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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.

Background	<p>I. <u>Infertility</u></p> <ul style="list-style-type: none">• Definition:<ul style="list-style-type: none">○ A disease (an interruption, cessation, or disorder of body functions, systems, or organs) of the reproductive tract which prevents the conception of a child or the ability to carry a pregnancy to delivery. It is defined by the failure to achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or Therapeutic Donor Insemination. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women aged 35 years or older.○ 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 when an individual is actively attempting to achieve a conception.○ 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)○ 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) <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 <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">• 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.• The cause of infertility cannot be determined in up to 10-20% of couples.• Female factors can further be divided into tubal (40%), ovulatory (40%), uterine (10%) and cervical (10%).• Cigarette smoking adversely affects fertility.
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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.
- 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 2019 demonstrates that the cumulative live birth per intended retrieval resulting in live births decreased progressively from:
 - 55.0% in females younger than 35 years;
 - 41.0% for females aged 35-37 years;
 - 26.8% for females aged 38-40 years;
 - 13.4% for females aged 41-42; and
 - 4.14% 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, 2020)
- 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/moderate male factor infertility
 - Unexplained infertility
 - Diminished ovarian reserve
 - Minimal or mild endometriosis
- 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 (unless otherwise indicated) 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; ASRM, 2020)
- 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, 2019)

- FSH level ≥ 15 mIU/ml; OR
- AMH level < 0.2 ng/ml (LaMarca, 2013); OR
- Antral follicle count < 3 (ASRM, 2021(a); LaMarca, 2013).
- 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

Individualized consideration should be given at all times to all parameters of ovarian reserve and the overall clinical picture.

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; ASRM, 2020)
- 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 peritubal 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 ≥ 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, 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, 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, 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 cryopreservation.

Approximately 5%-10% of males evaluated for infertility are azoospermic. (Schlegel,

	<p>1997; Schlegel, 1999)</p> <p><u>XII. Immune Therapies in Conjunction with ART</u></p> <p>There is a common belief that the maternal immune system is damaging in early pregnancy and needs suppressing. However, there is no high-quality evidence to support this notion, and the classical features of inflammation are not seen in decidua in early pregnancy.</p>
<p>General Indications</p>	<p>General Indications for Initial and Continuation of Infertility Treatment Coverage</p> <p>The below general infertility criteria are to be met for consideration of treatment:</p> <ul style="list-style-type: none"> • <u>Prognosis for conception must be $\geq 5\%$; AND</u> • No evidence of very poor or futile prognosis. Markers of very poor or futile prognosis include but are not limited to two or more of the following: <ul style="list-style-type: none"> ○ FSH level ≥ 15 mIU/ml ; OR ○ AMH level < 0.2 ng/ml (LaMarca, 2013); OR ○ Antral follicle count < 3 (ASRM, 2021(a);LaMarca, 2013); OR ○ The risk for aneuploidy for all embryos is $\geq 85\%$; AND • 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"> ○ 1 follicle ≥ 15 mm diameter for IUI ○ Minimum of 1 follicle ≥ 15 mm diameter for ART ○ [See also: Ovulation Induction, Ovarian Stimulation, ART] <p>Individualized consideration should be given at all times to all parameters of ovarian reserve and the overall clinical picture.</p> <ul style="list-style-type: none"> • Diminished ovarian reserve may be recognized by: <ul style="list-style-type: none"> ○ FSH level ≥ 10 mIU/ml; OR ○ AMH level < 1.0 ng/ml; OR ○ Antral follicle count < 7 (ASRM, 2021(a)). <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"> • Unexplained infertility: Two abnormal semen analyses (abnormal count and/or motility), ovulatory dysfunction; diminished ovarian reserve; compromise of the fallopian tubes; documented untreated or recurrent endometriosis; sexual dysfunction; abnormalities of the cervix or uterus that may interfere with conception. <p>Treatment (not including the use of a traditional surrogate or gestational carrier) <u>is not indicated</u> for females at significant risk for severe obstetrical or medical complications associated with carrying a pregnancy.</p> <p>The general infertility surgery criteria as listed below are to be met for consideration of treatment:</p> <ul style="list-style-type: none"> • Pelvic pain that is not responsive to conservative management; OR • Presence of a pelvic mass for which gynecologic diagnosis warrants surgical intervention; OR

	<ul style="list-style-type: none"> 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. <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 <35 and 6 months for individuals ≥ 35 years of age.</p> <p>[See also: Tubal Surgery and Surgery for Endometriosis]</p>
<p>Treatment Criteria</p>	<p><u>Ovulation Induction</u></p> <p>Ovulation induction is not indicated beyond the 6th ovulatory cycle regardless of which drug or combinations of drugs have been administered.</p> <p>[See also: IUI]</p> <p>A. Clomiphene citrate (Clomid[®], Serophene[®])</p> <ol style="list-style-type: none"> Clomiphene citrate <u>is indicated</u> to treat females with ovulatory dysfunction in the following situations: <ul style="list-style-type: none"> <u>Anovulation</u>; OR <u>Oligo-ovulation</u>; OR <u>Amenorrhea</u>; AND Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated Clomiphene citrate <u>is not indicated</u> in the following situations: <ul style="list-style-type: none"> Beyond the 6th 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 ≥17 mm in diameter); OR An estradiol level <100 pg/ml/follicle ≥15 mm in diameter <p>B. Letrozole (Femara[®])</p> <ol style="list-style-type: none"> Letrozole <u>is indicated</u> to treat females with ovulatory dysfunction in the following situations: <ul style="list-style-type: none"> <u>Anovulation</u>; OR <u>Oligo-ovulation</u>; OR <u>Amenorrhea</u>; AND Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated. Letrozole <u>is not indicated</u> in the following situations: <ul style="list-style-type: none"> Beyond the 6th 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 ≥17 mm in diameter). <p>C. Tamoxifen (Nolvadex[®], Soltamox[®])</p> <ol style="list-style-type: none"> Tamoxifen <u>is indicated</u> to treat females with ovulatory dysfunction in the following situations: <ul style="list-style-type: none"> Anovulation; OR

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

D. 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 6th ovulatory cycle; **OR**
 - When there are ≥ 4 follicles which are ≥ 15 mm in diameter from a previously gonadotropin-induced ovulation, despite a dosage adjustment (e.g., doses of gonadotropin down to 37.5 IU per day); **OR**
 - When used alone for females with unexplained infertility; **OR**
 - When there is a failure to respond to ovarian stimulation, (e.g., doses of gonadotropins up to 225 IU per day and no follicles ≥ 15 mm in diameter) [See also: [ART](#), [gonadotropin dose](#)]; **OR**
 - In lieu of clomiphene or letrozole to correct a thin endometrial lining (Dietterich, 2004; Kolibianakis, 2002; Assante, 2013); **OR**
 - An estradiol level < 100 pg/ml/follicle ≥ 15 mm in diameter.
3. Gonadotropins are not indicated:
- In total doses that exceed 225 IU/day for ovulation induction; **OR**
 - For duration of therapy that exceeds 14 days per cycle.
 - A longer than 14 day stimulation may be considered in the setting of hypothalamic amenorrhea.

I. Ovarian Stimulation

Controlled ovarian stimulation is not indicated beyond the cycle limitations listed below regardless of which drug or combinations of drugs have been administered. Ultrasound monitoring for ovarian stimulation using oral medications in conjunction with IUI is not medically necessary. (ASRM, 2020)

A. **Clomiphene citrate, letrozole and Tamoxifen**

1. Clomiphene citrate, letrozole and Tamoxifen are indicated to treat females only when used in conjunction with intrauterine insemination (IUI) in the following situations:
 - With unexplained infertility; **OR**
 - Minimal or mild endometriosis; **OR**
 - Diminished ovarian reserve

2. Clomiphene citrate, letrozole and Tamoxifen are not indicated in the following situations:
 - When used alone (without IUI) to treat females with unexplained infertility, diminished ovarian reserve, bilateral tubal factor infertility, unilateral isthmic, ampullary, fimbrial or peritubal compromise (e.g., loculated spill, dilatation, phimosis, occlusion), endometriosis, male factor infertility or recurrent pregnancy loss (absent an ovulatory disorder) when used alone (without IUI) (ASRM) [See also: [Recurrent Pregnancy Loss and Gonadotropins, IUI and ART](#)]; **OR**
 - In the setting where natural cycle IUI is indicated; **OR**
 - Beyond 3 cycles (Farquhar, 2018; ASRM, 2020)[See also: [IUI cycle limitations](#)]; **OR**
 - In the setting of very poor/futile prognosis; **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**
 - 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.
 - Gonadotropins are not indicated when used in the setting of unexplained infertility, diminished ovarian reserve, endometriosis, or male factor infertility.

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 isthmic, ampullary, fimbrial or peritubal compromise (e.g., loculated spill, dilatation, phimosis,

occlusion), isolated male factor infertility or recurrent pregnancy loss (McClamrock, 2012; ESHRE, 2013) [See also: [Recurrent Pregnancy Loss and IUI, Clomid, Letrozole and Tamoxifen, ART](#)]; **OR**

- In lieu of clomiphene or letrozole or Tamoxifen 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 with gonadotropins, (e.g., doses of gonadotropins up to 150 IU per day and no follicles ≥ 15 mm in diameter); **OR**
- An estradiol level <100 pg/ml/follicle ≥ 15 mm in diameter); **OR**
- When there are ≥ 4 follicles which are ≥ 15 mm in diameter from a previously gonadotropin-induced ovulation, despite a dosage adjustment; **OR**
- Beyond 3 cycles (Farquhar, 2018; ASRM, 2020)[See also: [IUI cycle limitations](#)]; **OR**
- In the setting of very poor/futile prognosis; **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 [See also: [Gonadotropins for ART](#)]; **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.

II. 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 when required

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

1. Failure to conceive within 12 therapeutic donor insemination cycles in a female <35 years old; **OR**
2. Failure to conceive within 6 therapeutic 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. (Carpinello et al, 2021) (Cycle limitations apply for unexplained infertility, diminished ovarian reserve, minimal to mild endometriosis and tubal factor infertility.)

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

4. When there is ovulatory dysfunction absent concomitant diminished ovarian reserve. Ovulation induction/therapeutic cervical or intrauterine donor insemination is not indicated beyond the sixth ovulatory cycle when insemination is otherwise indicated.

[See also: [IUI and Ovarian Stimulation, Ovulation Induction](#)]

III. **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 (ASRM, 2020), 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 (<5 million sperm/ml or < 1 million motile sperm after sperm preparation)
 4. Ovulatory dysfunction (unless associated with diminished ovarian reserve or absence of a male partner) absent a concomitant male factor, sexual dysfunction or cervical trauma (AHRQ, 2019)
 5. Bilateral tubal factor infertility
 6. Unilateral isthmic, ampullary, fimbrial or peritubal compromise (e.g., loculated spill, dilatation, 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 (See also: [Recurrent Pregnancy Loss and Gonadotropins, Oral Medications and ART](#))
 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 3 cycles (ASRM, 2020)
 - In the setting of very poor/futile prognosis, **OR**
 - When the diagnosis is limited exclusively to teratospermia unless <2% 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.
11. In the setting of ovulation induction (absent diminished ovarian reserve) where IUI is otherwise indicated, including donor insemination:
- Beyond 6 cycles
12. In the setting of ART in the following situations:
- To convert an ART cycle to IUI when at least 2 follicles ≥ 15 mm in diameter are present (particularly in the setting of diminished ovarian reserve or on the 2nd or greater ART cycle when maximal dosage of gonadotropins are being used); **OR**
 - Following an ART cycle that fails to result in conception due to poor ovarian response or poor quality oocytes or embryos; **OR**
 - Following ≥ 2 ART cycles that have failed to result in a conception despite good quality oocytes or embryos. (Reichman, 2013)

IV. Assisted Reproductive Technologies (ART)

A. Assisted Reproductive Technologies (ART) are indicated for the following:

1. Unexplained infertility
2. Diminished ovarian reserve
3. Tubal factor infertility
4. Male factor infertility
5. Endometriosis
6. Ovulatory dysfunction
 - When ovulation induction has not resulted in conception
 - Poor response to ovulation induction
 - Hyper-response to ovulation induction where there is a risk for ovarian hyperstimulation or a multiple gestation
7. Failure to achieve conception with any other treatment modality

B. Assisted Reproductive Technologies (ART) are not indicated in the following situations:

1. When using autologous oocytes in the setting of a very poor or futile prognosis or when using autologous or donor oocytes in female recipients who are ≥ 55 years of age due to the obstetrical and medical risks of pregnancy. (ASRM (d))
2. When there is a failure to respond to ovarian stimulation (e.g., as demonstrated by failure to achieve at least 3 follicles > 12 mm in diameter); **OR**
3. ART cycle does not demonstrate the attainment of at least one (1) embryo suitable for transfer (**Note:** an additional cycle may be considered when

	<p>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); OR</p> <ol style="list-style-type: none"> 4. Lack of viable spermatozoa; OR 5. Ovarian failure where a couple is attempting conception with their own gametes; OR 6. Recurrent pregnancy loss except in the setting of recurrent aneuploidy or ≥ 5 unexplained losses [See also: Recurrent Pregnancy Loss and IUI, Gonadotropins and Clomid, Letrozole and Tamoxifen]; OR 7. Numerous ≥ 2 ART cycles without adequate egg quality or production, fertilization and/or embryo quality or development; OR 8. When using autologous oocytes in the setting of very poor/futile prognosis. 9. Gonadotropins are not indicated: <ul style="list-style-type: none"> • In total doses that exceed 450 IU/day for controlled ovarian stimulation for ART (Nargund 2017; van Tilborg 2017; Youseff 2018; Gerber 2020); OR • For duration of therapy that exceeds 14 days per cycle. <p>C. Natural (unstimulated) Cycle Assisted Reproductive Technologies (ART) <u>are indicated</u> for all females under the age of 35 and all patients' ≥ 35 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"> 1. In the setting of diminished ovarian reserve in females ≥ 35 years of age; OR 2. There have been not more than 2 natural ART cycle attempts with a failure to obtain an embryo suitable for transfer; OR 3. There has been a failure to attain a conception following two natural cycle intended retrieval cycle starts. <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"> 1. Avoidance of ovarian hyperstimulation syndrome; OR 2. For pre-implantation genetic testing for a monogenic disorder (PGT-M) or aneuploidy screening (PGT-A) or testing for structural rearrangements (PGT-SR); OR 3. For enhancing the uterine environment. <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. A fresh cycle is indicated when there are < 8 previously frozen oocytes (M2) as long as those oocytes are not being used in conjunction with a fresh cycle. (Optum Expert Panel, 2023)</p> <p>G. Intracytoplasmic Sperm Injection (ICSI)</p> <p>ICSI <u>is indicated</u> for the following:</p> <ol style="list-style-type: none"> 1. Male factor infertility <ul style="list-style-type: none"> • "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) 2. After failed conventional insemination (either complete failure or lower-than-
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expected rates (<50%). (Palermo et al, 1999; Benadiva et al, 1999; Katrop et al, 1999; Optum Infertility Expert Panel 2018)

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)

4. Cases of IVF using pre-implantation genetic testing for monogenic disorders, aneuploidy (when a covered benefit) or structural rearrangements (PGT-M, PGT-A, PGT-SR). (Tucker, 2001; Thornhill, 2005; ICSI in 2006: Evidence and Evolution. Hum Reprod Update, 2005)

5. When using previously cryopreserved oocytes.

6. When using TESE/PESE (surgically) derived sperm (Silber et al, 1994; Mercant et al, 2011)

ICSI is not indicated for the following:

1. Unexplained infertility (Foong, 2006)

2. Advanced maternal age (Kim, 2007)

3. Low oocyte yield (Kim, 2007)

4. Repeat IVF attempts after documented poor ovarian stimulation (Roest et al, 1998; Kinzer, 2008; Westerlaken, 2005)

5. Routine IVF (Bhattacharya, 2001; Geng, 2020)

6. When the diagnosis is limited exclusively to teratospermia unless <2% strict morphology has been demonstrated on at least two semen analyses.

7. In the setting of PGT-A unless PGT-A is a covered benefit or there are other indications for ICSI

8. Cumulus cell removal is part of the ICSI process (Optum Expert Panel, 2023)

Assisted Hatching: Assisted hatching is not indicated/medically necessary

Endometrial Preparation for Frozen/Thaw Embryo Transfer Cycles

- Oral or injectable estrogen is indicated
- Gonadotropins are not indicated for use in the preparation of the endometrial lining unless there has been a failure to achieve a sufficient endometrial thickness (>6 mm) or trilaminar pattern with conventional preparation methods (e.g., estrogen and progesterone) followed by a modified natural cycle using oral medications (clomiphene or letrozole). (Optum Expert Panel, 2023)

H. Cryopreservation

Embryo or mature oocyte cryopreservation when this is a covered benefit is indicated:

1. In the prevention of ovarian hyperstimulation syndrome

2. In the context of elective single embryo transfer to freeze and store supernumerary embryos or otherwise when there are supernumerary embryos

3. In the context of pre-implantation genetic testing, allowing for the return of test results

4. In the presence of poor endometrial development
 5. When there is a failure to obtain sperm at the time of a fresh ART cycle at egg retrieval
 6. In the context of freeze only cycles:
 - All embryos are cryopreserved with the intent for subsequent transfer within a 6 month time period
 7. Medically necessary oocyte, sperm or embryo cryopreservation for individuals facing gonadotoxic therapy when this is a covered benefit. This may include individuals facing prolonged hormonal ovarian suppression such that at the conclusion of treatment they would be at risk for a significant decrease in fecundity
 8. Sperm cryopreservation of medically necessary surgically obtained (TESE, PESE, etc.) sperm
- Embryo or mature oocyte cryopreservation is not indicated:
1. For the purpose of embryo or oocyte accumulation or banking
 2. For planned oocyte cryopreservation unless specifically covered in plan documents

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 (Grade BB or better) regardless of the female’s age; **OR**
 - Previous live birth after an IVF cycle.
 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 3rd full ART embryo transfer cycle if the prognosis is favorable for females < 35 years of age; **OR**
 - A euploid embryo (Grade BB or better) is available for transfer.
 - For patients between 35 and 37 years of age, strong consideration should be made for a single-embryo 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 (Grade BB or better) is available for transfer.
 - For patients between 38 and 40 years of age, no more than three untested cleavage stage embryos or two blastocysts should be transferred.
5. Patients 41-42 years of age should plan to receive no more than four untested cleavage stage embryos or three blastocysts.
6. In women >43 years of age, there are insufficient data to recommend a limit on the number of embryos to transfer when the patient uses her own oocytes. Caution should be exercised as the risk associated with multiple pregnancy increases dramatically with advancing maternal age.

Blastocyst Transfer

Age	<35	35-37	38-40	41-42	Euploid Embryo (Grade BB or better)
1 st cycle (fresh or frozen)	1	1	2	3	1
2nd cycle (fresh or frozen)	1	1	2	3	1
3rd cycle (fresh or frozen)	1	2	2	3	1
No favorable prognosis embryos	2	2	3	3	

- 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.

	<p>3. For females ≥ 38 years of age:</p> <ul style="list-style-type: none"> • 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 available. • Only 1 euploid blastocyst should be transferred. <p>C. Multiple cleavage stage embryo transfer <u>is indicated</u> in the following situations (ASRM 2017):</p> <ol style="list-style-type: none"> 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. <ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> • 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. <p><u>Adjunct Procedures</u></p> <p><u>Due to insufficient evidence of efficacy, the following are unproven and not medically necessary for treating infertility:</u></p> <ul style="list-style-type: none"> • Co-culture of embryos (ECRI, 2022; Le Saint, 2019) • Cryopreservation of <i>immature</i> oocytes (eggs), ovarian tissue, or testicular tissue (ASRM, 2013) • EmbryoGlue® (Yung, 2021; Heymann, 2020) • In vitro maturation (IVM) of oocytes (Zheng, 2022; Siristatidis, 2018) • Uterine/endometrial receptivity testing (Liu, 2022; Riestenberg, 2021) • Treatments to improve uterine/endometrial receptivity (e.g., immunotherapy, endometrial scratching, uterine artery vasodilation) (van Hoogenhuijze, 2021; Lensen, 2019) <p>The following unproven adjuncts <u>are not indicated</u> when used in conjunction with an ART cycle unless otherwise medically indicated: They include but are not limited to Dehydroepiandrosterone, Testosterone, Growth Hormone, Aspirin, Heparin, antioxidants for the female partner, seminal plasma, platelet-rich plasma, intravenous immune globulin (IVIG), intralipid.</p> <p>Reproductive medicine (endometrial receptivity analysis), RNA gene expression profile, 238 genes by next-generation sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation (e.g., pre-receptive,</p>
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receptive, post-receptive) is not indicated.

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 including Fragile X
 - 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 (PGT-M or PGT-SR). PGT-M and PGT-SR may be considered a covered expense if the fetus is at risk for a genetic disorder. The medical condition being prevented must result in Significant Health Problems or Severe Disability and be caused by a single gene (PGT-M) or structural changes of a parents’ chromosome (PGT-SR). Significant Health Problems or Severe Disability is defined as: A disability or impairment that is physical or mental and substantially limits one or more major life activities. The impairment is expected to last at least 12 months or result in death. (Department of Labor; Office of Disability Employment Policy; Federal Government Definition for Social Security Disability Benefits)
- C. Pre-implantation genetic testing for aneuploidy is not indicated.
- D. “Assisted Hatching” is part of the biopsy procedure. (Optum Expert Panel, 2023)

VIII. Gestational Carrier

The use of a gestational carrier 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 and warrants the need for an ART cycle to obtain an embryo(s) (ASRM, 2017; Dar, 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 [See also: [General Indications for 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
3. In the presence of a significant male factor.
4. In an individual pursuing ART.
5. To treat mid or distal tubal occlusion by tubal cannulation.
6. To treat severe hydrosalpinges by neosalpingostomy.
7. To perform a fimbrioplasty, salpingostomy or neosalpingostomy for severe tubal disease or concomitant proximal and distal tubal occlusion.
8. Prior to ART in order to improve the result of ART treatment (except to treat hydrosalpinges prior to an ART cycle).

C. Additional infertility treatment (e.g., controlled ovarian stimulation, IUI or ART) is not indicated within 6 months of tubal surgery unless additional infertility factors have been identified or there is recurrence of tubal compromise as documented by a postoperative hysterosalpingogram, laparoscopy, etc. This also applies to tubal cannulation for both unilateral and bilateral proximal occlusion when tubal patency has been reestablished. (ASRM, 2021)

X. Surgery for Endometriosis [See also: [General Indications for Surgery](#)]

- 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 6 months of surgery 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

	<p>uterine cavity (FIGO classification 3) (Munro, 2011)</p> <ul style="list-style-type: none"> • 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 <p>B. Uterine Surgery is not indicated in the following situations:</p> <ol style="list-style-type: none"> 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. <p>C. Additional infertility treatment (e.g., controlled ovarian stimulation, IUI or ART) is not indicated within 6 months of surgery unless additional infertility factors have been identified or there is documentation of tubal compromise by a postoperative hysterosalpingogram, laparoscopy, etc. or recurrence of disease.</p> <p>XII. Male Factor Infertility</p> <p>A. Varicocele Repair/Varicolectomy (Schlegel 2020):</p> <p>Surgical varicolectomy <u>is indicated</u> in men attempting to conceive who have palpable varicocele(s), infertility, and abnormal semen parameters, except for azoospermic men.</p> <p>Varicolectomy <u>is not indicated</u> for men with non-palpable varicoceles detected solely by imaging.</p> <p>Varicolectomy <u>is not indicated</u> for men with clinical varicocele and non-obstructive azoospermia,</p> <p>B. Sperm Retrieval</p> <p>Surgical sperm aspiration <u>is indicated</u> for obstructive azoospermia in the setting of:</p> <ul style="list-style-type: none"> • Congenital absence of the vas deferens (carrier of cystic fibrosis gene (Jaffe, 1994), OR • Infection, OR • Vasectomy, OR • Trauma. <p>BY:</p> <ol style="list-style-type: none"> 1. Microsurgical epididymal sperm aspiration (MESA) (Schlegel, 1994, 2020; Tournaye, 1994) OR 2. Percutaneous epididymal sperm aspiration (PESA) (Craft, 1995), OR
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	<ol style="list-style-type: none"> 3. Open testicular biopsy (TESE) (Schlegel, 1997, 2020; Schlegel, 1999) OR 4. Percutaneous testicular sperm aspiration (TEFNA) (Persson, 1971), OR 5. Percutaneous testicular needle biopsy (PercBiopsy) (Sheynkin, 1998) <p>Surgical sperm aspiration by microdissection testicular sperm extraction (TESE) <u>is indicated</u> for non-obstructive azoospermia in the setting of:</p> <ul style="list-style-type: none"> • Maturation arrest, OR • Sertoli-only syndrome <p>BY:</p> <ol style="list-style-type: none"> 1. Microdissection testicular sperm aspiration (mTESE) OR 2. Open testicular biopsy (TESE) (Schlegel, 1997, 2020; Schlegel, 1999) OR 3. Percutaneous testicular sperm aspiration (TEFNA) (Persson, 1971), OR 4. Percutaneous testicular needle biopsy (PercBiopsy) (Sheynkin, 1998) <p>Men with retrograde ejaculation (RE) may be treated with:</p> <ul style="list-style-type: none"> • Sympathomimetics and alkalinization of urine with or without urethral catheterization, OR • Induced ejaculation, OR • Surgical sperm retrieval. <p>Men with aspermia may be treated with (Schlegel 2020):</p> <ul style="list-style-type: none"> • Surgical sperm extraction, OR • Induced ejaculation (sympathomimetics, vibratory stimulation or electroejaculation). <p>Surgical sperm aspiration <u>is not indicated</u> in the absence of azoospermia.</p> <p>C. Male Hypogonadotropic Hypogonadism</p> <p>Initial treatment with hCG injections (1,500-2,500 IU, twice weekly) is indicated followed by FSH, when indicated, after testosterone levels are normalized on hCG (Schlegel 2020).</p>
<p>Clinical Evidence</p>	<p><u>Ovulation Induction</u></p> <p>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</p>

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; ASRM, 2020)
- 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, 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; ASRM, 2020)

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 ± 3.8 mm vs. 3.4 ± 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)
- For anovulatory women, such as those with polycystic ovary syndrome, the most recent Cochrane review showed that letrozole compared to clomiphene citrate (CC) increased live birth rates (OR 1.68;95% CI 1.42–1.99) without increasing the multiple pregnancy rate (1.7% with CC vs 1.3% with letrozole; OR 0.69%;95% CI 0.41–1.16) (Franik 2018). A meta-analysis of 57 RCTs with 8,082 women also confirmed that letrozole resulted in significantly higher live birth rates compared to clomiphene and with a lower incidence of multiple gestation compared to gonadotropins, which had the greatest risk of multiple gestation (Wang 2018). However, if ovulation is not achieved using oral agents, low-dose exogenous gonadotropins may be considered to use for OI cycles with a strict cancellation policy. It is recommended to start at a low dose of 37.5–75 IU a day, with slow increases of dosing to achieve mono-follicular development. Further, cycle cancellation is strongly recommended for patients with >2 follicles 16 mm or if there are 3 intermediate sized follicles to reduce the risk of multiple gestation and ovarian hyperstimulation syndrome (ASRM 2020).

Treatments for Unexplained Infertility (ESHRE, 2022)

Clomiphene citrate or letrozole with timed intercourse vs. expectant management

- A randomized control study including 385 patients with UI, compared six months of expectant management (n=167) with clomiphene citrate (CC) and timed intercourse (n=173). Cumulative birth rate was 16% (26/167) with expectant management compared to 13% (23/173) with active treatment. Compared with expectant management, the adjusted hazard ratio (HR) for the time to a pregnancy leading to a live birth was 0.83 2145 (99% CI 0.42-1.63) (Bhattacharya et al, 2008). The cost-benefit study using this data by the same group also found no cost-benefit of clomiphene citrate over expectant management (Wordsworth et al, 2147 2011). In a four-arm RCT, including 155 couples with unexplained infertility, timed intercourse with CC for ovarian stimulation, with or without hCG for final oocyte maturation, was compared to timed intercourse and placebo, with or without hCG for final oocyte maturation. Pregnancy rates were significantly higher after timed intercourse with CC and hCG compared to placebo without hCG (19%) vs. 0/36 (0%) (Fisch et al, 1989).
- There are no relevant studies pertaining to letrozole but similar results would be expected.

Natural cycle IUI vs. expectant management

- One RCT compared IUI in a natural cycle with expectant management in couples with unexplained infertility. The live birth rate was not significantly different between IUI and expectant management (38/165 (23%) vs. 26/167 (16%)(Bhattacharya et al, 2008).

IVF vs. expectant management

- A systematic review and meta-analysis compared IVF with expectant management. The OR for live birth with one cycle of IVF compared to three months of expectant management was 22.0 (95% CI 2.56 to 189.38, n=51, 1 RCT). The OR for clinical pregnancy with one cycle of IVF compared to 3-6 months of expectant management was 3.24 (95% CI 1.07 to 9.80, 2 RCTs, n=86). Although the evidence is of low quality and insufficient, IVF is presently associated with a higher live birth rate than expectant management (Pandian et al, 2015). In a retrospective cohort study, 635 couples with unexplained infertility and female age ≥39 years were included. Couples undergoing immediate IVF treatment (n=359) were compared to couples waiting for about one year to start IVF treatment (n=276). No significant difference was found in live birth rate between immediate IVF treatment and waiting for about a year (70/359 (19%; 11 natural conception and 59 after IVF) vs. 57/276 (20.7%, 37 natural conception and 20 after IVF) (Carosso et al, 2022).

Gonadotropins for Unexplained Infertility

- The use of gonadotropins for ovarian stimulation in the treatment of unexplained infertility is not recommended. A recent systematic review and meta-analysis of 8 RCTs (2,989 women) showed no increase in live birth rates with gonadotrophins as compared to oral agents if gonadotropins were used in low doses or with a strict cancellation policy (Zolton 2020). However, if gonadotrophins were used in higher doses or without a strict cancellation policy, there was an increased pregnancy rate (RR 1.09) but with a concurrent increase in multiple gestations (RR 1.20 for higher doses and 1.15 for lax cancellation policy). Another meta-analysis demonstrated similar findings, indicating that gonadotropins had the highest live birth and ongoing pregnancy rates, but at the expense of a higher risk of multiple gestation (Danhof 2020).

Considering all the associated maternal and neonatal complications with multiples, this increase in the rates of pregnancy and live birth does not ameliorate the negative outcomes of a similar increase in multiple gestation. Based on these findings, a course of ovarian stimulation with oral medications and intrauterine insemination (IUI) would be appropriate followed by IVF for those not successful (Reindollar 2010, Goldman 2014).

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, intrauterine insemination and in vitro fertilization. (Harris, 2010; Wiser, 2012; ASRM, 2014)
- A systematic review and meta-analysis compared ovarian stimulation combined with IUI and expectant management in couples with unexplained infertility. The OR for cumulative live birth rate in couples with poor prognosis was 4.48 (95% CI 2.00-10.01, 1 RCT, n=201). The OR for live birth rate in couples with moderate prognosis was 0.82 (95% CI 0.45-1.49, 1 RCT, n=253). The OR for multiple pregnancy rate was 3.01 (95% CI 0.47-19.28, 2 RCTs, n=454) (Aveleke et al, 2020).
- 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 (≤ 3) number of clomiphene IUI cycles but should progress rapidly to ART. Females aged 35 and older should be advised to move directly to IVF. (ASRM, 2020; 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

	<p>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, 2020)</p> <ul style="list-style-type: none"> • 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 3rd 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 aged 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, unexplained infertility, and diminished ovarian reserve. Compared with normal ovarian reserve, treatment with oral antiestrogens for ovarian stimulation/IUI for patients with low ovarian reserve results in comparable follicular development and ongoing pregnancy rates for all age groups. When patients with low ovarian reserve are treated with gonadotropins for ovarian stimulation/IUI, multifollicular recruitment is less likely resulting in a significantly decreased ongoing pregnancy rate for patients aged $<$35 and 35-40 years but also a decrease in multifetal gestations. Overall, the ongoing pregnancy rates of 8.7% per oral antiestrogen cycle and 8.1% per injectable gonadotropin cycle in patients with low ovarian reserve are comparable with the expected rates in the general infertility population. (Romanski et al, 2022) • 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; Danhoff, 2018; Dankert, 2007; ASRM, 2020) • 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
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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)
- There is no evidence that ovarian stimulation in the setting of therapeutic donor insemination (absent ovulatory dysfunction of any other infertility factor) improved outcome. In a study involving 6,192 TDI cycles from 2,343 patients met inclusion criteria and were available for analysis (3,837 natural cycle and 2,355 ovarian stimulation). Ovarian stimulation involved the use of either clomiphene or letrozole but not gonadotropins. The probability of clinical and ongoing pregnancy was higher in the ovarian stimulation cohort compared with the natural cycle cohort (ovarian stimulation, 22.4% vs. natural cycle, 18.7% and ovarian stimulation, 15.4% vs. natural cycle, 14.9% respectively). However, ovarian stimulation significantly increased ongoing multiple gestations (ovarian stimulation, 10.8% vs. natural cycle, 2.4%). Ovarian stimulation in TDI cycles resulted in a <4% increase in clinical and <1% increase in ongoing pregnancy, and more than fourfold increase in ongoing multiple gestations. Natural cycle IUI should be considered as a first-line treatment for ovulatory women who need donor insemination. (Carpinello et al, 2021).
- 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)

Assisted Hatching

- Assisted hatching (AH) involves the artificial thinning or breaching of the ZP 15 and has been used as one technique to improve implantation and pregnancy rates following in vitro fertilization (IVF). Techniques have included mechanical opening of the zona pellucida, thinning with acidified Tyrode's solution, and more recently laser photoablation. Assisted hatching is commonly performed on the day of embryo transfer by full thickness laser-assisted hatching. While there may be a theoretical benefit to creating an opening for an embryo to escape and thus enhance the likelihood of improved implantation rates, the procedure may be associated with complications, including damage to the embryo and/or damage to individual blastomeres with reduction of embryo viability. Additionally, artificial manipulation of the zona pellucida has been associated with an increased risk of monozygotic twin pregnancy (Hershlag 1999, Shieve 2000). A review of multiple studies (ASRM 2021) evaluating pregnancy rates in an unselected patient population demonstrated that live birth rates are not significantly different between embryos that have undergone AH versus those that have not. In patients with a poor prognosis, the data is mixed about any improvement in pregnancy outcomes with laser AH. There is also moderate evidence that AH does not improve live-birth rates with frozen embryo transfers.

Use of Clinical Adjuncts in ART (Lensen, 2019; ESHRE, 2022)

- Numerous adjuncts have been utilized in an attempt to improve the follicular response to stimulation, fertilization, embryo development or implantation. Many studies have been poorly designed and demonstrate little to no improvement in outcomes. Specifically:
 - Dehydroepiandrosterone: The current evidence is too inconsistent

	<p>to draw any firm conclusions on the beneficial effect of DHEA for poor responders undergoing IVF. (Nagels, 2015; Kamath, 2020)</p> <ul style="list-style-type: none"> ○ Testosterone: Testosterone pretreatment has not been proven to be beneficial for poor responders and evidence from larger ongoing RCTs is awaited. (Nagels, 2015; Kamath, 2020) ○ Growth Hormone: There is a lack of strong evidence to support the use of adjuvant GH in ART. Furthermore, there is no agreement on the dosage and length of GH administration which have varied among the studies. (Choe, 2018; Kamath, 2020) ○ Aspirin: There is no proven efficacy for routine use of aspirin as an adjuvant in IVF treatment. (Siristatidis, 2016; Kamath, 2020) ○ Heparin: Its routine use as an adjuvant in the general population undergoing IVF is not supported by the current literature. (Akhtar, 2013; Kamath, 2020) ○ Low molecular weight heparin (LMWH): A systematic review and meta-analysis investigated the use of LMWH in patients with recurrent implantation failure (≥ 3 failed ET). Meta-analysis of the two included RCTs failed to show an effect of LMWH on both LIVE BIRTH RATE (RR 1.38; 95% CI 0.64 778 to 2.96, n=71) and Cumulative Pregnancy Rate (RR 1.39; 95% CI 0.87 to 2.23, n=218) (Busnelli et al, 2021). The observational study by Berker et al also failed to show a difference in live birth or pregnancy rates (Berker et al, 2011). ○ Antioxidants for the female partner: The current evidence does not support the routine use of supplemental antioxidants for women undergoing IVF. (Showell, 2017; Kamath, 2020) ○ Seminal Plasma: The Cochrane review that compiled these RCTs concluded that there was no clear evidence of a difference in LBR with seminal plasma application or exposure. (Ata, 2018; Kamath, 2020) ○ Platelet-rich Plasma: Use of PRP is not approved by the U.S. Food and Drug Administration and is therefore an off-label use. Currently, the use of PRP in reproductive medicine should be considered experimental. (Kamath, 2020; de Miguel-Gomez, 2021) ○ IVIG: Intravenous immunoglobulin (IVIG) is an important therapy in diverse autoimmune and inflammatory disorders, as well as primary immunodeficiencies. Its effects on the systemic immune system are complex and how it might affect the uterine immune system is completely unknown. A recent systematic review included two small trials evaluating the application of IVIG during ovarian stimulation or near the time of embryo transfer and reported no clinical benefit. (ASRM, 2018; DePlacedo, 2019; Galeotti, 2017; Stephenosn, 2000) ○ Intralipid: Intralipid is an emulsion of soybean oil, egg phospholipids and glycerin, commonly administered as intravenous nutrition for patients not able to tolerate an oral diet. Intralipid is thought to also modulate immune function and has been observed to reduce the probability of spontaneous abortion in a mouse model . A systematic
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review identified only a single trial: a double-blind RCT which found that giving intralipid to women with 'elevated NK cell levels' did not improve chemical pregnancy rate. (ASRM, 2018; Dakhly, 2016)

- Endometrial Receptivity Assay (ERA) (Lensen, 2019)
 - The ERA is a novel diagnostic test based on microarray technology, created by a single commercial enterprise. The test requires an appropriately timed endometrial biopsy to measure the endometrial expression of 248 genes. A prediction model is then applied to categorize the endometrium as one of: “receptive, pre-receptive, or proliferative”. This categorization then allows women to undergo a more “personalized” embryo transfer, where the exact timing of the transfer has been aligned to each woman’s personal window of implantation. The test has repeatedly demonstrated that women with recurrent implantation failure are more likely to suffer from a non-receptive endometrium, and approximately 25% of women with recurrent implantation failures are reported to have an altered implantation window. Additionally, the test applied to the same women biopsied in multiple cycles will consistently produce the same result (Ruiz-Alonso, 2013; Diaz-Gimeno, 2013). However, to date, only a single RCT has been completed, for which only interim and per-protocol analyses are available (Simon, 2016; Simon 2019). It is therefore not possible to confirm whether or not the ERA increases the probability of live birth. A recent study demonstrated no improvement in live birth rate when the ERA was utilized for the general ART population as a screening tool (Riestenberg, 2021)
 - A meta-analysis from 2022 included 11 studies and reported the prevalence of displaced “Window of Implantation” as 316 detected through endometrial receptivity test was 34% (95% CI 24-43%) in recurrent implantation failure/poor prognosis 317 patients (Liu, et al, 2022). In this patient population, comparable ongoing pregnancy rate (OPR)/LBR 318 was found between patients undergoing “personalized” embryo transfer (p-ET) with endometrial 319 receptivity testing and those with routine ET (40.7% vs. 49.6%; OR 0.94; 95% CI 0.70 to 1.26; 6 studies; 320 n=2552) (Liu et al, 2022). There is insufficient evidence to support the routine use of endometrial receptivity testing in ART.
 - Liu et al (2022) conducted a systematic review and meta-analysis to determine the prevalence of displaced window of implantation (WOI) in infertile women and the clinical utility of personalized embryo transfer (pET) guided by the endometrial receptivity array/analysis (ERA) on IVF/ICSI outcomes. The study included 11 published articles after meeting inclusion criteria. The estimate of the incidence of WOI displacement based on ERA was 38% in good-prognosis infertile patients (GPP) and 34% in repeated implantation failure (RIF), respectively. There was no difference in ongoing pregnancy rate (OPR)/live birth rate (LBR) between patients undergoing routine ET without ERA test and those who following pET with ERA (39.5 vs. 63.7%, OR 1.28, p=0.49, 95% CI 0.92-1.77, I²=0%) in relative GPP. The meta-analysis revealed that OPR/LBR of patients with RIF undergoing pET who had non-receptive ERA increased to the level of those undergoing standard embryo transfer

(sET) with receptive ERA (40.7 vs. 49.6%, OR 0.94, $p=0.85$, 95% CI 0.70-1.26, $I^2=0\%$). The authors concluded the ERA test as a promising tool. In patients with general good-prognosis ERA it may not be beneficial but personalized embryo transfer guided by ERA significantly increases the chances of pregnancy for non-receptive patients with RIF of endometrial origin. Limitations in the study include small sample size and heterogeneity in the studies and therefore more high-quality RCTs are needed to confirm the clinical utility of ERA.

- A Hayes (2022) Precision Medicine Research Brief examined the published peer-reviewed literature to evaluate the evidence related to the Endometrial Receptivity Analysis (ERA) test. The safety and clinical utility of this health technology cannot be made within this report as it would require a full-text review of the evidence. A full review of evidence may be justified depending on whether the health technology of interest is emerging, evolving, controversial, or disruptive and the degree to which it is a priority to clients.
- There is insufficient evidence supporting the safety and efficacy of uterine receptivity testing and/or treatment. More studies are needed to support improved outcomes such as successful pregnancies with delivery of liveborn children.

Endometrial Scratching

- Van Hoogenhuijze et al. (2021) conducted a non-blinded RCT (SCRaTCH trial) in women with one failed IVF/ICSI cycle to evaluate whether a single endometrial scratch using an endometrial biopsy catheter would lead to a higher live birth rate after the subsequent IVF/ICSI treatment compared to no scratch. Cumulative twelve month ongoing pregnancy leading to live birth rate was a secondary outcome. The women were randomized between January 2016 and July 2018, in total, 933 participants out of 1065 eligible were included in the study that took place in eight academic and 24 general hospitals. After the fresh transfer, 4.6% more live births were observed in the scratch compared to control group (110/465 versus 88/461, respectively). These data are consistent with a true difference of between 0.7% and $p9.9\%$ (95% CI), indicating that while the largest proportion of the 95% CI is positive, scratching could have no or even a small negative effect. Biochemical pregnancy loss and miscarriage rate did not differ between the two groups: in the scratch group 27/153 biochemical pregnancy losses and 14/126 miscarriages occurred, while this was 19/130 and 17/111 for the control group. After 12 months of follow-up, 5.1% more live births were observed in the scratch group (202/467 versus 178/466), of which the true difference most likely lies between 1.2% and $p11.4\%$ (95% CI). The authors note that the results of this study are an incentive for further assessment of the efficacy and clinical implications of endometrial scratching and if a true effect exists, it may be smaller than previously anticipated or may be limited to specific groups of women undergoing IVF/ICSI. The authors concluded that at present, endometrial scratching should not be performed outside of clinical trials and recommend further studies with larger sample sizes. Limitations include non-blinding of participants.
- Lensen et al. (2019a) summarized the current evidence for several add-on treatments suggested to improve endometrial receptivity. Immune therapies,

endometrial scratching, endometrial receptivity array, uterine artery vasodilation and human chorionic gonadotropin instillation were included in the assessment. Immune therapies addressed include corticosteroids, intravenous immunoglobulin (IVIG), granulocyte-colony stimulating factor and intralipid. The results suggest there is no robust evidence that these add-ons are effective or safe. Large randomized controlled trials are needed prior to introducing these IVF add-ons into routine practice.

- Lensen et al. (2019b) conducted a multicenter, open-label, randomized controlled trial evaluating the impact of endometrial scratching prior to IVF. Participants were randomly assigned in a 1:1 ratio to either endometrial scratching (n = 690) or no intervention (n = 674). The primary outcome was live birth. The frequency of live birth was 180 (26.1%) in the endometrial scratching group and 176 (26.1%) in the control group (adjusted odds ratio, 1.00; 95% confidence interval, 0.78 to 1.27). There were no significant between-group differences in the rates of ongoing pregnancy, clinical pregnancy, multiple pregnancy, ectopic pregnancy or miscarriage.
- In a Cochrane review, Nastri et al. (2015) conducted a review of RCTs comparing intentional endometrial injury before embryo transfer in women undergoing ART, versus a sham procedure or no intervention. Fourteen trials (n = 1063) were in the intervention groups and (n = 1065) were in the control groups. One study compared endometrial injury on the day of oocyte retrieval versus no injury, thirteen studies compared endometrial injury performed between day seven of the previous cycle and day seven of the embryo transfer (ET) cycle versus no injury. In studies comparing endometrial injury performed between day seven of the previous cycle and day seven of the ET cycle versus no intervention or a sham procedure, endometrial injury was associated with an increase in live birth or ongoing pregnancy rate (RR 1.42, 95% confidence interval (CI) 1.08 to 1.85; P value 0.01). There was no evidence of an effect on miscarriage. Endometrial injury was also associated with an increased clinical pregnancy rate (RR 1.34, 95% CI 1.21 to 1.61; P value 0.002). This suggests that if 30% of women achieve clinical pregnancy without endometrial injury, between 33% and 48% will achieve clinical pregnancy with this intervention. Endometrial injury was associated with increased pain. One study reported pain on a VAS scale, two studies reported the number of pain complaints after the procedure, one recorded no events in either group and the other reported that endometrial injury increased pain complaints. Results from the only RCT comparing endometrial injury on the day of oocyte retrieval versus no injury, reported that this endometrial injury markedly decreased live birth and clinical pregnancy. The authors concluded the procedure is mildly painful, there is no evidence of effect on miscarriage, multiple pregnancy or bleeding, and reduction of clinical and ongoing pregnancy rates is associated with endometrial injury on the day of oocyte retrieval. Additionally, moderate-quality evidence indicates that endometrial injury performed between day seven of the previous cycle and day seven of the ET cycle is associated with an improvement in live birth and clinical pregnancy rates in women with more than two previous embryo transfers. The authors states that although current evidence suggest benefit of endometrial injury, more evidence from well-designed trials that avoid instrumentation of the uterus in the preceding three months, do not cause endometrial damage in the control group, stratify the results for women with

and without recurrent implantation failure, and report live birth are needed.

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 meta-analysis on tubal cannulation demonstrated that the pooled (both unilateral and bilateral obstruction) cumulative clinical pregnancy rates were 22.3% (95% confidence interval [CI]: 17.8%–27.8%) at 6 months and increased slowly to achieve 26.4% (95% CI: 23.0%–30.2%) at 12 months, 27.9% (95% CI: 24.9%–31.3%) at 36 months, and 28.5% (95% CI: 25.5%–31.8%) at 48 months. The pooled (unilateral and bilateral obstruction) live-birth rate was 22% (95% CI: 18%–26%) and the pooled ectopic pregnancy rate was 4% (95% CI: 3%–5%) (26). In women with bilateral obstruction, the clinical pregnancy rate was 27% (95% CI: 23%–32%) (DeSilva, 2017). Relatively few women conceive naturally >6–12 months post cannulation. Consequently ART may be considered after 6 months to a year (depending upon age) after successful cannulation. The optimal treatment of unilateral proximal tubal occlusion has not been determined. One study reported similar pregnancy rates with ovarian stimulation and intrauterine insemination in patients with untreated unilateral proximal tubal occlusion and in those with unexplained infertility (Farhi, 2007). Therefore, there is no requirement for intervention with a unilateral proximal tubal obstruction with no distal abnormalities (ASRM, 2021)
- 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; ASRM, 2017)

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; ASRM, 2020)

- 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, 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, 2007; Luna, 2011).
- There is no data demonstrating the benefit of ICSI when used in women over 35 years of age (Kim, 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, 1998; Kinzer, 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. (ASRM, 2012; ASRM, 2020)
- In the setting of pre-implantation genetic testing (PGT) ICSI may be warranted to ensure mono-spermic fertilization (Thornhill, 2005; ICSI in 2006: evidence and evolution. Hum Reprod Update 2005; ASRM, 2020)
- 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, 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%

	<p>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)</p> <ul style="list-style-type: none"> • 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, 2013) • 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) • Strategies to improve live birth have primarily focused on maximizing embryo selection and endometrial synchrony. These strategies include PGT-A, freezing only embryo transfer cycles, endometrial synchrony testing, and time lapse imaging and other noninvasive embryo testing strategies. There is currently a lack of robust and consistent evidence that these strategies improve the chances of achieving a live birth. In addition, while strategies to improve live birth are aimed at improving the livebirth success of each embryo transfer, they are not necessary to reduce multiple gestation. Performing SET without additional embryo or endometrial testing reduces the multiple gestation rate down to the background 1–2% risk of monozygotic twins in ART (Gardner 2004, Styer 2008, Crinit 2005). Single embryo transfer, regardless of additional testing, should be considered the gold standard to reduce multiple gestation. Given the lack of robust evidence or conflicting evidence for many of these tests to improve clinical outcomes, they are currently not routinely recommended as a strategy to increase SET (ASRM 2022).
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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 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)

Pre-implantation Genetic Testing for Aneuploidy (PGT-A)

- Analysis of data from national assisted reproductive technology (ART) surveillance systems from 2011-2012 has found that the use of PGT-A is not associated with improved rates of clinical pregnancy or live birth after fresh autologous blastocyst transfer among women aged ≤37 years, irrespective of the indication (Chang 2016; Kushnir, 2016)
- Retrospective studies suggest a benefit of PGT-A testing, particularly in women up to age 43 years (improved live-birth rate per cycle start seen in women aged 38-40 years with PGT-A and implantation rates in women 40-43 years of age (implantation rate was 50.9% in euploid embryos compared with unscreened fresh [23.8%] and FET [25.4%] cycles) (Whitney, 2016; Lee, 2015)
- eSET: When comparing live-birth rates per elective single embryo transfer cycle in a 2015 study, there was no significant difference between groups (20.9% without PGT-A vs. 24.4% with PGT-A). (Ubaldi, 2017)
- Recurrent Pregnancy Loss (RPL): to date, the literature has not suggested an improved live-birth rate using PGT-A in RPL patients.
- One study found that applying PGT-A to patients with unexplained RPL (n=232) was not cost-effective when compared with expectant management (n=302); though PGT-A decreased miscarriage rates (7% vs 24%), the live-birth rate was not improved (40% vs 55%) (Murugappan, 2015)
- There are lingering concerns pertaining to the embryo biopsy and interpretation of the genetic testing. Specifically, these relate to the issues surrounding Mosaicism, Embryo Damage and the extremely challenging questions of false-positive testing and loss of euploid embryos between day 3

and blastulation all of which remain unanswered.

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). 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 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.

Co-Culture of Embryos

- Studies describe different techniques of co-culture, but no standardized method of co-culturing has been defined. Further studies are necessary to support the effects of co-culture on clinical outcomes.
- An ECRI (2022) Clinical Evidence Assessment report on endometrial coculture for treating infertility was inconclusive as there is limited studies on assessing its safety. The assessment reviewed all available literature through November

2022 and identified two RCTs, one nonrandomized comparative study, and two case series that reported on 2,684 patients. The conclusion findings suggests that there are insufficient studies to determine whether endometrial coculture improves the chances of assisted reproduction (AR) to result in a live birth. The controlled studies suggest coculture is not effective, but the findings are at high risk of bias and need validation. In addition, at least one of the studies indicates the procedure may result in multiple pregnancies.

- Le Saint et al. (2019, included in the ECRI 2022 Clinical Evidence Assessment) conducted a randomized, double-blind study of 207 patients undergoing an in-vitro fertilization or intracytoplasmic sperm injection (ICSI) protocol, which compared blastocyst quality between autologous endometrial co-culture (AECC) and conventional culture. The study found AECC significantly increased the quality of blastocysts compared to a conventional culture medium. However, the analysis was conducted on embryos rather than patients, there was no follow-up of children born following the treatments, and no significant differences were found in pregnancy and live birth rates.
- In a meta-analysis of 17 prospective, randomized trials, Kattal et al. (2008) evaluated the role of coculture in human IVF. Primary outcomes measured were implantation rates and pregnancy rates (clinical and ongoing). Secondary outcomes included evaluation of pre-embryo development based on average number of blastomeres per embryo. The pooled data of human trials on coculture demonstrate a statistically significant improvement in blastomere number, implantation rates and clinical and ongoing pregnancy rates. However, the authors acknowledged that confounding factors such as heterogeneity of cell lines and variability in culture media used limit the conclusions.
- Johnson et al. (2008) evaluated whether culture of immature human oocytes with and without autologous cumulus cells (CCs) in standard culture medium would provide additional oocytes for use in IVF procedure in 61 women. This study demonstrated good maturation of metaphase I (MI) oocytes but poor maturation of germinal vesicle (GV) oocytes in standard culture medium. The investigators concluded that these extended culturing techniques were inefficient in maturing and providing additional oocytes/embryos for patient use.
- A comparative study evaluated 517 women undergoing cumulus coculture and cumulus-aided embryo transfer with those who underwent cumulus coculture but did not undergo cumulus-aided embryo transfer. The study results demonstrated a significant increase in the implantation rate in the study group of 25.6% versus 14.5% in the control group and a significant increase in the pregnancy rate in the study group of 47.6% versus 34% in the control group (Parikh et al., 2006).

EmbryoGlue

- There is insufficient evidence supporting the clinical utility of EmbryoGlue. Further studies are needed to support improved clinical outcomes measures.
- Yung et al. (2021) performed a randomized, double blind, controlled trial, which compared the effects of hyaluronic acid (HA)–enriched transfer medium versus standard medium on live birth rate after frozen embryo transfer (FET). Five hundred and fifty infertile women, age 43 and under, were randomly placed in two groups. The first group used an HA enriched medium (EmbryoGlue), with an HA concentration of 0.5 mg/ml while the control group used the conventional G-2 (Vitrolife) medium with an HA concentration of 0.125mg/ml. The study found that live birth rates in both groups were

comparable; however, EmbryoGlue did not improve the live birth rates of FET when compared with standard medium.

- In a Cochrane systematic review, Heymann et al. (2020) evaluated whether adding adherence compounds to embryo transfer media could improve pregnancy outcomes, including improving live birth and decreasing miscarriage, in women undergoing assisted reproduction. Twenty-six RCTs with a total of 6704 participants were analyzed. The certainty of evidence was low to moderate overall. Compared to embryos transferred in media containing no or low (0.125 mg/mL) HA, the addition of HA concentrations (0.5 mg/mL) to the transfer media probably increases the live birth rate (RR 1.21, 95% CI 1.1 to 1.31; 10 RCTs, n = 4066; I² = 33%). This suggests that if the chance of live birth following no HA addition in media is assumed to be 33%, the chance following HA addition would be between 37% and 44%. The addition of HA may slightly decrease miscarriage rates (RR 0.82, 95% CI 0.67 to 1.00; 7 RCTs, n = 3091; I² = 66%). Adding HA to transfer media probably results in an increase in both clinical pregnancy (RR 1.16, 95% CI 1.09 to 1.23; 17 studies, n = 5247; I² = 40%) and multiple pregnancy rates (RR 1.45, 95% CI 1.24 to 1.70; 7 studies, n = 3337; I² = 36%). The effect of HA added to transfer media on the rate of total adverse events yielded uncertain results. The authors concluded the addition of HA as an adherence compound in embryo transfer media in ART improved clinical pregnancy and live birth rates, adding HA may slightly decrease miscarriage rates, HA had no clear effect on the rate of total adverse events and combining an adherence compound and transferring more than one embryo may increase multiple pregnancy rates. The authors recommend further studies of adherence compounds with single embryo transfers. Limitations include imprecision and/or heterogeneity.
- In a single center, prospective randomized study (n = 224), Hazlett et al. (2008) found that routine use of EmbryoGlue did not significantly improve pregnancy or implantation rates in non-selected patients receiving either a day 3 or day 5 embryo transfer compared with standard culture media. Future prospective randomized studies are needed to determine whether EmbryoGlue is beneficial in a selected patient population.
- In a prospective randomized clinical trial, Valojerdi et al. (2006) evaluated the efficacy of EmbryoGlue. A total of 815 patients were randomly allocated to the test group (embryos were treated with EmbryoGlue prior to intrauterine transfer) (n = 417) and the control group (embryos were not treated with EmbryoGlue) (n = 398). The clinical pregnancy and implantation rate increased significantly in the test group compared to the control group. More studies are needed to evaluate the effectiveness and safety of EmbryoGlue.

In Vitro Maturation of Oocytes

- Although preliminary results with in vitro maturation are promising, studies to date show that implantation and pregnancy rates are significantly lower than those achieved with standard IVF. Further evidence from well-designed trials is needed to determine the long-term safety and efficacy of the procedure.
- In a 2022 single- center, open-label randomized control trial, Zheng et al. sought to assess the effectiveness of in vitro maturation (IVM) in non-inferior cumulative live birth rates compared to those after standard in vitro fertilization (IVF) in infertile women with polycystic ovary syndrome (PCOS). A total of 351 women were randomly selected to receive one cycle of unstimulated IVM (n=175) or one cycle of standard IVF with a GnRH antagonist protocol and hCG as ovulatory trigger (n =176). Both groups received a freeze-all and single blastocyst transfer strategy. The researchers concluded that one cycle

of IVM without ovarian stimulation to be inferior to IVF with ovarian stimulation for women with infertility and PCOS in terms of 6-month cumulative ongoing pregnancy rates (22.3% vs. 50.6%; rate difference - 28.3%; 95% confidence interval [CI]: -37.9% to -18.7%). To evaluate the effectiveness and safety of other IVM protocols or multiple cycles of IVM compared to IVF, further RCTs should be evaluated due to limitations in the study. The limitations include IVM protocol constraint, decline in patient participation, primary outcome transfer timeframes, and ovarian stimulants.

- A Cochrane review by Siristatidis et al. (2018) compared outcomes associated with in vitro maturation (IVM) followed by vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) versus conventional IVF or ICSI, in women with polycystic ovarian syndrome (PCOS) undergoing ART. Though results are promising, there is still no evidence from randomized controlled trials upon which to base any practice recommendations regarding IVM before IVF or ICSI for women with PCOS. Clinical trials are ongoing.

Recurrent Pregnancy Loss

Treatment for unexplained recurrent pregnancy (RPL) loss should be considered in the context of a successful outcome with expectant management alone. No apparent cause for RPL is identified in 50%-70% of couples. The chance for a future successful pregnancy may exceed 50%-60% depending upon maternal age and the number of previous losses (Lund, 2012; ESHRE, 2017). Five years after the first consultation, 66.7% (95% CI 63.7-69.7) had achieved a live birth, increasing to 71.1% (95% CI 68.0-74.2) after 15 years. There was a significantly decreased chance of at least one subsequent live birth with increasing maternal age; of women aged 40 years or older, 41.7% (95% CI 29.8-56.1) achieved a live birth within 5 years compared to 81.3% (95% CI 69.2-90.7) of women aged 20–24 years. There was also a significant decrease in chance of a live birth by increasing number of miscarriages before first consultation ranging from 71.9% (95% CI 67.5-76.1) in women with 3 miscarriages to 50.2% (95% CI 40.5-60.8) in women with 6 or more previous miscarriages. Only women 40 years of age or older had a successful outcome over time of <60% at 10 years of follow-up after the first consultation (approximately 35% at 1 year of follow-up). Another study demonstrated a predicted percentage success rate of subsequent pregnancy according to age and previous miscarriage history (Brigham, 1999). Success rates ranged from 84% [CI:77-90] for a 30 year old with 2 previous miscarriages down to 42% [CI:22-62] to 42% [CI:22-62] for a 45 year old with 6 previous losses.

Surgical Sperm Aspiration

Surgical testicular sperm aspiration has been shown to be an effective treatment for nonobstructive azoospermia (Schlegel, 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, 1999)

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, 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, 2001)

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.

Varicocelectomy

Varicoceles have long been thought to be associated with male infertility. A recent meta-analysis observed higher estimated pregnancy rates for men undergoing repair of clinical varicocele compared to no treatment (Wang 2015). Pregnancy rates without treatment were assumed to be 17%, while rates were calculated to be 42% (95% CI 26% to 61%) with sub inguinal microsurgical varicocelectomy, 35% (95% CI 21% to 54%) with inguinal micro varicocelectomy, 37% (95% CI 22% to 58%) with inguinal open (non-microsurgical) surgery, and 37% (95% CI 19% to 61%) with laparoscopic surgery. For palpable varicoceles, observed the calculated estimated pregnancy rates were 52% (95% CI 24% to 83%) for sub inguinal micro varicocelectomy, 53% (95% CI 18% to 90%) for inguinal micro varicocelectomy, 55% (95% CI 27% to 88%) for inguinal open surgery, and 52% (95% CI 18% to 90%) for laparoscopic surgery. Another meta-analysis of ART outcomes evaluated the chance of pregnancy using ART for couples where men had varicocele repair relative to couples where the man had an untreated varicocele (Kirby, 2016). In these 7 non-randomized retrospective studies, only men with clinical varicoceles were considered. In this report by Kirby et al., the OR for pregnancy and live birth were 1.76-fold higher for men treated with varicocelectomy prior to ART.

In men with no palpable varicocele, surgical repair does not appear to be warranted. No demonstrable benefit of varicocele repair was observed in pregnancy or bulk seminal parameters with the exception of a possible small numerical effect on progressive sperm motility that is unlikely to be clinically important (Kim, 2016).

There is insufficient evidence to support varicocelectomy in the setting of a clinical varicocele and non-obstructive azoospermia. One study that reported return of adequate motile sperm in the ejaculate to avoid surgical sperm retrieval after varicocele repair had a success rate of only 9.6% (Schlegel, 2004).

Very Poor Prognosis/Futility

The American Society for Reproductive Medicine Ethics Committee defines “futility” in the treatment of infertility as a chance of live birth of <1% and differentiates futility from “very poor prognosis,” which is defined as a live birth rate between 1% and 5% (ASRM 2019).

Female fecundity decreases with increasing age. With aging, chromosome segregation errors during meiotic division are increasingly common and lead to the production of oocytes with an incorrect number of chromosomes, referred to as aneuploidy. Trophoctoderm biopsies of >15,000 blastocysts have shown that the rate of aneuploidy steadily increases after age 31 and reaches 85% at age 43 (Franasiak, 2014).

In an early study to determine the age-based chance of achieving a live birth in women aged >=40 years (n ¼ 2,705, ranging from 40–49 years, with mostly day 3 embryo transfers), the live birth rate per cycle start was 14% at the age of 40. This declined to

	<p>1%–2% at the age of 44–45, and to 0 over the age of 45 (8). Furthermore, the cumulative live birth rate (with an average of 2.3 IVF cycles) was 28% for IVF starting at age 40, declining to 2%–5% for IVF starting at the age of 44–45, and to 0 for IVF starting R45 years of age (Klipstein, 2005). The overall cancellation rate due to poor response was as high as 29% in the oldest patient population. Another study focusing on women 42 years of age (range, 42–47 years; n ¼ 843) demonstrated similar findings with (9) live birth rates per cycle of 4.2%, 3.3%, and 0.6% for women 42, 43, and 44 years old, respectively. There were no live births in women >= 44 years of age (Hourvitz, 2009). More recent studies demonstrated similar low pregnancy rates (0–2% live births per cycle start) in women aged 44– 45, and no live birth after the age of 45 (Gleicher, 2014; Alasmari., 2016). A multicenter longitudinal observational study, the rate of cycles with euploid blastocysts at the age of 44 and 45 was found to be 18% and 5%, respectively. The live birth rate was 57% per single frozen embryo transfer. The rate of live births per subsequent ART cycle (freeze all followed by a frozen/thaw embryo transfer cycle) and preimplantation genetic testing for aneuploidy followed by frozen embryo transfer was 10% at the age of 44 and 2% at the age of 45 (Ubaldi, 2017). In the same study, no euploid embryo was found in patients aged >45 years.</p> <p>In an IVF cycle, the possibility of obtaining a high-quality euploid blastocyst and a live birth directly correlates with the number of mature oocytes obtained (Ubaldi, 2017; Devesa, 2018; Drakopoulos, 2016; Polyzos 2018). Consequently, ovarian reserve represents a very important determinant for IVF success, most notably in older patients with a low euploid rate (Alviggi, 2016; ASRM, 2020). In younger women in their early 30s, for example, obtaining even a very small number of mature oocytes (1 to 3) per cycle can still yield a reasonable cumulative live birth rate (21%) (Drakopoulos, 2016). In contrast, according to a predictive model using 4,570 women with infertility aged >=38 years, 4 mature oocytes could result in a cumulative live birth rate per fresh IVF cycle of only 16% in women aged 38–39, 12% in women aged 40–41, 5% in women aged 42–43, and 1% in women aged >=44 years (Devesa, 2018).</p>
<p>Definitions</p>	<p>Amenorrhea: the complete lack of menstrual bleeding</p> <p>Anovulation: 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>Bicornuate uterus: a bifurcated uterus</p> <p>Endometriosis: 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>Fimbrioplasty: reconstructive surgery of the distal fimbriated end of the fallopian tube</p> <p>Hydrosalpinx: distal occlusion of a fluid filled fallopian tube. Often causes denudation of the tubal cilia.</p> <p>Medical Futility: “Futility” refers to treatment that has a ≤1% chance of achieving a live birth</p> <p>Male Factor Infertility: World Health Organization Reference Limits for Human Semen Characteristics Semen Parameter: One-Sided Lower Reference Limit (Fifth Centiles With 95% Confidence Intervals): Semen Volume 1.4 mL (1.3-1.5) Total Sperm Number 39 million per ejaculate (35-40) Sperm Concentration 16 million/mL (15-18 million/mL) Vitality 54% Live (50-56%)</p>

	<p>Progressive Motility 30% (29-31%)</p> <p>Total Motility (Progressive + Non-Progressive) 39% (40-43%)</p> <p>Morphologically Normal Forms 4.0% (3.9-4.0)</p> <ul style="list-style-type: none"> • Mild Male Factor: abnormalities in the semen analysis where the sperm concentration is ≥ 10 million/ml but < 15 million/ml and/or progressive motility is $\geq 30\%$ but $< 40\%$ or ≥ 5 million total motile sperm • Moderate Male Factor: abnormalities in the semen analysis where the sperm concentration is ≥ 5 million/ml but < 10 million/ml and/or progressive motility is $\geq 25\%$ but $< 30\%$ • Severe Male Factor: abnormalities in the semen analysis where the sperm concentration is < 5 million/ml or sperm preparation techniques result in a sperm concentration of < 1 million motile sperm/ml (Schlegel, 2020) • Isolated teratospermia is considered a male factor when there is $< 2\%$ normal morphology on at least two semen analyses 1-4 weeks apart <p>Metroplasty: surgical reconstruction of the uterus</p> <p>Neosalpingostomy: surgery to create a new opening in the distal end of the fallopian tube when there is complete fimbrial obstruction or obliteration</p> <p>Oligo-ovulation: Ovulatory menstrual cycles that are > 35 days apart</p> <p>Poor Prognosis: “Very poor prognosis” refers to treatment for which the odds of achieving a live birth are very low but not nonexistent ($> 1\%$ to $< 5\%$ per cycle). (ASRM, 2019)</p> <p>Recurrent Pregnancy Loss: Recurrent pregnancy loss is a disease distinct from infertility, defined by two or more failed pregnancies.</p> <p>Salpingitis isthmica nodosum: chronic nodular inflammation of the proximal fallopian tube often resulting in tubal occlusion</p> <p>Salpingectomy: partial or complete removal of a fallopian tube</p> <p>Salpingostomy: surgery to create an opening in the fallopian tube</p> <p>Septate uterus: a congenital anomaly with incomplete resorption of the medial uterine wall. Sometimes associated with recurrent pregnancy loss and possibly infertility</p> <p>Tubal Factor Infertility: 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>Unexplained Infertility: Infertility for which no causative factor has been identified</p> <p>Unicornuate uterus: a congenital anomaly with development of a hemi-uterus. Often associated with a rudimentary horn.</p> <p>Uterine Factor Infertility: 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 $< 1/4$ 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>Uterus didelphys: 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]

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.

Akhtar MA, Sur S, Raine-Fenning N, et al. Heparin for assisted reproduction. *Cochrane Database Syst Rev* 2013;8:CD009452.

Alasmari NM, Son WY, Dahan MH. The effect on pregnancy and multiples of transferring 1-3 embryos in women at least 40 years old. *J Assist Reprod Genet* 2016;33:1195-202.

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.

Alvigi C, Andersen CY, Buehler K, Conforti A, De Placido G, Esteves SC, et al, Poseidon Group (Patient-Oriented Strategies Encompassing Individualized Oocyte Number). A new more detailed stratification of low responder to ovarian stimulation: from a poor ovarian response to a low prognosis concept. *Fertil Steril* 2016;105:1452–3.

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* 2021;115:1143-50.

American Society for Reproductive Medicine (ASRM) Practice Committee opinion: Multiple gestation associated with infertility therapy. *Fertil Steril* 2022;117:498-511.

American Society for Reproductive Medicine (ASRM) Committee Opinion: Removal of myomas in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline. *Fertil Steril* 2017;108:416-25.

ASRM. The Practice Committee of the American Society for Reproductive Medicine: Definitions of infertility and recurrent pregnancy loss. *Fertil Steril* 2020;113:533-5.

ASRM. The Practice Committee of the American Society for Reproductive Medicine: Intracytoplasmic sperm injection (ICSI) for non-male factor infertility: a committee opinion. *Fertil Steril* 2020;114:239-45.

ASRM Practice Committee Guideline: Evidence based treatments for couples with unexplained infertility: a guideline. *Fertil Steril* 2020;113:305-22.

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* 2019;111:659-63.

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. Use of exogenous gonadotropins for ovulation induction in anovulatory women: a committee opinion *Fertil Steril* 2020;113:66–70..

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

ASRM. The Practice Committee of the American Society for Reproductive Medicine: Testing and interpreting measures of ovarian reserve. *Fertil Steril* 2020;114:1151–7.

ASRM Ethics Committee of the American Society for Reproductive Medicine. Fertility treatment when the prognosis is very poor or futile: an Ethics Committee opinion. *Fertil Steril* 2019;111:659–63. 2.

American Society for Reproductive Medicine (ASRM) Practice Committee of the American Society for Reproductive Medicine. The role of immunotherapy in in vitro fertilization: a guideline. *Fertil Steril* 2018; 110:387–400.

American Society for Reproductive Medicine (ASRM) Practice Committee of the American Society for Reproductive Medicine. Female age-related fertility decline. (*Fertil Steril* 2014;101:633–4.

American Society for Reproductive Medicine, the Society of Reproductive Biologists and Technologists, and the Society for Assisted Reproductive Technology. In vitro maturation: a committee opinion. *Fertil Steril*. 2021b Feb;115(2):298-304.

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.

Ata B, Abou-Setta AM, Seyhan A, Buckett W. Application of seminal plasma to female genital tract prior to embryo transfer in assisted reproductive technology cycles (IVF, ICSI and frozen embryo transfer). *Cochrane Database Syst Rev* 2018;2:CD011809.

Ayeleke RO, Asseler JD, Cohlen BJ, et al. Intra-uterine insemination for unexplained subfertility. *The Cochrane database of systematic reviews* 2020;3:Cd001838.

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.

Bhattacharya S, Harrild K, Mollison J et al. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. *BMJ (Clinical research ed)* 2008;337: a716.

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.
- Berker B, Taşkın S, Kahraman K, et al. The role of low-molecular-weight heparin in recurrent implantation failure: a prospective, quasi-randomized, controlled study. Fertil Steril. 2011;95: 2499-2502.
- 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.
- Bontekoe S, Heineman MJ, Johnson N, Blake D. Adherence compounds in embryo transfer media for assisted reproductive technologies. Cochrane Database Syst Rev. 2014 Feb 25;2:CD007421.
- Bravelle [package insert]. Parsippany, NY: Ferring Pharmaceuticals; June 2012.
- Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Hum Reprod 1999;14:2868–2871.
- Burrage J et al. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. BMJ (Clinical research ed) 2008;337: a716.
- Busnelli A, Somigliana E, Cirillo F, et al. Efficacy of therapies and interventions for repeated embryo implantation failure: a systematic review and meta-analysis. Sci Rep. 2021;11:1747.
- 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.
- Carpinello O, Jahandideh S, Yamasaki M, et al. Does ovarian stimulation benefit ovulatory women undergoing therapeutic donor insemination? (Fertil Steril 2021;115:638–45).
- Carosso AR, van Eekelen R, Revelli A, et al. Expectant Management Before In vitro Fertilization in Women Aged 39 or Above and Unexplained Infertility Does Not Decrease Live Birth Rates Compared to Immediate Treatment. Reproductive sciences (Thousand Oaks, Calif) 2022;29:1232-1240.
- 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.
- Chang J, Boulet SL, Jeng G, Flowers L, Kissin DM. Outcomes of in vitro fertilization with reimplantation genetic diagnosis: an analysis of the United States Assisted Reproductive Technology Surveillance Data, 2011-2012. Fertil Steril 2016;105:394–400. 10.
- 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.
- Choe SA, Kim MJ, Lee HJ, et al. Increased proportion of mature oocytes with sustained-release growth hormone treatment in poor responders: a prospective randomized controlled study. Arch Gynecol Obstet 2018;297:791-6.
- 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, Tsigiriotis 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.

Dakhly DM, Bavoumi YA, Sharkawy M, et al. Intralipid supplementation in women with recurrent spontaneous abortion and elevated levels of natural killer cells. *Int J Gynaecol Obstet* 2016;135:324–7.

Danhof NA, van Wely M, Repping S, et al. SUPER study group. Follicle stimulating hormone vs. clomiphene citrate in intrauterine insemination for unexplained subfertility: a randomized controlled trial. *Hum Reprod* 2018;33:1866–74.

Danhof NA, Wang R, van Wely M, van der Veen F, Mol BWJ, Mochtar MH. IUI for unexplained infertility-a network meta-analysis. *Hum Reprod Update* 2020;26:1–15

Dankert T, Kremer JA, Cohlen BJ, et al. A randomized clinical trial of clomiphene citrate vs. low dose recombinant FSH for ovarian hyperstimulation in intrauterine insemination cycles for unexplained and male subfertility. *Hum Reprod* 2007;22:792–7.

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.

de Miguel–Gomez M, Lopez-Martínez S, Campo H, et al. Comparison of different sources of platelet-rich plasma as treatment option for infertility-causing endometrial pathologies. *Fertil Steril* 2021;115:490-500.

den Hartog JE, Morre SA, Land JA. Chlamydia trachomatis-associated tubal factor subfertility: immunogenetic aspects and serological screening. *Hum Reprod Update* 2006.

De Placido G, Zullo F, Mollo A, et al. Intravenous immunoglobulin (IVIG) in the prevention of implantation failures. *Ann N Y Acad Sci* 1994;734:232–4. VOL. 112 NO. 6 / DECEMBER 2019.

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.

De Silva PM, Chu JJ, Gallos ID, Vidyasagar AT, Robinson L, Coomarasamy A. Fallopian tube catheterization in the treatment of proximal tubal obstruction: a systematic review and meta-analysis. *Hum Reprod* 2017;32:836–52.

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.

Devesa M, Tur R, Rodriguez I, Coroleu B, Martinez F, Polyzos NP. Cumulative live birth rates and number of oocytes retrieved in women of advanced age. A single centre analysis including 4500 women R38 years old. *Hum Reprod* 2018;33:2010–7.

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.

Diaz- Gimeno P, Ruiz-Alonso M, Blesa D, Bosch N, Martínez-Conejero JA, Alama P, et al. The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity. *Fertil Steril* 2013;99:508–17.

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.

Drakopoulos P, Blockeel C, Stoop D, Camus M, de Vos M, Tournaye H, et al. Conventional ovarian stimulation and single embryo transfer for IVF/ICSI. How many oocytes do we need to maximize cumulative live birth rates after utilization of all fresh and frozen embryos? *Hum Reprod* 2016;31:370–6.

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.

ECRI. Endometrial coculture for treating infertility. Plymouth Meeting (PA): ECRI; 2022 Dec 12. (Clinical Evidence Assessment).

ESHRE Unexplained Infertility Guideline 2022. In Press

ESHRE GOOD PRACTICE RECOMMENDATIONS ON RECURRENT IMPLANTATION FAILURE 2022. ESHRE working group on Recurrent Implantation Failure: Macklon N., Cimadomo D., de los Santos Molina M. J., et al. In Press

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.

European Society of Human Reproduction and Embryology (ESHRE) Guideline: Recurrent Pregnancy Loss. November, 2017.

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

Farhi J, Ben-Haroush A, Lande Y, Fisch B. Role of treatment with ovarian stimulation and intrauterine insemination in women with unilateral tubal occlusion diagnosed by hysterosalpingography. *Fertil Steril* 2007;88:396–400.

Farquhar CM, Liu E, Armstrong S, et al. Intrauterine insemination with ovarian stimulation vs. expectant management for unexplained infertility (TUI): a pragmatic, open-label, randomised, controlled, two-centre trial. *Lancet* 2018;391:441-50.

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.

Fauser 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. May 13, 2020 .

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.

Franik S, Eltrop SM, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2018;5:CD010287.

Franasiak JM, Forman EJ, Hong KH, et al. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophoctoderm biopsies evaluated with comprehensive chromosomal screening. *Fertil Steril* 2014;101:656–63.e1.

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.

Galeotti C, Kaveri SV, Bayry J. IVIG-mediated effector functions in autoimmune and inflammatory diseases. *Int Immunol* 2017;29:491–8.

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.

Geng T, Geng L, Ge C, Zhang T. The effect of ICSI in infertility couples with non-male factor: a systematic review and meta-analysis. *Journal of Assisted Reproduction and Genetics* (2020) 37:2929–2945.

Gerber R, Fazzari M, Kappy M, et al. Differential impact of controlled ovarian hyperstimulation on live birth rate in fresh versus frozen embryo transfer cycles: a Society for Assisted Reproductive Technology Clinic Outcome System study. *Fertil Steril* 2020; 114: 1225-1231.

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, Kushnir VA, Weghofer A, Barad DH. The “graying” of infertility services: an impending revolution nobody is ready for. *Reprod Biol Endocrinol* 2014;12:63.

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.

Goldman MB, Thornton KL, Ryley D, Alper MM, Fung JL, Hornstein MD, et al. A randomized clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment Trial (FORT-T). *Fertil Steril* 2014;101:1574-81.e1-2.

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 xcxi 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.

Hayes Inc. Precision Medicine Research Brief. ERA Endometrial Receptivity Analysis (Igenomix). Lansdale, PA: Hayes, Inc.; November 2022.

Hazlett WD, Meyer LR, Nasta TE, et al. Impact of EmbryoGlue as the embryo transfer medium. *Fertil Steril.* 2008 Jul;90(1):214-6.

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.

Hershlag A, Paine T, Cooper GW, Scholl GM, Rawlinson K, Kvapil G. Monozygotic twinning associated with mechanical assisted hatching. *Fertil Steril* 1999;71:144–6.

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.

Hourvitz A, Machtinger R, Maman E, Baum M, Dor J, Levron J. Assisted reproduction in women over 40 years of age: how old is too old? *Reprod Biomed Online* 2009;19:599–603.

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 JE, Higdon IJ HL, Boone WR. Effect of human granulosa cell co-culture using standard culture media on the maturation and fertilization potential of immature human oocytes. *Fertil Steril*. 2008 Nov;90(5):1674-9.
- 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.
- Kamath MS, Mascarenhas M, Franik S, et al. Clinical adjuncts in in vitro fertilization: a growing list. *Fertil Steril* 2019;112:978-86.
- 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.
- Kattal N, Cohen J, Barmat LI. Role of coculture in human in vitro fertilization: a meta-analysis. *Fertil Steril*. 2008 Oct;90(4):1069-76.
- 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.
- Kim HJ, Seo JT, Kim KJ et al: Clinical significance of subclinical varicocele in male infertility: Systematic review and meta-analysis. *Andrologia* 2016; 48: 654.
- 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.
- Kirby EW, Wiener LE, Rajanahally S et al: Undergoing varicocele repair before assisted reproduction improves pregnancy rate and live birth rate in azoospermic and oligospermic men with a varicocele: A systematic review and meta-analysis. *Fertil Steril* 2016; 106: 1338.
- 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.
- Klipstein S, Regan M, Ryley DA, Goldman MB, Alper MM, Reindollar RH. One last chance for pregnancy: a review of 2,705 in vitro fertilization cycles initiated in women age 40 years and above. *Fertil Steril* 2005;84:435–45. 9.
- 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.

Kushnir VA, Darmon SK, Albertini DF, et al. Effectiveness of in vitro fertilization with preimplantation genetic screening: a reanalysis of United States assisted reproductive technology data 2011-2012. *Fertil Steril* 2016;106:75–9.

La Marca A, Kamal Sunkara SK: Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. *Human Reprod* 2014; 20, 124-140.

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.

Lee HL, McCulloh DH, Hodes-Wertz B, et al. In vitro fertilization with preimplantation genetic screening improves implantation and live birth in women age 40 through 43. *J Assist Reprod Genet* 2015;32:435–44.

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.

Lensen S, Shreeve N, Barnhart K, et al. In vitro fertilization add-ons for the endometrium: it doesn't add up. *Fertil Steril* 2019;112:987–93.

Lensen S, Osavlyuk D, Armstrong S, et al. A randomized trial of endometrial scratching before in vitro fertilization. *N Engl J Med*. 2019b Jan 24;380(4):325-334.

Le Saint C, Crespo K, Bourdieu A, et al. Autologous endometrial cell co-culture improves human embryo development to high-quality blastocysts: a randomized controlled trial. *Reprod Biomed Online*. 2019 Mar;38(3):321-329.

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)

Liu Z, Lui X, Wang M et al. The clinical efficacy of personalized embryo transfer guided by the Endometrial Receptivity array/analysis on IVF/ICSI outcomes: A systematic review and meta-analysis. *Front Physiol* 2022; 13;841437.

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.

Lund M, Kamper-Jørgensen M, Nielsen HS, et al. Prognosis for live birth in women with recurrent miscarriage: what is the best measure of success? *Obstet Gynecol* 2012; 119:37–43.

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, 24th edition, Ambulatory Care, 2020.

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.

Merchant R, Gandhi G, Allahbadia GN. In-Vitro Fertilization/Intracytoplasmic sperm injection for male infertility

Deccan Fertility Clinic Rotunda-Center for Human Reproduction Mumbai India. Indian Journal of Urology Jan-Mar 2011;27:121-132.

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

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.

Murugappan G, Ohno MS, Lathi RB. Cost-effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained recurrent pregnancy loss. Fertil Steril 2015;103:1215–20.

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

Nagels HE, Rishworth JR, Siristatidis CS, et al. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database Syst Rev 2015;11:CD009749.

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.

Nastri CO, Lensen SF, Gibreel A, et al. Endometrial injury in women undergoing assisted reproductive techniques. Cochrane Database Syst Rev. 2015 Mar 22;(3):CD009517.

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.

Nojua-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.

Optum Fertility Solutions Expert Panel. April 19, 2023.

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, Gibreel A, Bhattacharya S. In vitro fertilisation for unexplained subfertility. *The Cochrane database of systematic reviews* 2015;2015: Cd003357.

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.

Parikh FR, Nadkarni SG, Naik NJ, et al. Cumulus coculture and cumulus-aided embryo transfer increases pregnancy rates in patients undergoing in vitro fertilization. *Fertil Steril*. 2006 Oct;86(4):839-47.

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, Wattanakumtornkul 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.

Polyzos NP, Drakopoulos P, Parra J, Pellicer A, Santos-Ribeiro S, Tournaye H, et al. Cumulative live birth rates according to the number of oocytes retrieved after the first ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection: a multicenter multinational analysis including 15,000 women. *Fertil Steril* 2018;110:661–70.e1

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: Guidance on the limits of the number of embryos to transfer: a committee opinion. *Fertil Steril* 2021;116:651-54.

Practice Committee of American Society for Reproductive Medicine and the Practice Committee of Society for Assisted Reproductive Technology. Guidance regarding gamete and embryo donation: a committee opinion. *Fertil Steril* 2021;115:1395-410.

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.

Practice Committee of the American Society for Reproductive Medicine, American Society for Reproductive Medicine: The role of assisted hatching in in vitro fertilization: a guideline *Fertil Steril* 2014;102:348–51.

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.

Richter KS, Shipley SK, McVearry 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.

Riestenberg C, Kroener L, Quinn M, et al. Routine endometrial receptivity array in first embryo transfer cycles does not improve live birth rate. *Fertil Steril* 2021;115:1001–6.

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.

Romanski P, Bortoletto P, Malmstem J, et al. Pregnancy outcomes after oral and injectable ovulation induction in women with infertility with a low antimullerian hormone level compared with those with a normal antimullerian hormone level. *Fertil Steril* 2022;118:1048–56.

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.

Ruiter-Ligeti J, Dahan M, Steiner N, et al. Is intrauterine insemination a viable treatment option for women over 43 years old? An analysis by ovarian stimulation protocol and sperm source. *Journal of Assisted Reproduction and Genetics* (2020) 37:3103–3107.

Ruiz-Alonso M, Blesa D, Diaz-Gimeno P, Gomez E, Fernandez-Sanchez M, Carranza F, et al. The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. *Fertil Steril* 2013;100:818–24.

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.

Schieve LA, Meikle SF, Peterson HB, Jeng G, Burnett NM, Wilcox LS. Does assisted hatching pose a risk for monozygotic twinning in pregnancies conceived through in vitro fertilization? *Fertil Steril* 2000;74:288–94.

- 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.
- Schlegel PN and Kaufmann J: Role of varicocelectomy in men with nonobstructive azoospermia. Fertil Steril 2004;81:1585.
- Schlegel PN, Sigman M, Collura B, Et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I. Fertil Steril 2020; in press
- Schlegel PN, Sigman M, Collura B, Et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part II. Fertil Steril 2020; in press
- Schlegel P, Sigman M, Collura B et al. Diagnosis and Treatment of Infertility in Men: AUA/ ASRM Guideline part III. Fertil Steril 2020; in press
- 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.
- Showell MG, Mackenzie-Proctor R, Jordan V, Hart RJ. Antioxidants for female subfertility. *Cochrane Database Syst Rev* 2017;7:CD007807.
- Silber S, Zsolt P, Liu NJ, et al. Conventional in-vitro fertilization versus intracytoplasmic sperm injection for patients requiring microsurgical sperm aspiration. *Human Reproduction*.1994;9(9):1705-09.
- Simon C, Vladimirov IK, Castillon Cortes G, et al. Prospective, randomized study of the endometrial receptivity analysis (ERA) test in the infertility work-up to guide personalized embryo transfer versus fresh transfer or deferred embryo transfer. *Fertil Steril* 2016;106: e46–7.
- Simon C, Gomez C, Cabanillas S, Vladimirov IK, Castillon G, Giles J, et al. In vitro fertilization with personalized blastocyst transfer versus frozen or fresh blastocyst transfer: a multicenter, randomized clinical trial. *Fertil Steril* 2019;112:e56.
- Siristatidis CS, Basios G, Pergialiotis V, Vogiatzi P. Aspirin for in vitro fertilization. *Cochrane Database Syst Rev* 2016;11:CD004832.
- Siristatidis CS, Maheshwari A, Vaidakis D, Bhattacharya S. In vitro maturation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction. *Cochrane Database Syst Rev*. 2018 Nov 15;11:CD006606.
- Society for Assisted Reproductive Technology: National Data Summary 2011. Available at: https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reporting_year+2017.
- 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.
- Stephenson MD, Fluker MR. Treatment of repeated unexplained in vitro fertilization failure with intravenous immunoglobulin: a randomized, placebo-controlled Canadian trial. *Fertil Steril* 2000;74:1108–13.
- 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.
- Styer AK, Wright DL, Wolkovich AM, Veiga C, Toth TL. Single-blastocyst transfer decreases twin gestation without affecting pregnancy outcome. *Fertil Steril* 2008;89:1702–8.
- 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.
- Ubaldi FM, Capalbo A, Colamaria S, et al. Reduction of multiple pregnancies in the advanced maternal age population after implementation of an elective single embryo transfer policy coupled with enhanced embryo selection: pre- and post-intervention study. *Hum Reprod* 2015;30:2097–106.
- Ubaldi FM, Cimadomo D, Capalbo A, Vaiarelli A, Buffo L, Trabucco E, et al. Preimplantation genetic diagnosis for aneuploidy testing in women older than 44 years: a multicenter experience. *Fertil Steril* 2017;107:1173–80.
- 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 Hoogenhuijze NE, Mol F, Laven JSE et al. Endometrial scratching in women with one failed IVF/ICSI cycle-outcomes of a randomised controlled trial (SCRaTCH). *Hum Reprod*. 2021 Jan 1;36(1):87-98.
- 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.
- Wang R, Kim BV, van Wely M, Johnson NP, Costello MF, Zhang H, et al. Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis. *BMJ* 2017;356:j138.
- 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, Fiddelers 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.
- Wang J, Xia SJ, Liu ZH et al: Inguinal and subinguinal micro-varicocele, the optimal surgical management of varicocele: A meta-analysis. *Asian J Androl* 2015; 17: 74.
- 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.
- Whitney JB, Schiewe MC, Anderson RE. Single center validation of routine blastocyst biopsy implementation. *J Assist Reprod Genet* 2016;33:1507–13.

Wordsworth S, Buchanan J, Mollison J, et al. Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost-effective? *Human reproduction (Oxford, England)* 2011;26: 369- 2259 375.

World Health Organization. *WHO Laboratory Manual for the Examination of Human Semen and Semen-Cervical Mucus Interaction*. 4th 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.

Zheng X, Guo W, Zeng L, et al. In vitro maturation without gonadotropins versus in vitro fertilization with hyperstimulation in women with polycystic ovary syndrome: a non-inferiority randomized controlled trial. *Hum Reprod*. 2022 Jan 28;37(2):242-253.

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.

Zolten JR, Lindner PG, Terry N, DeCherney AH, Hill MJ. Gonadotropins versus oral ovarian stimulation agents for unexplained infertility: a systematic review and meta-analysis. *Fertil Steril* 2020;113:417–25.e1.

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.
1.1	12/05/2013	Confidentiality statement added to footer
1.2	01/30/2014	Minor edits made to verbiage per EP recommendations.
2.0	02/26/2014	Infertility Surgery and eSET incorporated into this document.
2.1	06/26/2014	Minor edits made to verbiage and clarification of age groups for applicable ART cycles.
2.1	07/14/2014	Governing control number of document changed from PR4069 to PR4221.
3.0	07/14/2014	Updated with new information on letrozole.
3.1	10/13/2014	Minor changes to guideline verbiage.
4.0	07/09/2015	Guideline review and update. New information on tubal factor infertility, letrozole, thin endometrial lining, PCOS and teratospermia added.
4.1	10/02/2015	Clinical evidence and references updated.
5.0	05/05/2016	Policy revision with additional indications for use of letrozole, gonadotropins, eSET and use of preimplantation genetic testing.

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5.1	06/22/2016	Minor changes to guideline verbiage.
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.
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.
7.0	05/03/2018	Annual review with revisions. 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 ≥ 44 years was added, non-indications for IUI and donor insemination were revised, additional information on natural cycle IUI has been provided.
7.1	10/01/2018	Replaces JA22214780.
8.0	08/27/2018	Interim review with revisions. 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 updated.
9.0	06/26/2019	Guideline review with revisions. 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 ≥ 40 years of age. Clarified male factor infertility indication in natural cycle IUI and unilateral tubal factor infertility in IUI.
9.1	12/10/2019	Isolated teratospermia added to male factor infertility definition.
10.0	02/11/2020	Guideline update. 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.
11.0	05/15/2020	Guideline review and update. The definition of infertility was revised, ultrasound monitoring was added as not medically necessary in ovarian stimulation with oral medications in conjunction with IUI, added Clomid and letrozole as not indicated when natural cycle IUI is indicated, ICSI indication added when previously cryopreserved oocytes are used, and adjunct treatments not indicated when used in conjunction with ART were added.
12.0	11/10/2020	Interim update. The definition of infertility was revised.
13.0	05/05/2021	Annual guideline review with revisions. Added information regarding immune therapies, tamoxifen in ovulation induction and stimulation, non-indication for

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		gonadotropins, IVIG and intralipids as unproven in ART, male infertility, and tubal cannulation as not indicated for mid or distal tubal occlusion. eSET information updated to reflect ASRM recommendations and preimplantation genetic testing wording correlated with the federal definition of disability. PGT for aneuploidy, ERA, RNA gene expression profile, 238 genes sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation added as not indicated.
14.0	01/06/2022	Interim guideline review with revisions. Revised: general indications for infertility treatment and use of autologous or donor oocytes for females ≥ 55 years of age as not indicated; removed Clomid, letrozole and Tamoxifen for unilateral tubal factor infertility from previous salpingectomy or proximal tubal occlusion; standardized maximum number of cycles in ovarian stimulation and IUI to three regardless of age; removed age parameters for IUI in the setting of sexual dysfunction or cervical trauma; removed age parameters for use of autologous oocytes; and added the need for an ART cycle for gestational carriers.
15.0	05/05/2022	Annual guideline review with revisions. Updated SART registry data, added statement on individualized assessment of patients, diminished ovarian reserve added as an indication for IUI, revised examples of poor prognosis/fertility and diminished ovarian reserve, clarified language regarding tubal compromise, added assisted hatching as not medically necessary, added ICSI as not indicated in the setting of PGT-A unless PGT-A is a covered benefit, added a section on endometrial prep, added Fragile X to PGT section, added tubal surgery not indicated prior to ART except for hydrosalpinges and revised WHO reference limits to diagnose male factor infertility.
16.0	05/04/2023	Annual guideline review with revisions. Added information on IUI as not indicated in the setting of ovulatory dysfunction and ovulation induction. Added additional unproven adjunct procedures, ICSI as indicated when using surgically derived sperm and cryopreservation of sperm as medically necessary when surgically obtained, cumulus cell removal as part of the ICSI process, assisted hatching as art of the biopsy procedure, fresh cycle indicated when < 8 previously frozen oocytes, and use of modified natural cycle prior to gonadotropins for preparation of endometrial lining. Removed age limits and revised timelines for additional infertility treatment after surgery and removed the use of gonadotropins as initial treatment for diminished ovarian reserve.
17.0	08/09/2023	Interim review. In background section under indications for IUI, removed “unilateral tubal factor infertility due to previous salpingectomy or proximal tubal occlusion” and added “moderate” male factor infertility to mild male factor infertility in order to accurately align with the treatment criteria section.