2008)

Figure 4: Oxidative Stress In ART Setting (Chu et al., 2005)
• Support of the uterine lining with hormones to permit and sustain pregnancy
• In certain cases, these additional procedures can be employed:
  • Intracytoplasmic sperm injection (ICSI) to increase the chance for fertilization
  • Assisted hatching of embryos to potentially increase the chance of embryo attachment ("implantation") (Dain et al., 2011 and Rova et al., 2012)
  • Embryo cryopreservation (freezing)
  • The success of IVF largely depends on growing multiple eggs at once:
  • Injections of the natural hormones FSH and/or LH (gonadotropins) are used for this purpose
  • Additional medications are used to prevent premature ovulation
  • An overly vigorous ovarian response can occur, or conversely an inadequate response.

**Cycle Preceding ART Cycle:** (Picaud et al., 2012)
• Sometimes oral contraceptives are begun.
• Sometimes a GnRH agonist (e.g. Lupron®) is initiated.
• Sometimes a mock transfer is performed to identify potential problems in embryo transfer.
• Occasionally, an IVF cycle starts with a cycle day of the menstrual period without other medications.

**ART Cycle**
• Prestimulation treatment
• Ovarian stimulation with gonadotropins (e.g. Bravelle®, Menopur®, Follistim®, Reproprotex®, Gonal-F®, Follistim AQ pen, and/or Gonal-F RFF Pen)
• Monitoring follicle development with ultrasound and serum hormone levels
• Final oocytes maturation and hCG administration (Profasi®, Pregnyl®, Novarel® or Ovidrel®)
• Transvaginal oocyte retrieval
• Insemination
• Embryo transfer
• Progesterone supplementation (Hamdan et al., 2015)
• Pregnancy test Early pregnancy follow-up

**ART Medications**
Several medications are used in a typical IVF cycle. These medicines belong to several categories and each are an important part of a stimulated cycle. The types and amount of medications used vary according to the medication protocol prescribed by physician.

**GnRH Agonists**
Gonadotropin releasing hormone (GnRH) is a hormone produced in the brain that indirectly stimulates ovarian function. Agonists of GnRH are synthetic forms of this hormone which do not directly induce follicle development or ovulation but which have become very important in ART therapy, (Perkins et al., 2015)

**GnRH Antagonists**
Antagonists of GnRH are also available (Cetrotide® and Antagon®). These are started later in the cycle than Lupron® and directly and immediately inhibit FSH and LH production. Protocols that use these medications may require fewer injections. (McLernon et al., 2010) Ultrasound measurements of follicular growth are used to determine when to start these medicines.

**Gonadotropins**
To increase likelihood of pregnancy through ART, multiple oocytes must be produced. This is accomplished through the administration of gonadotropins, hormonal medications that directly stimulate the ovaries. Stimulation can be achieved with a variety of drug regimens. Gonadotropin medications come in several forms; Reprovin® and Menopur® are a combination of FSH and LH. They replace a woman's own LH and FSH which are normally produced by the pituitary gland. Bravelle®, Follistim® AQ Cartridge for use with Follistim Pen®, Follistim® AQ Vial, Gonal-F®, and Gonal-F® RFF Pen are preparations that contain only FSH. (Kresowik et al., 2011) This process ensures uniform purity and potency. Because the dose of hormones that are used in ART is greater than what the body normally produces, the ovaries typically develop more than one oocyte as occurs in a natural cycle.

**Human Chorionic Gonadotropin**
Human chorionic gonadotropin (hCG) is an injectable medication that is administered to complete oocyte maturation. The brand names for hCG are Profasi®, Ovidrel®, Novarel®, and Pregnyl®. Human chorionic gonadotropin is structurally similar to the LH that is produced by a woman's pituitary gland. It acts on the ovary in a manner similar to a woman's own LH. (Shah et al., 2011) Human chorionic gonadotropin, like LH, stimulates the final maturation of the oocytes in the follicle. It also stimulates progesterone production from the ovary after egg retrieval. This progesterone is important to prepare the uterus for implantation of the embryo.

**ART procedures**
**In Vitro Fertilization (IVF)**
This type of treatment, the first to be introduced in 1978 still remains as the mainstay of ART today. The object of IVF is to add sperm to eggs in the laboratory (instead of the Fallopian tube) in situations where the normal pathway via the Fallopian tubes is damaged or absent, or sperm is not functioning normally. The process of IVF requires a significant time contribution and is emotionally stressful. When performed for the correct reasons, it offers a pregnancy (success) rate of approximately 30-50% percent per single attempt, (Kalra et al., 2011). Units specializing in ART undertake this type of treatment. A treatment cycle requires the stimulation of multiple eggs in the ovary using drugs such as clomiphene citrate, HMG, FSH GnRH agonists/antagonists and/or hCG. At an appropriate time, eggs are collected either by ultrasound as an outpatient procedure, or rarely by laparoscopy. The sperm is collected, prepared and added to the eggs in the laboratory, (Abma et al., 1997 and Barbieri et al., 1999). Once fertilization and division of the eggs has occurred, usually after forty-four hours, normally one or two embryos are replaced into the mother's uterus by means of a thin plastic tube (transfer catheter) inserted via the vagina and cervix.
**GIFT** - GIFT is short for Gamete Intrafallopian Transfer, and it was once a very common and popular form of ART. However, it is not used that much anymore. GIFT is where the woman’s eggs and man’s sperm are combined in a lab. The eggs are then inserted into the fallopian tubes. In GIFT treatments, the fertilization takes place inside a woman’s body and not inside a lab, (Biljan et al., 1999) GIFT is a good option for couples who want a more natural ART treatment, that allows the fertilization to take place inside the woman’s body naturally.

**ZIFT** - ZIFT is short for Zygote Intrafallopian Transfer, and it is much like GIFT. The eggs are mixed with the sperm in a lab, and then placed back inside the woman’s fallopian tubes. The difference with ZIFT is that the eggs are not inserted back into the woman’s body until the eggs have already been fertilized. As with GIFT, this process was once very popular, (Centers for Disease Control and Prevention, 2002 and Confino et al., 1990) but has now become less common with the increased success of IVF.

**ICSI** - ICSI is short for Intracytoplasmic Sperm Injection, and it is most commonly used for couples with serious problems with the man’s sperm. ICSI represents one of the major advances in human reproduction and ART that occurred in the 90's. It differs from IVF by what happens once the eggs and sperm reaches the laboratory. Essentially a single moving sperm is injected into a single mature egg. Thus the couple requires very few sperm for this type of therapy. (Evenson and Wixon, 2005) ICSI has opened up treatment to a whole new group of patients in whom classical IVF was unsuccessful. This includes males with very low sperm counts (< 5 million / ml), males with antisperm antibody problems, couples who have had failed fertilisation at IVF. Once embryos are formed, embryo transfer is identical to IVF (de La Rochebrochard et al., 2006).

**Embryo Freezing and Replacement (Transfer)**

Advances in freezing technology allow unused embryos, provided they are structurally normal, to be frozen and stored. Embryos can be stored for years without any apparent defects occurring. These can be thawed and replaced in normal cycles greatly simplifying the patient's treatment cycle and costs. At this time it would appear that the pregnancy rate from frozen embryos is lower than that from fresh embryos. Unfortunately at the time of writing while some eggs have been successfully frozen the technology has not reached the same level as that for embryos and is not a routine clinical procedure. In Australia, a grading system based on embryo morphology is commonly used to select the healthiest embryos for injection into the uterus trans vaginally. After embryo transfer, the female is treated with progesterone daily for up to the 10th week of pregnancy (or alternative regimens) to assist implantation and maintenance of pregnancy. The number of embryos transferred depends on the practice of the provider and the age and preferences of the treated couple. Any remaining healthy embryos may be frozen for storage (cryopreservation) for thawing and transfer at a later date if needed.

**Blastocyst Culture**

The embryo is usually replaced at the 2-8 cell stage of development. The blastocyst (multicellular stage with fluid...
compartment) stage may be reached by prolonging the culture of the embryo in the laboratory for a longer period and if it reaches the blastocyst stage can be transferred to the uterus at that time. This scientific approach helps in selecting the embryo(s) with a greater chance of succeeding. To achieve this degree of development special laboratory conditions are required. (Guzick et al., 2001)

Intrauterine insemination- Intrauterine insemination (IUI) involves the placement of washed sperm into the uterus under ultrasound guidance to bypass the natural cervical mucus barrier. It is performed under sedation as an outpatient procedure with or without controlled ovarian hyperstimulation (COH). It is designed to bring a high concentration of sperm into close contact with one oocyte (after natural ovulation) or with multiple oocytes (after COH). (Kidd et al., 2001; Klonoff-Cohen et al., 2004 and Kovacs et al., 1978) The main indications for IUI with COH are in the treatment of unexplained infertility where investigations have excluded an obstructive cause (at least one open fallopian tube) and severe male factor infertility.

Advantages are that the procedure is less invasive and better tolerated than IVF. Disadvantages are that the procedure has been associated with a lower success rate and higher multiple pregnancy rate than IVF. However, the use of low-dose COH regimens with abandonment of insemination when more than three dominant follicles develop may be expected to reduce the latter. In Australia, best practice involves ovarian stimulation with low-dose clomiphene citrate (usually 50–100mg daily) or FSH alone (usually 50–75 IU daily), with IUI treatment only when one or two dominant follicles are present on the day of HCG administration.

Surrogacy/Gestational Carrier

A pregnancy may be carried by the egg donor (traditional surrogate) or by another woman who has no genetic relationship to the baby (gestational carrier). If the embryo is to be carried by a surrogate, pregnancy may be achieved through preimplantation Genetic Diagnosis (PGD). (Johnson et al., 2004)

In addition the embryo can undergo certain genetic tests before it is returned to the mother's uterus during IVF/ICSI cycles to exclude certain genetic problems and this is referred to as Pre-implantation Genetic Diagnosis (PGD). (Johnson et al., 2004)

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Success rates on ART for some fertility clinics. According to The U.S. Centers for Disease Prevention (CDC) collects that affect the success rate of ART include:

- Age of the partners
- Reason for infertility
- Clinic
- Type of ART
- If the egg is fresh or frozen
- If the embryo is fresh or frozen

The U.S. Centers for Disease Prevention (CDC) collects success rates on ART for some fertility clinics. According to the 2006 CDC report on ART, the average percentage of ART cycles that led to a live birth were:

- 39% in women under the age of 35
- 30% in women aged 35-37
- 21% in women aged 37-40
- 11% in women aged 41-42

ART can be expensive and time-consuming. But it has allowed many couples to have children that otherwise would not have been conceived. The most common complication of ART is multiple fetuses. But this is a problem that can be prevented or minimized in several different ways. (Paulson et al., 2001)

Success Rates

Success varies with many factors. The age of the woman is the most important factor, when women are using their own eggs. Success rates decline as women age, specifically after the mid-30’s. Part of this decline is due to a lower chance of getting pregnant from ART, and part is due to a higher risk of miscarriage with increasing age, especially over age 40.

Success rates vary with the number of embryos transferred. However, transferring more and more embryos at one time does not increase the chance of live birth significantly, but may only increase the risk of a multiple pregnancy, and its associated risks, (Peters et al., 1992). The impact of the number of embryos that are transferred also varies with the age of the woman. SART, in conjunction with, The American Society for Reproductive Medicine (ASRM), has published guidelines for the recommended number of embryos to transfer. Patients may require several cycles of treatment to have a baby, (Petrozza et al., 1997) Success rates remain fairly constant over several cycles, but may vary greatly between individuals. It is important to note that patient characteristics vary among programs; therefore, success rates should not be used to compare treatment centers.

Risks of Art

The medical risks of ART depend upon each specific step of the procedure. The following are some of the primary risks of ART procedures:

Ovarian stimulation carries a risk of hyperstimulation, where the ovaries become swollen and painful. Fluid may accumulate in the abdominal cavity and chest, and the woman may feel bloated, nauseated, and experience vomiting or lack of appetite. Up to 30% of woman undergoing ovarian stimulation have a mild case of ovarian hyperstimulation syndrome (OHSS) that can be managed with over-the-counter painkillers and a reduction in activity. (Pittaway et al., 1983) In moderate OHSS, women develop or accumulate fluid within the abdominal cavity, and gastrointestinal symptoms may occur. These women are monitored closely, but generally do very well with simple outpatient management. The condition tends to resolve without intervention unless pregnancy occurs, in which case recovery may be delayed for several weeks. Up to 2% of women develop severe OHSS characterized by excessive weight gain, fluid accumulation in the abdomen and chest, electrolyte abnormalities, over-concentration of the blood, and, in rare

Donation

Artificial Insemination (AI)- Any procedure in which human sperm are introduced into the reproductive tract of a woman by a non-coital method other than as part of an IVF or GIFT procedure, (Misell et al., 2006)

Donor Insemination (DI)- Introduction of sperm which has been donated, from a man other than the woman’s partner, into the reproductive tract of a woman by a non-coital method, (Misell et al., 2006)

Donation- A process by which a person who has the responsibility to make decisions about the keeping or use of any gametes or embryo gives consent for their use by another person or persons.

In ART there are three types of donation - egg, sperm or embryo.

- **Donor embryo**: A fertilised egg where the sperm and oocyte used do not belong to the couple attempting to conceive. A donor embryo may be donated from a couple, or may be made up from a donated oocyte and donated sperm.

- **Donor sperm**: Sperm not belonging to the male partner of the couple attempting to conceive. The donor may or may not be known to the couple, (Mitwally et al., 2005)

- **Donor oocyte**: An unfertilised egg not belonging to the female member of the couple attempting to conceive. The donor may or may not be known to the couple.

How often is assisted reproductive technology (ART) successful

Success rates vary and depend on many factors. Some things that affect the success rate of ART include:

- Age of the partners
- Reason for infertility
- Clinic
- Type of ART
- If the egg is fresh or frozen
- If the embryo is fresh or frozen

Figure 12. Gestational Surrogacy, (Legro et al., 2007)
cases, the development of blood clots, kidney failure, or death. (Schlaff et al., 1990)

Safety of ART

Research about the safety of ART compared to spontaneous pregnancies is based on observational studies that compare outcomes for couples achieving pregnancy with ART with those achieving pregnancy spontaneously. As outlined in the following, these studies show that ART procedures are associated with greater health risks for the mother and child than spontaneous pregnancies. These risks are largely associated with the use of controlled ovarian hyperstimulation regimens and multiple embryo transfers in ART, for example, OHSS, and complications due to multiple pregnancies. Other differences observed in antenatal and perinatal outcomes may reflect differences between fertile and subfertile couples. (Stumpf et al., 1980; Styer et al., 2008) such as maternal age and paternal sperm abnormalities, rather than the independent effects of ART. However, research is ongoing to confirm or exclude an association between ART, in particular ICSI, and the risk of congenital malformations.

Ethics

Some couples find it difficult to stop treatment despite very bad prognosis, resulting in futile therapies. This may give ART providers a difficult decision of whether to continue or refuse treatment Tietze et al., 1957. Some assisted reproductive technologies can in fact be harmful to both the mother and child. Posing a psychological and a physical health risk, which may impact the ongoing use of these treatments. The adverse effects may cause for alarm, and they should be tightly regulated to ensure candidates are not only mentally, but physically prepared, (Titionally, et al., 2003)

The role of the ART ethical guidelines in the regulation of ART

The Ethical guidelines on the use of assisted reproductive technology in clinical practice and research 2007 underpin the regulation of ART practice within Australia. Accreditation of ART treatment centres by the Reproductive Technology Accreditation Committee (RTAC) is the basis of a nationally consistent approach for overseeing ART clinical practice. (Watson et al., 1994) RTAC accreditation requires ART treatment centres to comply with government laws and guidelines concerning the practice of ART. The ART Guidelines are included in this requirement. RTAC was established by the Fertility Society of Australia.

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 oocyte activation, sperm selection by hyaluronic acid-binding assays and pronuclear transfer for overcoming mitochondrial disease. Although the same could be said for all areas of medicine, assisted reproductive technology in particular has developed a very strong commercial backing. It is therefore particularly important to ensure that all new technologies are adequately and rigorously tested for both safety and efficiency, ideally before being used clinically. While not all of the techniques discussed here are routinely offered, many are reserved for use in patients with repeated IVF failure. The use of largely experimental techniques particularly in a vulnerable cohort of patients further highlights the need for the risks and benefits to be fully investigated.

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