

**Clinical Performance Guideline**  
**Fertility Solutions**  
**Infertility**

**Medical Necessity Guideline**

**Purpose:** To provide an understanding of infertility treatment, issues surrounding infertility surgery, and issues surrounding multiple embryo transfers among individuals faced with the potential loss of fertility.

**Goals:** To provide an evidence-based approach to infertility management, infertility surgery, and the use of single embryo transfer in addition to describing the limitations of and recommendations for infertility treatment.

<b>Background</b>	<p><b>I. <u>Infertility</u></b></p> <ul style="list-style-type: none"> <li>• Definition: <ul style="list-style-type: none"> <li>○ The inability to achieve a successful pregnancy following 1 year of unprotected intercourse or therapeutic donor insemination in cases where the female is &lt;35 years of age; or following 6 months of unprotected intercourse or therapeutic donor insemination for females ≥35 years of age. (ASRM)</li> <li>○ The presence of an identified infertility factor should allow for immediate treatment, obviating the need for the waiting period to meet the definition of infertility.</li> <li>○ Recurrent pregnancy loss is a disease distinct from infertility, defined by two or more failed pregnancies. When the cause is unknown, each pregnancy loss merits careful review to determine whether specific evaluation may be appropriate. (ASRM)</li> <li>○ For purposes of determining when evaluation and treatment for infertility or recurrent pregnancy loss are appropriate, pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathologic examination. (ASRM)</li> </ul> </li> </ul> <p>Artificial donor insemination may (refer to specific benefit language) be considered diagnostic in terms of meeting the definition of infertility for females without a male partner who do not otherwise have an identified infertility factor. Such artificial insemination is limited to not more than 12 inseminations for females &lt;35 years of age and not more than 6 inseminations for females 35 years of age and older. In this context, ovarian stimulation is not indicated as the insemination is being performed in a natural cycle. (The above does not apply to any individual with an infertility diagnosis as such individual would be subject to the medical necessity infertility clinical guidelines when medical necessity review is part of the infertility benefit.)</p> <ul style="list-style-type: none"> <li>• The causes of infertility may be attributable to the female in 40% of cases, to the male in 40% of cases and to a combination of both male and female factors in 10% of cases.</li> <li>• The cause of infertility cannot be determined in up to 10-20% of couples.</li> <li>• Female factors can further be divided into tubal (40%), ovulatory (40%), uterine (10%) and cervical (10%).</li> <li>• Cigarette smoking adversely affects fertility.</li> </ul>
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- Endometriosis is associated with infertility; however, the mechanism of impaired fertility in the presence of minimal disease has not been clearly elucidated.
- If a hysterosalpingogram (HSG) is performed, particularly with an oil-based dye (Dreyer 2017), for diagnostic evaluation of infertility, there is an increased chance of fertility (10% over the ensuing 6 months) as thin, filmy adhesions may be lysed by the dye injected into the tubes, which will allow them to become patent.
- Luteal phase deficiency has never been established as a cause of infertility.
- It has never been demonstrated that antibodies against sperm in either the male or female partner is a cause of infertility.
- It has never been demonstrated that asymptomatic infection of the male or female genital tract can cause infertility.
- The spontaneous conception rate for the “normal” couple is 25% per ovulatory cycle.
- Fecundity declines gradually after age 32 and more precipitously after age 37. National data from the SART registry 2016 demonstrates that the cumulative live birth per intended retrieval resulting in live births decreased progressively from:
  - 47.6% in females younger than 35 years;
  - 34.8% for females aged 35-37 years;
  - 21.8% for females aged 38-40 years;
  - 11.2% for females aged 41-42; and
  - 3.3% for females over the age of 42. The age-related decline in fertility is accompanied by a significant increase in the rates of aneuploidy and spontaneous abortion. (SART, 2016)
- The post-coital test has never been demonstrated to correlate with pregnancy outcome and should only be used in cases where the outcome will significantly affect treatment strategy. The test may be considered useful in cases of suspected sexual dysfunction.

## **II. Intrauterine Insemination**

Intrauterine insemination (IUI) involves the placement of washed, motile sperm directly into the uterine cavity.

- Indications for IUI:
  - Sexual dysfunction
  - Sequelae of cervical trauma
  - Mild male factor infertility
  - Unexplained infertility
  - Minimal or mild endometriosis
  - Unilateral tubal factor infertility due to a previous salpingectomy or proximal tubal occlusion.
- Historically, controlled ovarian stimulation (COS) with clomiphene citrate or gonadotropins combined with intrauterine insemination (IUI) has provided less invasive options before proceeding to IVF.
- A traditional approach involved 3 cycles of clomiphene/IUI followed by 3 cycles of gonadotropin/IUI before pursuing IVF.
- Gonadotropin/IUI is associated with an increased risk for multiple gestation

(30%) including high-order multiple births (8.1%). (Gleicher, 2000)

- The pregnancy rate per cycle for gonadotropin/IUI is 9%. (Guzick, 1998,1999)
- The pregnancy rate per cycle for clomiphene/IUI is 7%.
- Conception, when it occurs, is achieved within 4 clomiphene or gonadotropin/IUI cycles in 90% of cases. (Chaffkin, 1991)
- The cumulative pregnancy rate for gonadotropin/IUI treatment is 33%.
- The cumulative pregnancy rate for clomiphene/IUI treatment for women <35 is 25%. (Dovey, 2008; Ecohard, 2000)
- IUI with controlled ovarian stimulation may be effective in increasing live birth rate in women with minimal or mild endometriosis. (Nulsen, 1993; Tummon, 1997)
- Skipping gonadotropin/IUI in the traditional approach and moving instead directly to IVF yields a significant increase in pregnancy rate and time to conception while decreasing overall costs. (Goldman, 2010; Reindollar, 2010)
- Gonadotropin/IUI should not be used for treatment given the increased cost of medication, risk for a multiple gestation and a cumulative pregnancy rate that is only slightly higher compared to clomiphene/IUI. (Goldman, 2010)
- Several studies have not demonstrated a benefit for IUI in the context of ovulation induction in the treatment of PCOS. (AHRQ, 2019)

### **III. Poor Prognosis and Futility**

Examples where continued treatment may be futile: (ASRM, 2006)

- Markedly elevated FSH levels
  - $\geq 20$  for women < 40
  - $\geq 15$  for women  $\geq 40$ 
    - FSH levels should be evaluated in the context of other markers of ovarian reserve, such as AMH, AFC and response to prior ovarian stimulation
    - In the absence of a history of prior ovarian stimulation, a cycle of ART may be considered, especially in women age <35.
- Lack of viable spermatozoa
- Ovarian failure where a couple is attempting conception with their own gametes
- Numerous ART cycles without adequate egg production, fertilization and/or embryo development

### **IV. Treatment in the Natural Cycle**

- Natural cycle treatment assumes:
  - Normal ovulatory function with spontaneous (unstimulated) ovulation
  - At least one patent fallopian tube
  - Normal uterine cavity
- Treatment options in the natural cycle encompass:
  - Timed coitus
  - Cervical insemination
  - Intrauterine insemination (IUI)

- Assisted reproductive technologies (ART)

- Cervical insemination in the natural cycle may be beneficial in cases involving sexual dysfunction
- Intrauterine insemination may be useful in cases involving cervical trauma (e.g., cervical ablation, following a wide cervical cone biopsy)
- There is no evidence that, absent sexual dysfunction or cervical trauma, natural cycle (i.e., no ovarian stimulation) IUI has any benefit over appropriately timed heterosexual intercourse. (Helmerhorst, 2005)
- Natural cycle IUI may be considered in the setting of donor insemination when no other infertility factor is present.

#### **V. Tubal Surgery**

- Tubal disease accounts for 25%–35% of female factor infertility, with more than half of the cases due to salpingitis. (Honore, 1999)
- A history of ectopic pregnancy, pelvic inflammatory disease (PID), endometriosis, or prior pelvic surgery raises the index of suspicion for tubal factor infertility.
- For patients with no risk factors, a negative chlamydia antibody test indicates that there is less than a 15% likelihood of tubal pathology. (denHartog 2006)
- Although a laparoscopy is considered the best method to determine tubal patency, 3% of women diagnosed with bilateral tubal occlusion conceived spontaneously. (Mol 1999)
- Proximal tubal blockage accounts for 10%-25% of tubal disease. (Honore 1999)
- A hysterosalpingogram (HSG) may have a therapeutic effect, with higher fecundity rates reported for several months after the procedure when patency of at least one fallopian tube is demonstrated. (Johnson 2009)
- Distal tubal disease involves hydrosalpinges, tubal phimosis, fimbrial and peri-tubal adhesions.
- Tuboplasty is not appropriate for severe tubal disease or with both proximal and distal tubal disease.
- There are no adequate trials comparing pregnancy rates with tubal surgery vs. ART.
- The advantages of tubal surgery are that it is mostly a one-time intervention and that patients may attempt conception monthly without further intervention.
- The disadvantages of tubal surgery are that it involves an invasive procedure with concomitant associated risks of bleeding, infection, organ damage, and risk of anesthesia. In addition, patients may need to wait at least 6 months up to 2 years to see the maximum beneficial outcome from surgery in terms of cumulative pregnancy rates. Finally, there is a risk of recurrence of tubal pathology (e.g. adhesion formation, occlusion of the fallopian tube(s) as well as a higher risk for an ectopic pregnancy).
- Time to pregnancy is an important consideration when contemplating tubal surgery. Corrective tubal surgery even for the most favorable prognoses may

not be appropriate for women  $\geq 35$  years. (Feinberg 2008)

#### **VI. Endometriosis**

- The evidence for performing surgery with the sole intent of increasing live birth rate indicates that a relatively large number of women need to be treated to gain an additional pregnancy in women with minimal or mild endometriosis. (Jacobson 2010)
- Operative laparoscopy, including adhesiolysis is effective in increasing the pregnancy/live birth rate compared to diagnostic laparoscopy. (Jacobson 2010)
- While the removal of endometriosis in women with minimal or mild endometriosis in women undergoing a laparoscopy for other indications may improve pregnancy, implantation and live birth rates compared to those undergoing a diagnostic laparoscopy alone, there is no conclusive evidence to support laparoscopy for asymptomatic women with the only aim to diagnose and subsequently treat peritoneal endometriosis in order to improve the result of the ART treatment. (ESHRE 2013, Falcone 2011, Opøien 2011)
- The comparative effectiveness of various surgical techniques is not well studied.
- Endometriosis does not adversely affect pregnancy rates with ART.
- Pregnancy rates for patients with minimal or mild endometriosis are not different from patients with tubal factor infertility in ART cycles.

#### **VII. Uterine Factor**

- The septate uterus is the most common congenital anomaly of the uterus and is associated with the highest incidence of reproductive failure. (Raga 1997)
- The avascular nature of the uterine septum may represent a less than optimal environment for implantation.
- A unicornuate uterus represents only 4.4% of uterine anomalies.
- A bicornuate uterus, while associated with a higher incidence of pregnancy loss, rarely requires surgery. (Taylor 2008)
- The uterus didelphys has a good prognosis for conception and rarely requires surgery. (Taylor 2008)
- Little is known about the association of endometrial polyps and fertility.
- Intrauterine adhesions are associated with poor reproductive outcome. (Schenker 1982)
  - Surgery improves fertility and reduces pregnancy loss.
- Uterine myomas are common and mostly asymptomatic.
  - Large fibroids may impede access to the ovary during ART.
  - Fibroids that distort the uterine cavity may reduce ART pregnancy rates.
  - It is unclear whether or not large fibroids that do not distort the uterine

cavity may reduce ART pregnancy rates in some patients.

### **VIII. Elective Single Embryo Transfer (eSET)**

Assisted reproductive technology (ART) poses a major risk of multiple pregnancy and birth that is associated with adverse maternal and infant outcomes.

The principal reason behind the large number of multiple pregnancies after in-vitro fertilization (IVF) is the practice of transferring more than one embryo within the uterus in order to maximize pregnancy rates. (ASRM 2012, Criniti 2005, Pandian 2009)

Twin pregnancies and higher order gestations are associated with an increased risk of:

- Preeclampsia
- Hypertension
- Preterm labor
- Premature rupture of membranes
- Low birth weight (<2,500 g)
- Operative delivery
- Fetal death and/or
- Cerebral palsy. (Mullin 2010)

Even though eSET requires subsequent frozen embryo transfer cycle(s) if the initial fresh cycle is unsuccessful, it is prudent to promote elective single blastocyst embryo transfer as a means of reducing the frequency of multiple gestations and the associated risks of poor maternal and birth outcomes. (Johnson 2013; Sunderam 2012).

- Numerous countries have adopted regulations that mandate eSET resulting in a twin gestation rate of <5%.
- Pregnancy rates for eSET are comparable to multiple embryo transfer. (Thurin 2004)
- Although pregnancy outcome diminishes with increasing maternal age, all age groups should be considered for blastocyst stage eSET (Niinimaki 2012, Kato 2012) particularly in the context of preimplantation genetic testing or other technologies that enhance the embryo selection process.

### **IX. Gestational Carrier**

Gestational surrogacy involves third party reproduction that is distinct from sperm or egg donation. A gestational carrier is genetically not related to the embryo and serves merely as the host to carry the pregnancy. In contrast, in traditional surrogacy, the surrogate is genetically related to the embryo having been the source of the egg that has been fertilized either through artificial insemination or in vitro fertilization. A traditional surrogate may be utilized when the intended parent(s) lacks both eggs and a uterus, for example in the setting of a single male or same sex male couple wishing to have a family. There are a myriad of medical conditions that would warrant the use of a gestational carrier. These include but are not limited to: congenital or iatrogenic absence of the uterus; a severe müllerian anomaly; unexplained or failed treatment of



recurrent pregnancy loss (2 or more losses); unexplained recurrent implantation failure (3 or more failed assisted reproductive technology (ART) cycles); maternal medical conditions where carrying a pregnancy may pose a serious risk to the mother or fetus; maternal medications that pose a risk of teratogenicity; prior poor obstetrical history. (Dar et al 2015).

The medical aspects of a gestational carrier cycle are fairly standard and involve the intended parent(s) undertaking an ART cycle, fertilization of the oocytes, embryo culture and ultimately the transfer of an embryo(s) to the gestational carrier. These embryos may be either fresh or previously frozen. The gestational carrier's uterus must be prepared to receive the embryos and the transfer must be synchronized to embryo development. This typically involves the administration of both estrogen and progesterone to promote appropriate endometrial development and receptivity.

In addition to the medical aspects there are additional factors that must be taken into consideration in the setting of a gestational carrier (and traditional surrogate) cycle. The intended parents should undergo medical, legal and psychological counseling as should separately the gestational carrier (Reilly, 2007; Dermount et al., 2010). A legal contract between the intended parent(s) and the gestational carrier should be in place to avoid the potential of future issues pertaining to maternity and parental rights and obligations. Matters pertaining to compensation should be clearly addressed. The gestational carrier should undergo appropriate infectious disease screening (ASRM and SART 2013). The GC and her partner (if applicable) should undertake informed consent and fully understand the process, risks and benefits of all procedures including the number of embryos to be transferred, maternal complications of pregnancy, possible adverse outcomes, etc. (ASRM, 2013, 2017; Dar et al 2015).

#### **X. Cryopreservation**

Human embryo cryopreservation dates back to the 1980s when embryos were frozen at various stages of development ranging from the pronuclear to cleavage stage. The process involved a slow freezing protocol that yielded mixed results and less than ideal thaw survival (<60%) and subsequent live births. Over the past 10 years, with the introduction of vitrification technology, survival rates have climbed to well over 90% with live birth rates approaching 45% (SART 2016 National Preliminary Report). More recently, cryopreservation of mature oocytes has proven to be effective for those individuals who for moral/ethical/religious reasons are opposed to freezing embryos (with the potential of later having to face the issue of discarding embryos that have not been transferred) as well as for medically indicated fertility preservation for those individuals facing gonadotoxic treatment. The ability to freeze embryos is a necessary component of elective single embryo transfer as supernumerary embryos must be frozen and stored for later sequential transfer if needed. Embryo cryopreservation is also a vital component of pre-implantation genetic testing given the lag time from embryo biopsy to result reporting. Finally, while not a covered benefit, embryo banking/accumulation may be logical in cases of diminished ovarian reserve or advanced maternal age in order to obtain an adequate supply of embryos for later use when future fresh retrievals might otherwise yield few or poor quality oocytes/embryos.

#### **XI. Surgical Sperm Aspiration**

Surgical sperm aspiration is the surgical removal of sperm to obtain high quality sperm in adequate numbers to be used in assisted reproductive technology cycles and/or

	<p>cryopreservation.</p> <p>Approximately 5%-10% of males evaluated for infertility are azoospermic. (Schlegel, 1997; Schlegel, 1999)</p>
<p><b>General Indications</b></p>	<p><b><u>General Indications for Initial and Continuation of Infertility Treatment Coverage</u></b></p> <p>The below general infertility criteria are to be met for consideration of treatment:</p> <ul style="list-style-type: none"> <li>• <u>Prognosis for conception must be <math>\geq 5\%</math>; AND</u></li> <li>• No evidence of significant diminished ovarian reserve. Markers of significant diminished ovarian reserve include but are not limited to (one or more of the following within the previous 6 months):             <ul style="list-style-type: none"> <li>○ FSH level <math>\geq 15</math> mIU/ml if <math>\geq 35</math> years of age; <b>OR</b></li> <li>○ FSH level <math>\geq 20</math> mIU/ml if <math>&lt; 35</math> years of age; <b>OR</b></li> <li>○ AMH level <math>&lt; 0.3</math> ng/ml; <b>OR</b></li> <li>○ Antral follicle count <math>&lt; 7</math>(ASRM (a)); <b>AND</b></li> </ul> </li> <li>• If there has been monitored, medicated-stimulated infertility treatment within the previous 6 months it must demonstrate adequate ovarian response to stimulation. Examples include but are not limited to:             <ul style="list-style-type: none"> <li>○ 1 follicle <math>\geq 15</math> mm diameter for IUI</li> <li>○ Minimum of 1 follicle <math>\geq 15</math> mm diameter for ART</li> </ul> </li> </ul> <p>The general infertility surgery criteria as listed below are to be met for consideration of treatment:</p> <ul style="list-style-type: none"> <li>• Pelvic pain that is not responsive to conservative management; <b>OR</b></li> <li>• Presence of a pelvic mass for which gynecologic diagnosis warrants surgical intervention; <b>OR</b></li> <li>• As an alternative treatment modality to the Assisted Reproductive Technologies (ART) particularly for individuals who are averse to pursuing ART for religious, social or financial concerns.</li> </ul> <p>In the absence of other infertility factors or recurrence of disease additional infertility treatment is not indicated following infertility surgery for 12 months for individuals <math>&lt; 35</math> and 6 months for individuals <math>\geq 35</math> years of age.</p> <p>Infertility treatment is warranted when an infertility factor has been identified. This would include but is not limited to:</p> <ul style="list-style-type: none"> <li>• Two abnormal semen analyses (abnormal count and/or motility), ovulatory dysfunction; compromise of the fallopian tubes; documented untreated or recurrent endometriosis; sexual dysfunction; abnormalities of the cervix or uterus that may interfere with conception.</li> </ul> <p>Treatment is not indicated in the setting of using autologous oocytes in females' <math>\geq 44</math> years of age. (UnitedHealthcare Infertility Services Coverage Determination Guidelines July 1, 2019 ; MCG 23<sup>rd</sup> ed, 2019))</p>
<p><b>Treatment Criteria</b></p>	<p><b><u>I. Ovulation Induction</u></b></p> <p><b>Ovulation induction is not indicated beyond the 6<sup>th</sup> ovulatory cycle regardless of which drug or combinations of drugs have been administered.</b></p> <p>A. <b>Clomiphene citrate (Clomid<sup>®</sup>, Serophene<sup>®</sup>)</b></p>



1. Clomiphene citrate is indicated to treat females with ovulatory dysfunction in the following situations:
  - Anovulation; **OR**
  - Oligo-ovulation; **OR**
  - Amenorrhea; **AND**
  - Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated
2. Clomiphene citrate is not indicated in the following situations:
  - Beyond the 6<sup>th</sup> clomiphene citrate induced ovulatory cycle; **OR**
  - When there is a failure to respond to ovarian stimulation after appropriate dosage adjustment, (e.g., doses of clomiphene citrate up to 250 mg per day and no follicles  $\geq 17$  mm in diameter); **OR**
  - An estradiol level  $< 100$  pg/ml/follicle  $\geq 15$  mm in diameter

**B. Letrozole (Femara®)**

1. Letrozole is indicated to treat females with ovulatory dysfunction in the following situations:
  - Anovulation; **OR**
  - Oligo-ovulation; **OR**
  - Amenorrhea; **AND**
  - Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated.
2. Letrozole is not indicated in the following situations:
  - Beyond the 6<sup>th</sup> letrozole induced ovulatory cycle; **OR**
  - When used alone for females with unexplained infertility; **OR**
  - When there is a failure to respond to ovarian stimulation, (e.g., no follicles  $\geq 17$  mm in diameter).

**C. Gonadotropins**

1. Gonadotropins are indicated to treat females with ovulatory dysfunction in the following situations:
  - Anovulation; **OR**
  - Oligo-ovulation; **OR**
  - Amenorrhea; **AND**
  - Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated; **AND**
  - Failure to ovulate with clomiphene citrate **and** letrozole.
    - PCOS, anovulatory or oligo-ovulatory patients who fail to ovulate with clomiphene after dosage adjustment up to 150 mg per day should attempt ovulation induction with letrozole before proceeding to gonadotropins.
    - Patients diagnosed with hypothalamic amenorrhea (failure to withdraw to progesterone) who demonstrate hypoestrogenemia may move directly to gonadotropins.
2. Gonadotropins are not indicated in the following situations:
  - Beyond the 6<sup>th</sup> gonadotropin induced ovulatory cycle; **OR**
  - When there are  $\geq 4$  follicles which are  $\geq 15$  mm in diameter from a

	<p>previously gonadotropin-induced ovulation, despite a dosage adjustment (e.g., doses of gonadotropin down to 37.5 IU per day); <b>OR</b></p> <ul style="list-style-type: none"><li>• When used alone for females with unexplained infertility; <b>OR</b></li><li>• When there is a failure to respond to ovarian stimulation, (e.g., doses of gonadotropins up to 225 IU per day and no follicles <math>\geq</math> 15 mm in diameter); <b>OR</b></li><li>• In lieu of clomiphene or letrozole to correct a thin endometrial lining (Dietterich, 2004; Kolibianakis, 2002; Assante, 2013); <b>OR</b></li><li>• An estradiol level <math>&lt;</math>100 pg/ml/follicle <math>\geq</math>15 mm in diameter.</li></ul> <p>3. Gonadotropins <u>are not indicated</u>:</p> <ul style="list-style-type: none"><li>• In total doses that exceed 225 IU/day for ovulation induction; <b>OR</b></li><li>• For duration of therapy that exceeds 14 days per cycle.<ul style="list-style-type: none"><li>• A longer than 14 day stimulation may be considered in the setting of hypothalamic amenorrhea.</li></ul></li></ul> <p><b>II. <u>Controlled Ovarian Stimulation</u></b></p> <p><b>Controlled ovarian stimulation is not indicated beyond the cycle limitations listed below regardless of which drug or combinations of drugs have been administered.</b></p> <p><b>A. Clomiphene citrate and letrozole</b></p> <p>1. Clomiphene citrate and letrozole <u>are indicated</u> to treat females only when used in conjunction with intrauterine insemination (IUI) in the following situations:</p> <ul style="list-style-type: none"><li>• With <u>unexplained infertility</u>; <b>OR</b></li><li>• Minimal or mild endometriosis; <b>OR</b></li><li>• Diminished ovarian reserve; <b>OR</b></li><li>• <u>Male factor infertility</u>; <b>OR</b></li><li>• Unilateral tubal factor infertility due to a previous salpingectomy or proximal tubal occlusion.<ul style="list-style-type: none"><li>○ Patency of one fallopian tube must be demonstrated and there should be no evidence of peritubal adhesions or anything that may compromise tubal function.</li></ul></li></ul> <p>2. Clomiphene citrate and letrozole <u>are not indicated</u> in the following situations:</p> <ul style="list-style-type: none"><li>• To treat females with <u>unexplained infertility</u>, diminished ovarian reserve, bilateral tubal factor infertility, unilateral mid or distal tubal compromise (obstruction, phimosis, adhesions), endometriosis, <u>male factor infertility</u> or recurrent pregnancy loss (absent an ovulatory disorder) when used alone (without IUI) (ASRM); <b>OR</b></li><li>• Beyond 4 cycles for females <math>&lt;</math>38 years of age (Chaffkin, 1991; Dovey, 2008; ASRM, 2013); <b>OR</b></li><li>• Beyond 2 cycles for females 38-39 years of age (ASRM, 2006, 2013; Hendricks, 2006; Harris, 2010; Wiser, 2012); <b>OR</b></li><li>• For females <math>\geq</math>40 years of age (Liu, 2018; Harris, 2010; Wiser, 2016; MCG, 2019 ); <b>OR</b></li></ul>
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- In the setting of very poor/futile prognosis, defined as:
  - FSH level  $\geq 15$  mIU/ml if  $\geq 40$  years of age or FSH level  $\geq 20$  mIU/ml if  $< 40$  years of age (Fertility Solutions Expert Panel);
    - FSH levels should be evaluated in the context of other markers of ovarian reserve, such as AMH, AFC and response to prior ovarian stimulation

**OR**

- Following ART cycles that fail to result in conception due to poor ovarian response or poor quality oocytes or embryos.

### **B. Gonadotropins**

1. Gonadotropins are indicated when used only in conjunction with intrauterine insemination in the following situations:
  - To treat females with diminished ovarian reserve that have not responded to clomiphene citrate or letrozole; **OR**
  - Initial treatment for women with diminished ovarian reserve; **OR**
  - In the setting of unilateral tubal disease due to a previous salpingectomy or proximal tubal occlusion when there is no evidence of tubal compromise on the patent side when at least 2 cycles of oral agents (clomiphene or letrozole) have failed to yield a dominant follicle on the side with a patent fallopian tube.
2. Gonadotropins are not indicated when used alone or in conjunction with intrauterine insemination (IUI) in the following situations:
  - To treat females with unexplained infertility, endometriosis, bilateral tubal factor infertility, unilateral mid or distal tubal compromise (obstruction, phimosis, adhesions), male factor infertility or recurrent pregnancy loss (McClamrock, 2012; ESHRE, 2013); **OR**
  - In lieu of clomiphene or letrozole to correct a thin endometrial lining. (Dietterich, 2004; Kolibianakis, 2002; Assante, 2013; Gingold, 2015), **OR**
  - When there is a failure to respond to ovarian stimulation, (e.g., doses of gonadotropins up to 150 IU per day and no follicles  $\geq 15$  mm in diameter); **OR**
  - An estradiol level  $< 100$  pg/ml/follicle  $\geq 15$  mm in diameter); **OR**
  - When there are  $\geq 4$  follicles which are  $\geq 15$  mm in diameter from a previously gonadotropin-induced ovulation, despite a dosage adjustment; **OR**
  - Beyond 4 cycles for females  $< 38$  years of age (Chaffkin, 1991; Dovey, 2008; ASRM, 2013); **OR**
  - Beyond 2 cycles for females 38-39 years of age (ASRM, 2006, 2013; Hendricks, 2006; Harris, 2010; Wisner, 2012); **OR**
  - For females  $> 40$  years of age (; Harris, 2010, Liu, 2018; Wisner, 2016; MCG, 2019); **OR**
  - In the setting of very poor/futile prognosis, defined as:
    - FSH level  $\geq 15$  mIU/ml if  $\geq 40$  years of age or FSH level  $\geq 20$  mIU/ml if  $< 40$  years of age (Fertility Solutions Expert

Panel);

- FSH levels should be evaluated in the context of other markers of ovarian reserve, such as AMH, AFC and response to prior ovarian stimulation

**OR**

- Following ART cycles that fail to result in conception due to poor ovarian response or poor quality oocytes or embryos.
3. Gonadotropins are not indicated:
- In total doses that exceed 150 IU/day for controlled ovulation stimulation; **OR**
  - For duration of therapy that exceeds 14 days per cycle.

**Note:** *Gonadotropins may be utilized in the face of ovulatory dysfunction, see above section ovulation induction.*

### **III. Therapeutic Donor Insemination**

A. Therapeutic donor insemination is indicated in the following situations:

1. Male factor infertility; **OR**
2. Failure of fertilization with ART; **OR**
3. Female without a male partner (*when this is a covered benefit*) upon meeting the definition of infertility

B. Therapeutic cervical or intrauterine donor insemination is not indicated in the following situations:

1. Failure to conceive within 12 donor insemination cycles in a female <35 years old; **OR**
2. Failure to conceive within 6 donor insemination cycles in a female ≥35 years old;

**AND**

There are no other infertility factors.

In the absence of any known infertility factor, therapeutic donor insemination is not indicated in conjunction with ovarian stimulation. (Cycle limitations apply for unexplained infertility, minimal to mild endometriosis and tubal factor infertility.)

3. Cervical donor insemination is not indicated when using frozen sperm.

### **IV. Intrauterine Insemination (IUI)**

A. Intrauterine insemination (IUI) in a natural (unstimulated) cycle is indicated when no other confounding infertility factors exist in any one (1) of the following situations:

1. Sexual dysfunction
2. Cervical trauma
3. Therapeutic donor insemination
4. Mild to moderate male factor (AHRQ, 2019)

B. Intrauterine insemination (IUI) in a natural (unstimulated) cycle is not indicated in the treatment of unexplained infertility, diminished ovarian reserve, ovulatory dysfunction, tubal factor infertility, endometriosis or severe male factor infertility.

- C. Intrauterine insemination (IUI) in conjunction with controlled ovarian stimulation is indicated in any one (1) of the following situations:
1. Unexplained infertility
  2. Mild and moderate male factor infertility
  3. Minimal or mild endometriosis
  4. Unilateral proximal tubal occlusion absent any compromise of the patent fallopian tube
  5. Diminished ovarian reserve
- D. Intrauterine insemination (IUI) is not indicated in any one (1) of the following situations:
1. >1 insemination per cycle (Osuna, 2004; Albrozi, 2003; Tonguc, 2010)
  2. Isolated teratospermia unless there is <2% normal morphology on at least two semen analyses
  3. Severe male factor infertility (< 1 million motile sperm after sperm preparation)
  4. Ovulatory dysfunction absent a concomitant male factor, sexual dysfunction or cervical trauma (AHRQ, 2019)
  5. Bilateral tubal factor infertility
  6. Unilateral mid or distal tubal compromise (e.g., loculated spill, phimosis, occlusion)
  7. Moderate or severe endometriosis (ESHRE, 2013) unless treatment has previously been rendered and there is documentation of at least one uncompromised fallopian tube
  8. Recurrent pregnancy loss
  9. In the setting of unexplained infertility, diminished ovarian reserve, unilateral tubal factor infertility or mild to moderate male factor infertility or minimal or mild endometriosis in the following situations:
    - Beyond 4 cycles for females <38 years of age (Chaffkin, 1991; Dovey, 2008; ASRM, 2013; Merviel, 2010; Dickey, 2003); **OR**
    - Beyond 2 cycles for females 38-39 years of age (ASRM, 2006, 2013; Hendricks, 2006; Harris, 2010; Wisner, 2012); **OR**
    - Females  $\geq 40$  years of age (Liu, 2018; Wisner, 2016; Harris, 2010; MCG, 2019); **OR**
    - In the setting of very poor/futile prognosis, defined as:
      - FSH level  $\geq 15$  mIU/ml if  $\geq 40$  years of age or FSH level  $\geq 20$  mIU/ml if <40 years of age (Fertility Solutions Expert Panel); **OR**
    - When the diagnosis is limited exclusively to teratospermia unless 0% strict morphology has been demonstrated on at least two semen analyses.
  10. In the setting of sexual dysfunction or cervical trauma when there are no other confounding infertility factors, in the following situations:
    - Beyond 12 cycles in a female <35 years old; **OR**
    - Beyond 6 cycles in a female  $\geq 35$  years old.
  11. In the setting of ART in the following situations:
    - To convert an ART cycle to IUI when at least 2 follicles  $\geq 15$  mm in diameter are present (particularly in the setting of diminished

	<p>ovarian reserve or on the 2<sup>nd</sup> or greater ART cycle when maximal dosage of gonadotropins are being used); <b>OR</b></p> <ul style="list-style-type: none"> <li>• Following an ART cycle that fails to result in conception due to poor ovarian response or poor quality oocytes or embryos; <b>OR</b></li> <li>• Following <math>\geq 2</math> ART cycles that have failed to result in a conception despite good quality oocytes or embryos. (Reichman, 2013)</li> </ul> <p><b>V. Assisted Reproductive Technologies (ART)</b></p> <p>A. Assisted Reproductive Technologies (ART) <u>are indicated</u> for the following:</p> <ol style="list-style-type: none"> <li>1. <u>Unexplained infertility</u></li> <li>2. Diminished ovarian reserve</li> <li>3. <u>Tubal factor infertility</u></li> <li>4. <u>Male factor infertility</u></li> <li>5. Endometriosis</li> <li>6. Ovulatory dysfunction <ul style="list-style-type: none"> <li>• When ovulation induction has not resulted in conception</li> <li>• Poor response to ovulation induction</li> <li>• Hyper-response to ovulation induction where there is a risk for ovarian hyperstimulation or a multiple gestation</li> </ul> </li> <li>7. Failure to achieve conception with any other treatment modality</li> </ol> <p>B. Assisted Reproductive Technologies (ART) <u>are not indicated</u> in the following situations:</p> <ol style="list-style-type: none"> <li>1. When using autologous oocytes in females <math>\geq 44</math> years of age or when using donor oocytes in female recipients who are <math>\geq 55</math> years of age. (ASRM (d)) (However, oocytes or embryos derived from oocytes that were retrieved prior to age 44 and subsequently cryopreserved may be utilized up to age <math>\leq 55</math>.)</li> <li>2. When there is a failure to respond to ovarian stimulation (e.g., as demonstrated by failure to achieve at least 3 follicles <math>&gt;12</math> mm in diameter); <b>OR</b></li> <li>3. ART cycle does not demonstrate the attainment of at least one (1) embryo suitable for transfer (<b>Note:</b> an additional cycle may be considered when there is a significant change in treatment protocol after 1 such cycle including, but not limited to, a change in gonadotropin dosage that does not exceed pharma guidelines, a change in agonist/antagonist protocol or a change in the clinical presentation); <b>OR</b></li> <li>4. Lack of viable spermatozoa; <b>OR</b></li> <li>5. Ovarian failure where a couple is attempting conception with their own gametes; <b>OR</b></li> <li>6. Recurrent pregnancy loss except in the setting of recurrent aneuploidy or <math>\geq 5</math> unexplained losses; <b>OR</b></li> <li>7. Numerous <math>\geq 2</math> ART cycles without adequate egg quality or production, fertilization and/or embryo quality or development; <b>OR</b></li> <li>8. When using autologous oocytes in the setting of very poor/futile prognosis, defined as follows (Fertility Solutions Expert Panel): <ul style="list-style-type: none"> <li>• FSH level <math>\geq 15</math> mIU/ml if <math>\geq 40</math> years of age</li> <li>• FSH level <math>\geq 20</math> mIU/ml if <math>&lt;40</math> years of age</li> </ul> </li> </ol>
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	<p>9. Gonadotropins are not indicated:</p> <ul style="list-style-type: none"> <li>• In total doses that exceed 450 IU/day for controlled ovulation stimulation (Nargund 2017; van Tilborg 2017; Youseff 2018); <b>OR</b></li> <li>• For duration of therapy that exceeds 14 days per cycle.</li> </ul> <p>C. Natural (unstimulated) Cycle Assisted Reproductive Technologies (ART) <u>are indicated</u> for all females under the age of 35 and all patients' <math>\geq 35</math> years of age with normal ovarian reserve.</p> <p>D. Natural cycle IVF <u>is not indicated</u>:</p> <ol style="list-style-type: none"> <li>1. In the setting of diminished ovarian reserve in females <math>\geq 35</math> years of age; <b>OR</b></li> <li>2. There have been not more than 2 natural ART cycle attempts with a failure to obtain an embryo suitable for transfer; <b>OR</b></li> <li>3. There has been a failure to attain a conception following two natural cycle intended retrieval cycle starts.</li> </ol> <p>E. Freezing of ALL oocytes or embryos (<i>when this is a covered benefit</i>) <u>is indicated</u> in the following situations:</p> <ol style="list-style-type: none"> <li>1. Avoidance of ovarian hyperstimulation syndrome; <b>OR</b></li> <li>2. For pre-implantation genetic testing for a monogenic disorder (PGT-M) or aneuploidy screening (PGT-A) or testing for structural rearrangements (PGT-SR); <b>OR</b></li> <li>3. For enhancing the uterine environment.</li> </ol> <p>F. Fresh oocyte retrievals are not indicated when previously frozen oocytes (M2) or embryos of at least BB grading quality (or equivalent) are available for transfer and if tested, are genetically normal.</p> <p>G. Intracytoplasmic Sperm Injection (ICSI)</p> <p>ICSI <u>is indicated</u> for the following:</p> <ol style="list-style-type: none"> <li>1. Male factor infertility <ul style="list-style-type: none"> <li>• "Male factor" infertility is seen as an alteration in sperm concentration and/or motility and/or morphology in at least two sperm analyses, collected 1 and 4 weeks apart. (WHO, 1999)</li> </ul> </li> <li>2. After failed conventional insemination (either complete failure or lower-than-expected rates (&lt;50%). (Palermo et al, 1999; Benadiva et al, 1999; Katrop et al, 1999; Optum Infertility Expert Panel 2018)</li> <li>3. Failed attempts at traditional IVF or conventional insemination when the quality of the ovarian stimulation was not the main cause of failure. (Van der Westerlaken et al, 2005)</li> <li>4. Cases of IVF using pre-implantation genetic testing for monogenic disorders, aneuploidy or structural rearrangements (PGT-M, PGT-A, PGT-SR). (Tucker et al, 2001; Thornhill et al, 2005; ICSI in 2006: Evidence and Evolution. Hum Reprod Update, 2005)</li> </ol> <p>ICSI <u>is not indicated</u> for the following:</p> <ol style="list-style-type: none"> <li>1. Unexplained infertility (Foong et al, 2006)</li> <li>2. Advanced maternal age (Kim et al, 2007)</li> <li>3. Low oocyte yield (Kim et al, 2007)</li> <li>4. Repeat IVF attempts after documented poor ovarian stimulation (Roest et al, 1998; Kinzer et al, 2008; Westerlaken et al, 2005)</li> <li>5. Routine IVF (Bhattacharya et al, 2001)</li> </ol>
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	<p>6. When the diagnosis is limited exclusively to teratospermia unless &lt;2% strict morphology has been demonstrated on at least two semen analyses.</p> <p>H. Cryopreservation Embryo or mature oocyte cryopreservation when this is a covered benefit <u>is indicated</u>:</p> <ol style="list-style-type: none"> <li>1. In the prevention of ovarian hyperstimulation syndrome</li> <li>2. In the context of elective single embryo transfer to freeze and store supernumerary embryos</li> <li>3. In the context of pre-implantation genetic testing, allowing for the return of test results</li> <li>4. In the presence of poor endometrial development</li> <li>5. When there is a failure to obtain sperm at the time of a fresh ART cycle at egg retrieval</li> <li>6. In the context of freeze only cycles: <ul style="list-style-type: none"> <li>• All embryos are cryopreserved with the intent for subsequent transfer within a 6 month time period</li> </ul> </li> <li>7. Medically necessary cryopreservation for individuals facing gonadotoxic therapy when this is a covered benefit</li> </ol> <p>Embryo or mature oocyte cryopreservation <u>is not indicated</u>:</p> <ol style="list-style-type: none"> <li>1. For the purpose of embryo or oocyte accumulation or banking</li> <li>2. For planned oocyte cryopreservation unless specifically covered in plan documents</li> </ol> <p>I. Surgical Sperm Aspiration Surgical sperm aspiration <u>is indicated</u> for obstructive azoospermia in the setting of:</p> <ol style="list-style-type: none"> <li>1. Congenital absence of the vas deferens (carrier of cystic fibrosis gene (Jaffe, 1994), OR</li> <li>2. Infection, OR</li> <li>3. Vasectomy, OR</li> <li>4. Trauma</li> </ol> <p>BY:</p> <ol style="list-style-type: none"> <li>1. Microsurgical epididymal sperm aspiration (MESA) (Schlegel, 1994; Tournaye, 1994) OR</li> <li>2. Percutaneous epididymal sperm aspiration (PESA) (Craft, 1995), OR</li> <li>3. Open testicular biopsy (TESE) (Schlegel, 1997; Schlegel, 1999) OR</li> <li>4. Percutaneous testicular sperm aspiration (TEFNA) (Persson, 1971), OR</li> <li>5. Percutaneous testicular needle biopsy (PercBiopsy) (Sheynkin, 1998)</li> </ol> <p>Surgical sperm aspiration <u>is indicated</u> for non-obstructive azoospermia in the setting of:</p> <ol style="list-style-type: none"> <li>1. Maturation arrest, OR</li> <li>2. Sertoli-only syndrome</li> </ol> <p>BY:</p> <ol style="list-style-type: none"> <li>1. Microdissection testicular sperm extraction (mTESE), OR</li> <li>2. Open testicular biopsy (TESE) (Schlegel, 1997; Schlegel, 1999) OR</li> </ol>
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3. Percutaneous testicular sperm aspiration (TEFNA) (Persson, 1971), OR
4. Percutaneous testicular needle biopsy (PercBiopsy) (Sheynkin, 1998)

Surgical sperm aspiration Is not indicated:

1. In the absence of azoospermia

## **VI. Elective Single Embryo Transfer (eSET)**

A. Elective single blastocyst embryo transfer (eSET) is indicated in the following situations (AHRQ, ASRM):

1. Patients with a favorable prognosis as defined as:
  - Expanded day 5 or 6 blastocysts with well-defined inner-cell mass and trophoctoderm as defined by the individual embryology laboratory **AND** one of the following:
    - Embryo(s) or eggs available and suitable for cryopreservation; **OR**
    - Presence of one or more euploid embryos regardless of the female's age.
2. All patients undergoing ovum donation where the donor is <35 years of age.
3. For females <35-37 years of age eSET is further indicated by one of the following:
  - On the 1st full ART embryo transfer cycle; **OR**
  - On the 2nd full ART embryo transfer cycle if the prognosis is favorable for females <35 years of age; **OR**
  - On the 3<sup>rd</sup> full ART embryo transfer cycle if the prognosis is favorable for females < 35 years of age; **OR**
  - A euploid embryo is available for transfer.
4. For females 38-40 years of age eSET is further indicated:
  - On the 1st full ART embryo transfer cycle if the prognosis is favorable as defined above; **OR**
  - A euploid embryo is available for transfer.

Age	<35	35-37	38-40	41-42	Euploid Embryo
1 <sup>st</sup> cycle (fresh or frozen)	1	1	1	2	1
2nd cycle (fresh or frozen)	1	1	2	2	1

<b>3rd cycle (fresh or frozen)</b>	<b>1</b>	<b>2</b>	<b>2</b>	<b>3</b>	<b>1</b>
<b>No favorable prognosis embryos</b>	<b>2</b>	<b>2</b>	<b>3</b>	<b>3</b>	

**B. Multiple blastocyst embryo transfer is indicated in the following situations (AHRQ):**

1. The transfer of 2 blastocyst embryos may be considered if no favorable prognosis embryos are available.
2. For females 35-37 years of age:
  - On the 3rd full ART embryo transfer cycle the transfer up to 2 embryos may be considered.
3. For females  $\geq 38$  years of age:
  - The transfer of up to 2 blastocyst embryos may be considered if there is only one favorable prognosis embryo.
  - The transfer of 3 blastocyst embryos may be considered if there are no favorable prognosis embryos are available.
  - Only 1 euploid blastocyst should be transferred.

**C. Multiple cleavage stage embryo transfer is indicated in the following situations (ASRM 2017):**

1. For females <35 years of age with a favorable prognosis no more than 1 embryo should be transferred. All others should have no more than 2 embryos transferred
2. For females <35-37 years of age with a favorable prognosis no more than 1 embryo should be transferred.
  - Females with fewer than 2 high quality embryos should have no more than 3 embryos transferred.
3. For females 38-40 years of age with a favorable prognosis no more than 3 embryos should be transferred.
  - All others should have no more than 4 embryos transferred.
4. For females 41 - 42 years of age with a favorable prognosis no more than 4 embryos should be transferred. All others should have no more than 5 embryos transferred.

**VII. Pre-Implantation Genetic Testing**

- A. Pre-implantation genetic testing for a monogenic disorder or structural rearrangement (PGT-M, PGT-SR) for the diagnosis of known genetic disorders only when the fetus is at risk for the genetic disorder or there is a risk for recurrent pregnancy loss. This would include, but is not limited to the following:

1. Autosomal dominant disorders;
  2. Sex-linked (X or Y chromosome) disorders;
  3. Autosomal recessive diseases for which very specific mutations in heterozygosity can lead to a phenotype;
  4. Recessive disorders (e.g. Spinal Muscular Atrophy) where it is not atypical for an affected child to have inherited one of the deletions in a de novo fashion.
  5. Unbalanced and balanced translocations (where there is a risk for the balanced translocation to become unbalanced).
  6. At least one intended parent is a carrier for a mitochondrial condition.
- B. Check the benefit documents and state mandates for coverage of pre-implantation genetic diagnosis (PGD). PGD may be considered a covered expense if the fetus is at risk for a genetic disorder.

### **VIII. Gestational Carrier**

The use of a gestational carrier (when this is a covered benefit) is medically indicated when a specific condition precludes the intended parent from carrying a pregnancy or when carrying a pregnancy has a significant risk of death or harm to the woman or the fetus. A medical indication must be clearly documented in the patient's medical record with evidence of appropriate specialist (e.g. maternal fetal medicine) consultation. The use of a gestational carrier is indicated in the following situations (ASRM, 2017; Dar et al, 2015):

1. Absence of the uterus (congenital or acquired and not as part of a sterilization procedure)
2. Significant uterine anomaly including but not limited to
  - a. Irreparable Asherman's syndrome
  - b. Unicornuate uterus, bicornuate uterus, uterus didelphys and variants thereof with a history of recurrent(2 or more) pregnancy loss
  - c. Unicornuate rudimentary uterine horn
  - d. Irreparable submucosal leiomyomata uteri or other leiomyomata that would result in pregnancy loss or an inability to conceive
  - e. Irreparable cervical incompetence
3. Absolute medical contraindication to pregnancy
  - a. e.g. pulmonary hypertension
4. Serious medical condition that would be exacerbated by pregnancy or cause significant risk to the fetus
5. Serious obstetrical condition that would cause significant risk to the fetus including but not limited to:
  - a. History of uterine rupture
  - b. History of severe Rh sensitization
6. Endometrial factors such as failed, unexplained multiple (3 or more) ART cycles despite the transfer of good quality embryos (recurrent implantation failure)
7. Recurrent (5 or more) unexplained pregnancy losses
8. Maternal use of teratogenic medications
9. Prior poor obstetrical history

### **IX. Tubal Surgery**

- A. Tubal surgery is indicated in the following situations (ASRM, 2015):
1. To treat proximal tubal occlusion with selective salpingography or

hysteroscopy with tubal cannulation in an individual not pursuing ART.

- There is good evidence to support HSG as the standard first line test to assess tubal patency, but it is limited by false-positive diagnoses of proximal tubal blockage.
2. To treat hydrosalpinges prior to an ART cycle by salpingectomy or proximal tubal occlusion.
  3. To treat distal tubal disease in an individual not pursuing ART.
- B. Tubal surgery is not indicated in the following situations:
1. When the intent of surgery is to enhance fertility in the absence of an infertility treatment benefit.
  2. To treat proximal tubal occlusion for the following:
    - Salpingitis isthmica nodosum in the presence of a compromised distal tube
    - Chronic salpingitis
    - Obliterative fibrosis
    - Women over the age of 35
    - In the presence of a significant male factor
    - In an individual pursuing ART
  3. To treat severe hydrosalpinges by neosalpingostomy.
  4. To perform a fimbrioplasty, salpingostomy or neosalpingostomy for severe tubal disease or concomitant proximal and distal tubal occlusion.
- C. Additional infertility treatment (e.g., controlled ovarian stimulation, IUI or ART) is not indicated within 12 months of tubal surgery for women <35 years of age or within 6 months for women ≥35 years of age unless additional infertility factors have been identified or there is recurrence of tubal compromise as documented by a postoperative hysterosalpingogram, laparoscopy, etc.

#### **X. Surgery for Endometriosis**

- A. Surgery for Endometriosis is indicated in the following situations:
1. When there are gynecologic indications for surgery such as:
    - Pelvic pain that is not responsive to conservative management; **OR**
    - Presence of a pelvic mass and/or pain for which gynecologic diagnosis otherwise warrants surgical intervention; **OR**
    - An alternative for women who do not wish to pursue ART.
- B. Surgery for Endometriosis in asymptomatic women is not indicated in the following situations:
1. When the intent of surgery is to enhance fertility in the absence of an infertility treatment benefit.; **OR**
  2. Where the only aim is to diagnose and subsequently treat peritoneal endometriosis in order to improve the result of ART treatment; **OR**



3. To perform an aspiration or cystectomy of an endometrioma prior to ART unless there are other gynecologic indications for surgery; **OR**
4. To resect deep nodular implants of endometriosis prior to ART in order to improve the result of ART treatment.

C. Additional infertility treatment (e.g., controlled ovarian stimulation, IUI or ART) is not indicated within 12 months of surgery for women <35 years of age or within 6 months for women ≥35 years of age unless additional infertility factors have been identified or there is documentation of tubal compromise by a postoperative hysterosalpingogram, laparoscopy, etc. or recurrence of disease.

#### **XI. Uterine Surgery**

A. Uterine Surgery is indicated in the following situations:

1. To treat a uterine septum that extends >1cm from the superior uterine wall; **OR**
2. To treat a unicornuate uterus based upon symptomatology associated with the presence of a functional rudimentary horn; **OR**
3. To treat uterine polyps; **OR**
4. To treat uterine adhesions; **OR**
5. To treat the following:
  - Submucosal myomas (FIGO classification 0 through 2) (Munro 2011)
  - Intramural myomas that protrude into or significantly distort the uterine cavity (FIGO classification 3) (Munro 2011)
  - Myomas that limit access to the ovary, occlude the Fallopian tube(s), or are located at the myometrial/endometrial junction
  - Large (≥ 4 cm) myomas following a failed ART cycle

B. Uterine Surgery is not indicated in the following situations:

1. When the intent of surgery is to enhance fertility in the absence of an infertility treatment benefit; **OR**
  2. To treat a uterine septum that extends ≤ 1 cm from the superior uterine wall (an arcuate or sub-septate uterus); **OR**
  3. To treat a bicornuate uterus; **OR**
  4. To treat a uterus didelphys; **OR**
  5. To treat subserosal or pedunculated fibroids prior to ART in order to improve the result of ART treatment.
- C. Additional infertility treatment (e.g., controlled ovarian stimulation, IUI or ART) is not indicated within 12 months of surgery for women <35 years of age or within 6 months for women ≥35 years of age unless additional infertility factors have been identified or there is documentation of tubal compromise by a postoperative hysterosalpingogram, laparoscopy, etc. or recurrence of disease.

**Clinical Evidence**
**Ovulation Induction**

Anovulatory females or those with oligomenorrhea or amenorrhea who wish to conceive should be treated with agents that induce ovulation once specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated. Clomiphene citrate or letrozole is the initial agent of choice. Letrozole has been shown to have increased efficacy in the setting of PCOS. (Legro, 2014) Dosage adjustments should be based exclusively upon ovulatory response, and not be based upon failure to conceive. A failure to have an ovulatory response to clomiphene or letrozole may warrant a trial of gonadotropins. If a woman has not conceived within 6 ovulatory cycles, a move to IVF would be the next treatment option. Gonadotropin treatment regimens should employ optimal stimulation regimens that ideally yield no more than 2 mature follicles. Females who do not conceive within 6 ovulatory cycles, are poor or hyper-responders to gonadotropin therapy should be directed to ART. (VanVoorhis, 1998)

**Ovarian Reserve**

- Ovarian reserve testing may consist of baseline FSH and estradiol levels, and measurement of anti-Müllerian hormone and antral follicle counts. (Nardo, 2009)
- FSH levels over 10mIU/ml may be considered as suspect for diminished ovarian reserve. (ACOG, 2008)
- Menopausal levels of FSH range from 25.8 – 134.8 mIU/ml (NLM)
  - High FSH= 16.7 mIU/ml
  - Moderately high FSH = 11.7 mIU/ml
  - Normal FSH= <10 mIU/ml (IRP 78/549) (ASRM, 2012a,b)
    - FSH levels in and of themselves may not be solely and entirely predictive of pregnancy outcome particularly in women < 35 years of age as ovarian reserve reflects oocyte quantity and not quality (Steiner, 2017)
    - FSH levels should be evaluated in conjunction with additional predictors of cycle success including anti-Müllerian hormone (AMH), antral follicle count (AFC) as well as follicular response to stimulation and in the case of assisted reproductive technology (ART), oocyte quantity and quality
- Delivery rates for women with diminished ovarian reserve in excess of defined threshold levels of FSH are reported to be approximately 1%. (Scott, 2004)
  - Older women (age >40 years) with an elevated FSH (on day 3 of the menstrual cycle) may not be candidates for undergoing ART, as they may have significantly lower implantation rates and clinical pregnancy rates, compared with a normal day 3 FSH in the same age category. (Luna et al, 2007)
- A lower antral follicle count is associated with infertility. (Rosen, 2011)
- Decreased ovarian reserve does not constitute an absolute contraindication to treatment. (ASRM, 2012a)

**Letrozole**

- There is no evidence that controlled ovarian stimulation with Letrozole is superior to clomiphene for patients with unexplained infertility undergoing IUI. A multi-center randomized clinical trial involving 900 couples with unexplained infertility demonstrated rates of conception, clinical pregnancy and live births were statistically significantly lower than those in the standard therapy group (the combined clomiphene and gonadotropin groups). The rate of multiple gestations was not significantly reduced among women treated with letrozole. Letrozole was found to be non-inferior to clomiphene in terms of conception, clinical pregnancy and live birth rates. While clomiphene treatment resulted in a high incidence of hot flashes (30.9% vs. 16.8%) compared to letrozole, letrozole treatment demonstrated a higher rate of headaches (41.9% vs. 34.9% and joint or limb pain (5.8% vs. 2.7%) compared to clomiphene. (Badawy, 2009; Diamond, 2015)
- Letrozole is contraindicated in women with premenopausal endocrine status, in pregnancy, and/or lactation due to potential for fetal malformations. According to the manufacturer (Novartis) the drug should only be used for its primary indication- breast cancer therapy for postmenopausal women. Secondary to concerns about teratogenicity, the FDA issued a strong label warning against the use of letrozole in reproductive age women seeking pregnancy. However, a study concluded that there was no overall difference in the rates of major and minor malformations between clomiphene and letrozole, but it appeared that congenital cardiac anomalies were less frequent in the letrozole group. (Tulandi, 2006)
- Two meta-analyses comparing letrozole with clomiphene as a first-line agent for ovarian stimulation demonstrated no difference in pregnancy and live birth rates (Donghong, 2011; Misso, 2012). As compared with clomiphene, letrozole was associated with higher live-birth (27.5% vs. 19.1%) and ovulation rates (88.5% vs. 76.6%) among infertile women with the polycystic ovary syndrome who were treated for up to 5 menstrual cycles (Legro, 2014).
- Letrozole compared to clomiphene demonstrated a lower incidence of hot flushes (20.3% vs. 33%) but a higher incidence of fatigue (21.7% vs. 14.9%) and dizziness (12.3% vs. 7.6%) and a lesser, but not significant, increase in endometrial thickness ( $2.4 \pm 3.8$  mm vs.  $3.4 \pm 3.7$  mm) (Legro, 2014)
- A randomized trial of 900 women with unexplained infertility treated with letrozole demonstrated a lower clinical pregnancy rate (22.4% v. 28.3%), lower singleton gestation rate (16.1% v. 22%) and a higher multiple gestation rate (13.4% v. 9.4%) compared to women treated with clomiphene. Side effects were also different with letrozole resulting in a higher incidence of abdominal bloating (18.6% v. 16.8%), breast pain (7.2% v. 6.4%), headaches (41.9% v. 34.9%) and joint or limb pain (5.8% v. 2.7%) but a lower incidence of constipation (2.7% v. 9.4%) and hot flashes (16.8% v. 30.9%) compared to clomiphene. (Diamond, 2015)

#### **Intrauterine Insemination**

- Cervical factor infertility may be subject to a trial of IUI, but should move to treatment with ART if IUI is not successful within 4 cycles. (Guzick,1999)
- Natural cycle IUI and controlled ovarian stimulation with clomiphene or letrozole with IUI are equally effective in the treatment of mild to moderate male factor infertility (AHRQ 2019)
- For unexplained infertility, a retrospective cohort study of 1738 women

undergoing 4199 treatment cycles using both clomiphene citrate and intrauterine insemination reported that pregnancy rates decrease with advancing maternal age and with subsequent treatment cycles. The authors concluded that it is reasonable to offer a limited number of cycles of clomiphene citrate and intrauterine insemination as first-line therapy in younger women with tubal patency without regard to ovulatory status (Dovey, 2008). Studies of women 40 years and older report age-related decline in fecundity and cumulative live birth rates with controlled ovarian stimulation and intrauterine insemination. (Harris, 2010; Wisner, 2012)

- Natural cycle IUI: The use of IUI appears to improve cycle fecundity when combined with ovarian stimulation. In one trial comparing intercourse with insemination in a natural cycle, conceptions occurred in 6 of 145 (4.1%) IUI cycles and 3 of 123 (2.4%) intercourse cycles ( $P=.46$ ) (Kirby, 1991). One would need to provide 100/2.71 or 37 cycles of IUI therapy to obtain a single additional pregnancy compared with control cycles. (ASRM, 2006)
- Unexplained infertility in females under the age of 35 may initially be addressed with a limited ( $\leq 3$ ) number of clomiphene IUI cycles but should progress rapidly to ART. Females age 35 and older should be advised to move directly to IVF. (ASRM, 2006; Hendricks, 2006)
- When used in combination with IUI, CC seems to be beneficial compared with expectant management. One study randomized 67 females with unexplained infertility to CC/IUI or expectant management for up to 8 cycles. Fourteen patients achieved pregnancy with CC/IUI treatment over 148 cycles (9.5% pregnancy rate per cycle), compared with 5 patients managed expectantly (over 150 cycles; 3.3% pregnancy rate per cycle). In a more recent trial, 475 females were observed for up to 3 cycles of CC/IUI. There were 123 pregnancies over 1,294 cycles and 98 ongoing or live births (7.6% ongoing or live births per cycle). Up to three cycles is a common therapeutic regimen before progressing to more aggressive therapies. (ASRM, 2013)
- After 6 cycles of gonadotropin/IUI the cumulative pregnancy rate ranges from 0 to 48.5%. (Merviel, 2010; Aboulghar, 2001)
- The pregnancy rate per cycle appears to diminish after the 3<sup>rd</sup> cycle. (Merviel, 2010)
- After 3 cycles of gonadotropin/IUI 39.2 to 87% of conceptions will have occurred. (Merviel, 2010; Aboulghar, 2001; Sahakyan, 1999; Dickey, 2003)
- After 4 cycles of gonadotropin/IUI 89 to 98% of conceptions will have occurred. (Merviel, 2010; Aboulghar, 2001; Sahakyan, 1999; Nuojua-Huttunen, 1999; Dickey, 2003)
- Women age 38-39 years old have a diminished prognosis following 2 gonadotropin/IUI cycles and women  $\geq 40$  years have a diminished prognosis after one cycle. (Sahakyan, 1999; Harris, 2010)
- Women  $\geq 41$  years old have a diminished prognosis with clomiphene citrate/IUI treatment. (Aboulghar, 2001)
- Clomiphene citrate may be as effective as gonadotropins when used in conjunction with IUI in cases of cervical factor, mild male factor and unexplained infertility.
- Pregnancy rates for Clomid/IUI (2%-19.3%) do not differ from those

involving gonadotropin/IUI (7%-19.2%) or low dose (75 IU/day) gonadotropin/IUI (8.7%-16.3%) but the incidence of twin gestations is markedly reduced (12.5% vs. 28.6% and 29.3% respectively). (McClamrock, 2012)

- Controlled ovarian stimulation and IUI may increase the live birth rate 5.6 fold in women with minimal or mild endometriosis compared to expectant management. (Tummon, 1997)
- ART is recommended for women with moderate or severe endometriosis. (ESHRE, 2013)
- Cumulative pregnancy rates within 4 cycles are 51.44% and 25.4% for clomiphene and gonadotropins respectively (the difference in pregnancy rates is not statistically significant). (Ecochard, 2000; Guzik, 1999; Reindollar 2010, 2011)
- There is no evidence that, absent sexual dysfunction, cervical trauma or mild male factor infertility natural cycle (i.e., no ovarian stimulation) IUI has any benefit over appropriately timed heterosexual intercourse.
- Natural cycle IUI may be considered in the setting of donor insemination when no other infertility factor is present.
- There is no evidence from the published studies that intrauterine insemination is an effective treatment for cervical hostility. (Helmerhorst, 2009)
- A single timed insemination per cycle is sufficient as there is no benefit to additional inseminations per cycle. (Osuna, 2004; Albrozi, 2003; Tonguc, 2010)
- There is no evidence in published studies that reverting to treatment with IUI following failed ART cycles due to poor ovarian response, poor quality oocytes or embryos has been proven to be clinically effective.
- IVF compared with IUI presents superior pregnancy rates in the setting of two or more follicles. (Reichman, 2013)

#### **Treatment in the Natural Cycle**

- There is no evidence in the medical literature that timed coitus based upon serial ultrasound monitoring of follicular development improves pregnancy outcome. (ASRM, 2006, 2012a, 2012b; Lewis, 2004)
- Natural cycle ART may have some benefit in individuals who prefer to avoid ovarian stimulation.
  - Pregnancy rate per cycle ranges from 9.8 to 19.2%. (Schimberni, 2009; Gordon, 2013)
  - Live birth rate per initiated cycle ranges from 0 (age group >42) to 15.2% (age group <35). (Gordon, 2013)
    - Across all age groups the cumulative live birth rate per cycle is reported as 2.6% with a live birth rate per patient ranging from 6.8 to 7.9% and the probability of a live birth reaching only 5.8% after 4 consecutive treatment cycles. (Polyzos, 2012)
    - Live birth rates per intended retrieval are 13.9% for

females <35 years of age, 10.7% for females 35-37 years of age, 7.1% for females 38-40 years of age, 4.1% for females 41-42 years of age and 0.6% for females >42 years of age with corresponding implantation rates of 32.7%, 34.7%, 23.8% 14.9% and 5.1% respectively.

- In the setting of diminished ovarian reserve, however, the live birth rates drop dramatically to 13.9%, 3.4%, 6.1%, 2.5% and 0.5% respectively. (SART, 2016)
- Cycle cancellation rates range from 46 (age group <35) to 77% (age group >42) (Gordon, 2013) More recent data demonstrate cancellation rates ranging from 23.4% to 27%. (SART, 2015)

**Embryo Banking and Use of Frozen Embryos**

- There is no evidence in the medical literature to support the practice of repeated ART cycles for the purpose of accumulating (banking) embryos for later use (egg retrievals without a fresh or frozen embryo transfer) with the exception of freeze all cycles for medical necessity.
- It is clinically appropriate and cost effective to utilize all frozen embryos for transfer prior to another fresh ART cycle. (Forman, 2013; Richter, 2006; Shapiro, 2011, 2013)

**Tubal Disease**

- Studies treating patients with bilateral proximal tubal occlusion showed that the obstruction is relieved in about 85% of the tubes with tubal cannulation and that about half of the patients conceive. Approximately a third of the opened tubes subsequently re-occlude. (Honore 1999, Pinto 2003)
- A good prognosis for distal tubal surgery is associated with patients who have no more than limited filmy adnexal adhesions, mildly dilated tubes (<3 cm) with thin and pliable walls, and a lush endosalpinx with preservation of the mucosal folds. (AFS 1988)
- Intrauterine pregnancy rates after neosalpingostomy for mild hydrosalpinges range from 58% to 77% but decreases to 0% to 22% for severe disease. The corresponding ectopic pregnancy rates range from 2%-8% and 0%-17% respectively. (Nackley 1998)
- Hydrosalpinges have been demonstrated to lower pregnancy, implantation and delivery rates. (Camus 1999, Zeyneloglu 1998)
- Laparoscopic salpingectomy or tubal occlusion has been demonstrated to restore pregnancy and live birth rates to those of women without a hydrosalpinx. (Dechaud 1998, Kontoravdis 2006, Strandell 1999)

**Endometriosis**

- The cumulative spontaneous pregnancy rate within 3 years (life table analysis) after surgery has been reported to range from 46% to 77% for moderate endometriosis and 44% to 74% for severe endometriosis. (Adamson 1994, Nezhat 1989, Vercellini 2006)
- There is no evidence to support the use of adjunctive hormonal therapy to improve pregnancy rates prior to or following surgery for endometriosis. (Furness 2004)



- ART pregnancy rates for women with moderate or severe endometriosis are lower than those for patients with tubal factor infertility. (Barnhart 2002)
- There is no medical evidence that laparoscopic aspiration or cystectomy of an endometrioma prior to ART shows any benefit over expectant management with regard to the clinical pregnancy rate. (Benschop 2010)
- Although the presence of bilateral endometriomas at the time of ART affects responsiveness to hyperstimulation, the quality of the oocytes retrieved and the chances of pregnancy are not affected. (Benaglia 2013)
- There is no evidence that resection of deep nodular implants of endometriosis prior to ART improves pregnancy outcome. (Bianchi 2009, Papaleo 2011)

#### **Uterine Factor**

- 79% of pregnancies in patients with a uterine septum may end in miscarriage. (Homer 2000)
- The role of metroplasty in the treatment of infertility is not clear. (Pabuccu 2004)
- ART appears to be less successful in women with a septate uterus. (Lavergne 1996)
- There is no evidence to support resection of a uterine septum that extends <1cm (sub-septate or arcuate uterus) from the superior uterine wall.
- In the largest series of women with a unicornuate uterus who were infertile or had recurrent pregnancy loss, the live birth rate in those with a communicating rudimentary horn was 15%, with a non-communicating rudimentary horn 28%, and with a rudimentary horn without a cavity 35%. (Akar 2005)
- Polypectomy may improve spontaneous pregnancy rates. (Perez-Medina 2005)
- Polyps <2 cm do not appear to affect ART outcome adversely. (Taylor 2008)
- One large study of intrauterine adhesions demonstrated a term pregnancy rate of 81.3% among women with mild disease, 66.0% among women with moderate disease, and 31.9% of those with severe disease following surgical treatment. (Schenker 1982)
- Sub-mucosal and intramural fibroids that protrude into the uterine cavity are associated with decreased pregnancy and implantation rates both of which improve following myomectomy. (Garcia 1984; Goldenberg 1995)
- Subserosal and intramural myomas that do not distort the uterine cavity do not appear to affect ART outcome adversely. (Dietterich 2000, Surrey 2001; Yarali 2002; Wang 2004; Klatsky 2007)
- A review suggests that fibroids with a submucous or an intracavitary component are associated with decreased fertility and increased spontaneous abortion rates. Myomectomy (either hysteroscopic, laparoscopic, or abdominal) is of value for submucosal fibroids. (Olive & Pritts 2010)

#### **Intracytoplasmic Sperm Injection (ICSI)**

ICSI is a safe and effective treatment of male factor infertility. While the diagnostic criteria used to identify male factor infertility fail to predict decreased or absent

fertilization in assisted reproductive technology (ART) studies to date support the safety and efficacy of ICSI to treat various male factor conditions. (ASRM 2012.) The rationale for using ICSI in other situations is to avoid a failure of fertilization. In the setting of unexplained infertility, a large meta-analysis demonstrated a fertilization rate per oocyte retrieved of 67.5% using ICSI vs. 47.8% allocated to conventional insemination (Johnson, 2012) Other studies while demonstrating a higher fertilization rate with ICSI compared to conventional fertilization (58% vs. 47%) have shown no difference in clinical pregnancy or live birth rates (Bhattacharya, 2001)

- In the setting of unexplained infertility, current evidence does not demonstrate any significant improvement in fertilization rate, embryo quality, implantation rate, clinical pregnancy rate or live-birth rate (Foong et al 2006).
- In the setting of low oocyte yield, two controlled studies comparing conventional insemination vs. ICSI demonstrated no difference in fertilization rates, fertilization failure, embryo quality, mean embryos per patient, clinical pregnancy rates and miscarriage rates (Kim et al 2007; Luna 2011).
- There is no data demonstrating the benefit of ICSI when used in women over 35 years of age (Kim et al 2007).
- There is evidence to support the use of ICSI when there has been a failure of fertilization with conventional insemination. While subsequent conventional insemination may result in fertilization rates ranging from 30%-97% the fertilization rate may be correlated with number of follicles, oocytes retrieved and mature oocytes (Roest et al 1998; Kinzer et al 2008). A prospective study however demonstrated a marked improvement in fertilization with ICSI (48%) compared to conventional insemination (115).
- There is no data regarding the use of ICSI when using cryopreserved oocytes. Nevertheless, changes in the zona pellucida associated with the freezing process may affect fertilization with conventional insemination, thus warranting the use of ICSI.
- In the setting of pre-implantation genetic testing (PGT) ICSI may be warranted to ensure mono-spermic fertilization (Tucker et al 200; Thornhill et al 2005; ICSI in 2006: evidence and evolution. Hum Reprod Update 2005)
- While an argument has been made that the use of ICSI should be used for all patients to minimize the risk for fertilization failure, a well powered, multi-center, randomized controlled trial demonstrated that the fertilization rate per oocyte retrieved was actually higher with conventional insemination compared to ICSI (Bhattacharya et al 2001).

#### **Efficacy of eSET**

- Single embryo transfer is most applicable for transfer of blastocyst-stage embryos as these appear to have higher implantation rates compared to cleavage-stage embryos. (Papanikolaou 2006, Blake 2007, Zech 2007)
- Compared with DET-conceived infants, eSET-conceived singletons are less likely to be born either preterm (RCT-based relative risk [RR] 0.37, 95% confidence interval [CI] 0.25–0.55) or with low birth weight (RCT-based RR 0.25, 95% CI 0.15–0.45; cohort study RR 0.51, 95% CI 0.29–0.91). (Grady

2012)

- Following implementation of a mandatory eSET program, eSET fresh transfers have resulted in clinical pregnancy rates of 67.7% (Csokmay 2011) and a live-birth rate of 64.6% (Kresowik 2011) with a significant reduction in multiple-birth rate to 3-4%.
- The transfer of a single euploid blastocyst embryo yields comparable pregnancy rates to untested double blastocyst transfer (Forman 2013) and yield pregnancy rates comparable to egg donation cycles. (Griffo)
- Some studies suggest a lower initial pregnancy rate for eSET compared to two embryo transfer (Pandian 2009; McLernon 2010, van Montfoort 2006), but cumulative pregnancy rates are similar (54.7% for eSET vs. 49% for a double transfer). (Criniti 2005, Henman 2005, le Lannou 2006)
- eSET in women under 37 resulted in increased cumulative live birth compared with multiple embryo transfer. In women aged between 37 and 40, CLBR in eSET group was similar with that in MET group. In both age groups, eSET reduced multiple birth rates.(Fujimoto, 2015)
- Double embryo or more was associated with a significantly increased risk for multiple pregnancy, placenta accreta, preterm premature rupture of membrane, cesarean section (CS), pre-term birth, low birth weight, small for gestational age, and early neonatal death compared with single embryo transfer. (Takeshima, 2016)
- Double frozen blastocyst transfer yielded a higher live birth per transfer, but 33% of births from double frozen blastocyst transfer were twins versus only 0.6% of single FBT. Double frozen blastocyst transfer was associated with statistically significant increases in preterm birth and low birth weight, the latter of which was statistically significant even when the analysis was limited to singletons. Of the blastocysts transferred via single frozen blastocyst transfer, 38% resulted in a liveborn child versus only 34% with double frozen blastocyst transfer. This suggests that two single FBTs would result in more liveborn children with significantly fewer preterm births when compared with double frozen blastocyst transfer. (Devine, 2015)

#### **Double Embryo Transfer**

- In a randomized controlled study the twin rate with blastocyst transfer following double embryo transfer (DET) was 47% vs. 0% for eSET. (Gardner 2004)
- Multiple gestation rates of 50% to > 60% have been reported following the transfer of two top quality blastocysts. (Gardner 2004, Crinit 2005, Balaban 2000, Gardner 2000)
- Pregnancy rates are similar for autologous eSET versus double blastocyst transfer (65%-76% vs. 63%-79%). (Salame 2011)

#### **Blastocyst Stage Embryos**

- Other studies demonstrate high implantation rates (65%) and live birth rates (54%) when supernumerary blastocysts are available for cryopreservation. (Hill 2013, Mullin 2012, Dare 2004,)
- Extended embryo culture allows transfer of embryos with the highest implantation potential. (Balaban 2000, Shapiro 2000)
- Blastocyst has been found to achieve higher implantation and live birth rates

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compared with cleavage stage embryos. (Gardner 2007, Blake 2007, Papanikolaou 2008.

- Favorable (>50%) pregnancy rates have been reported for single blastocyst transfer in women >35 years of age. (Davis 2008, Shapiro 2000)

### **Cryopreservation**

Traditionally, embryos are usually transferred in the same IVF cycle in which oocytes are collected. More recently there has been a shift in practice towards favoring freezing of the entire cohort of good quality embryos (Weinerman and Mainigi, 2014; Chen, 2016; Shapiro, 2014a, b). In such “freeze only” cycles, all good quality embryos are frozen and transferred at a later stage (Aflatoonian 2012; Doody, 2014). Among the advantages of using frozen embryo transfer (FET) cycles is the associated reduction in ovarian hyperstimulation syndrome (OHSS) and/or the facilitation of pre-implantation genetic testing (Devroey, 2011; Maheshwari, 2012; Roque, 2015). Additionally, delay of transfer to a later FET cycle may be associated with an improvement of receptivity for implantation of the uterine environment in the presence, for example of a premature progesterone elevation or thin endometrial lining (Shapiro 2010; Shapiro 2011; Shapiro 2011). Of additional and perhaps greater import is the need to freeze supernumerary embryos in the context of elective single embryo transfer cycles.

Cumulative live birth rates appear to be similar to those of a fresh transfer of cleavage stage embryos (45.6% vs 46.4%, but are superior when blastocyst stage embryos are transferred/cryopreserved (45.3% vs 65.7%) (Zhu 2011; Maheshwari 2012; Zacca 2018). Other studies have demonstrated comparable live birth outcomes for fresh vs. frozen/thaw transfer cycles (Chen 2016; Vuong 2018).

From a neonatal perspective numerous registry studies and meta-analyses have demonstrated that infants resulting from fresh autologous ET have reduced birth weight, increased risk of low birth weight, and other perinatal risks associated with birth weight when compared with infants resulting from the transfer of frozen-thawed embryos. FET cycles yield increases in birth weights ranging from 80g to 250 g (Ishihara 2010; Kalra 2011; Wennerholm 2013; Nakashima 2013; Li 2014; Schwarze 2015; Shapiro 2016)

Mature oocyte cryopreservation was recognized as being appropriate treatment as defined in this document by the American Society for Reproductive medicine in 2013 (ASRM 2013). Utilization of cryopreserved autologous oocytes leads to similar outcomes, including pregnancy rates compared to women undergoing IVF with frozen embryo transfer (45.5% vs 52.3%) (Alvarez 2015) Several studies, however, have also have observed decreased success with oocyte vitrification in women of advanced age. A large Italian retrospective cohort study of 450 couples undergoing oocyte thaw cycles using previously vitrified supernumerary oocytes found that maternal age was inversely correlated with delivery rates (Rienzi 2012). Another report also noted that ongoing pregnancy rates in 182 oocyte vitrification/warming cycles were significantly lower in women over 40 years of age (Ubaldi 2010). In this study, age stratified cumulative pregnancy rates per transfer were: 48.6% in %34 year-olds, 24.1% in 35–37 year-olds, 23.3% in 38–40 year-olds, and 22.2% in 41–43 year-olds. In summary, success rates with oocyte cryopreservation appear to decline with maternal age consistent with the clinical experience using fresh oocytes.

### **Surgical Sperm Aspiration**

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	<p>Surgical testicular sperm aspiration has been shown to be an effective treatment for nonobstructive azoospermia (Schlegel PN, 1997). In 1999, Schlegel et al demonstrated successful sperm retrieval in 35% of random testicular biopsy cases and 52% in micro testicular biopsy. This shows that microsurgical testicular sperm aspiration is 1.5 time more effective than random biopsy of the testicle for nonobstructive azoospermia. (Schlegel PN, 1999)</p> <p>For the surgical treatment of obstructive azoospermia, microsurgical epididymal sperm aspiration (MESA) has been found to be the optimal method as it yields the highest clinical pregnancy rates and greatest number of retrieved sperm. (Sheynkin, 1998) (Bernie AM, 2013) A live birth rate of 39% using MESA-ICSI vs 24% live birth rate using TESE-ICSI demonstrates a significantly higher birth rate with MESA. (van Wely, 2015) Cayan et al suggest that cryopreserved/thawed sperm retrieved through MESA and used with ICSI produces similar success rates when compared to fresh sperm retrieved through MESA. They found no significant difference in fertilization rates (58.4% for fresh sperm and 62% for frozen thawed sperm), clinical pregnancy rates (31.6% for fresh sperm and 36.8% for frozen thawed sperm), and live birth rates (21.1% for fresh sperm and 36.8% for frozen thawed sperm). (Cayan S, 2001)</p> <p>After a search of the current literature, there are no studies comparing pregnancy outcome rates using sperm obtained through surgical methods vs sperm obtained through ejaculation.</p>
<p><b>Definitions</b></p>	<p><b>Amenorrhea:</b> the complete lack of menstrual bleeding</p> <p><b>Anovulation:</b> the lack of ovulatory menstrual cycles. Females with anovulation may still have periodic bleeding but these episodes are not associated with prior ovulation</p> <p><b>Bicornuate uterus:</b> a bifurcated uterus</p> <p><b>Endometriosis:</b> a condition where endometrial implants are located external to the uterine cavity. Often but not always associated with pain, pelvic adhesions, ovarian cysts</p> <p><b>Fimbrioplasty:</b> reconstructive surgery of the distal fimbriated end of the fallopian tube</p> <p><b>Hydrosalpinx:</b> distal occlusion of a fluid filled fallopian tube. Often causes denudation of the tubal cilia.</p> <p><b>Medical Futility:</b> “Futility” refers to treatment that has a <math>\leq 1\%</math> chance of achieving a live birth</p> <p><b>Male Factor Infertility:</b></p> <ul style="list-style-type: none"> <li>• <b>Mild Male Factor:</b> abnormalities in the semen analysis where the sperm concentration is <math>\geq 10</math> million/ml but <math>&lt; 15</math> million/ml and/or progressive motility is <math>\geq 30\%</math> but <math>&lt; 40\%</math> or <math>\geq 5</math> million total motile sperm</li> <li>• <b>Moderate Male Factor:</b> abnormalities in the semen analysis where the sperm concentration is <math>\geq 5</math> million/ml but <math>&lt; 10</math> million/ml and/or progressive motility is <math>\geq 25\%</math> but <math>&lt; 30\%</math></li> <li>• <b>Severe Male Factor:</b> abnormalities in the semen analysis where the sperm concentration is <math>&lt; 5</math> million/ml or sperm preparation techniques result in a sperm concentration of <math>&lt; 1</math> million motile sperm/ml</li> <li>• Isolated teratospermia is considered a male factor when there is <math>&lt; 2\%</math> normal morphology on at least two semen analyses 1-4 weeks apart</li> </ul> <p><b>Metroplasty:</b> surgical reconstruction of the uterus</p> <p><b>Neosalpingostomy:</b> surgery to create a new opening in the distal end of the fallopian tube when there is complete fimbrial obstruction or obliteration</p>



	<p><b>Oligo-ovulation:</b> Ovulatory menstrual cycles that are &gt;35 days apart</p> <p><b>Poor Prognosis:</b> “Very poor prognosis” refers to treatment for which the odds of achieving a live birth are very low but not nonexistent (&gt;1% to &lt;5% per cycle). (ASRM, 2006)</p> <p><b>Recurrent Pregnancy Loss:</b> Recurrent pregnancy loss is a disease distinct from infertility, defined by two or more failed pregnancies.</p> <p><b>Salpingitis isthmica nodosum:</b> chronic nodular inflammation of the proximal fallopian tube often resulting in tubal occlusion</p> <p><b>Salpingectomy:</b> partial or complete removal of a fallopian tube</p> <p><b>Salpingostomy:</b> surgery to create an opening in the fallopian tube</p> <p><b>Septate uterus:</b> a congenital anomaly with incomplete resorption of the medial uterine wall. Sometimes associated with recurrent pregnancy loss and possibly infertility</p> <p><b>Tubal Factor Infertility:</b> Infertility that is caused by or associated with compromise of one or both fallopian tubes. This may be due to peritubal or fimbrial adhesions, blockage, or phimosis (narrowing)</p> <p><b>Unexplained Infertility:</b> Infertility for which no causative factor has been identified</p> <p><b>Unicornuate uterus:</b> a congenital anomaly with development of a hemi-uterus. Often associated with a rudimentary horn.</p> <p><b>Uterine Factor Infertility:</b> Infertility that is caused by or associated with compromise of the uterine (endometrial) cavity. This may be due to intrauterine lesions such as polyps, sub-mucosal leiomyomata, or synechiae (adhesions). Intramural, subserosal and external pedunculated leiomyoma have not been proven to be associated with infertility unless the endometrial cavity is distorted or they compromise a fallopian tube. Congenital anomalies such as a septate, bicornuate, unicornuate or didelphic uterus tend to be associated with recurrent pregnancy loss. A sub-septate (septum extending &lt;1/4 the length of the uterine cavity) or arcuate (minimal indentation of the superior aspect of the uterus) are not associated with infertility or pregnancy loss.</p> <p><b>Uterus didelphys:</b> a congenital anomaly with a double uterus, sometimes with a double cervix and double vagina</p>
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### ***Bibliography***

Aboulghar M, Mansour R, Serour G, et al. Controlled ovarian hyperstimulation and intrauterine insemination for treatment of unexplained infertility should be limited to a maximum of three trials. *Fertil Steril* 2001;75:88–91.

ACOG. The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists and The Practice Committee of the American Society for Reproductive Medicine: Age-related fertility decline: a committee opinion. *American Society for Reproductive Medicine* 2008.

Adamson DG, Pasta DJ. Surgical treatment of endometriosis-associated infertility: meta-analysis compared with survival analysis. *Am J Obstet Gynecol.* 1994 Dec;171(6):1488-504.

Aflatoonian A, Oskouian H, Ahmadi S, Oskouian L. Can fresh embryo transfers be replaced by cryopreserved-thawed embryo transfers in assisted reproductive cycles? A randomized controlled trial. *J Assist Reprod Genet* 2010;27:357–63.

Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services, National Guideline Clearinghouse | Fertility: assessment and treatment for people with fertility problems. [http://guideline.gov/content.aspx?f=rss&id=43841&osrc=12\[5/20/2013 9:54:47 AM\]](http://guideline.gov/content.aspx?f=rss&id=43841&osrc=12[5/20/2013 9:54:47 AM])

Agency for healthcare research and quality (AHRQ), U.S. Department of Health and Human Services, National Guideline Clearinghouse Comparative Effectiveness Review Number 217 Management of Infertility. AHRQ Publication No. 19-EHC014-EF May 2019.

Akar ME, Bayar D, Yildiz S, Ozel M, et al. Reproductive outcome of women with unicornuate uterus. *Aust N Z J Obstet Gynaecol* 2005;45:148–50.

Albrozi S, Motazedian S, Parsanezhad M, et al. Comparison of the effectiveness of single intrauterine insemination (IUI) versus double IUI per cycle in infertile patients. *Fertil Steril* 2003. 80:595-99.

Alvarez JP, Akopians AI, Wang ET, et al. Outcomes of utilized autologous cryopreserved oocytes. *Fertil Steril* 2015; 104:e267-8.

American Fertility Society (AFS). The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies and intrauterine adhesions. *Fertil Steril* 1988;49:944–55.

American Society for Reproductive Medicine (ASRM) Committee Opinion: Role of tubal surgery in the era of assisted reproductive technology. *Fertil Steril* 2012;97:539-45.

American Society for Reproductive Medicine (ASRM) Practice Committee opinion: Multiple gestation associated with infertility therapy. *Fertil Steril* 2012;97(4):825-834.

American Society for Reproductive Medicine (ASRM) Committee Opinion: Myomas and reproductive function. *Fertil Steril* 2008;90:S125-30.

ASRM. The Practice Committee of the American Society for Reproductive Medicine: Definitions of infertility and recurrent pregnancy loss. *Fertil Steril* 2013;99:63

ASRM. The Practice Committee of the American Society for Reproductive Medicine: Effectiveness and treatment for unexplained infertility. *Fertil Steril* 2006; 86; S114.

ASRM (a). The Practice Committee of the American Society for Reproductive Medicine: Testing and interpreting measures of ovarian reserve. *Fertil Steril* 2015;103(3):e9-e17.

ASRM (b). The Ethics Committee of the American Society for Reproductive Medicine. Fertility Treatment When the Prognosis is Very Poor or Futile: a Committee Opinion. *Fertil Steril* 2012;98:e6–e9.

ASRM (c). The Practice Committee of the American Society for Reproductive Medicine: Use of Clomiphene Citrate in Infertile Females: a Committee Opinion. *Fertil Steril* 2013; 100: 341-8.

ASRM (d). The Ethics Committee of the American Society for Reproductive Medicine. Oocyte or embryo donation to women of advanced reproductive age: an ethics committee opinion. *Fertil Steril* 2016;106:e3-e7.

ASRM. The Practice Committee of the American Society for Reproductive Medicine: Gonadotropins for ovulation induction. 2019 in press.

ASRM Mature Oocyte Cryopreservation: A guideline. *Fertil Steril* 2013;99:37-43.

Assante A, Coddington CC, Schenck LL, Stewart EA. Thin endometrial stripe does not affect the likelihood of achieving pregnancy in clomiphene citrate/intrauterine insemination cycles. *Fertil Steril* 2013 Dec;100(6):1610-4.

Baart E, Martini E, Eijkemans M, et al. Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial. *Human Reprod* 2007 Apr; 22(4): 980-8.

Badawy A, Elnashar A, Totongy M. Clomiphene citrate or aromatase inhibitors for superovulation in women with unexplained infertility undergoing intrauterine insemination: a prospective randomized trial. *Fertil Steril*. 2009 Oct;92(4):1355-9.

Balaban B, Urman B, Sertac A, Alatas C, Aksoy S, Mercan R. Blastocyst quality affects the success of blastocyst-stage embryo transfer. *Fertil Steril* 2000;74:282–7.

Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. *Fertil Steril* 2002; 77:1148–1155.

Bhattacharya S, Hamilton MP, Shaaban M, Khalaf Y, Seddler M, et al. Conventional in-vitro fertilization versus intracytoplasmic sperm injection for the treatment of non-male-factor infertility: a randomised controlled trial. *Lancet* 2001;357:2075–9.

Benadiva CA, Nulsen J, Siano L, Jennings J, Givargis HB, Maier D. Intracytoplasmic sperm injection overcomes previous fertilization failure with conventional in vitro fertilization. *Fertil Steril* 1999;72:1041–4.



- Benaglia LB, Bermejo A, Somigliana E, et al. In vitro fertilization outcome in women with unoperated bilateral endometriomas. *Fertil Steril* 2013;99:1714–9.
- Benschop L, Farquhar C, van der Poel N et al. Interventions for women with endometrioma prior to assisted reproductive technology. *Cochrane Database Syst Rev* 2010:CD008571.
- Bernie AM, et al. Microsurgical epididymal sperm aspiration: indications, techniques and outcomes. *Asian J Androl.*, 2013;15(1;40-43).
- Bianchi PH, Pereira RM, Zanatta A, et al. Extensive excision of deep infiltrative endometriosis before in vitro fertilization significantly improves pregnancy rates. *J Minim Invasive Gynecol* 2009; 16:174–180.
- Blake DA, Farquhar CM, Johnson N, et al. Cleavage stage versus blastocyst stage embryo transfer in assisted conception. *Cochrane Database Syst Rev* 2007;4:CD002118.
- Bravelle [package insert]. Parsippany, NY: Ferring Pharmaceuticals; June 2012.
- Camus E, Poncelet C, Goffinet F, et al. Pregnancy rates after in-vitro fertilization in cases of tubal infertility with and without hydrosalpinx: a meta-analysis of published comparative studies. *Hum Reprod* 1999;14:1243–9.
- Cayan S, Lee D, Conaghan J, Givens CA, Ryan IP, et al. A comparison of ICSI outcomes with fresh and cryopreserved epididymal spermatozoa from the same couples. *Hum Reprod.* 2001;16:495-9.
- Chaffkin LM, Nulsen JC, Luciano AA, et al. A comparative analysis of the cycle fecundity rates associated with combined human menopausal gonadotropin (hMG) and intrauterine insemination (IUI) versus either hMG or IUI alone. *Fertil Steril* 1991;55:252–7.
- Chen Z-J, Shi Y, Sun Y, Zhang B, Liang X, Cao Y, Yang J, Liu J, Wei D, Weng N et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. *N Engl J Med* 2016;375:523–533.
- Cooper TG, Noonan E, von Eckerdstein S, et al. M: World Health Organization reference values for human sperm characteristics. *Human Reprod Update* 2010; 16: 231-245.
- Craft IL, Khalifa Y, Boulos A, Pelekanos M, Foster C, Tsigotis M. Factors influencing the outcome of in vitro fertilization with percutaneous aspirated epididymal spermatozoa and intracytoplasmic sperm injection in azoospermic men. *Hum Reprod* 1995;10:1791–4.
- Crawford S, Boulet SL, Mneimneh AS, et al. Costs of achieving live birth from assisted reproductive technology: a comparison of sequential single and double embryo transfer approaches. *Fertil Steril* 2016 Feb;105(2):444–50.
- Criniti A, Thyer A, Chow G, Lin P, Klein N, Soules M. Elective single blastocyst transfer reduces twin rates without compromising pregnancy rates. *Fertil Steril.* 2005;84:1613–1619.
- Csokmay JM, Hill MJ, Chasin RJ et al. Experience with a patient-friendly, mandatory, single-blastocyst transfer policy: the power of one. *Fertil Steril* 2011;96:580–4.
- Dar S, Lazer T, Swanson S et al: Assisted reproduction involving gestational surrogacy: an analysis of the medical, psychosocial and legal issues: experience from a large surrogacy program. *Human Reproduction* 2015; 30: 345-352.
- Dare MR, Crowther CA, Dodd JM et al. Single or multiple embryo transfer following in vitro fertilization for improved neonatal outcome: A systematic review of the literature. *Aust NZ J Obstet Gynaecol* 2004; 44: 283-291.
- Davis LB, Lathi RB, Westphal LM, Milki AA. Elective single blastocyst transfer in women older than 35. *Fertil Steril* 2008;89:230–1.
- Dechaud H, Daures JP, Arnal F, et al. Does previous salpingectomy improve implantation and pregnancy rates in patients with severe tubal factor infertility who are undergoing in vitro fertilization? A pilot prospective randomized study. *Fertil Steril* 1998;69:1020–5.
- den Hartog JE, Morre SA, Land JA. Chlamydia trachomatis-associated tubal factor subfertility: immunogenetic aspects and serological screening. *Hum Reprod Update* 2006.
- Dermount S, van deWiel H, Heintz P, Jansen K, Ankum W. Non-commercial surrogacy: an account of patient management in the first Dutch Centre for IVF Surrogacy, from 1997 to 2004. *Hum Reprod* 2010;25:443–449.
- Devine S, Connell MT, Richter KS, et al. Single vitrified blastocyst transfer maximizes liveborn children per embryo while minimizing preterm birth. *Fertil Steril.* 2015 Jun;103(6):1454–60.

Devroey P, Polyzos NP, Blockeel C. An OHSS-Free Clinic by segmentation of IVF treatment. *Hum Reprod* 2011;26:2593–2597.

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, clomiphene or gonadotropin for unexplained infertility. *N Engl J Med* 2015;373:1230-40.

Dickey RP, Taylor SN, Lu PY, et al. The number of cycles of gonadotropin-intrauterine insemination should be tailored to follicular response. *Fertil Steril* 2003; 80: S213.

Dietterich C, Wang W, Shucoski K, Check JH. The relationship of endometrial thickness and pregnancy in infertile women treated without in vitro fertilization. *Fertil Steril*. 2004 Apr;81 Suppl 3:S7-31.

Dietterich C, Check JH, Choe JK, et al. The presence of small uterine fibroids not distorting the endometrial cavity does not adversely affect conception outcome following embryo transfer in older recipients. *Clin Exp Obstet Gynecol* 2000;27:168–70.

Donghong H, Fengyan J. Meta-analysis of letrozole versus clomiphene citrate in polycystic ovary syndrome. *Reprod BioMedicine Online* 2011;23:91–6.

Doody KJ. Cryopreservation and delayed embryo transfer-assisted reproductive technology registry and reporting implications. *Fertil Steril* 2014; 102:27–31.

Dovey S, Sneeringer RM, Penzias AS. Clomiphene citrate and intrauterine insemination: analysis of more than 4100 cycles. *Fertil Steril* 2008;90:2281–6.

Dreyer K, van Rijswijk J, Mijatovic V, et al. Oil based or water based contrast for hysterosalpingography in infertile women. *NEJM* 2017;376: 2043-2052.

Ecochard R, Mathieu C, Royere D, et al. A randomized prospective study comparing pregnancy rates after clomiphene citrate and human menopausal gonadotropin before intrauterine insemination. *Fertil Steril* 2000; 73:90-93.

Ethics Committee of the American Society for Reproductive Medicine Consideration of the gestational carrier: a committee opinion. *Fertil Steril* 2013;99:1838–41.

European Society of Human Reproduction and Embryology (ESHRE) Guideline: Management of Women with Endometriosis. September 2013.

Falcone T, Lebovic DI. Clinical management of endometriosis. *Obstet Gynecol* 2011;118:691–705.

Fauque P, Jouannet P, Davy C, Guibert J, et al. Cumulative results including obstetrical and neonatal outcome of fresh and frozen-thawed cycles in elective single versus double fresh embryo transfers. *Fertil Steril* 2010;94:927-935.

Fausser BC, Nargund G, Anderson AN, et al. Mild ovarian stimulation for IVF: 10 years later. *Human Reprod*. 2010 Nov; 25(11): 2678-84.

Feinberg EC, Levens ED, DeCherney AH. Infertility surgery is dead: only the obituary remains? *Fertil Steril* 2008 Jan;89(1):232-6.

Fertility Solutions Expert Panel. June 26, 2019 .

Follistim AQ [package insert]. Roseland, NJ: Organon USA Inc.; August 2012

Fisch P, Casper RF, Brown SE, et al. Unexplained infertility: evaluation of treatment with clomiphene citrate and human chorionic gonadotropin. *Fertil Steril* 1989;51:828–33.

Foong SC, Fleetham JA, O'Keane JA, Scott SG, Tough SC, Greene CA. A prospective randomized trial of conventional in vitro fertilization versus intracytoplasmic sperm injection in unexplained infertility. *J Assist Reprod Genet* 2006;23:137–40.

Forman EJ, Hong KH, Ferry KM, et al. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. *Fertil Steril* 2013; 100: 100-7.

Fujimoto A, Morishima K, Harada M, et al. Elective single-embryo transfer improves cumulative pregnancy outcome in young patients but not in women of advanced reproductive age. *J Assist Reprod Genet*. 2015 Dec;32(12):1773–1779.

Furness S, Yap C, Farquhar C, et al. Pre and post-operative medical therapy for endometriosis surgery. *Cochrane Database Syst Rev* 2004;CD003678.

Garcia CR, Tureck RW. Submucosal leiomyomas and infertility. *Fertil Steril* 1984;42:16–9.

Gardner DK, Surrey E, Minjarez D, Leitz A, Stevens J, Schoolcraft WB. Single blastocyst transfer: a prospective randomized trial. *Fertil Steril* 2004;81: 551–5.

Gingold JA, Lee JA, Rodriguez Purata R, et al. Endometrial pattern, but not endometrial thickness, affects implantation rates in euploid embryo transfers. *Fertil Steril* 2015;104:620-8.

Gleicher N, Oleske DM, Tur-Kaspa I, et al. Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. *N Engl J Med* 2000;343:2–7.

Goldenberg M, Sivan E, Sharabi Z, et al. Outcome of hysteroscopic resection of submucous myomas for infertility. *Fertil Steril* 1995;64:714–6.

Goldman MB, Regan MM, Berger MJ, et al. The natural history of infertility treatment in a state with mandated insurance coverage: the fast track and standard treatment (FASTT) trial. *Fertil Steril* 2010; 94: 888-899.

Gonal-F [package insert]. Rockland, MA: EMD Serono, Inc.; December 2011.

Gordon J, DiMattina M, Reh A, et al. Utilization and success rates of unstimulated in vitro fertilization in the United States: an analysis of the Society for Assisted Reproductive Technology database. *Fertil Steril* 2013; 100:392-395.

Grady R, Alavi N, Vale R et al. Elective single embryo transfer and perinatal outcomes: a systematic review and meta-analysis. *Fertil Steril* 2012;97:324–31.

Griffo J, Hodes-Wertz B, Lee H-L. Single thawed euploid embryo transfer improves IVF pregnancy, miscarriage, and multiple gestation outcomes and has similar implantation rates as egg donation. *J Assist Reprod Genet.* 2013 Feb;30(2):259-64.

Gurgan T, Kis xnis cxi H, Yarali H, et al. The value of human menopausal gonadotropin treatment in patients with unexplained infertility. *Int J Gynaecol Obstet* 1991;35:327–30.

Guzick DS, Sullivan MW, Adamson GD, et al. Efficacy of treatment for unexplained infertility. *Fertil Steril* 1998; 70; 207-213.

Guzick DS, Carson SA, Coutifaris C, et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network. *N Engl J Med* 1999;340:177–83.

Harris ID, Missmer SA, Hornstein MD: Poor success of gonadotropin-induced controlled ovarian hyperstimulation and intrauterine insemination for older women. *Fertil Steril* 2010;94:144–148.

Helmerhorst FM, Van Vliet HA, Gornas T, et al. Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples. *Cochrane Database Syst Rev.* 2005 Oct 9;(4):CD002809.

Hendriks DJ, Mol, Laszlo BJ, Bancsi FJ, et al. The Clomiphene Citrate challenge test for the prediction of poor ovarian response and nonpregnancy in patients undergoing in vitro fertilization: a systematic review. *Fertil Steril* 2006; 86; 807-818.

Henman M, Catt JW, Wood T, et al. Elective transfer of single fresh blastocysts and later transfer of cryostored blastocysts reduces the twin pregnancy rate and can improve the in vitro fertilization live birth rate in younger women. *Fertil Steril* 2005;84:1620–7.

Hill MJ, Richter KS, Heitmann RJ et al. Number of supernumerary vitrified blastocysts is positively correlated with implantation and live birth in single-blastocyst embryo transfers. *Fertil Steril* 2013;99:1631–6.

Homer HA, Li TC, Cooke ID. The septate uterus: a review of management and reproductive outcome. *Fertil Steril* 2000;73:1–14.

Honore GM, Holden AE, Schenken RS. Pathophysiology and management of proximal tubal blockage. *Fertil Steril* 1999;5:785–95.

Intracytoplasmic sperm injection (ICSI) in 2006: evidence and evolution. *Hum Reprod Update* 2007;13:515–26.

- Ishihara O, Araki R, Kuwahara A, Itakura A, Saito H, Adamson GD. Impact of frozen-thawed single-blastocyst transfer on maternal and neonatal outcome: an analysis of 277,042 single-embryo transfer cycles from 2008 to 2010 in Japan. *Fertil Steril* 2014;101:128–33.
- Jacobson TZ, Duffy JM, Barlow D, et al. Laparoscopic surgery for subfertility associated with endometriosis. *Cochrane Database Syst Rev* 2010:CD001398.
- Jaffe T, Oates RD. Genetic abnormalities and reproductive failure. In: Lipshultz LI, ed. *Urologic clinics of North America*. Philadelphia: W.B. Saunders Company, 1994.
- Johnson N, Vanderkerchove P, Lilford R, et al. Tubal flushing for subfertility. *Cochrane Database Syst Rev* 2009;1:CD003718.
- Johnson LNC, Sasson IE, Sammel MD and Dokras A: Does intracytoplasmic sperm injection (ICSI) improve the fertilization rate and decrease the total fertilization failure rate in couples with well-defined unexplained infertility? *Fertil Steril* 2012;98: S286.
- Johnston J, Gusmano MK. Why we should all pay for fertility treatment: an argument from ethics and policy. *Hastings Cent Rep* 2013;43(2):18-21.
- Jun SH, Ginsurg ES, Racowsky C, et al. Uterine leiomyomas and their effect on in vitro fertilization outcome. *J Assist Reprod Genet* 2001;18:139–43.
- Kalra SK, Ratcliffe SJ, Coutifaris C, Molinaro T, Barnhart KT. Ovarian stimulation and low birth weight in newborns conceived through in vitro fertilization. *Obstet Gynecol* 2011;118:863–71.
- Kastrop PM, Weima SM, Van Kooij RJ, Te Velde ER. Comparison between intracytoplasmic sperm injection and in-vitro fertilization (IVF) with high insemination concentration after total fertilization failure in a previous IVF attempt. *Hum Reprod* 1999;14:65–9.
- Kato K, Takehara Y, Segawa T et al. Minimal ovarian stimulation combined with elective single embryo transfer policy: age-specific results of a large, single-centre, Japanese cohort. *Reproductive Biology and Endocrinology* 2012,10:35.
- Kim HH, Bundorf MK, Behr B, McCallum SW. Use and outcomes of intracytoplasmic sperm injection for non-male factor infertility. *Fertil Steril* 2007;88:622–8.
- Kirby CA, Flaherty SP, Godfrey BM, Warnes GM, Matthews CD. A prospective trial of intrauterine insemination of motile spermatozoa versus timed intercourse. *Fertil Steril* 1991;56:102-7.
- Klatsky PC, Lane DE, Ryan IP, et al. The effect of fibroids without cavity involvement on ART outcomes independent of ovarian age. *Hum Reprod* 2007;22:521–6.
- Kolibianakis EM, Fatemi HM, Osmanagaoglu K, et al. Is endometrial thickness, assessed on the day of HCG administration, predictive of ongoing pregnancy in patients undergoing intrauterine insemination after ovarian stimulation with clomiphene citrate? *Fertil Steril* 2002;78 Suppl 1:S151-S152.
- Kontoravdis A, Makrakis E, Pantos K, et al. Proximal tubal occlusion and salpingectomy result in similar improvement in in vitro fertilization outcome in patients with hydrosalpinx. *Fertil Steril* 2006;86:1642–9.
- Kresowik J, Stegmann B, Sparks AE et al. Five-years of a mandatory single-embryo transfer (mSET) policy dramatically reduces twinning rate without lowering pregnancy rates. *Fertil Steril* 2011;96:1367–9.
- Lavergne N, Aristizabal J, Zarka V, et al. Uterine anomalies and in vitro fertilization: what are the results? *Eur J Obstet Gynecol Reprod Biol* 1996;68:29–34.
- Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *NEJM* 2014;371:119-29.
- Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2013 Dec;98(12):4565-92.
- le Lannou D, Griveau JF, Laurent MC, et al. Contribution of embryo cryopreservation to elective single embryo transfer in IVF-ICSI. *Reprod Biomed Online* 2006;13:368–75.
- Lewis V, Queenan J, Hoeger K, et al. Clomiphene Citrate monitoring for intrauterine insemination: a randomized trial. *Fertil Steril* 2004; 85: 401-406.

Li Z, Wang YA, Ledger W, Edgar DH, Sullivan EA. Clinical outcomes following cryopreservation of blastocysts by vitrification or slow freezing: a population-based cohort study. *Hum Reprod* 2014;29:2794–801.

Liu KE, Case A. Advanced reproductive age and fertility. (No. 346). *Journal of Obstetrics and Gynaecology Canada* 2017;39(8):685-695. DOI: 10.1016/j.jogc.2016.12.004. (Reaffirmed 2018 May)

Luna M, Bigelow C, Duke M, Ruman J, Sandler B, Grunfeld L, Copperman AB. Should ICSI be recommended routinely in patients with four or fewer oocytes retrieved? *J Assist Reprod Genet* 2011;28(10):911–5.

Luna M, Grunfeld L, Mukherjee T, et al. Moderately elevated levels of basal follicle-stimulating hormone in young patients predict low ovarian response, but should not be used to disqualify patients from attempting in vitro fertilization. *Fertil Steril* 2007;87:782–787.

Maheshwari A, Pandey S, Shetty A, Hamilton M, Bhattacharya S. Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis. *Fertil Steril* 2012;98:368–377.e1-9.

McClamrock HD, Jones HW Jr., Adashi, EY. Ovarian stimulation and intrauterine insemination at the quarter centennial: implications for the multiple births epidemic. *Fertil Steril* 2012;97:802–9.

MCG, 23<sup>rd</sup> edition, Ambulatory Care, 2019.

McLernon DJ, Harrild K, Bergh C et al. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. *BMJ* 2010;341:c6945.

Merck & Co, Inc., Whitehouse Station, NJ Follistim® AQ (follitropin beta injection) prescribing information. Available at: [https://www.merck.com/product/usa/pi\\_circulars/f/follistim\\_aq\\_cartridge/follistim\\_cartridge\\_pi.pdf](https://www.merck.com/product/usa/pi_circulars/f/follistim_aq_cartridge/follistim_cartridge_pi.pdf)

Merviel P, Heraud MH, Grenier N, et al. Predictive factors for pregnancy after intrauterine insemination (IUI): An analysis of 1038 cycles and a review of the literature. *Fertil Steril* 2010;93:79–88.

Misso ML, Wong JL, Teede HJ, Hart R, Rombauts L, Melder AM. Aromatase inhibitors for PCOS: a systematic review and meta-analysis. *Hum Reprod Update* 2012;18:301–12.

Mol BW, Collins JA, Burrows EA, et al. Comparison of hysterosalpingography and laparoscopy in predicting fertility outcome. *Hum Reprod* 1999;14:1237–42.

Mullin CM, Fino ME, Talebjan S et al. Comparison of pregnancy outcomes in elective single blastocyst transfer versus double blastocyst transfer stratified by age. *Fertility and Sterility* 2010; 93: 1837-1843.

Mullin C, Berkeley AS, Grifo JA. Supernumerary blastocyst cryopreservation: a key prognostic indicator for patients opting for an elective single blastocyst transfer (eSBT). *J Assist Reprod Genet* 2012;29:783–8.

Munro MG, Critchley HO, Frasaer IS, FIGO Menstrual Disorders Working Group. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. *Fertil Steril* 2011 Jun;95(7):2204-8.

Nackley AC, Muasher SJ. The significance of hydrosalpinx in in vitro fertilization. *Fertil Steril* 1998;69:373–84.

Nakashima A, Araki R, Tani H, Ishihara O, Kuwahara A, Irahara M, et al. Implications of assisted reproductive technologies on term singleton birth weight: an analysis of 25,777 children in the national assisted reproduction registry of Japan. *Fertil Steril* 2013;99:450–5.

Nardo LG, Gelbaya TA, Wilkinson H, et al. Circulating basal anti Müllerian hormone levels as predictor of ovarian response in females undergoing ovarian stimulation for in vitro fertilization. *Fertil Steril* 2009;92:1586-1593.

Nargund G, Datta AK and Fauser BCJM. Mild Stimulation for in vitro fertilization. *Fertil Steril* 2017;108: 558-67.

Nezhat C, Crowgey S, Nezhat F. Videolaseroscopy for the treatment of endometriosis associated with infertility. *Fertil Steril* 1989;51:237–240.

Niinimäki M, Suikkari AM, Makinen S et al. Elective single-embryo transfer in women aged 40–44 years. *Human Reproduction* 2013;28:331–335.

NLM. National Library of Medicine, <http://www.nlm.nih.gov/medlineplus/ency/article/003710.htm>.

Nicopoulos JD and Abdalla H. Poor response cycles: when should we cancel? Comparison of outcome between egg collection, intrauterine insemination conversion, and follow-up cycles after abandonment. *Fertil Steril* 2011;95:68–71.



- Norian JM, Levens ED, Richter KS, et al. Conversion from assisted reproductive technology to intrauterine insemination in low responders: Is it advantageous. *Fertil Steril* 2010; 94:2073-7.
- Nulsen JC, Walsh S, Dumez S et al. A randomized and longitudinal study of human menopausal gonadotropin with intrauterine insemination in the treatment of infertility. *Obstet Gynecol* 1993; 82:780–786.
- Nuojua-Huttunen S, Tomas C, Bloigu R, et al. Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome. *Hum Reprod* 1999;14:698–703.
- Olive DL & Pritts EA. Fibroids and reproduction. *Semin Reprod Med*. 2010 May;28(3):218-27.
- Opøien HK, Fedorcsak P, Byholm T et al. Complete surgical removal of minimal and mild endometriosis improves outcome of subsequent IVF/ICSI treatment. *Reprod Biomed Online* 2011; 23:389–395.
- Osuna C, Matorras R, Pijoin IJ, et al. One versus two inseminations per cycle in intrauterine insemination with sperm from patients' husbands: a systematic review of the literature. *Fertil Steril* 2004; 82:17-24.
- Pabuccu R, Gomel V. Reproductive outcome after hysteroscopic metroplasty in women with septate uterus and otherwise unexplained infertility. *Fertil Steril* 2004;81:1675–8.
- Pal L, Jindal S, Witt B, Santoro N. Less is more: increased gonadotropin use for ovarian stimulation adversely influences clinical pregnancy and live birth after in vitro fertilization. *Fertil Steril*. 2008 Jun;89(6):1694-701.
- Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet* 1999;340:17–8.
- Pandian Z, Marjoribanks J, Ozturk O, et al. Number of embryos for transfer following in vitro fertilization or intracytoplasmic sperm injection: summary of a Cochrane review. *Fertil Steril*. 2014 Aug;102(2):345–7.
- Pandian Z, Bhattacharya S, Ozturk O, Serour G, Templeton A. Number of embryos for transfer following in-vitro fertilization or intra-cytoplasmic sperm injection. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD003416. DOI: 10.1002/14651858.CD003416.pub3.
- Papaleo E, Ottolina J, Viganò P, et al. Deep pelvic endometriosis negatively affects ovarian reserve and the number of oocytes retrieved for in vitro fertilization. *Acta Obstet Gynecol Scand* 2011;90:878–884.
- Papanikolaou EG, Camus D, Kolibianakis EM, et al. In vitro fertilization with single blastocyst-stage versus cleavage-stage embryos. *N Engl J Med*. 2006;354:1139–1146.
- Papanikolaou EG, Kolibianakis EM, Tournaye H, et al. Live birth rates after transfer of equal number of blastocysts or cleavage-stage embryos in IVF. A systematic review and meta-analysis. *Hum Reprod* 2008;23:91–99.
- Perez-Medina T, Bajo-Arenas J, Salazar F, et al. Endometrial polyps and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. *Hum Reprod* 2005;20:1632–5.
- Persson PS, Ahren C, Obrant KO. Aspiration biopsy smear of testis in azoospermia: Cytological versus histological examination. *Scand J Urol Nephrol* 1971;5:22–6.
- Pinto AB, Hovsepian DM, Wattanakupornkul S, et al. Pregnancy outcomes after fallopian tube recanalization: oil-based versus water-soluble contrast agents. *J Vasc Interv Radiol* 2003;14:69–74.
- Polyzos N, Blockeel C, Verpoest W, et al. Live birth rates following natural cycle IVF in women with poor ovarian response according to the Bologna criteria. *Hum Reprod* 2012;27S:30.
- Practice Committee of the American Society for Reproductive Medicine: Elective single embryo transfer. *Fertil Steril* 2012;97:835–42.
- Practice Committee of the American Society for Reproductive Medicine: Criteria for number of embryos to transfer: a committee opinion. *Fertil Steril* 2013;99:44–6.
- Practice Committee of American Society for Reproductive Medicine and the Practice Committee of Society for Assisted Reproductive Technology. Recommendations for gamete and embryo donation: a committee opinion. *Fertil Steril* 2013;99:47–62.
- Practice Committee of the American Society for Reproductive Medicine and Practice Committee of the Society for Assisted Reproductive Technology. Recommendations for practices utilizing gestational carriers: a committee opinion. *Fertil Steril* 2017;107: e3–10.

- Raga F, Bauset C, Remohi J, et al. Reproductive impact of congenital Mullerian anomalies. *Hum Reprod* 1997;12:2277–2281.
- Reichman DE, Gunnala V, Meyer L, et al. In vitro fertilization versus conversion to intrauterine insemination in the setting of three or fewer follicles: how should patients proceed when follicular response falls short of expectation? *Fertil Steril* 2013;100:94–9.
- Reilly DR. Surrogate pregnancy: a guide for Canadian prenatal health care providers. *CMAJ* 2007;176:483–485.
- Reindollar RH, Regan MM, Neumann PJ, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. *Fertil Steril* 2010;94:888–99.
- Reindollar RH, Thornton KL, Ryley D, et al. A randomized clinical trial to determine optimal infertility therapy in couples when the female partner is 38-42 years: preliminary results from the forty and over infertility treatment trial (FORT-T). *Fertil Steril* 2011;96:S1.
- Rienzi L, Cobo A, Paffoni A, Scarduelli C, Capalbo A, Vajta G, et al. Consistent and predictable delivery rates after oocyte vitrification: an observational longitudinal cohort multicentric study. *Hum Reprod* 2012;27:1606–12.
- Roest J, Van Heusden AM, Zeilmaker GH, Verhoeff A. Treatment policy after poor fertilization in the first IVF cycle. *J Assist Reprod Genet* 1998;15:18–21.
- Roque M, Valle M, Guimaraes F, Sampaio M, Geber S. Cost-effectiveness of the freeze-all policy. *JBRA Assist Reprod* 2015a;19:125–130.
- Rosen MP, Johnstone E, Addauan-Andersen C, et al. A lower antral follicle count is associated with infertility. *Fertil Steril* 2011; 95: 1950-52.
- Richter KS, Shipley SK, McVeary I, et al. Cryopreserved embryo transfers suggest that endometrial receptivity may contribute to reduced success rates of later developing embryos. *Fertil Steril* 2006;86:862–6.
- Sahakyan M, Harlow BL, Hornstein MD. Influence of age, diagnosis, and cycle number on pregnancy rates with gonadotropin-induced controlled ovarian hyperstimulation and intrauterine insemination. *Fertil Steril* 1999; 72: 500-504.
- Salame Y, Devreker F, Imbert R et al. Contribution of cryopreservation in a mandatory SET policy: analysis of 5 years of application of law in an academic IVF center. *J Assist Reprod Genet* 2011; 28:1059–1066.
- SART - Society for Assisted Reproductive Technology: National Clinic Summary, 2016. [https://www.sartcorsonline.com/rptCSR\\_PublicMultYear.aspx?reportingYear=2016](https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2016).
- Schimberni M, Morgia F, Colabianchi J, et al. Natural cycle in vitro fertilization in poor responder patients: a survey of 500 consecutive cycles *Fertil Steril* 2009; 92: 1297-1301.
- Schlegel PN, Su LM. Physiologic consequences of testicular sperm extraction. *Hum Reprod* 1997;12:1688–92.
- Schlegel PN. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. *Hum Reprod* 1999;14:131-5.
- Schlegel PN, Berkeley AS, Goldstein M, Cohen J, Alikani M, Adler A, et al. Epididymal micropuncture with in vitro fertilization and oocyte micromanipulation for the treatment of unreconstructable obstructive azoospermia. *Fertil Steril* 1994;61:895–901.
- Schwarze JE, Crosby JA, Zegers-Hochschild F. Effect of embryo freezing on perinatal outcome after assisted reproduction techniques: lessons from the Latin American Registry of Assisted Reproduction. *Reprod Biomed Online* 2015;31:39–43.
- Schwarzler P, Zech H, Auer M, Pfau K, Gobel G, Vanderzwalmen P, et al. Pregnancy outcome after blastocyst transfer as compared to early cleavage stage embryo transfer. *Hum Reprod*. 2004;19:2097–2102.
- Scott, RT. Diminished ovarian reserve and access to care. *Fertil Steril* 2004; 81:1489-1492.
- Shapiro BS, Daneshmand ST, Garner FC, et al. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. *Fertil Steril* 2011;96:344–348.
- Shapiro BS, Daneshmand ST, Restrepo H, et al. Matched-cohort comparison of single-embryo transfers in fresh and frozen-thawed embryo transfer cycles *Fertil Steril* 2013;99:389–92.



Shapiro BS, Harris DC, Richter KS. Predictive value of 72-hour blastomere cell number on blastocyst development and success of subsequent transfer based on the degree of blastocyst development. *Fertil Steril* 2000;73:582–6.

Shapiro BS, Richter KS, Harris DC, Daneshmand ST. Influence of patient age on the growth and transfer of blastocyst-stage embryos. *Fertil Steril* 2002;77:700–5.

Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Embryo cryopreservation rescues cycles with premature luteinization. *Fertil Steril* 2010;93:636–41.

Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. *Fertil Steril* 2011; 96:344–8.

Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: A prospective randomized trial comparing fresh and frozen-thawed embryo transfers in high responders. *Fertil Steril* 2011;96: 516–8.

Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Clinical rationale for cryopreservation of entire embryo cohorts in lieu of fresh transfer. *Fertil Steril* 2014a;102:3–9.

Shapiro BS, Daneshmand ST, Bedient CE, Gaarner FC. Comparison of birth weights in patients randomly assigned to fresh or frozen-thawed embryo transfer *Fertil Steril* 2016;106:317-21

Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Frozen embryo transfer following 'Freeze All' is a superior therapy to another fresh transfer in patients with prior fresh embryo implantation failure. *Fertil Steril* 2014b;101:e6.

Sheynkin YR, Ye Z, Menendez S, Liotta D, Veeck LL, Schlegel P. Controlled comparison of percutaneous and microsurgical sperm retrieval in men with obstructive azoospermia. *Hum Reprod* 1998;13:3086–9.

Society for Assisted Reproductive Technology: National Data Summary 2011. Available at: [https://www.sartcorsonline.com/rptCSR\\_PublicMultYear.aspx?ClinicPKID=0](https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?ClinicPKID=0).

Steiner AZ, Prtichard D, Stanczyk FZ, et al. Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. *JAMA* 2017; 318: 1367-1376.

Strandell A, Lindhard A, Waldenstrom U, et al. Hydrosalpinx and IVF outcome: a prospective, randomized multicentre trial in Scandinavia on salpingectomy prior to IVF. *Hum Reprod* 1999;14:2762–9.

Sunderam S, Kissin DM, Flowers L et al. Assisted reproductive technology surveillance--United States, 2009. *MMWR Surveill Summ* 2012;61(7):1-23.

Surrey ES, Lietz AK, Schoolcraft WB. Impact of intramural leiomyomata in patients with a normal endometrial cavity on in vitro fertilization. *Fertil Steril* 2001;75:405–10.

Takehima K, Jwa SC, Saito H, et al. Impact of single embryo transfer policy on perinatal outcomes in fresh and frozen cycles—analysis of the Japanese Assisted Reproduction Technology registry between 2007 and 2012. *Fertil Steril* 2016 Feb;105(2):337–46.

Taylor E, Gomel V. The uterus and fertility. *Fertil Steril* 2008; 89: 1-16.

Thornhill AR, deDie-Smulders CE, Geraedts JP, Harper JC, Harton GL, et al. ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)'. *Hum Reprod* 2005;20:35–48.

Thurin A, Hausken J, Hillensjo T, Jablonowska B, Pinborg A, Strandell A, et al. Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization. *N Engl J Med*. 2004;351:2392–2402.

Tonguc E, Var T, Onalan G, et al. Comparison of the effectiveness of single versus double intrauterine insemination with three different timing regimens. *Fertil Steril* 2010; 94: 1267-70.

Tournaye H, Devroey P, Liu J, Nagy Z, Lissens W, Van Steirteghem A. Microsurgical epididymal sperm aspiration and intracytoplasmic sperm injection: a new effective approach to infertility as a result of congenital absence of the vas deferens. *Fertil Steril* 1994;61:1045–51.

Tucker M, Graham J, Han T, Stillman R, Levy M. Conventional insemination versus intracytoplasmic sperm injection. *Lancet* 2001;358:1645–6.

- Tulandi T, Martin J, Al-fadhli R, Kabli N, Forman R, Hitkari J, et al. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. *Fertil Steril* 2006;85:1761–5.
- Tummon IS, Asher LJ, Martin JS et al. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. *Fertil Steril* 1997; 68:8–12.
- Ubaldi F, Anniballo R, Romano S, Baroni E, Albricci L, Colamaria S, et al. Cumulative ongoing pregnancy rate achieved with oocyte vitrification and cleavage stage transfer without embryo selection in a standard infertility program. *Hum Reprod* 2010;25:1199–205.
- Van der Westerlaken, Helmerhorst F, Dieben S, Naaktgeboren N. Intracytoplasmic sperm injection as treatment for unexplained total fertilization failure or low fertilization after conventional in vitro fertilization. *Fertil Steril* 2005;83:612–7.
- Van Voorhis BJ, Stovall DW, Allen BD, et al. Cost-effective treatment of the infertile couple. *Fertil Steril* 1998; 70: 995-1005.
- Vercellini P, Fedele L, Aimi G, et al. Reproductive performance, pain recurrence and disease relapse after conservative surgical treatment for endometriosis: the predictive value of the current classification system. *Hum Reprod* 2006;21:2679–2685.
- Wang W, Check JH. Effect of corporal fibroids on outcome following embryo transfer in donor-oocyte recipients. *Clin Exp Obstet Gynecol* 2004;31:263–4.
- Wiser A, et al. Ovarian stimulation and intrauterine insemination in women aged 40 years or more. *Reproductive Biomedicine Online* 2012;24(2):170-3.
- van Montfoort AP, Fiddelaers AA, Janssen JM, Derhaag G, Dirksen C, Dunselman G, et al. In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double embryo transfer: a randomized controlled trial. *Hum Reprod* 2006;21:338–43.
- Van Tilborg TC, Torrance HL, Oudshoorn SC, et al. Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 1: The predicted poor responder. *Human Reprod* 2017; 32:2496-505.
- Van Wely M, Barbey N, Meissner A, Repping S, Silber S. Live birth rates after MESA or TESE in men with obstructive azoospermia: is there a difference?, *Hum Reprod* 2015;30:761-766.
- Vuong LN, Dang VQ, Ho TM, Huynh BG, Ha DT, Pham TD, et al. IVF transfer of fresh or frozen embryos in women without polycystic ovaries. *N Engl J Med* 2018;378:137–47.
- Wennerholm UB, Henningsen AK, Romundstad LB, Bergh C, Pinborg A, Skjaerven R, et al. Perinatal outcomes of children born after frozen thawed embryo transfer: a Nordic cohort study from the CoNARTaS group. *Hum Reprod* 2013;28:2545–53.
- Weinerman R, Mainigi M. Why we should transfer frozen instead of fresh embryos: the translational rationale. *Fertil Steril* 2014;102:10–18.
- World Health Organization. WHO Laboratory Manual for the Examination of Human Semen and Semen-Cervical Mucus Interaction. 4<sup>th</sup> ed. Cambridge: Cambridge University Press; 1999. pp. 1–86.
- Yarali H, Bukulmez O. The effect of intramural and subserous uterine fibroids on implantation and clinical pregnancy rates in patients having intracytoplasmic sperm injection. *Arch Gynecol Obstet* 2002;266:30–3.
- Youseff M A-F; van Wiley M, Mochtar M, et al: Low dosing of gonadotropins in in vitro fertilization cycles for women with poor ovarian reserve: systematic review and meta-analysis. *Fertil Steril* 2018; 109: 289-301.
- Zacca C, Bazzochi A, Pennetta F, et al: Cumulative live birth rate in freeze-all cycles is comparable to that of a conventional embryo transfer policy at the cleavage stage but superior at the blastocyst stage. *Fertil Steril* 2018; 110:703-9.
- Zech NH, Lejeune B, Puissant F, et al. Prospective evaluation of the optimal time for selecting a single embryo for transfer: day 3 versus day 5. *Fertil Steril* 2007;88:244–6.
- Zeyneloglu HB, Arici A, Olive D. Adverse effects of hydrosalpinx on pregnancy rates after in vitro fertilization-embryo transfer. *Fertil Steril* 1998;70:492–9.
- Zhu D, Zhang J, Cao S, Zhang J, Heng BC, Huang M, et al. Vitrified-warmed blastocyst transfer cycles yield higher pregnancy and implantation rates compared with fresh blastocyst transfer cycles—time for a new embryo transfer strategy? *Fertil Steril* 2011;95:1691–5.



### Revision History

The following are approved changes incorporated into the revision numbers indicated below.

Revision	Date	Description of Change
1.0	12/01/2013	New medical necessity document (CE)
1.1	12/05/2013	Confidentiality statement added to footer (LW)
1.2	01/30/2014	Minor edits made to verbiage per EP recommendations. (CE)
2.0	02/26/2014	Infertility Surgery and eSET incorporated into this document. (CE)
2.1	06/26/2014	Minor edits made to verbiage and clarification of age groups for applicable ART cycles per AD. (CE)
2.1	07/14/2014	Governing control number of document changed from PR4069 to PR4221.(CE)
3.0	07/14/2014	Updated by AD with new information on letrozole. (LW)
3.1	10/13/2014	Minor changes to guideline verbiage by AD. (CE)
4.0	07/09/2015	Guideline review and update by AD. New information on tubal factor infertility, letrozole, thin endometrial lining, PCOS and teratospermia added. (CE)
4.1	10/02/2015	Clinical evidence and references updated by AD. (CE)
5.0	05/05/2016	Policy revision with additional indications for use of letrozole, gonadotropins, eSET and use of preimplantation genetic testing by AD. (LW)
5.1	06/22/2016	Minor changes to guideline verbiage by AD. (MB)
5.2	09/12/2016	Clarification on cycle limitations, removal of PCOS Rotterdam criteria and clarification on when tubal and/or endometriosis surgery is not covered by AD. (MB)
6.0	05/04/2017	Guideline review and revision with revised antral follicle count as part of consideration for infertility treatment, addition of FSH and age parameters to define very poor/futile prognosis, addition of age parameters for autologous and donor oocytes in ART, and clarification on coverage of therapeutic donor insemination, IUI with moderate or severe endometriosis, and ART with repeat pregnancy loss by AD. (MB)
7.0	05/03/2018	Annual review with revisions by AD. SART data was updated, post-coital test indications were revised, FSH, AMH and antral count levels as infertility indicators were revised, ICSI information added, eSET cycles for women aged 41-42 were revised, information on multiple cleavage stage embryo transfers was revised, verbiage of no infertility benefits for autologous oocytes in females $\geq 44$ years was added, non-indications for IUI and donor insemination were revised, additional information on natural cycle IUI has been provided. (CE)
7.1	10/01/2018	Replaces JA22214780. (CE)
8.0	08/27/2018	Interim review with revisions by AD. Information on Gestational Carrier added, clarification that natural cycle IVF is not indicated after failure of two natural cycle ART attempts, definition of infertility expanded and age for ART

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		updated. (CE)
9.0	06/26/2019	Guideline review with revisions by AD. Added information on surgical sperm aspiration, cryopreservation, non-indication in controlled ovarian stimulation, markers of ovarian reserve, indication for natural cycle IUI, isolated teratospermia as non-indication in IUI and ICSI, indication for pre-implantation genetic testing, 14-day gonadotropin stimulation for hypothalamic amenorrhea and lack of benefit for ovulation induction in IUI for PCOS. Revised FSH levels as indication or poor prognosis and fertility, definition of mild male factor infertility and terminology of pre-implantation genetic testing. Removed allowance for a controlled ovarian stimulation and IUI cycle for women $\geq$ 40 years of age. Clarified male factor infertility indication in natural cycle IUI and unilateral tubal factor infertility in IUI. (CE)
9.1	12/10/2019	Isolated teratospermia added to male factor infertility definition. (CE)
10.0	02/11/2020	Guideline update by AD. Added information to infertility definition section applicable to artificial donor insemination for females without male partners who otherwise do not have an identified infertility factor. (CE)