The Use of In Vitro Fertilization in the Management of Male Infertility: What the Urologist Needs to Know

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Infertility affects approximately 10% to 20% of reproductive-age couples, many of whom may present initially to a urologist. Some couples may be treated medically to increase spontaneous conception rates; however, many will require more aggressive management with in vitro fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI). IVF involves ovarian stimulation, oocyte retrieval, and fertilization outside of the body; ICSI involves injecting one sperm into the oocyte to promote fertilization. Here we provide a brief overview of IVF and ICSI along with a discussion of the risks involved to facilitate the counseling and care of the infertile couple.

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KEY WORDS

In vitro fertilization • Intracytoplasmic sperm injection • Male infertility

Infertility, defined as the inability to conceive within 12 months of unprotected intercourse, affects approximately 10% to 20% of reproductive-age couples.[1] As couples defer childbearing until later ages and as the obesity epidemic grows, the incidence of infertility is likely to continue to rise.[2,3] Male factor infertility is estimated to contribute to two-thirds of all cases. Of men seeking care for infertility, 18.1% reported being diagnosed with male factor infertility and 13.7% with a sperm or semen problem.[4]

The evaluation for male infertility includes a thorough history and physical examination, and the mainstay of diagnostic testing continues to be the semen analysis. If abnormalities are noted on semen analysis, further testing is warranted to evaluate for possible etiologies. Where applicable, treatment is initiated with the goal of improving semen quality and male fertility. Previously, in cases in which semen quality remained profoundly impaired, the successful treatment for male factor infertility was once limited to donor insemination.

The development of in vitro fertilization (IVF) revolutionized the management of female infertility. As powerful a tool as this proved to be, however, IVF fertilization rates remained poor in the presence of compromised semen parameters. A significant breakthrough in the treatment of severe male infertility was the development of intracytoplasmic sperm injection (ICSI) in 1992.[5] By allowing the injection of a single sperm into each oocyte, ICSI provides the possibility of genetic offspring to men who have very scant numbers of motile sperm on semen analysis or who require surgical harvesting.

From its inception, assisted reproduction has involved a gynecologist and an embryologist. The urologist is a critical collaborator for the treatment of couples with male factor infertility. Sperm harvested by microsurgical epididymal sperm aspiration, testicular sperm aspiration, or biopsy can be used to fertilize harvested oocytes by ICSI. The urologist may be the first to evaluate a couple for infertility, and will certainly be involved if sperm harvesting is indicated. Therefore, this article reviews the process of assisted reproduction by IVF/ICSI for urologists who may be seeing patients with infertility issues.

Fertility Evaluation

A basic infertility evaluation should be performed in both the male and female partner concurrently and includes a history and physical examination. Routine testing for causes of female infertility includes an evaluation of ovulatory status, evaluation of the fallopian tubes and uterine cavity, transvaginal pelvic ultrasound, and evaluation of ovarian reserve. Ovulatory status can be reasonably assured by the presence of normal cyclic menstrual cycles accompanied by premenstrual symptoms; however, basal body temperature charting, the use of urinary luteinizing hormone (LH) kits, or midluteal progesterone level can be used in uncertain cases. Evaluation of thyroid-stimulating hormone and prolactin levels should be considered, as abnormal values can affect ovulation. The uterine cavity and tubal patency are most often initially evaluated by hysterosalpingogram.

Ovarian reserve testing includes measurement of early follicular phase serum follicle-stimulating hormone (FSH), estradiol (E_2), and anti-Mullerian hormone (AMH). AMH is produced by the granulosa cells of the primary and preantral follicle and does not vary significantly during the menstrual cycle. Subsequently, it can be obtained at any time and can predict poor response to ovarian stimulation if low.[6] An ovarian antral follicle count completes the ovarian reserve testing and is easily obtained during a transvaginal ultrasound (TVUS).

The initial laboratory test for the evaluation of the infertile male is the semen analysis. This should be collected after 3 to 5 days of abstinence and two assessments should be performed as variation in semen quality occurs even in normal men. Typically evaluated parameters include ejaculate volume, sperm density, sperm motility, and sperm morphology.

The initial laboratory test for the evaluation of the infertile male is the semen analysis. This should be collected after 3 to 5 days of abstinence and two assessments should be performed as variation in semen quality occurs even in normal men. Typically evaluated parameters include ejaculate volume, sperm density, sperm motility, and sperm morphology. The lower limits of normal as defined by the World Health Organization are: semen volume 1.5 mL, total sperm number 39 million/ejaculate, sperm concentration 15 M/mL, total motility 40%, progressive motility 32%, and morphologically normal forms 4%.[7] Hormonal evaluation is indicated in men with sperm concentration $<$ 10 M/mL or with clinical evidence of an endocrinopathy. Genetic evaluation by karyotype and for Y chromosome microdeletions should be considered in men with sperm concentration $<$ 10 M/mL, and cystic fibrosis genetic testing should be performed in men with congenital absence of the vas deferens.

Ovarian Stimulation and IVF

Once all testing has been completed, recommendations for treatment can then be made. Oral or injectable pharmacologic agents may be used to promote ovulation of a single mature oocyte in anovulatory or oligo-ovulatory women (ovulation induction) or to promote the development and ovulation of multiple mature oocytes in women with normal ovulatory menstrual cycles (supra-ovulation). This can be coupled with intrauterine insemination (IUI) or timed intercourse to further increase pregnancy rates.

IVF is often reserved for couples that fail less aggressive therapy; however, it is the first-line treatment for those with tubal factor or severe male factor infertility (in conjunction with ICSI). ICSI is the process of injecting a single sperm into an oocyte to promote fertilization. The process involves stripping the surrounding cumulus cells from the oocyte, stabilizing the oocyte with a micropipette, and

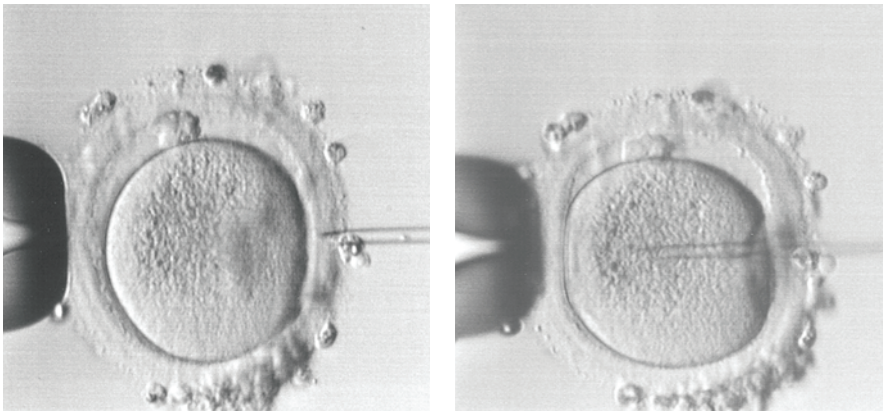

Figure 1. Intracytoplasmic sperm injection (photographs courtesy of Brent Barrett, PhD, HCLD, Boston IVF, Boston, MA).

injecting a single selected sperm directly into the cytoplasm of the oocyte (Figure 1). Because only one viable sperm is needed per mature oocyte, ICSI provides the possibility of genetic offspring even to those with severely compromised semen parameters. IVF/ICSI is also required for those couples undergoing preimplantation genetic testing (PGD) for specific chromosomal abnormalities. PGD may be pursued by any couple with a known genetic mutation and a desire to avoid transmitting that mutation onto their offspring. For example, couples in which both partners are carriers for cystic fibrosis (autosomal recessive inheritance) or in which one carries a *BRCA* gene mutation (autosomal dominant inheritance) may pursue IVF/ICSI with PGD in order to identify unaffected embryos that may then be used to create a pregnancy.

Severely abnormal semen parameters may be an indication for the application of IVF/ICSI. Pregnancy rates with IUI decrease with total motile spermatozoa $<$ 5 million[8] and total motility $<$ 30%.[9] In contrast, successful fertilization and pregnancy can be accomplished with very few motile sperm through the process of IVF/ICSI. Indications for ICSI include oligospermia $<$ 5 M/mL, cases of azoospermia in which sperm can be harvested from the epididymis or testes, and failed fertilization in a prior IVF cycle. Some clinicians also employ ICSI in the management of couples with unexplained infertility undergoing IVF. In addition, ICSI is used when PGD is performed. Prior to embryo biopsy for PGD, the oocyte is stripped of its surrounding cumulus cells to reduce genetic contamination. Fertilization by conventional means (placing sperm with the oocyte) is reduced once the cumulus cells have been removed.[10] In addition to maintaining fertilization rates, ICSI also eliminates the possibility of polyspermic fertilization and contamination of the embryo biopsy by sperm adherent to the embryo.

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IVF involves the removal of oocytes from the ovary, fertilization outside of the body, and transfer of the embryo into the uterus. The first successful pregnancy from IVF was delivered in 1978.[11] At that time, laparoscopy was performed in a natural menstrual cycle to obtain the ovulatory oocyte that was then fertilized and transferred back to the uterus. Shortly thereafter, practitioners began using gonadotropins to promote the development of multiple follicles to increase the yield of oocytes per cycle. Improvements in, and the increased availability of, TVUS increased the ease of oocyte retrieval and allowed for improved monitoring of follicular development.

The process of modern day IVF involves several steps: multifollicular development, prevention of spontaneous ovulation, oocyte maturation, oocyte retrieval, fertilization, and embryo transfer.

Multifollicular Development

Exogenous gonadotropin administration overrides the intrinsic mechanisms that normally result in monofollicular growth during the menstrual cycle. The use of pituitary extract to induce ovulation in the human was first described in 1958 by Gemzell and colleagues.[12] Urinary extracts from postmenopausal women containing FSH and LH (human menopausal gonadotropins [HMG]) began to be used in the 1960s for ovulation induction. Not long after the report of successful IVF in 1978, the use of gonadotropins for ovarian hyperstimulation was implemented to increase the number of oocytes obtained for IVF. Problems with the use of pituitary or urinary sources of gonadotropins included limited supply, possible transmission of disease, impurity, and difficulty standardizing the amount of hormone in each batch of product. As the field of molecular biology progressed, the development of recombinant gonadotropins improved upon the safety and standardization of therapy. Currently, gonadotropin preparations include urinary HMG, highly immunopurified urinary gonadotropin,

and recombinant gonadotropins. Exogenous gonadotropin is administered daily by subcutaneous injection over approximately 7 to 10 days during an IVF cycle to promote multifollicular development.

Prevention of Spontaneous Ovulation

In a normal menstrual cycle, rising E_2 levels result in an LH surge that causes the receptive oocyte to proceed through meiosis to the metaphase II stage where it awaits fertilization. The LH surge also causes rupture of the dominant follicle and ovulation of the oocyte. The use of exogenous gonadotropins for multifollicular development results in prematurely elevated E_2 levels, which will trigger premature luteinization of the follicle and premature ovulation.

A gonadotropin-releasing hormone (GnRH) agonist or antagonist is utilized in IVF cycles to prevent premature ovulation and allow for the timed collection of mature oocytes. GnRH agonists cause an initial flare of FSH and LH secretion that is then followed by down-regulation and desensitization of the GnRH receptor at the level of the pituitary. IVF protocols that use a GnRH agonist for suppression of an endogenous LH surge typically start the GnRH agonist several days before exogenous gonadotropins. In contrast, GnRH antagonists cause immediate suppression of endogenous gonadotropin release and are typically initiated after exogenous gonadotropin stimulation has begun.

Oocyte Maturation

As exogenous gonadotropin is given, a cohort of follicles will begin to respond and grow in size. In a normal ovulatory cycle, the LH surge triggers the resumption of meiosis and ovulation. In an IVF cycle, the endogenous LH surge is suppressed to prevent premature luteinization and ovulation. Subsequently, an LH surge needs to be induced prior to oocyte aspiration to allow for the collection of mature oocytes. Prior to the development of recombinant LH, urinary human chorionic gonadotropin (hCG) was the best option for inducing LH activity. Current options include urinary hCG, recombinant hCG, recombinant LH, or a GnRH agonist. A GnRH agonist will cause an LH surge by the flare of gonadotropin release prior to down-regulation of the GnRH receptor; however, it can only be used to trigger an LH surge in a protocol where a GnRH antagonist was used for pituitary suppression.

Oocyte Retrieval

Approximately 36 hours after hCG or GnRH agonist administration, oocyte harvesting is performed. This is typically performed via TVUS-guided needle aspiration. The timing of oocyte retrieval is critical: collection performed too early results in an increased number of immature oocytes; if collection is performed too late, the oocytes may have already been ovulated.

Fertilization

Fertilization is performed shortly after oocyte retrieval either by conventional IVF or by ICSI. In conventional fertilization, each oocyte is incubated with approximately 50,000 sperm and fertilization is allowed to occur naturally. For ICSI, one sperm is selected for injection into each oocyte. The tail of the sperm is broken both for ease of manipulation and to initiate the acrosome reaction allowing for fertilization. The oocyte is stripped of its surrounding cumulus cells, stabilized by a micropipette, and injected with the sperm. Approximately 18 hours later, the oocytes are examined for fertilization.

Sperm may be obtained from ejaculated semen or may be surgically retrieved from the epididymis or testis in cases of azoospermia. Approximately 70% of retrieved oocytes will fertilize given normal semen parameters by conventional fertilization. Reported fertilization rates vary for ICSI, but are generally comparable with that of conventional fertilization. Several studies show no difference in fertilization rates for surgically harvested sperm compared with sperm obtained from the ejaculate (73% vs 75%, respectively, in one study[13]). Results regarding fertilization rates by type of azoospermia (obstructive vs nonobstructive) have been conflicting, however, a meta-analysis of nine studies published in 2004 found a significantly improved fertilization rate (relative risk [RR] 1.18; 95% confidence interval [CI], 1.13-1.23; $P < .01$) and clinical pregnancy rate (RR 1.36; 95% CI, 1.10-1.69; $P = .01$) in men with obstructive azoospermia compared with nonobstructive azoospermia.[14]

Embryo Grading and Transfer

The embryos are evaluated by light microscopy for progression in development and cellular morphologic features at set time points following fertilization. Features typically assessed include cell number, degree of cellular fragmentation, and symmetry.[15] Embryos should develop within a normal time frame; most will be 2-cell at 28 hours, 4-cell at 43 hours, 8-cell at 54 hours, and blastocyst formation occurs between day 4 and day 5. Embryo transfer is usually performed on day 2 or 3 after fertilization or at the blastocyst stage, depending on the number and grade of embryos available. The decision of which embryos to transfer and when to transfer is a collaborative effort between the embryologist and reproductive endocrinologist.

The embryo transfer itself is technically fairly simple to perform and can be done with or without ultrasound guidance. The embryo(s) to be transferred are loaded into a catheter that is then passed through the cervix and into the uterine cavity. Ultrasound may be used to guide placement and measure the distance from the tip of the catheter to the top of the endometrial cavity prior to depositing the embryo(s) into the uterus. Factors shown to affect pregnancy rates include the presence of blood on the catheter on completion (suggesting trauma), uterine contractions seen on ultrasound, and distance of the catheter tip from the top of the endometrial cavity.[16,17]

Among IVF cycles in which nondonor oocytes were used in a fresh embryo transfer, women aged < 35 years have the highest success rates with a PR of 46.2% and LBR of 40.1%. Success rates decline significantly with age, with women aged > 42 years having a 9.1% PR and 4.2% LBR per cycle.

Success Rates

Since 1992, all clinics performing IVF have been required to provide outcome data to the Centers for Disease Control and Prevention, allowing for comparison of national and center-specific data over time. This information can be easily accessed by the public at www.cdc.gov or www.sart.org.

Pregnancy rates (PR) and live birth rates (LBR) from IVF are highly dependent on the age of the female partner. Available data indicate that the percentage of cycles resulting in pregnancy and the percentage of cycles resulting in live births has not changed significantly over the past 4 years. Among IVF cycles in which nondonor oocytes were used in a fresh embryo transfer, women aged < 35 years have the highest success rates with a PR of 46.2% and LBR of 40.1% (Table 1). Success rates decline significantly with age, with women aged > 42 years having a 9.1% PR and 4.2% LBR per cycle. The use of donor oocytes eliminates the reduction in pregnancy success seen with advancing age, with a 54.9% LBR per fresh embryo transfer regardless of the carrier's age.[18]

TABLE 1

2011 National Pregnancy and Live Birth Data

Fresh Embryos From Nondonor Oocytes

Age (y)	< 35	35-37	38-40	41-42	> 42
Cycles resulting in pregnancy (%)	46.2	38.5	29.3	19.5	9.1
Cycles resulting in live birth (%)	40.1	31.9	21.6	12.2	4.2
Average number of embryos transferred	1.9	2.1	2.5	3.0	3.1
Live births with twins (%)	30.8	26.7	21.1	14.9	10.6
Live births with triplets or more (%)	1.2	1.3	1.3	0.7	0

Data from Society for Assisted Reproductive Technology.[18]

Maternal Risks of IVF

Ovarian hyperstimulation syndrome (OHSS) is a self-limiting but possibly life-threatening condition and is characterized by ovarian enlargement, elevated sex steroids, and vascular permeability resulting in third-spacing of fluid and intravascular dehydration. Severe OHSS occurs in 0.5% to 5% of IVF cycles, and can result in multisystem organ failure and thromboembolism.[19] Risk factors for OHSS include young age, low body weight, polycystic ovarian syndrome, high or rapidly rising E_2 levels, and a history of previous OHSS. Women with OHSS who successfully conceive typically have a longer and more severe course related to rising serum hCG levels.

Strategies to reduce the risk of OHSS include cycle cancellation, allowing E_2 levels to decrease before administering hCG for follicle maturation, using a GnRH antagonist protocol in which a GnRH agonist is used for follicle maturation, freezing all embryos and postponing embryo transfer until E_2 levels normalize, and administering a dopamine agonist after oocyte retrieval.[20,21] Enlarged ovaries from ovarian hyperstimulation are infrequently prone to rupture and torsion as well as hemorrhage due oocyte aspiration.

Maternal risks of pregnancy achieved by IVF include increased risk of ectopic pregnancy, preeclampsia, placenta previa, placental abruption, gestational diabetes, and cesarean delivery.[22-26] Abnormal placentation has been suggested as a possible etiology for many of the adverse outcomes following IVF.

Fetal Risks of IVF

Perhaps the most significant fetal risk associated with assisted reproduction technology (ART) is that of multifetal gestation and resultant prematurity. Multifetal gestation, whether conceived naturally or by IVF, is a widely accepted risk factor for adverse fetal outcomes, including perinatal morbidity, prematurity, low birth weight (LBW), neonatal intensive care unit admission, and congenital defects.

Not surprisingly, IVF twins have increased risk of adverse pregnancy outcomes compared with IVF singletons. In the United States in 2004, more than 60% of IVF twins were delivered preterm and more than 50% were of LBW, compared with 14% and 9.3% of IVF singletons, respectively.[22] The Danish birth cohort registry data of IVF twin pregnancies found a 10-fold greater risk of preterm delivery (< 37 weeks) and a sevenfold greater risk of very preterm delivery (< 32 weeks) compared with IVF singletons.[27] Recent studies comparing outcomes for spontaneously conceived twins and IVF twins found no difference in maternal or neonatal outcomes,[28-30] suggesting that the risk conferred by multigestation overshadows any risk conferred by ART itself in these pregnancies. Elective single embryo transfer greatly reduces the chance of multifetal gestation and is increasingly used to reduce the risks involved with IVF.

IVF singletons do have increased adverse perinatal outcomes. A meta-analysis from 2004 including 12,283 IVF and 1.9 million spontaneously conceived singletons showed higher odds of perinatal mortality (odds ratio [OR] 2.2; 95% CI, 1.6-3.0), preterm birth (PTB) (OR 2.0; 95% CI, 1.7-2.2), LBW (OR 1.8; 95% CI, 1.4-2.2), very low birth weight (VLBW) (OR 2.7; 95% CI, 2.3-3.1), and small for gestational age infants (OR 1.6; 95% CI, 1.3-2.0) among IVF singletons.[24] These associations have been substantiated in several studies.[22-26] In addition, there is a growing body of evidence to suggest an increase risk of birth defects among infants conceived by ART,[31,32] and a recent large study by Davies and colleagues found an increased risk of cerebral palsy (OR 2.66; 95% CI, 1.79-3.94) although the absolute risk remained low (0.5%).[31]

The potential reasons for this association are areas of active research and include underlying infertility, supraphysiologic hormonal levels at the time of implantation, and embryo culture and manipulation. A recent large meta-analysis found infertility itself increased the risk of PTB among spontaneously conceived singletons (OR 1.35; 95% CI, 1.22-1.50),[33] and Davies and colleagues showed women with a history of infertility to have increased risk of birth defects (OR 1.25; 95% CI, 1.01-1.56).[31] The suggestion that supraphysiologic hormonal levels at the time of implantation may negatively impact pregnancy is supported by studies showing decreased rates of LBW and PTB in frozen embryo transfer and donor oocyte IVF compared with fresh autologous IVF cycles.[34,35] Identifying the modifiable factors of ART that impart increased maternal and fetal risk will allow for future risk reduction.

Risks of ICSI

Several studies have found slight increases in the number of chromosomal anomalies among couples with infertility, particularly among men with severe male factor infertility. Foresta and colleagues found a higher incidence of Y chromosome microdeletions, particularly in the azoospermia factor region, among men with oligospermia.[36] Infertile men may also be carriers of other genetic mutations that are currently unrecognized. The use of testicular sperm extraction techniques and ICSI has made fertility a possibility even in severe cases of oligospermia, but it also makes transmission of these genetic deletions possible. In addition, there have been several case series reporting an increased incidence of rare genetic imprinting disorders among ART children, particularly with the use of ICSI. Cases reported include Angelman syndrome and Beckwith-Wiedemann syndrome.[37]

The recent study by Davies and colleagues found an increased risk of birth defects in women who conceived with assistance compared with those who conceived spontaneously (8.3% vs 5.8%, OR 1.29; 95% CI, 1.16-1.41). However, when evaluated by type of ART (IVF vs ICSI), only ICSI was associated with a significantly increased risk of birth defects (OR 1.57; 95% CI, 1.3-1.9).[31]

Conclusions

The management of couples suffering from profound male factor infertility was revolutionized by the advent of IVF and ICSI. Severe male factor infertility can be successfully treated by ICSI using ejaculated sperm or from sperm-harvesting procedures. This has allowed many men who previously had little hope of fathering children to successfully achieve that goal. The process of IVF involves ovarian stimulation for mulifollicular growth, pituitary suppression to prevent premature luteinization and ovulation, triggering the resumption of meiosis to achieve maturity of the ova, harvesting oocytes by a minor surgical procedure, and fertilization by either conventional methods or ICSI. Success rates for IVF are affected most significantly by female age and can be easily accessed online for individual sites. Maternal risks of IVF include OHSS, ectopic pregnancy, placental abruption,

hypertensive disorders of pregnancy, gestational diabetes, and cesarean delivery. Fetal risks of IVF and ICSI include risks associated with multiple gestation, prematurity, LBW, birth defects, and imprinting disorders. The modifiable factors contributing to these risks are actively being investigated. Although risks of adverse outcomes are higher in pregnancies achieved through ART, the absolute risks are still fairly low, making IVF an acceptable treatment option to many infertile couples. ■

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MAIN POINTS

- In vitro fertilization (IVF) involves the removal of oocytes from the ovary by ultrasound-guided transvaginal follicle aspiration, fertilization outside of the body, and the transfer of the resultant embryo(s) into the uterine cavity.
- Intracytoplasmic sperm injection (ICSI) involves isolating a previously harvested oocyte and injecting a single sperm into it to promote fertilization.
- Success rates for IVF are highly dependent on the age of the female partner.
- Individual clinic success rates are available to the public at www.sart.org and www.cdc.gov.
- Maternal risks of IVF include ovarian hyperstimulation syndrome, ectopic pregnancy, placental abruption, hypertensive disorders of pregnancy, gestational diabetes, and cesarean delivery.
- Fetal risks of IVF and ICSI include risks associated with multiple gestation, prematurity, low birth weight, birth defects, and imprinting disorders.