Purpose: To provide an understanding of infertility treatment among individuals faced with the potential loss of fertility.

Goals: To provide an evidence-based approach to infertility management and describe 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.

- 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.

- 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
  - Cervical trauma
  - Mild male factor infertility
  - Unexplained infertility
  - Minimal or mild endometriosis

- Historically, super-ovulation 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%.
- 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.
- The cumulative pregnancy rate for gonadotropin/IUI treatment is 33%.
- The cumulative pregnancy rate for clomiphene/IUI treatment for women <35 is 25%.
- 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.
- Gonadotropin/IUI should not be used for treatment given the increased cost of medication, risk for a multiple gestation and a cumulative

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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.
- Natural cycle IUI may be considered in the setting of donor insemination or mild male factor when no other infertility factor is present.
<table>
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<th>General Indications for Initial and Continuation of Infertility Treatment Coverage</th>
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| **General Indications**

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:
  - 1 follicle ≥ 15 mm diameter for IUI
  - Minimum of 1 follicle ≥15 mm diameter for ART

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<th>Treatment Criteria</th>
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| **I. Ovulation Induction**

**A. Clomiphene citrate (Clomid®, Serophene®)**

1. Clomiphene citrate is indicated to treat females with ovulatory dysfunction in the following situations:
   - **Anovulation; OR**
   - **Oligo-ovulation; OR**
   - **Amenorrhea; AND**
   - Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated

2. Clomiphene citrate is not indicated in the following situations:
   - Beyond the 6th clomiphene citrate induced ovulatory cycle; **OR**
   - When there is a failure to respond to ovarian stimulation after appropriate dosage adjustment, (e.g., doses of clomiphene citrate up to 200 mg per day and no follicles ≥17 mm in diameter); **OR**
   - An estradiol level <100 pg/ml/follicle ≥15 mm in diameter

**B. Letrozole (Femara®)**

1. Letrozole is indicated to treat females with ovulatory dysfunction in the following situations:
   - **Anovulation; OR**
   - **Oligo-ovulation; OR**
   - **Amenorrhea; AND**
   - Other specific causative factors (e.g., thyroid disease, hyperprolactinemia) have been excluded or treated; **AND**
• Clomiphene citrate results in a thin endometrial lining (<7 mm); OR
• 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); OR
- Beyond 4 cycles for females <38 years of age; OR
- Beyond 2 cycles for females 38-40 years of age; OR
- Beyond 1 cycle for females >40 years of age in the setting of diminished ovarian reserve, unexplained infertility, or male factor infertility; 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:
- 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;
   - 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
   2. Severe male factor infertility
   3. Moderate or severe endometriosis
   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; OR
      • Beyond 2 cycles for females 38-40 years of age; OR
      • Beyond 1 cycle for females >40 years of age
   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
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. **Uterine Surgery**

A. Uterine surgery is indicated for the following:
   1. Sub-mucous myomas
   2. Polyps
   3. Intrauterine adhesions
   4. Congenital anomalies

B. Uterine surgery is not indicated for the following:
   1. Sub-septate uterus
   2. Arcuate uterus

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**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)
- A lower antral follicle count is associated with infertility (Rosen, 2011)
- Decreased ovarian reserve does not constitute an absolute contraindication to treatment (ASRM, 2012a)

**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-Huttunen, 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 (Cochrane Database, 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 not 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)

### 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

**Medical Futility:** “Futility” refers to treatment that has a \( \leq 1\% \) chance of achieving a live birth

**Male Factor Infertility:**

- **Mild Male Factor:** abnormalities in the semen analysis where the sperm concentration is \( \geq 10 \) million/ml but \( < 15 \) million/ml and/or progressive motility is
≥ 30% but <40%

- **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 ≥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 <2 million motile sperm/ml

**Oligo-ovulation:** Ovulatory menstrual cycles that are >35 days apart

**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, 2006)

**Recurrent Pregnancy Loss:** Recurrent pregnancy loss is a disease distinct from infertility, defined by two or more failed pregnancies.

**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)

**Unexplained Infertility:** Infertility for which no causative factor has been identified

**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 leiomyomata 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.

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

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<th>Date</th>
<th>Description of Change</th>
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<td>1.0</td>
<td>12/01/2013</td>
<td>New medical necessity Guideline that replaces the following guidelines: Natural Cycle, Treatment of Unexplained Infertility, Ovarian Stimulation, Limiting Infertility Treatment in Patients with Poor Prognosis, and Intrauterine Insemination (Eckard, Cookie)</td>
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<td>Effective date added to header and footer. (Wetherbee, Lynn)</td>
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<td>1.2</td>
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