Clinical Performance Guideline
Infertility
Effective 5/1/2014

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

I. Infertility

- Definition: the inability to conceive following 1 year of unprotected intercourse or therapeutic donor insemination in cases where the female is ≤ 35 years of age or following 6 months of unprotected intercourse or therapeutic donor insemination for females > 35 years of age. (ASRM)
- 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.
- 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 for diagnostic evaluation of infertility, there is an increased chance of fertility (10% over the ensuing 6 months) as thin, filmy adhesions may be lysed by the dye injected into the tubes, which will allow them to become patent.
- Luteal phase deficiency has never been established as a cause of infertility.
- It has never been demonstrated that antibodies against sperm in either the male or female partner is a cause of infertility.
- It has never been demonstrated that asymptomatic infection of the male or female genital tract can cause infertility.
- The spontaneous conception rate for the “normal” couple is 25% per ovulatory cycle.
- Fecundity declines gradually after age 32 and more precipitously after age 37. National data from the SART registry 2011 demonstrates that the percentage of embryo transfers resulting in live births decreased...
progressively from 46.3% in females younger than 35 years to 38.4% for females aged 35-37 years, 27.5% for females aged 38-40 years, 16.6% for females aged 41-42, and 6.5% 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, 2011)

- 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 or to assess the need for IUI when clomiphene citrate is being utilized to induce ovulation or treat unexplained infertility (10% of females treated with clomiphene may exhibit a significant reduction in cervical mucus).

II. Intrauterine Insemination

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

- Indications for IUI:
  - Sexual dysfunction
  - Sequelae of cervical trauma
  - Mild male factor infertility
  - Unexplained infertility
  - Minimal or mild endometriosis

- Historically, controlled ovarian stimulation (COS) with clomiphene citrate or gonadotropins combined with intrauterine insemination (IUI) has provided less invasive options before proceeding to IVF.

- A traditional approach involved 3 cycles of clomiphene/IUI followed by 3 cycles of gonadotropin/IUI before pursuing IVF.

- Gonadotropin/IUI is associated with an increased risk for multiple gestation (30%) including high-order multiple births (8.1%). (Gleicher, 2000)

- The pregnancy rate per cycle for gonadotropin/IUI is 9%. (Guzick, 1998, 1999)

- The pregnancy rate per cycle for clomiphene/IUI is 7%.

- Conception, when it occurs, is achieved within 4 clomiphene or gonadotropin/IUI cycles in 90% of cases. (Chaffkin, 1991)

- The cumulative pregnancy rate for gonadotropin/IUI treatment is 33%.

- The cumulative pregnancy rate for clomiphene/IUI treatment for women <35 is 25%. (Dovey, 2008; Ecohard, 2000)

- IUI with controlled ovarian stimulation may be effective in increasing live birth rate in women with minimal or mild endometriosis. (Nulsen, 1993; Tummon, 1997)

- Skipping gonadotropin/IUI in the traditional approach and moving instead directly to IVF yields a significant increase in pregnancy rate and time to conception while decreasing overall costs. (Goldman, 2010; Reindollar, 2010)
Gonadotropin/IUI should not be used for treatment given the increased cost of medication, risk for a multiple gestation and a cumulative pregnancy rate that is only slightly higher compared to clomiphene/IUI. (Goldman, 2010)

III. Poor Prognosis and Futility

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

- Markedly elevated FSH levels
  - ≥19 for women < 40
  - >15 for women ≥ 40
    - FSH levels should be evaluated in the context of other markers of ovarian reserve, such as AMH, AFC and response to prior ovarian stimulation
    - In the absence of a history of prior ovarian stimulation, a cycle of ART may be considered, especially in women age <35.

- Lack of viable spermatozoa
- Ovarian failure where a couple is attempting conception with their own gametes
- Numerous ART cycles without adequate egg production, fertilization and/or embryo development

IV. Treatment in the Natural Cycle

- Natural cycle treatment assumes:
  - Normal ovulatory function with spontaneous (unstimulated) ovulation
  - At least one patent fallopian tube
  - Normal uterine cavity

- Treatment options in the natural cycle encompass:
  - Timed coitus
  - Cervical insemination
  - Intrauterine insemination (IUI)
  - Assisted reproductive technologies (ART)

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

### General Indications for Initial and Continuation of Infertility Treatment Coverage

The below general infertility criteria are to be met for consideration of treatment:

- **Prognosis for conception must be ≥ 5%**: AND
- Adequate ovarian reserve. Markers of adequate reserve include but are not limited to (one or more of the following within the previous 6 months):
  - FSH level < 15 mlU/ml if >35 years of age; OR
  - FSH level <20 mlU/ml if ≤ 35 years of age; OR
  - AMH level > 0.3 ng/ml; OR
  - Antral follicle count > 7; 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:
The general infertility surgery criteria as listed below are to be met for consideration of treatment:

- pelvic pain that is not responsive to conservative management; OR
- presence of a pelvic mass for which gynecologic diagnosis warrants surgical intervention; OR
- 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.

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.

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<th>Treatment Criteria</th>
<th>I. Ovulation Induction</th>
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<td>A. Clomiphene citrate <em>(Clomid®, Serophene®)</em></td>
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<td>1. Clomiphene citrate is indicated to treat females with ovulatory dysfunction in the following situations:</td>
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<td>- Amenorrhea; AND</td>
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<td>- Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated</td>
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<td>2. Clomiphene citrate is not indicated in the following situations:</td>
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<td>- Beyond the 6th clomiphene citrate induced ovulatory cycle; OR</td>
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<td>- 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</td>
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<td>- An estradiol level &lt;100 pg/ml/follicle ≥15 mm in diameter</td>
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<td>B. Letrozole <em>(Femara®)</em></td>
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<td>- Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated; AND</td>
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<td>- Clomiphene citrate results in a thin endometrial lining (&lt;7 mm); OR</td>
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• Demonstrates an adverse reaction to clomiphene citrate

2. Letrozole is not indicated in the following situations:
   • Beyond the 6th letrozole induced ovulatory cycle; OR
   • When used alone for females with unexplained infertility; OR
   • When there is a failure to respond to ovarian stimulation, (e.g., no follicles ≥17 mm in diameter); OR
   • An estradiol level <100 pg/ml/follicle ≥15 mm in diameter

C. Gonadotropins
   1. Gonadotropins are indicated to treat females with ovulatory dysfunction in the following situations:
      • Anovulation; OR
      • Oligo-ovulation; OR
      • Amenorrhea; AND
      • Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated; AND
      • Failure to ovulate with either clomiphene citrate or letrozole.
   2. Gonadotropins are not indicated in the following situations:
      • Beyond the 6th gonadotropin induced 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); OR
      • An estradiol level <100 pg/ml/follicle ≥15 mm in diameter.

II. Controlled Ovarian Stimulation
   A. Clomiphene citrate and letrozole
      1. Clomiphene citrate and letrozole 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
         • Male factor infertility
      2. Clomiphene citrate and letrozole are not indicated in the following situations:
         • To treat females with unexplained infertility, endometriosis, or male factor infertility when used alone (without IUI) (ASRM); OR
         • Beyond 4 cycles for females <38 years of age (Chaffkin, 1991);
Dovey, 2008; ASRM, 2013); OR
- Beyond 2 cycles for females 38-40 years of age (ASRM, 2006, 2013; Hendricks, 2006; Harris, 2010; Wiser, 2012); OR
- Beyond 1 cycle for females >40 years of age in the setting of diminished ovarian reserve, unexplained infertility, or male factor infertility (ASRM, 2006; Hendricks, 2006; Harris, 2010; Sahakyan, 1999; Aboulghar, 2001); OR
- Following ART cycles that fail to result in conception due to poor ovarian response or poor quality oocytes or embryos.

3. Letrozole may only be utilized in lieu of clomiphene citrate if: (Badawy, 2009; Donghong, 2011; Misso, 2012)
   - There are contraindications to the use of clomiphene citrate; OR
   - Clomiphene citrate results in a thin endometrial lining (<7mm).

B. Gonadotropins
1. Gonadotropins are indicated when used alone or in conjunction with intrauterine insemination in the following situations:
   - To treat females with diminished ovarian reserve that have not responded to clomiphene citrate or letrozole; OR
   - Initial treatment for women with diminished ovarian reserve.
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 or male factor infertility (McClamrock, 2012; ESHRE, 2013); 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); 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
   - Following ART cycles that fail to result in conception due to poor ovarian response or poor quality oocytes or embryos.

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

III. Therapeutic Donor Insemination
A. Therapeutic donor insemination is indicated in the following situations:
   1. Male factor infertility; OR
   2. Failure of fertilization with ART; OR
   3. Female without a male partner (when this is a covered benefit)
B. Therapeutic donor insemination (cervical or intrauterine) is not indicated in the following situations:
1. Failure to conceive within 12 donor insemination cycles in a female <35 years old; OR
2. Failure to conceive within 6 donor insemination cycles in a female ≥35 years old.

### IV. Intrauterine Insemination (IUI)

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

1. Sexual dysfunction
2. Cervical trauma
3. Mild male factor infertility
4. Therapeutic donor insemination

**B.** Intrauterine insemination (IUI) in a natural (unstimulated) cycle is not indicated in the treatment of unexplained 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

**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. Severe male factor infertility
3. Moderate or severe endometriosis (ESHRE, 2013)
4. In the setting of unexplained infertility or mild to moderate male factor infertility or minimal or mild endometriosis in the following situations:
   - Beyond 4 cycles for females <38 years of age (Chaffkin, 1991; Dovey, 2008; ASRM, 2013; Merviel, 2010; Dickey, 2003); OR
   - Beyond 2 cycles for females 38-40 years of age (ASRM, 2006, 2013; Hendricks, 2006; Harris, 2010; Wiser, 2012); OR
   - Beyond 1 cycle for females >40 years of age (ASRM, 2006; Hendricks, 2006; Harris, 2010; Sahakyan, 1999; Aboulghar, 2001)
5. In the setting of sexual dysfunction or cervical trauma when there are no other confounding infertility factors, in the following situations:
   - Beyond 12 cycles in a female <35 years old; OR
   - Beyond 6 cycles in a female ≥35 years old
6. 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; 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)

V. Assisted Reproductive Technologies (ART)

A. Assisted Reproductive Technologies (ART) are indicated for the following:
   1. Unexplained infertility
   2. Tubal factor infertility
   3. Male factor infertility
   4. Endometriosis
   5. 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
   6. Recurrent pregnancy loss
   7. Failure to achieve conception with any other treatment modality

B. Assisted Reproductive Technologies (ART) are not indicated in the following situations:
   1. 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
   2. ART cycle does not demonstrate the attainment of at least one (1) embryo suitable for transfer; OR
   3. Lack of viable spermatozoa; OR
   4. Ovarian failure where a couple is attempting conception with their own gametes; OR
   5. Numerous ≥ 2 ART cycles without adequate egg production, fertilization and/or embryo development; OR
   6. In a female ≥45 years of age using autologous oocytes

C. Natural (unstimulated) Cycle Assisted Reproductive Technologies (ART) are indicated for previous poor responders as defined below:
   1. 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
   2. When a stimulated ART cycle does not demonstrate the attainment of at least one (1) embryo suitable for transfer; AND
   3. There have been <2 natural ART cycle attempts

D. Freezing of ALL oocytes or embryos (when this is a covered benefit) is indicated in the following situations:
   1. Avoidance of ovarian hyperstimulation syndrome; OR
   2. For pre-implantation genetic diagnosis (PGD) or screening (PGS); OR
3. For enhancing the uterine environment
E. Fresh oocyte retrievals are not indicated when previously frozen oocytes or embryos are available for transfer

VI. Tubal Surgery
A. Tubal surgery is indicated in the following situations:
   1. to treat proximal tubal occlusion with selective salpingography or hysteroscopy with tubal cannulation.
   2. to treat hydrosalpinges prior to an ART cycle by salpingectomy or proximal tubal occlusion.
B. Tubal surgery is not indicated in the following situations:
   1. to treat proximal tubal occlusion for the following:
      • Salpingitis isthmica nodosum in the presence of a compromised distal tube
      • Chronic salpingitis
      • Obliterative fibrosis
      • Women over the age of 35
      • In the presence of a significant male factor.
   2. to treat severe hydrosalpinges by neosalpingostomy.
   3. to perform a fimbrioplasty, salpingostomy or neosalpingostomy for severe tubal disease or concomitant proximal and distal tubal occlusion.

VII. Surgery for Endometriosis
A. Surgery for Endometriosis is indicated in the following situations:
   1. when there are gynecologic indications for surgery such as;
      • pelvic pain that is not responsive to conservative management; OR
      • presence of a pelvic mass and/or pain for which gynecologic diagnosis otherwise warrants surgical intervention; OR
      • as 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. where the only aim is to diagnose and subsequently treat peritoneal endometriosis in order to improve the result of ART treatment; OR
   2. to perform an aspiration or cystectomy of an endometrioma prior to ART unless there are other gynecologic indications for surgery; OR
3. to resect deep nodular implants of endometriosis prior to ART in order to improve the result of ART treatment.

VIII. Uterine Surgery

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

B. Uterine Surgery is not indicated in the following situations:
   1. to treat a uterine septum that extends ≤ 1 cm from the superior uterine wall (an arcuate or sub-septate uterus); OR
   2. to treat a bicornuate uterus; OR
   3. to treat a uterus didelphys; OR
   4. to treat subserosal or pedunculated fibroids prior to ART in order to improve the result of ART treatment.

IV. Elective Single Embryo Transfer (eSET)

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

- Patients with a favorable prognosis as defined as:
  - Expanded day 5 or 6 blastocysts with well-defined inner-cell mass and trophoderm AND one of the following:
    - Embryo(s) or eggs available and suitable for cryopreservation;
    - Presence of one or more euploid embryos.
  - All patients undergoing ovum donation where the donor is < 35 years of age.
- **For females <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
  - Additional selection methodologies (e.g. pre-implantation genetic testing) have been utilized for females ≥ 35 years of age.
- **For females 37-42 years of age** eSET is further indicated on the 1st full ART embryo transfer cycle if the prognosis is favorable as defined above
  - OR
  - Additional selection methodologies (e.g. pre-implantation genetic testing) have been utilized on the 2nd cycle.

Multiple blastocyst embryo transfer is indicated in the following situations (AHRQ):
- **For females <37-40 years of age**:
  - The transfer of 2 blastocyst embryos may be considered if no favorable prognosis embryos are available;
    - On the 3rd full ART embryo transfer cycle the transfer up to 2 embryos may be considered.
- **For females 40-42 years of age**:
  - The transfer of up to 2 blastocyst embryos may be considered if there is only one favorable prognosis embryo;
    - The transfer of 3 blastocyst embryos may be considered if there are no favorable prognosis embryos are available;
      - Only 1 euploid blastocyst should be transferred.

Multiple cleavage stage embryo transfer is indicated in the following situations (ASRM 2013):
- **For females <35-37 years of age** with a favorable prognosis no more than 2 embryos should be transferred.
  - Females with fewer than 2 high quality embryos should have no more than 3 embryos transferred.
- **For females 38-40 years of age** with a favorable prognosis no more than 3 embryos should be transferred.
  - Females with ≤ 2 high quality embryos should have no more than 4 embryos transferred.
For females 41 - 42 years of age with a favorable prognosis no more than 4 embryos should be transferred.

**Clinical Evidence**

### Ovulation Induction

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

### Ovarian Reserve

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

• Decreased ovarian reserve does not constitute an absolute contraindication to treatment. (ASRM, 2012a)

**Letrozole**

• There is no evidence that controlled ovarian stimulation with Letrozole is superior to clomiphene for patients with unexplained infertility undergoing IUI. (Badawy, 2009)

• 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)

• Currently, it is unknown whether letrozole or clomiphene is more effective for ovulation induction in patients with PCOS.

**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)

• For unexplained infertility, a retrospective cohort study of 1738 women undergoing 4199 treatment cycles using both clomiphene citrate and intrauterine insemination reported that pregnancy rates decrease with advancing maternal age and with subsequent treatment cycles. The authors concluded that it is reasonable to offer a limited number of cycles of clomiphene citrate and intrauterine insemination as first-line therapy in younger women with tubal patency without regard to ovulatory status (Dovey, 2008). Studies of women 40 years and older report age-related decline in fecundity and cumulative live birth rates with controlled ovarian stimulation and intrauterine insemination. (Harris, 2010; Wiser, 2012)

• 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 age 35 and older should be advised to move directly to IVF. (ASRM, 2006; Hendricks, 2006)

• When used in combination with IUI, CC seems to be beneficial compared with expectant management. One study randomized 67 females with unexplained
infertility to CC/IUI or expectant management for up to 8 cycles. Fourteen patients achieved pregnancy with CC/IUI treatment over 148 cycles (9.5% pregnancy rate per cycle), compared with 5 patients managed expectantly (over 150 cycles; 3.3% pregnancy rate per cycle). In a more recent trial, 475 females were observed for up to 3 cycles of CC/IUI. There were 123 pregnancies over 1,294 cycles and 98 ongoing or live births (7.6% ongoing or live births per cycle). Up to three cycles is a common therapeutic regimen before progressing to more aggressive therapies. (ASRM, 2013)

- After 6 cycles of gonadotropin/IUI the cumulative pregnancy rate ranges from 0 to 48.5%. (Merviel, 2010; Aboulghar, 2001)

- The pregnancy rate per cycle appears to diminish after the 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-Hutunen, 1999; Dickey, 2003)

- Women age 38-39 years old have a diminished prognosis following 2 gonadotropin/IUI cycles and women ≥ 40 years have a diminished prognosis after one cycle. (Sahakyan, 1999; Harris, 2010)

- Women ≥ 41 years old have a diminished prognosis with clomiphene citrate/IUI treatment. (Aboulghar, 2001)

- Clomiphene citrate may be as effective as gonadotropins when used in conjunction with IUI in cases of cervical factor, mild male factor and unexplained infertility.

- Pregnancy rates for Clomid/IUI (2%-19.3%) do not differ from those involving gonadotropin/IUI (7%-19.2%) or low dose (75 IU/day) gonadotropin/IUI (8.7%-16.3%) but the incidence of twin gestations is markedly reduced (12.5% vs. 28.6% and 29.3% respectively). (McClamrock, 2012)

- Controlled ovarian stimulation and IUI may increase the live birth rate 5.6 fold in women with minimal or mild endometriosis compared to expectant management. (Tummon, 1997)

- ART is recommended for women with moderate or severe endometriosis. (ESHRE, 2013)

- Cumulative pregnancy rates within 4 cycles are 51.44% and 25.4% for clomiphene and gonadotropins respectively (the difference in pregnancy rates is not statistically significant). (Ecochard, 2000; Guzik, 1999; Reindollar 2010, 2011)

- There is no evidence that, absent sexual dysfunction, cervical trauma or mild male factor infertility natural cycle (i.e., no ovarian stimulation) IUI has any benefit over appropriately timed heterosexual intercourse.

- Natural cycle IUI may be considered in the setting of donor insemination.
when no other infertility factor is present.

- There is no evidence from the published studies that intrauterine insemination is an effective treatment for cervical hostility. (Helmerhorst, 2009)

- A single timed insemination per cycle is sufficient as there is no benefit to additional inseminations per cycle. (Osuna, 2004; Albrozi, 2003; Tonguc, 2010)

- There is no evidence in published studies that reverting to treatment with IUI following failed ART cycles due to poor ovarian response, poor quality oocytes or embryos has been proven to be clinically effective.

- IVF compared with IUI presents superior pregnancy rates in the setting of two or more follicles. (Reichman, 2013)

**Treatment in the Natural Cycle**

- There is no evidence in the medical literature that timed coitus based upon serial ultrasound monitoring of follicular development improves pregnancy outcome. (ASRM, 2006, 2012a, 2012b; Lewis, 2004)

- Natural cycle ART may have some benefit in previous poor responders
  - 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)
  - Cycle cancellation rates range from 46 (age group <35) to 77% (age group >42) (Gordon, 2013)

**Embryo Banking and Use of Frozen Embryos**

- There is no evidence in the medical literature to support the practice of repeated ART cycles for the purpose of accumulating (banking) embryos for later use (egg retrievals without a fresh or frozen embryo transfer) with the exception of freeze all cycles for medical necessity.

- It is clinically appropriate and cost effective to utilize all frozen embryos for transfer prior to another fresh ART cycle. (Forman, 2013; Richter, 2006; Shapiro, 2011, 2013)

**Tubal Disease**

- Studies treating patients with bilateral proximal tubal occlusion showed that
the obstruction is relieved in about 85% of the tubes with tubal cannulation and that about half of the patients conceive. Approximately a third of the opened tubes subsequently re-occlude. (Honore 1999, Pinto 2003)

- A good prognosis for distal tubal surgery is associated with patients who have no more than limited filmy adnexal adhesions, mildly dilated tubes (<3 cm) with thin and pliable walls, and a lush endosalpinx with preservation of the mucosal folds. (AFS 1988)
- Intrauterine pregnancy rates after neosalpingostomy for mild hydrosalpinges range from 58% to 77% but decreases to 0% to 22% for severe disease. The corresponding ectopic pregnancy rates range from 2%-8% and 0%-17% respectively. (Nackley 1998)
- Hydrosalpinges have been demonstrated to lower pregnancy, implantation and delivery rates. (Camus 1999, Zeyneloglu 1998)
- Laparoscopic salpingectomy or tubal occlusion have 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)

**Efficacy of eSET**
• Single embryo transfer is most applicable for transfer of blastocyst-stage embryos as these appear to have higher implantation rates compared to cleavage-stage embryos. (Papanikolaou 2006, Blake 2007, Zech 2007)
• Compared with DET-conceived infants, eSET-conceived singletons are less likely to be born either preterm (RCT-based relative risk [RR] 0.37, 95% confidence interval [CI] 0.25–0.55) or with low birth weight (RCT-based RR 0.25, 95% CI 0.15–0.45; cohort study RR 0.51, 95% CI 0.29–0.91). (Grady 2012)
• Following implementation of a mandatory eSET program, eSET fresh transfers have resulted in clinical pregnancy rates of 67.7% (Csokmay 2011) and a live-birth rate of 64.6% (Kresowik 2011) with a significant reduction in multiple-birth rate to 3-4%.
• The transfer of a single euploid blastocyst embryo yields comparable pregnancy rates to untested double blastocyst transfer (Forman 2013) and
yield pregnancy rates comparable to egg donation cycles. (Griffo)

- Some studies suggest a lower initial pregnancy rate for eSET compared to two embryo transfer (Pandian 2009; McLernon 2010, van Montfoort 2006), but cumulative pregnancy rates are similar (54.7% for eSET vs. 49% for a double transfer). (Criniti 2005, Henman 2005, le Lannou 2006)

**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, Criniti 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)

**Definitions**

**Amenorrhea:** the complete lack of menstrual bleeding

**Anovulation:** the lack of ovulatory menstrual cycles. Females with anovulation may still have periodic bleeding but these episodes are not associated with prior ovulation

**Bicornuate uterus:** a bifurcated uterus

**Endometriosis:** a condition where endometrial implants are located external to the uterine cavity. Often but not always associated with pain, pelvic adhesions, ovarian cysts

**Fimbrioplasty:** reconstructive surgery of the distal fimbriated end of the fallopian tube

**Hydrosalpinx:** distal occlusion of a fluid filled fallopian tube. Often causes denudation of the tubal cilia.

**Medical Futility:** “Futility” refers to treatment that has a ≤1% chance of achieving a live birth

**Male Factor Infertility:**

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


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Tummon IS, Asher L, 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.


Version History
The following are approved changes incorporated into the version numbers indicated below.

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Description of Change</th>
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<tr>
<td>1.0</td>
<td>12/01/2013</td>
<td>New medical necessity document (Eckard, C)</td>
</tr>
<tr>
<td>1.1</td>
<td>12/05/2013</td>
<td>Confidentiality statement added to footer (Wetherbee, Lynn)</td>
</tr>
<tr>
<td>1.2</td>
<td>01/30/2014</td>
<td>Minor edits made to verbiage per EP recommendations (Eckard, C)</td>
</tr>
<tr>
<td>2.0</td>
<td>02/26/2014</td>
<td>Infertility Surgery and eSET incorporated into this document (Eckard, C)</td>
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