Clinical Policy Bulletin:
Infertility

Revised April 2014

Number: 0327

Policy

1. For purposes of this entire policy, Aetna covers diagnostic infertility services to determine the cause of infertility and treatment only when specific coverage is provided under the terms of a member’s benefits plan. All coverage is subject to the terms and conditions of the plan. The following discussion is applicable only to members whose plans cover infertility services.

2. For purposes of this policy, a member is considered infertile if he or she is unable to conceive or produce conception after 1 year of frequent, unprotected heterosexual sexual intercourse, or 6 months of frequent, unprotected heterosexual sexual intercourse if the female partner is over age 35 years. Alternately, a woman without a male partner may be considered infertile if she is unable to conceive or produce conception after at least 12 cycles of donor insemination (6 cycles for women aged 35 or older). However, this definition of infertility may vary due to state mandates and plan customization; please check plan documents.

3. Note: Most plans exclude coverage of infertility services for couples in which either of the partners has had a previous sterilization procedure, with or without surgical reversal, and for females who have undergone a hysterectomy. Individuals who have undergone genital gender reassignment surgery (female to male or male to female) are considered to have undergone elective sterilization and are also not eligible for infertility services under these benefit plans. Please check benefit plan descriptions for details. In addition, infertility services for persons who have undergone voluntary sterilization procedures are not covered because such services are not considered treatment of disease. The inability to conceive in a couple who has undergone a voluntary sterilization procedure, including tubal sterilization or vasectomy, with or without surgical reversal, is not the result of disease but the result of an elective procedure intended to prevent conception.

4. Note: Some plans exclude coverage of infertility services using a woman’s own eggs for women with poor ovarian reserve, as determined by measurement of serum FSH, a marker of ovarian reserve. Ovarian responsiveness is determined by measurement of an unmedicated day 3 FSH obtained within the prior 6 months if the woman is older than age 35 or within the prior 12 months if the woman is 35 years of age or younger. Under these plans, for women who are less...
than age 40, the day 3 FSH must be less than 19 mIU/mL in their most recent lab test to use their own eggs. For women age 40 and older, their unmedicated day 3 FSH must be less than 19 mIU/mL in all prior tests to use their own eggs. Please check benefit plan descriptions. In addition, infertility services for women with natural menopause in women age 40 years and older are not covered as such services are not considered treatment of disease. Women with ovarian failure who are less than 40 years of age are considered to have premature ovarian failure (also known as premature ovarian insufficiency, primary ovarian insufficiency, or hypergonadotropic hypogonadism). Advanced reproductive technology (in vitro fertilization) services are considered medically necessary for women with premature ovarian failure who are less than 45 years of age.

5. Infertility services are considered not medically necessary once pregnancy is established and a fetal heartbeat is detected. Infertility services beyond 8 weeks of pregnancy are not considered medically necessary.

I. **Females: Basic Infertility Services**

The following services are considered medically necessary for diagnosis and/or treatment of infertility.

A. History and physical examination

B. Laboratory studies:

1. Anti-sperm antibodies (e.g., immunobead or mixed antiglobulin method)
2. Chlamydia trachomatis screening (See CPB 0433 - Chlamydia Trachomatis - Screening and Diagnosis)
3. Fasting and 2 hours post 75 gram glucose challenge levels
4. Lipid panel (total cholesterol, HDL cholesterol, triglycerides)
5. Post-coital testing (PCT) (Simms-Huhner test) of cervical mucus
6. Rubella serology
7. Testing for viral status (HIV, hepatitis B, hepatitis C)
8. Serum hormone levels

   a. Androgens (testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEA-S) if there is evidence of hyperandrogenism (e.g., hirsuitism, acne, signs of virilization) or ovulatory dysfunction
   b. Gonadotropins (serum follicle-stimuating hormone [FSH], luteinizing hormone [LH]) for women with irregular menstrual cycles (see Appendix for medical necessity limitations) or age-related ovulatory dysfunction. **Note:** Aetna considers urinary FSH testing to be experimental and investigational. Serum, not urinary, FSH is the standard of care for determination of menopausal status (AAACE, 1999; NAMS, 2000; SOGC, 2002)
   c. Human chorionic gonadotrophin (hCG) (see Appendix for medical necessity limitations)
   d. Prolactin for women with an ovulatory disorder, galactorrhea, or a pituitary tumor
   e. Progestins (progesterone, 17-hydroxyprogesterone) (see Appendix for medical necessity limitations)
   f. Estrogens (estradiol) (see Appendix for medical necessity limitations)
g. Thyroid stimulating hormone (TSH) for women with symptoms of thyroid disease
h. Adrenocortitrophic hormone (ACTH) for ruling out Cushing's syndrome or Addison's disease in women who are amenorrheic
i. Clomiphene citrate challenge test

9. Karyotype testing for couples with recurrent pregnancy loss (2 or more consecutive spontaneous abortions) (See CPB 0348 - Recurrent Pregnancy Loss)

10. The following laboratory studies are considered experimental and investigational:

a. Anti-mullerian hormone
b. Antiprothrombin antibodies (See CPB 0662 - Antiprothrombin Antibody Testing)
c. Embryotoxicity assay (See CPB 0348 - Recurrent Pregnancy Loss)
d. Endometrial receptivity testing (e.g., endometrial receptivity array (ERA), integrin testing, beta-3 integrin test)
e. Uterine and endometrial receptivity testing (Endometrial function test (EFT) (cyclin E and p27) and E-tegrity)
f. Measurement of natural killer cell activity
g. Reproductive immunophenotyping
h. Serum inhibin B measurement (value in assessing ovarian reserve is uncertain).

Note: Many plans exclude coverage of home pregnancy tests and home ovulation test kits. Please check benefit plan descriptions.

C. Diagnostic procedures:

The following diagnostic procedures are considered medically necessary:

1. CT or MR imaging of sella turcica is considered medically necessary if prolactin is elevated
2. Endometrial biopsy
3. Hysterosalpingography (hysterosalpingogram (HSG)) or hysterosalpingo-contrast-ultrasonography to screen for tubal occlusion. Note: Sonohysterosalpingography or saline hysterosalpingography (e.g., Femvue) are considered experimental and investigational to screen for tubal occlusion because of a lack of reliable evidence of effectiveness.
4. Hysteroscopy, salpingoscopy (falloscopy), hydrotubation where clinically indicated
5. Laparoscopy and contrast dye to assess tubal and other pelvic pathology, and to follow-up on hysterosalpingography abnormalities
6. Sonohysteroscopy to evaluate the uterus
7. Ultrasound (e.g., ovarian, transvaginal, pelvic) (see Appendix for medical necessity limitations)
8. Monitoring of ovarian response to ovulatory stimulants:

   a. Estradiol (see Appendix for medical necessity limitations)
   b. FSH (see Appendix for medical necessity limitations)
   c. hCG quantitative (see Appendix for medical necessity limitations)
   d. LH assay (see Appendix for medical necessity limitations)
   e. Progesterone (see Appendix for medical necessity limitations)
f. Serial ovarian ultrasounds are considered medically necessary for cycle monitoring (see Appendix for medical necessity limitations).

D. Non-surgical treatments:

The following non-surgical treatments are considered medically necessary:

1. Aromatase inhibitors (e.g., anastrozole [Arimidex], exemestane [Aromasin], and letrozole [Femara])
2. Corticosteroids (e.g., dexamethasone, prednisone)
3. Estrogens (e.g., estrone and conjugated estrogens [Premarin])
4. Hepatitis B vaccination of partners of people with hepatitis B
5. Lutropin alfa (Luveris) for use in combination with human FSH to stimulate follicular development in infertile hypo-gonadotropic hypo-gonadal women or in women with a profound LH deficiency defined as LH less than 1.2 International Units/L
6. Metformin (Glucophage) for women with WHO Group II anovulatory disorders such as polycystic ovarian syndrome
7. Progestins (oral, topical gel (8% progesterone) (Crinone 8%, Prochive 8%) or intramuscular progestins and progesterone vaginal suppositories (Endometrin), see CPB 0510 - Progestins)
8. Prolactin inhibitors (bromocriptine (Parlodel), cabergoline (Dostinex), pergolide (Permax)) for women with ovulatory disorders due to hyperprolactinemia
9. Rubella vaccination of women susceptible to rubella
10. Tamoxifen (Novaldex) or oral clomiphene citrate (Clomid, Serophene) for ovulation induction.

Note: The medications listed above may not be covered for members without pharmacy benefit plans; in addition, some pharmacy benefit plans may exclude or limit coverage of some or all of these medications. Please check benefit plan descriptions for details.

The following non-surgical treatments are considered experimental and investigational:

Leukocyte immunization (immunizing the female partner with the male partner's leukocytes) (See CPB 0348 - Recurrent Pregnancy Loss); and

Dehydroepiandrosterone (DHEA); and

FSH manipulation of women with elevated FSH levels. (An elevated FSH level is a marker of reduced ovarian reserve, as occurs with advancing age. Elevated FSH-related (i.e., age-related) infertility has not been proven to be affected by interventions to reduce FSH levels.); and

Parenteral administration of lipids.

E. Infertility surgery:

1. Hysteroscopic adhesiolysis for women with amenorrhea who are found to have intrauterine adhesions
2. Hysteroscopic or fluoroscopic tubal cannulation (salpingostomy, fimbrioplasty), selective salpingography plus tubal catheterization, or transcervical balloon
tuboplasty for women with proximal tubal obstruction (See CPB 0347 -
Transcervical Balloon Tuboplasty)
3. Laparoscopic cystectomy for women with ovarian endometriomas
4. Laparoscopy for treatment of pelvic pathology
5. Open or laparoscopic resection, vaporization, or fulguration of endometriosis
   implants plus adhesiolysis in women with endometriosis
6. Ovarian wedge resection or ovarian drilling for women with WHO Group II ovulation
   disorders such as polycystic ovarian syndrome who have not responded to
   clomiphene citrate
7. Removal of myomas, uterine septa, cysts, ovarian tumors, and polyps
8. Surgical tubal reconstruction (unilateral or bilateral tubal microsurgery, laparoscopic
   tubal surgery, tuboplasty and tubal anastomosis) for women with mid or distal tubal
   occlusion and for women with proximal tubal disease where tubal cannulation has
   failed or where severe proximal tubal disease precludes the likelihood of successful
   cannulation
9. Tubal ligation (salpingectomy) for women with hydrosalpinges who are
   contemplating in vitro fertilization, as this has been demonstrated to improve the
   chance of a live birth before in-vitro fertilization treatment
10. Cervicectomy/trachelectomy is an acceptable alternative to hysterectomy for
    treatment of early stage (IA2 or small IB1) cervical adenocarcinoma in women who
    wish to preserve their fertility.
11. Bariatric surgery is considered experimental and investigational as a treatment for
    infertility (see CPB 0157 - Obesity Surgery).
12. Uterine transplant is considered experimental and investigational as a treatment for
    infertility.

II. Females: Additional Infertility Services

The following additional services (referred to in some plans as "Comprehensive Infertility
Services") may be considered medically necessary if the member is unable to conceive after
Treatment with Basic Infertility Services, or if the member's diagnosis suggests that there is no
reasonable chance of pregnancy as a result of Basic Infertility Services.

A. Injectable medications (See CPB 0020 - Injectable Medications)

1. Gonadotropin releasing hormone (GnRH) (luteinizing hormone releasing hormone
   (LHR-H)) by intermittent subcutaneous injections or by GnRH infusion pump
   (See CPB 0501 - Gonadotropin-Releasing Hormone Analogs and Antagonists for
   additional information and limitations.)
   - Gonadorelin (Synarel, Factrel)
   - Goserelin (Zoladex)
   - Leuprolide (Lupron)

Considered medically necessary for the following indications:

- For use, in addition to gonadotropin stimulation, in pituitary down-regulation
  as part of in-vitro fertilization treatment (Note: coverage of GnRH for this
  indication is limited to plans that cover advanced reproductive technologies.
  Please check benefit plan descriptions for details.)
Pulsatile administration of gonadotropin-releasing hormone is considered medically necessary in women with WHO Group I ovulation disorders (hypothalamic pituitary failure, characterized by hypothalamic amenorrhea or hypogonadotropic hypogonadism) (see Appendix for WHO classification of ovulation disorders).

2. Gonadotropins

- Human chorionic gonadotropin (hCG) (A.P.L., Novarel, Pregnyl, Ovidrel, Chorex, Choron)
- Human menopausal gonadotropin (hMG) (menotropins) (LH and FSH) (Menopur, Repronex)
- Urofollitropins (human FSH) (Fertinex, Bravemle) and recombinant follitropin (recombinant FSH) (Follitropin alfa (Gonal-F); Follitropin beta (Follistim)).

* Note on least cost brands of follitropin: There are several brands of FSH on the market. There is a lack of reliable evidence that any one brand of FSH is superior to other brands for medically necessary indications. Bravelle (urofollitropin alfa for injection), Gonal-F and Gonal-F RFF (recombinant follitropin alfa for injection) brands of FSH ("least cost brands of FSH") are less costly to Aetna. Consequently, because other brands of FSH such as Follistim and Follistim AQ (recombinant follitropin beta) are more costly than these least cost brands of FSH, and least cost brands of FSH are at least as likely to produce equivalent therapeutic results, no other brand of FSH will be considered medically necessary unless the member has a contraindication or intolerance to at least two of the least cost brands of FSH.

Gonadotropins are considered medically necessary for the following indications:

- Clomiphene plus gonadotropins may be considered medically necessary in women who do not ovulate using clomiphene alone
- For use in pituitary down-regulation as part of in-vitro fertilization (Note: coverage of gonadotropins for this indication is limited to plans that cover advanced reproductive technologies. Please check benefit plan descriptions for details.)
- Pulsatile administration of gonadotropins are considered medically necessary for women with WHO Group I ovulation disorders (hypothalamic pituitary failure, characterized by hypothalamic amenorrhea or hypogonadotropic hypogonadism)
- Women with WHO Group II ovulation disorders such as polycystic ovary syndrome who do not ovulate with clomiphene citrate or tamoxifen. (See Appendix for WHO classification of ovulation disorders).

Human chorionic gonadotropin (hCG) is considered experimental and investigational for in vitro fertilization with frozen-thawed embryos.

3. Gonadotropin releasing hormone (GnRH) antagonists
GnRH antagonists (ganirolex acetate (Antagon), cetrolex acetate (Cetrotide)) are considered medically necessary for women undergoing assisted reproduction techniques (ART) to prevent premature LH surge in women undergoing controlled ovarian stimulation with gonadotropins, allowing the follicles to mature for planned oocyte collection. (Note: coverage of GnRH antagonists for this indication is limited to plans that cover advanced reproductive technologies. Please check benefit plan descriptions for details.)

4. Growth hormone for infertility treatment is considered experimental and investigational. There is inadequate evidence that the use of adjuvant growth hormone treatment during ovulation induction improves pregnancy rates. See CPB 0170 - Growth Hormone (GH) and Growth Hormone Antagonists.

5. Intravenous immunoglobulins are considered experimental and investigational for treatment of infertility. See CPB 0348 - Recurrent Pregnancy Loss; and CPB 0206 - Parenteral Immunoglobulins.

6. Drainage of ovarian cyst for infertility treatment is considered experimental and investigational.

7. In-vitro maturation (IVM) of oocytes for infertility treatment is considered experimental and investigational.

Note: Many plans exclude coverage for infertility injectable medications; other plans may limit coverage of ovulation induction cycles with menotropins to six (6) per lifetime. Please check plan documents for details.

B. Artificial insemination: See section IV below.

III. Males: Infertility Services

The following services are considered medically necessary for diagnosis and/or treatment of infertility in men:

A. History and physical examination

B. Laboratory studies:

1. Anti-sperm antibodies (e.g., immunobead or mixed antiglobulin method)

2. Cultures
   a. Prostatic secretion
   b. Semen
   c. Urine

3. Serum hormone levels
   a. 17-hydroxyprogesterone
   b. Adrenal cortical stimulating hormone (ACTH)
   c. Androgens (testosterone, free testosterone)
   d. Estrogens (e.g., estradiol, estrone)
   e. Gonadotropins (FSH, LH)
   f. Growth hormone (GH)
g. Prolactin for men with reduced sperm counts, galactorrhea, or pituitary tumors
h. Sex hormone binding globulin (SHGB) for men with signs and symptoms of hypogonadism and low normal testosterone levels. (SHGB is not indicated in the routine evaluation of male infertility)
i. Thyroid stimulating hormone (TSH) for men with symptoms of thyroid disease.

4. Semen analysis (volume, pH, liquefaction time, sperm concentration, total sperm number, motility (forward progression), motile sperm per ejaculate, vitality, round cell differentiation (white cells versus germinal), morphology, viscosity, agglutination) is considered medically necessary for the evaluation of infertility in men. Because of the marked inherent variability of semen analyses, an abnormal result should be confirmed by at least one additional sample collected one or more weeks after the first sample.

- For men with abnormal semen analysis exposed to gonadotoxins, up to 4 semen analyses are considered medically necessary.
- For men with a normal initial semen analysis, a repeat semen analysis is considered medically necessary if there is no pregnancy 4 months after the initial normal semen analysis.
- If the result of the first semen analysis is abnormal and the man has not been exposed to gonadotoxins, up to 2 repeat confirmatory tests may be considered medically necessary.

5. Vasography
6. Semen leukocyte analysis (e.g., Endtz test, immunohistochemical staining)
7. Seminal fructose

Note: Seminal alpha-glucosidase, zinc, citric acid, and acid phosphatase are considered experimental and investigational.

8. Blood test for cytogenetic analysis (karyotype and FISH) in men with severe deficits of semen quality or azoosperma (for consideration of ICSI)
9. Cystic fibrosis mutation testing in men with congenital absence of vas deferens
10. Y chromosome microdeletion analysis in men with severe deficits of semen quality or azoosperma (for consideration of ICSI). Note: Y chromosome microdeletion analysis is not routinely indicated before ICSI, and is subject to medical necessity review
11. Post-coital test (PCT) (Simms-Huhner test) of cervical mucus
12. Sperm function tests:

a. Sperm penetration assay (zona-free hamster egg penetration test)

Note: The following sperm function tests are considered experimental and investigational:

a. Acrosome reaction test
b. Comet assay
c. Computer-assisted sperm analysis (CASA)/computer-assisted sperm motion analysis
d. Hemizona assay
e. Hyaluronan binding assay
f. Hypoosmotic swelling test
g. In vitro testing of sperm penetration
h. Reactive oxygen species (ROS) test
i. Sperm chromatin assay
j. Sperm DNA condensation test
k. Sperm DNA fragmentation assay
l. Sperm nucleus maturation
m. TUNEL assay

13. Karyotyping of couples with recurrent pregnancy loss (defined as 2 or more consecutive spontaneous abortions) (See CPB 0348 - Recurrent Pregnancy Loss) and for men with severe deficits in semen quality or nonobstructive azoospermia (for consideration of ICSI).

14. Testing for viral status (HIV, hepatitis B, hepatitis C)

C. Diagnostic procedures:

1. CT or MR imaging of sella turcica if prolactin is elevated
2. Scrotal exploration
3. Scrotal (testicular) ultrasound (See CPB 0532 - Scrotal Ultrasonography)
4. Testicular biopsy
5. Transrectal ultrasound (See CPB 0001 - Transrectal Ultrasound)
6. Vasography
7. Venography.

Note: Fine needle aspiration (“mapping”) of testes, and microdissection of the zona are considered experimental and investigational because their efficacy have not been established.

D. Treatments:

1. Endocrine management
   a. Androgens (testosterone) for persons with documented androgen deficiency
   b. Anti-estrogens (tamoxifen (Nolvadex)) for men with elevated estrogen levels
   c. Clomiphene (Clomid, Serophene)
   d. Corticosteroids (e.g., dexamethasone, prednisone)
   e. Prolactin inhibitors (bromocriptine (Parlodel), cabergoline (Dostinex)) for persons with hyperprolactinemia
   f. Thyroid hormone replacement for men with thyroid deficiency.

2. Injectable Endocrine Management:
   a. Human chorionic gonadotropins (hCG) (Novarel, Pregnyl) are considered medically necessary for the following indications: 1) male infertility due to
hypogonadotropic hypogonadism (select cases of hypogonadism secondary to pituitary deficiency); or 2) prepubertal cryptorchidism not due to anatomic obstruction.

b. Human menopausal gonadotropins (hMG) (menotropins) (Menopur, Repronex) are considered medically necessary for use with human chorionic gonadotropin for the induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure.

c. Gonadotropin releasing hormone (GnRH) (luteinizing hormone releasing hormone (LHRH)), by intermittent subcutaneous injections or by GnRH infusion pump, are considered medically necessary for men with infertility due to hypogonadotropic hypogonadism (see CPB 0501 - Gonadotropin-Releasing Hormone Analogs and Antagonists for additional information and limitations)

d. Urofollitropins (human FSH) (Bravette) and recombinant follitropin products (recombinant FSH) (follitropin alfa (Gonal-F, Gonal-F RFF); follitropin beta (Follistim, Follistim AQ))* are considered medically necessary for use with human chorionic gonadotropin for the induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure.

*Note on least cost brands of follitropin (FSH): There are several brands of follitropin (FSH) on the market. There is a lack of reliable evidence that any one brand of FSH is superior to other brands for medically necessary indications. Bravette (urofollitropin alfa for injection), Gonal-F and Gonal-F RFF (recombinant follitropin alfa for injection) brand of FSH ("least cost brand of FSH") are less costly to Aetna. Consequently, because other brand of FSH, such as Follistim Follistim AQ (recombinant follitropin beta) are more costly than these least cost brand of FSH, and the least cost brands of FSH are at least as likely to produce equivalent therapeutic results, no other brands of FSH will be considered medically necessary unless the member has a contraindication or intolerance to at least two of the least cost brands of FSH.

Human chorionic gonadotropin (hCG) (Novarel, Pregnyl), human menopausal gonadotropin (hMG) (Menopur, Repronex), urofollitropin (Bravette) and recombinant follitropins (Gonal-F, Gonal-F RFF, Follistim and Follistim AQ) are considered experimental and investigational for idiopathic male infertility (i.e., for men without documented hypogonadotropic hypogonadism), idiopathic microphallus and all other indications in men because they have not been found to be effective for those indications.

Ovidrel (recombinant chorionic gonadotropin alpha, rhCG), Cetrotide (cetrorelix acetate), Ganirelix (ganirelix acetate), and Luveris (lutropin alpha) are considered experimental and investigational for use in males, including but not limited to any type of male infertility.

Note: Many plans that otherwise cover infertility treatments exclude coverage for infertility injectable medications. Please check benefit plan descriptions.
3. Antibiotics for men with an identified infection (Note: Intra-prostatic antibiotic injection is considered experimental and investigational)

4. Varicocelectomy (spermatic vein ligation) (See CPB 0413 - Percutaneous Embolization of Varicocele)

5. Spermatocoeleectomy and hydrocelectomy

6. Surgical repair of vas deferens: vasovasostomy

Note: Most plans exclude coverage for reversal of sterilization procedures. This would include vasectomy. Please check benefit plan descriptions for details.

7. Surgical correction of epididymal blockage for men with obstructive azoospermia.
   a. Epididymectomy
   b. Epididymovasostomy
   c. Excision of epididymal tumors and cysts
   d. Epididymostomy.

8. Transurethral resection of ejaculatory ducts (TURED) for obstruction of ejaculatory ducts

9. Orchiopexy

10. Alpha sympathomimetic agents (for retrograde ejaculation) (e.g., phenylephrine, imipramine)

11. Hepatitis B vaccination of partners of people with hepatitis B

12. For impotence treatments, see CPB 0007 - Erectile Dysfunction.

Note: Under most Aetna benefit plans, self-administered prescription medications are covered under the pharmacy benefit. Please check benefit plan descriptions.

IV. Artificial Insemination

A. Aetna considers artificial insemination (intra-cervical insemination or intra-uterine insemination [IUI]) medically necessary for infertile couples with mild male-factor fertility problems, unexplained infertility problems, minimal to mild endometriosis, medically refractory erectile dysfunction or vaginismus preventing intercourse, couples where the man is HIV positive and undergoing sperm washing, or couples undergoing menotropin ovarian stimulation.

B. Aetna considers clomiphene-citrate-stimulated artificial insemination (intra-cervical insemination or IUI) medically necessary for infertile women with WHO Group II ovulation disorders such as polycystic ovarian syndrome who ovulate with clomiphene citrate but have not become pregnant after ovulation induction with clomiphene.

C. Aetna considers double IUI not medically necessary because it offers no clear benefit over single IUI in the overall clinical pregnancy rate in couples with unexplained infertility.

D. Aetna considers direct intra-peritoneal insemination, fallopian tube sperm transfusion, intra-follicular insemination, and the use of sperm precursors (i.e., round or elongated spermatid nuclei, immature sperm) in the treatment of infertility experimental and investigational because their effectiveness has not been established.

E. Aetna considers electroejaculation medically necessary DME to overcome total anejaculation secondary to neurologic impairment, which most commonly occurs among members with the following conditions:
   - Diabetic neuropathy
- Prior retroperitoneal surgery (most commonly retroperitoneal lymphadenectomy as a treatment of testicular cancer)
- Spinal cord injury.

F. Donor insemination is considered medically necessary for the following indications:

- Non-obstructive azoospermia
- Obstructive azoospermia
- Severe deficits in semen quality in couples who do not wish to undergo intracytoplasmic sperm injection (ICSI)
- Severe rhesus isoimmunization
- Where there is a high risk of transmitting a genetic disorder in the male partner to the offspring.*
- Where there is a high risk of transmitting an infectious disease (such as HIV) to the partner or offspring.*

Notes:

Many Aetna plans that otherwise cover infertility services exclude coverage of fees associated with donor insemination (including semen donor recruitment, selection and screening, and cryostorage of sperm). In addition, cryopreservation of semen not covered as it is not considered treatment of disease. Please check benefit plan descriptions for details.

* Some plans limit coverage of donor insemination to couples who are infertile. Under these plans, donor insemination would not be covered for these indications (infectious disease in male partner, high risk of transmitting a genetic disorder) as these do not meet the contractual definition of infertility. Please check benefit plan descriptions.

Note: Some Aetna benefit plans may exclude coverage of artificial insemination (AI). For Aetna benefit plans that cover artificial insemination, coverage is typically limited to six (6) cycles per lifetime. Please check benefit plan descriptions.

V. Advanced Reproductive Technology

The following Advanced Reproductive Technologies (ART) procedures are considered medically necessary for women with infertility that meet either of the following criteria:

A. Women who have failed to conceive after a trial of ovarian stimulation:

1. For women less than 37-years of age or younger, six cycles of ovarian stimulation (with or without intrauterine insemination); or
2. For women 38 to 39 years of age, three cycles of ovarian stimulation (with or without IUI); or
3. For women 40 years of age or older, no trial of ovarian stimulation is required; or

B. Couples for whom natural or artificial insemination would not be expected to be effective and ART would be expected to be the only effective treatment, including:

1. Men with azoospermia or severe deficits in semen quality or quantity (see Appendix); or
2. Women with tubal factor infertility:
Infertility

a. Bilateral tubal disease (e.g., tubal obstruction, absence, or hydrosalpinges).
b. Endometriosis stage 3 or 4.
c. Failure to conceive after pelvic surgery with restoration of normal pelvic anatomy (see section 1. E above for pelvic surgery procedures for infertility):
   i. After trying to conceive for 6 months if less than 40 years of age;
   ii. After trying to conceive for 3 months if 40 years of age or older.

d. Infertility resulting from ectopic pregnancy
e. Ectopic pregnancy occurring during infertility treatment.
f. Unilateral hydrosalpinx with failure to conceive:
   i. After trying to conceive for 12 months if less than 40 years of age;
   ii. After trying to conceive for 6 months if 40 years of age or older.

3. Inadvertent ovarian hyperstimulation (estradiol level was greater than 1,000 pg/ml plus greater than 3 follicles greater than 16 mm or 4 to 8 follicles greater than 14 mm or a larger number of smaller follicles) during preparation for a planned stimulated IUI cycle in women less than 40 years of age with a diagnosis other than polycystic ovarian syndrome. In women 40 year of age or older, it is not generally medically necessary to convert an IUI cycle to in-vitro fertilization (IVF) due to ovarian hyperstimulation.

**Note:** Coverage is limited to plans with an ART benefit; please check benefit plan descriptions.

**Note on coverage of ART for preimplantation genetic diagnosis (PGD):** The procedure to obtain the cell sample for PGD (i.e., the embryo biopsy) is covered when medical necessity criteria for PGD are met as set forth in CPB 0358 - Invasive Prenatal Diagnosis of Genetic Diseases. However, under plans that limit coverage of ART to persons who are infertile, the IVF procedure (i.e., the procedures and services required to create the embryos to be tested and the transfer of the appropriate embryos back to the uterus after testing) is covered only for persons with ART benefits who are infertile (please check benefit plan descriptions) and meet medical necessity criteria for ART.

A. IVF with embryo transfer is considered medically necessary when criteria for ART are met. IVF with embryo transfer includes:

1. Embryo transfer (transcervical transfer back to the donor) (including cryopreserved embryo transfer)
2. Frozen embryo transfer (FET) *(Note: It may be considered medically necessary to freeze embryos not transferred during a stimulated IVF treatment cycle, and to transfer the embryos before the next stimulated treatment cycle because this will minimize ovulation induction and egg collection, both of which carry risks for the woman and use more resources).* Before proceeding to the next fresh ART cycle, FET using cryopreserved embryos must be used if an adequate number of 3 or more cryopreserved embryos of a similar developmental stage are available *(see Appendix 4 for women 35 years of age or older)*
3. Oocyte (egg) insemination in laboratory dish
4. Oocyte (egg) retrieval via laparoscope or transvaginal needle aspiration of follicles
5. Sperm preparation and capacitation
6. Intra-cytoplasmic sperm injection (ICSI) is medically necessary where there is azoospermia or oligospermia (obstructive or non-obstructive), severe deficits in semen quality or quantity (see Appendix), or for couples where a previous IVF treatment cycle has resulted in failed or poor (see Appendix) fertilization. (For use of ICSI in preimplantation genetic diagnosis, see CPB 0358 - Invasive Prenatal Diagnosis of Genetic Diseases).

7. Assisted hatching is considered medically necessary for any of the following indications:

   a. Age greater than 38 years; or
   b. Multiple (2 or more) failed IVF attempts; or
   c. Thickened zona pellucida.

8. Note on IVF cycles for embryo banking: IVF cycles for the sole purpose of embryo banking (where none of the embryos that are suitable for transfer are used in the current cycle in which they are created, but are frozen for use in a future cycle) is not considered treatment of disease and is not covered.

B. Gamete intra-fallopian transfer (GIFT) is considered medically necessary as an alternative to IVF for women with female factor infertility. GIFT includes:

   1. Immediate loading of the eggs into a transfer catheter with sperm and insertion into the member’s fallopian tube via the same laparoscope (the member must have at least 1 patent fallopian tube for this method to be an effective treatment for infertility)
   2. Oocyte (egg) retrieval via laparoscope.

GIFT is considered experimental and investigational for person with male factor infertility or unexplained infertility problems because there is insufficient evidence to recommend GIFT over IVF for these indications.

C. Zygote intra-fallopian transfer (ZIFT), tubal embryo transfer (TET), pronuclear stage tubal embryo transfer (PROUST) is considered medically necessary as an alternative to IVF for women with female factor infertility.

ZIFT is considered experimental and investigational for persons with male factor infertility or unexplained infertility problems because there is insufficient evidence to recommend ZIFT over IVF for these indications.

D. Specialized sperm retrieval techniques (including vasal sperm aspiration, microsurgical epididymal sperm aspiration (MESA), percutaneous epididymal sperm aspiration (PESA), electroejaculation, testicular sperm aspiration (TESA), microsurgical testicular sperm extraction (TESE), seminal vesicle sperm aspiration, and sperm recovery from bladder or urine for retrograde ejaculation) are considered medically necessary to overcome anejaculation or azoospermia.

Note: Most plans exclude coverage of infertility services for persons who have undergone sterilization. This would include sperm retrieval for men who have undergone vasectomy. Please check benefit plan descriptions for details.
E. Oocyte donation is considered medically necessary for managing infertility problems associated with the following conditions, when the infertile member is the intended recipient of the resulting embryos:

1. Bilateral oophorectomy;
2. Gonadal dysgenesis including Turner syndrome;
3. High-risk of transmitting a genetic disorder from the female partner to the offspring;
4. IVF treatment failure
5. Ovarian failure following chemotherapy or radiotherapy; or
6. Premature ovarian failure (failure of ovulation in woman younger than 40 years of age) (considered medically necessary until the woman with POF is 45 years of age).

Note: Many Aetna plans that otherwise cover infertility services exclude coverage of fees associated with oocyte donation, including recruitment and selection of donors, ovarian stimulation of donors, collection of oocytes from donors, and screening and storage of donor oocytes. Please check benefit plan descriptions for details. Under plans with benefits for IVF that have this exclusion, medically necessary IVF services are covered only once an embryo is created from the donor egg.

F. Cryopreservation of oocytes or embryos is considered medically necessary in women facing infertility due to chemotherapy, pelvic radiotherapy, or other gonadotoxic therapies. Routine use of oocyte cryopreservation in lieu of embryo cryopreservation, oocyte cryopreservation to circumvent reproductive aging in healthy women, and laser-assisted necrotic blastomere removal from cryopreserved embryos are considered experimental and investigational. Note: Some Aetna plans have a specific contractual exclusion of coverage of any charges associated with embryo cryopreservation or storage of cryopreserved embryos. Please check benefit plan descriptions. In addition, cryopreservation of embryos and oocytes (other than short-term cryopreservation of embryos that are necessary for contemporaneous use in infertile persons currently under active fertility treatment, or use of cryopreserved embryos or oocytes in women facing infertility due to chemotherapy or other gonadotoxic therapies) is not considered treatment of disease and is not covered.

G. Cryopreservation of sperm is considered medically necessary in men facing infertility due to chemotherapy, pelvic radiotherapy, or other gonadotoxic therapies. Sperm cryopreservation to circumvent reproductive aging in healthy men is considered experimental and investigational. Note: Some Aetna plans have a specific contractual exclusion of coverage of any charges associated with sperm cryopreservation or storage. Please check benefit plan descriptions. In addition, cryopreservation of sperm (other than cryopreserved sperm in men facing infertility due to chemotherapy or other gonadotoxic therapies) is not considered treatment of disease and is not covered.

H. The following procedures are considered experimental and investigational:

1. EmbryoGlue
2. Partial zonal dissection (PZD)
3. Subzonal sperm insertion (SUZI)

Note: A cycle of ART defined in the CPB may be any of the following: IVF (with fresh embryos), IVF/frozen embryo transfer, GIFT or ZIFT.
Note on elective single embryo transfer: In order to reduce the number of high-order multiple pregnancies, current guidelines from the American Society for Reproductive Medicine (ASRM, 2009) recommend elective single embryo transfer for women under the age of 35 who have no prior IVF cycles or who have had a previous IVF cycle that was successful in producing a pregnancy (i.e., documentation of fetal heartbeat) and who have excess embryos of sufficient quality to warrant cryopreservation. For women who meet these criteria who elect transfer of a single fresh embryo, Aetna will consider transfer of 1 cryopreserved embryo immediately subsequent to the fresh embryo transfer as part of the same IVF cycle, under plans that limit the number of IVF cycles that are covered. Please check benefit plan descriptions for details.

See also: CPB 0189 - Genetic Counseling, and CPB 0323 - Preconceptional Sex Selection Techniques.

Appendix

Laboratory Services:

The following numbers of laboratory services per cycle are considered medically necessary.

<table>
<thead>
<tr>
<th></th>
<th>Natural monitoring</th>
<th>Clomid monitoring</th>
<th>Clomid IUI</th>
<th>Inj Mon Cycle</th>
<th>Inj IUI</th>
<th>IVF</th>
<th>GIFT</th>
<th>FET Code</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transvaginal ultrasound</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>FSH</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>LH</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Progesterone</td>
<td>2*</td>
<td>2*</td>
<td>2*</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>hCG</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>


*Note: More than 2 progesterone measurements may be medically necessary for infertile women with irregular and prolonged menstrual cycles. For infertile women with regular menstrual cycles, a mid-luteal serum progesterone measurement (day 21 of a 28-day cycle) is considered medically necessary. For infertile women with irregular menstrual cycles, this test would need to be repeated at the mid-luteal phase and weekly thereafter until the next menstrual cycle starts.

Table: Female Gonadotropin Injectable Vial Management:

<table>
<thead>
<tr>
<th>Brand Names</th>
<th>Strength</th>
<th>Insemination Quantity†</th>
<th>ART Quantity‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Gonadotropins/Menotropins (Initial Cycle*)</td>
<td></td>
</tr>
</tbody>
</table>
### Examples:
- Follistim, Gonal F, Bravelle, etc.

<table>
<thead>
<tr>
<th>Example</th>
<th>Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 IU</td>
<td>20 ampules (up to 35 ampules if FSH level is greater than 12 and less than 19)</td>
</tr>
<tr>
<td>75 IU</td>
<td>20 to 30 ampules (up to 40 ampules if FSH level is greater than 12 and less than 19)</td>
</tr>
<tr>
<td>75 IU</td>
<td>40 ampules (up to 50 ampules if FSH level is greater than 12 and less than 19)</td>
</tr>
<tr>
<td>75 IU</td>
<td>10 ampules</td>
</tr>
<tr>
<td>150 IU, 300 IU, 450 IU, 600 IU, 900 IU, 450 IU MDV</td>
<td>15 ampules</td>
</tr>
</tbody>
</table>

### Luteinizing Hormone (Initial Cycle*)
- Less than age 35 years: 1 to 10 ampules
- Age 35 to 39 years: 10 to 15 ampules
- Age 40 years and older: 15 to 20 ampules

### Luteinizing Hormone (Initial Cycle*)
- Less than age 35 years: 1 to 10 ampules
- Age 35 to 39 years: 10 to 15 ampules
- Age 40 years and older: 15 to 20 ampules

### HCG subcutaneous injections (Initial Cycle*)
- Ovidrel 250 mcg 1 to 2 PFS 1 to 2 PFS

### HCG intramuscular injections (Initial Cycle*)
- HCG low dose 50 IU vial 1 vial 1 vial
<table>
<thead>
<tr>
<th></th>
<th>10 IU vial</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples:</td>
<td></td>
<td>5000 U</td>
<td>1 vial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10,000 U</td>
<td>1 vial</td>
</tr>
</tbody>
</table>

**GnRH Antagonists (Initial Cycle*)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>250 ug/0.5 ml</th>
<th>3 PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganiirelix acetate</td>
<td></td>
<td>4 PFS</td>
<td></td>
</tr>
<tr>
<td>(prefilled syringe)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>0.25 mg</th>
<th>1 to 7 PFS</th>
<th>1 to 7 PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetrotide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>3.0 mg</th>
<th>1 PFS</th>
<th>1 PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetrotide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: ART: advanced reproductive technology; BMI: body mass index; FSH: follicle stimulating hormone; HCG: human chorionic gonadotropin; IU: international units; MDV: multiple dose vial; PCOS: polycystic ovarian syndrome; PFS: prefilled syringe; U: units.

Notes:

* Refills based upon documentation in cycle sheets.

** Some plans exclude infertility services for ovarian failure; please check benefit plan descriptions.

† Assumes intra-uterine insemination cycle uses medication for 10 days

‡ Assumes ART cycle uses medication for 10 days.

§ For different concentrations use 75 IU as a base.

Table: Male Gonadotropin Injectable Vial Management:

<table>
<thead>
<tr>
<th>Brand Names</th>
<th>Strength</th>
<th>Dose</th>
<th>Length of approval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follitropins*</td>
<td></td>
</tr>
<tr>
<td>Gonal-F</td>
<td>450 unit MDV, 1050 unit MDV</td>
<td>After normalization of serum testosterone levels, use Gonal F concomitantly with hCG: 150 units three times a week; maximum dose</td>
<td>6 months</td>
</tr>
<tr>
<td>Follistim AQ</td>
<td></td>
<td>6 months</td>
<td></td>
</tr>
</tbody>
</table>

http://qawww.aetna.com/cpb/medical/data/300_399/0327_draft.html 11/03/2014
**Infertility**

<table>
<thead>
<tr>
<th>75 unit SDV, 150 unit SDV 150, 300, 600, 900 unit multi dose cartridges</th>
<th>300 units three times a week for up to 18 months After normalization of serum testosterone levels, use Follistim AQ concomitantly with hCG: 450 units per week (or 225 units twice a week or 150 units three times a week).</th>
</tr>
</thead>
</table>

**hCG intramuscular injections**

| Examples: Pregnyl, Novarel, hCG | 10,000 u | Varies: 500-1000 units three times per week x 3 weeks followed by same dose twice a week x 3 weeks OR 4000 units three times per week for 6-9 months, following which dosage may be decreased to 2000 units three times per week for an additional 3 months | 6 months |

*Concomitant recombinant follitropin and human chorionic gonadotropin therapy should be continued for at least 3 to 4 months before improvement in spermatogenesis can be expected.*

**Definitions:**

For purposes of this policy, the following definitions will be used:

**Classification of ovulatory disorders:**

Anovulation and oligo-ovulation are ovulatory disorders that are estimated to cause 21% of female fertility problems. The World Health Organization classifies ovulation disorders into 3 groups.

- **Group I:** hypothalamic pituitary failure (hypothalamic amenorrhea or hypogonadotrophic hypogonadism).
- **Group II:** hypothalamic pituitary dysfunction (predominately polycystic ovary syndrome).
- **Group III:** ovarian failure.

**Embryo Quantity and Quality in ART Cycles:**

Embryo quantity and quality are considered adequate if an ART cycle produces 3 or more embryos for transfer, each of which are at least 6 to 8 cells (for day 3 transfers) of reasonable quality (grade B or its equivalent) with less than 50% fragmentation.

**Fertilization Rates in IVF Cycles:**

Fertilization rates are considered poor if IVF cycles result in less than 50% fertilization.
Ovarian Reserve in Response to Gonadotropin Stimulation:

Ovarian reserve is considered normal if 3 or more follicles develop and estrogen levels are greater than 500 mIU/ml following ovarian hyperstimulation with gonadotropins. Diminished ovarian reserve is indicated by peak estrogen levels less than 500 mIU/ml or fewer than 3 mature follicles are available at the time of stimulation and retrieval.

Semen Quality and Quantity:

Deficits in semen quantity are considered severe if there are less than 10 million total motile sperm per ejaculate (unwashed specimen) or less than 3 million total motile sperm (washed specimen) on 2 separate occasions at least 2 weeks apart. Deficits in semen quality are considered severe if there are less than 4 % normal forms using Kruger strict morphology.

Table: Semen Analysis: World Health Organization Reference Values

<table>
<thead>
<tr>
<th>semen volume: 1.5 ml or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH: 7.2 or more</td>
</tr>
<tr>
<td>sperm concentration: 15 million spermatozoa per ml or more</td>
</tr>
<tr>
<td>total sperm number: 39 million spermatozoa per ejaculate or more</td>
</tr>
<tr>
<td>total motility (percentage of progressive motility and non-progressive motility): 40 % or more</td>
</tr>
<tr>
<td>motile or 32 % or more with progressive motility</td>
</tr>
<tr>
<td>vitality: 58 % or more live spermatozoa</td>
</tr>
<tr>
<td>sperm morphology (percentage of normal forms): 4 % or more.</td>
</tr>
</tbody>
</table>

Table: Limits on the Number of Embryos to Transfer

Before proceeding to the next fresh ART cycle, frozen embryo transfer (FET) using cryopreserved embryos must be used if the following numbers of cryopreserved embryos are available:

<table>
<thead>
<tr>
<th>Less than 35</th>
<th>35 to 37 years</th>
<th>37 to 39 years</th>
<th>40 years &amp; older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleavage-stage embryos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable*</td>
<td>1 to 2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>All others</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Blastocysts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable*</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>All others</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

* Favorable = first cycle of IVF, good embryo quality, excess embryos available for cryopreservation, or previous successful IVF cycle.


Background

No fertility treatment other than oocyte donation has been shown to be effective for women over 40 years of age with compromised ovarian reserve. Elevated follicle-stimulating hormone (FSH) and estradiol levels are independent predictors of poor prognosis in older women. Common criteria for normal ovarian reserve are an early follicular phase FSH level of less than 10 mIU/ml and an estradiol concentration...
level of less than 80 pg/ml (ASRM, 2002). Higher cut-off values for FSH have been reported (as high as 20 to 25 mIU/ml for FSH) because of the use of different FSH assay reference standards. Women with diminished ovarian reserve experience decreased responses to ovulation induction, require higher doses of gonadotropin, have higher in-vitro fertilization (IVF) cycle cancellation rates, and experience lower pregnancy rates through IVF.

Aetna covers ovarian stimulation medications and techniques only for women who have a biologic capacity to effectively respond to ovarian stimulation. Serum FSH is a marker of ovarian responsiveness. Ovarian responsiveness is determined by measurement of an unmedicated day 3 FSH obtained within the prior 6 months if the woman is older than age 35 or in the prior 12 months if the individual is age 35 or younger. In women greater than age 40, any single FSH greater than 19mIU/mL, regardless of subsequent test results that may be lower than 19mIU/mL, are indicative of ovarian insufficiency. In women less than age 40, ovarian responsiveness is demonstrated by any unmedicated day 3 FSH of less than 19mIU/mL. Younger women with a day 3 FSH less than 19mIU/mL have the capacity to respond to ovarian stimulation, even if they have had other day 3 FSH measurements greater than 19 mIU/mL.

Guidelines from the Society for Reproductive Medicine and Society for Assisted Reproductive Technology (Pfeifer et al., 2013) recommend that oocyte cryopreservation with appropriate counseling is recommended in patients facing infertility due to chemotherapy or other gonadotoxic therapies. The guidelines state that more widespread clinic-specific data on the safety and efficacy of oocyte cryopreservation in donor populations are needed before universal donor oocyte banking can be recommended. The guidelines state that there are not yet sufficient data to recommend oocyte cryopreservation for the sole purpose of circumventing reproductive aging in healthy women. The guidelines state that more data are needed before this technology should be used routinely in lieu of embryo cryopreservation.

The ACOG practice bulletin on bariatric surgery and pregnancy (2009) stated that bariatric surgery should not be considered a treatment for infertility.

Although anti-mullerian hormone (AMH) levels appears to be associated with declining ovarian function, there is no consensus on the appropriate threshold value. An assessment by the Institute for Clinical and Health Policy (Pichon-Riviere, et al., 2009) found no clear evidence on the usefulness of AMH in the assisted reproduction program clinical practice setting. The assessment found less evidence for the utility of AMH in other clinical practice settings. Guidelines from the American Society for Reproductive Medicine (2012) concluded “There is mounting evidence to support the use of AMH as a screening test for poor ovarian response, but more data are needed. There is emerging evidence to suggest that a low AMH level (e.g., undetectable AMH) has high specificity as a screen for poor ovarian response but insufficient evidence to suggest its use to screen for failure to conceive.”

Steiner (2009) stated that serum and urinary markers of ovarian reserve -- follicular phase inhibin B, FSH, and anti-mullerian hormone (AMH) levels -- are physiologically associated with ovarian aging, decline with chronologic age, and appear to predict later stages of reproductive aging including the menopause transition and menopause. In infertile women, they can be used to predict low oocyte yield and treatment failure in women undergoing IVF. These markers seem to be affected by common ovarian toxicants, such as smoking, which advance the age at menopause. Although available for commercial use, home test kits have not been shown to predict fertility or infertility in the general population. Clinical use of these markers is limited by the variety of assays, lack of definitive thresholds, and their intercycle variability in older women. Results should be conveyed with caution when highly discrepant with age, in the obese, and in women with irregular menstrual cycles. The author stated that
further research is needed to assess their predictive value for determining fertility in the general population.

Nelson et al (2009) stated that individualization of controlled ovarian stimulation (COS) for assisted conception is complicated by variable ovarian response to FSH. These researchers hypothesized that AMH may facilitate treatment strategies for women undergoing COS, to optimize safety and clinical pregnancy rates. A prospective cohort study of 538 patients in 2 centers with differential COS strategies based on a centralized AMH measurement was performed. Anti-Müllerian hormone was associated with oocyte yield after ovarian stimulation in both centers, and a "reduced" AMH (1 to less than 5 pmol/L) was associated with a reduced clinical pregnancy rate. Women with a "normal" AMH (5 to less than 15 pmol/L) treated with a long GnRH-agonist protocol (both centers) showed a low incidence of excess response (0 %) and poor response (0 %). In women with "high" AMH (greater than 15 pmol/L), the antagonist protocol eliminated the need for complete cryo-preservation of embryos due to excess response (p < 0.001) and showed a higher fresh cycle clinical pregnancy rate than agonist cycles odds ratio (OR) 4.40 (95 % confidence interval [CI]: 1.95 to 9.93), p < 0.001. The authors concluded that the use of circulating AMH to individualize treatment strategies for COS may result in reduced clinical risk, optimized treatment burden and maintained pregnancy rates, and is worthy of prospective randomized examination.

Nardo et al (2009) evaluated the clinical value of basal AMH measurements compared with other available determinants, apart from chronologic age, in the prediction of ovarian response to gonadotropin stimulation. Women undergoing their first cycle of controlled ovarian hyperstimulation (COH) for IVF were subject of this study. Basal levels of FSH and AMH as well as antral follicle count (AFC) were measured in 165 subjects. All patients were followed prospectively and their cycle outcomes recorded. Main outcome measures included predictive value of FSH, AMH, and AFC for extremes of ovarian response to stimulation. Out of the 165 women, 134 were defined as normal responders, 15 as poor responders, and 16 as high responders. Subjects in the poor response group were significantly older than those in the other 2 groups. Anti-Müllerian hormone levels and AFC were markedly raised in the high responders and decreased in the poor responders. Compared with FSH and AFC, AMH performed better in the prediction of excessive response to ovarian stimulation-AMH area under receiver operating characteristic curve (ROC(AUC)) 0.81, FSH ROC(AUC) 0.66, AFC ROC (AUC) 0.69. For poor response, AMH (ROC(AUC) 0.88) was a significantly better predictor than FSH (ROC(AUC) 0.63) but not AFC (ROC(AUC) 0.81). Anti-Müllerian hormone prediction of ovarian response was independent of age and polycystic ovarian syndrome (PCOS). Anti-Müllerian hormone cutoffs of greater than 3.75 ng/ml and less than 1.0 ng/ml would have modest sensitivity and specificity in predicting the extremes of response. The authors concluded that circulating AMH has the ability to predict excessive and poor response to stimulation with exogenous gonadotrophins. Overall, this biomarker is superior to basal FSH and AFC, and has the potential to be incorporated in to work-up protocols to predict patient's ovarian response to treatment and to individualize strategies aiming at reducing the cancellation rate and the iatrogenic complications of COH.

Su and associates (2010) examined if AMH and inhibin B were impacted by breast cancer treatment by comparing cancer survivors to age-matched control women and determined the association between these hormones and post-chemotherapy menstrual pattern. Breast cancer patients (n = 127) with American Joint Committee on Cancer stage I to III disease who were pre-menopausal at diagnosis were enrolled post-chemotherapy and observed. The primary end point was chemotherapy-related amenorrhea (CRA) (greater than or equal to 12 months of amenorrhea following chemotherapy). Matched pair analyses compared AMH, inhibin B, and FSH levels between cancer and age-matched control subjects. Associations between hormones, CRA status, and change in CRA status over time were assessed. The median age of the patients at chemotherapy was 43.2 years (range of 26.7 to 57.8 years). At enrollment, median follow-up since chemotherapy was 2.1 years, and 55 % of subjects had
CRA. Compared with age-matched controls, cancer subjects had significantly lower AMH (p = 0.004) and inhibin B (p < 0.001) and higher FSH (p < 0.001). Inhibin B (p = 0.001) and AMH (p = 0.002) were found to be significantly associated with risk of CRA, even after controlling for FSH. Anti-mullerian hormone was significantly lower (p = 0.03) and FSH was significantly higher (p = 0.04) in menstruating subjects who developed subsequent CRA. The authors concluded that AMH and inhibin B are 2 additional measures of post-chemotherapy ovarian function in late reproductive-aged breast cancer survivors. They stated that with further research and validation, these hormones may supplement limited current tools for assessing and predicting post-chemotherapy ovarian function.

In a Cochrane review, Duffy et al (2010) the effectiveness of adjuvant growth hormone (GH) in IVF protocols. These investigators searched the Cochrane Menstrual Disorders and Subfertility Groups trials register (June 2009), the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 2, 2009), MEDLINE (1966 to June 2009), EMBASE (1988 to June 2009) and Biological Abstracts (1969 to June 2009). All randomized controlled trials were included if they addressed the research question and provided outcome data for intervention and control participants. Assessment of trial risk of bias and extraction of relevant data was performed independently by 2 reviewers. A total of 10 studies (440 subfertile couples) were included. Results of the meta-analysis demonstrated no difference in outcome measures and adverse events in the routine use of adjuvant GH in IVF protocols. However, meta-analysis demonstrated a statistically significant difference in both live birth rates and pregnancy rates favoring the use of adjuvant GH in IVF protocols in women who are considered poor responders without increasing adverse events, OR 5.39, 95 % CI: 1.89 to 15.35 and OR 3.28, 95 % CI: 1.74 to 6.20 respectively. The authors concluded that although the use of GH in poor responders has been found to show a significant improvement in live birth rates, they were unable to identify which sub-group of poor responders would benefit the most from adjuvant GH. The result needs to be interpreted with caution, the included trials were few in number and small sample size. Thus, before recommending GH adjuvant in IVF, further research is needed to fully define its role.

Guidelines from the American Society for Reproductive Medicine (2012) concluded that "inhibin B is not a reliable measure of ovarian reserve" and that "the routine use of inhibin B as a measure of ovarian reserve is not recommended."

In a meta-analysis, Toulis et al (2010) evaluated the diagnostic accuracy of inhibin B and AMH as markers of persistent spermatogenesis in men with non-obstructive azoospermia (NOA). A search was conducted in the electronic databases MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials from inception through June 2009. A total of 36 different studies reported data on the predictive value of 1 or more index markers (serum inhibin B: 32 studies, seminal inhibin B: 5 studies, serum AMH: 2 studies, seminal AMH: 4 studies) and were included in the systematic review. Nine studies, which had serum inhibin B as index marker, met the predefined criteria and were included in the meta-analysis. Serum inhibin B showed a sensitivity of 0.65 (95 % CI: 0.56 to 0.74) and a specificity of 0.83 (CI: 0.64 to 0.93) for the prediction of the presence of sperm in testicular sperm extraction (TESE). When the pre-test probability of 41 % was incorporated in a Fagan's nomogram, resulted in a positive post-test probability of 73 % and a negative post-test probability of 23 % for the presence of sperm in TESE. The authors concluded that serum inhibin B can not serve as a stand-alone marker of persistent spermatogenesis in men with NOA. Although limited, evidence on serum AMH and serum/seminal AMH do not support their diagnostic value in men with NOA.

Steiner et al (2011) generated estimates of the association between markers of ovarian aging and natural fertility in a community sample at risk for ovarian aging. Women aged 30 to 44 years with no history of infertility who had been trying to conceive for less than 3 months provided early-follicular phase serum and urine (n = 100). Subsequently, these women kept a diary to record menstrual bleeding and intercourse and conducted standardized pregnancy testing for up to 6 months. Serum was
analyzed for estradiol, FSH, AMH, and inhibin B. Urine was analyzed for FSH and estrone 3-glucuronide. Diary data on menstrual cycle day and patterns of intercourse were used to calculate day-specific fecundability ratios. Sixty-three percent of participants conceived within 6 months. After adjusting for age, 18 women (18%) with serum AMH levels of 0.7 ng/ml or less had significantly reduced fecundability given intercourse on a fertile day compared with women with higher AMH levels (fecundability ratio 0.38; 95% CI: 0.08 to 0.91). The day-specific fecundability for women with early-follicular phase serum FSH values greater than 10 mIU/ml compared with women with lower FSH levels was also reduced, although nonsignificantly (11% of women affected; fecundability ratio 0.44; 95% CI: 0.08 to 1.10). The association with urinary FSH was weaker (27% women affected; fecundability ratio 0.61; 95% CI: 0.26 to 1.26), and the associations for the other markers were weaker still. The authors concluded that early-follicular phase AMH appears to be associated with natural fertility in the general population. Moreover, they stated that larger studies are needed to confirm these findings and to explore the way the different endocrine markers interact as potential joint predictors of fertility.

In a meta-analysis, Polyzos and associates (2010) examined the effect of double versus single intrauterine insemination (IUI) per treatment cycle in women with unexplained infertility. Main outcome measure was clinical pregnancy rates per couple. Electronic searches of the Cochrane Central Trials Registry and Medline without year and language restriction through March 2009 were performed; hand searching of the abstract books of the European Society of Human Reproduction and Embryology and American Society for Reproductive Medicine annual meetings (2001 to 2008) was carried out. A total of 6 randomized trials, involving 829 women, were included in the analysis. Fifty-four (13.6%) clinical pregnancies were recorded for treatment with double IUI and 62 (14.4%) for treatment with single IUI. There was no significant difference between the single and double IUI groups in the probability for clinical pregnancy (OR, 0.92; 95% CI: 0.58 to 1.45; p = 0.715). The authors concluded that double IUI offers no clear benefit in the overall clinical pregnancy rate in couples with unexplained infertility.

Guerini et al (2005) reported that in chronic prostatitis there are many causes that may provoke a therapeutical failure of a systemic antibiotic treatment. At the moment a consensus has not been reached on the effectiveness of the many therapeutical options that are available with not one of these approaches being effective in all patients. In the authors' view the main causes of treatment failure are the well-known hurdle to antibiotic diffusion inside the glandular parenchyma associated with the so-called intra-prostatic bacterial biofilms and the possible presence of local auto-immune reactions. Given this background, these researchers tested ultrasound-guided intra-prostate infiltration of a cocktail of antibiotics and betamethasone, for a therapeutical options. A total of 320 patients, referred for treatment because of symptoms indicative of chronic prostatitis, were enrolled in this study. The inclusion criteria were the severity of the symptoms and the failure of repeated cycles of antibiotics in the previous 12 months. At the initial consultation patients completed the NIH Prostatitis Symptoms Index (NIH-CPSI). All underwent: (i) digital rectal examination (DRE), (ii) transrectal prostatic ultrasound scan (TRUS), (iii) uroflowmetry, (iv) cultures of first voiding and after prostatic massage urine and cultures of sperm for saprophytic and pathogen germs, yeasts and protozoa, (v) DNA amplification with polymerase chain reaction (PCR) on urine and sperm, for Chlamydia trachomatis, Mycoplasmas (Ureaplasma urealyticum and Mycoplasma hominis), Gonococcus, HPV and HCV. Patients on the basis of laboratory results received a cocktail of antibiotics associated with betamethasone. The cocktail was administered as prostate infiltration. Administration was repeated after 7 and 14 days. Final assessment of the effectiveness of therapy included not only the NIH-CPSI scores but also the patient's subjective judgement expressed as a "percentage overall improvement". The percentage judgements were arbitrarily divided into 4 classes: (i) 0 to 30 %: no improvement (Class I); (ii) 30 to 50 %: satisfactory improvement (Class II); (iii) 50 to 80 %: good improvement (Class III); and (iv) 80 to 100 %: cured (Class IV). Statistical analysis of the results showed 68 % of patients were included in the Class IV and 13 % were non-responders (Class I). The authors concluded that this is one of the more valid therapeutical approaches to chronic bacterial or abacterial prostatitis; but it also required more studies.
McGrath et al (2009) stated that cycle-dependent fluctuations in natural killer (NK) cell populations in endometrium and circulation may differ, contributing to unexplained infertility. They conducted a study whereby NK cell phenotypes were determined by flow cytometry in endometrial biopsies and matched blood samples. While circulating and endometrial T cell populations remained constant throughout the menstrual cycle in fertile and infertile women, circulating NK cells in infertile women increased during the secretory phase. However, increased expression of CD94, CD158b (secretory phase), and CD158a (proliferative phase) by endometrial NK cells from infertile women was observed. These changes were not reflected in the circulation. In infertile women, changes in circulating NK cell percentages were found exclusively during the secretory phase and not in endometrium; cycle-related changes in NK receptor expression were observed only in infertile endometrium. While having exciting implications for understanding NK cell function in fertility, these data emphasized the difficulty in attaching diagnostic or prognostic significance to NK cell analyses in individual patients.

Winger et al (2011) examined if quantification of peripheral blood Treg cell levels could be used as an indicator of miscarriage risk in newly pregnant women with a history of immunologic reproductive failure. A total of 54 pregnant women with a history of immunologic infertility and/or pregnancy loss were retrospectively evaluated (mean age of 36.7 +/- 4.9 years, 2.8 +/- 2.5 previous miscarriages; 1.5 +/- 1.9 previous IVF failures). Twenty-three of these women experienced another first trimester miscarriage, and 31 of these women continued their current pregnancies past 12 weeks ("pregnancy success"). The following immunologic parameters were assessed in the first trimester: NK cell 50:1 cytotoxicity, CD56 (+) 16 (+) CD3 (-) (NK), CD56 (+) CD3 (+) (NK-T), TNFα/IL-10, IFNγ/IL-10, CD4 (+) CD25 (-) Foxp3 (+), total CD4 (+) Foxp3 (+) (CD4 (+) CD25 (+) Foxp3 +), and CD4 (+) CD25 (+) Foxp3 (+) levels. Patients with successful ongoing pregnancies experienced an mean (CD4 (+) CD25 (+) Foxp3 (+)) "Treg" level of 0.72 +/- 0.52 %, while those that miscarried in the first trimester experienced a mean Treg level of 0.37 +/- 0.29 % (p = 0.005). Markers not significantly different between the loss and success groups were NK 50:1 cytolysis (p = 0.63), CD56 (+) 16 (+) 3 (+) NK cells (p = 0.63), CD56 (+) 3 (+) NK-T (p = 0.30), TNFα/IL-10 (p = 0.13), IFNγ/IL-10 (p = 0.63), and CD4 (+) 25 (-) Foxp3 (+) cells (p = 0.10), although total CD4 (+) Foxp3 (+) levels remained significant (p = 0.02) and CD4 (+) 25 (+) Foxp3 (+) showed the most significant difference (p = 0.005). Mean day of blood draw was 49.2 +/- 36.1 days pregnant (median of 39.0 days). In addition, patients with a low Treg level (less than 0.7 %) in the first trimester experienced a significantly lower ongoing pregnancy rate than those with a higher Treg level (greater than 0.7 %) in the first trimester [44 % (15/34) versus 80 % (16/20); p = 0.01]. Of the 18 successful pregnancies with sequential Treg results, 85 % (11/13) showed a T-regulatory-cell-level increase (mean Treg change 0.33 +/- 0.32), while only 40 % (2/5) of the failed pregnancies showed a Treg increase (mean Treg change -0.08 +/- 0.28; p = 0.02). The authors concluded that from these data, they proposed that CD4 (+) CD25 (+) Foxp3 (+) T regulatory cells may serve as a superior pregnancy marker for assessing miscarriage risk in newly pregnant women. Moreover, they stated that larger follow-up studies are needed for confirmation.

In a prospective, randomized controlled trial, Ben-Meir et al (2010) examined if supplementation with hCG throughout the secretory phase of hormonally modulated cycles of frozen-thawed embryos might positively affect the outcome of such cycles. Patients were randomly divided into 2 groups by the last digit of their identification number. Group A received the authors' standard protocol for endometrial preparation, whereas group B patients were given an additional 250 microg of recombinant hCG on day of progesterone (P) initiation, the day of embryo transfer, and 6 days later. Throughout the cycle, and to compare between the groups, serial ultrasound examinations and hormonal tests of E(2) and P serum levels were obtained. Main outcome measures were implantation and clinical pregnancy rates (PR). A total of 165 patients were enrolled in this study -- 78 in the control group and 87 in the hCG-treated group. Progesterone levels and endometrial thickness were similar throughout the cycle in both groups. The E(2) level was significantly higher in group B on the day of embryo transfer and 6 days
later. The PRs did not differ between the 2 groups (28.2 % and 32.2 % for groups A and B, respectively). Similarly, the implantation rates were comparable between the groups (12.7 % and 14.9 %, respectively). The authors concluded that no advantage was found concerning PR and implantation rate by supplementing the secretary phase with hCG in patients undergoing transfer of frozen-thawed embryo in hormonally modulated cycles.

In a systematic review and meta-analysis, Momeni et al (2011) evaluated the relationship between endometrial thickness on the day of hCG administration and pregnancy outcome in in-vitro fertilization cycles. These investigators identified 484 articles using Cochrane library, PubMed, Web of Science, and Embase searches with various key words including endometrial thickness, pregnancy, assisted reproductive technology, endometrial pattern, and in-vitro fertilization. A total of 14 studies with data on endometrial thickness and outcome were selected, representing 4,922 cycles (2,204 pregnant and 2,718 non-pregnant). The meta-analysis with a random effects model was performed using comprehensive meta-analysis software. These researchers calculated the standardized mean difference, odds ratio (OR), and 95 % confidence intervals (CIs). There was a significant difference in the mean endometrial thickness between pregnant and non-pregnant groups (p < 0.001), with a standardized mean difference of 0.4 mm (95 % CI: 0.22 to 0.58). The OR for pregnancy was 1.40 (95 % CI: 1.24 to 1.58). The authors concluded that the mean endometrial thickness was significantly higher in pregnant women compared to non-pregnant. The mean difference between 2 groups was less than 1 mm, which may not be clinically meaningful. Moreover, they stated that although there may be a relationship between endometrial thickness and pregnancy, implantation potential is probably more complex than a single ultrasound measurement can determine.

van der Linden et al (2011) determined the relative safety and effectiveness of methods of luteal phase support in subfertile women undergoing assisted reproductive technology (ART). These investigators searched the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, CINAHL, Database of Abstracts of Reviews of Effects (DARE), LILACS, conference abstracts on the ISI Web of Knowledge, OpenSigle for grey literature from Europe, and ongoing clinical trials registered online. The final search was in February 2011. Randomized controlled trials of luteal phase support in ART investigating progesterone, hCG or GnRH agonist supplementation in IVF or intra-cytoplasmic sperm injection (ICSI) cycles. Quasi-randomized trials and trials using frozen transfers or donor oocyte cycles were excluded. These researchers extracted data per women and 3 review authors independently assessed risk of bias. They contacted the original authors when data were missing or the risk of bias was unclear; and they entered all data in 6 different comparisons. These investigators calculated the Peto odds ratio (Peto OR) for each comparison. A total of 69 studies with 16,327 women were included. The authors assessed most of the studies as having an unclear risk of bias, which we interpreted as a high-risk of bias. Because of the great number of different comparisons, the average number of included studies in a single comparison was only 1.5 for live birth and 6.1 for clinical pregnancy. Five studies (746 women) compared hCG versus placebo or no treatment. There was no evidence of a difference between hCG and placebo or no treatment except for ongoing pregnancy: Peto OR 1.75 (95 % CI: 1.09 to 2.81), suggesting a benefit from hCG. There was a significantly higher risk of ovarian hyper-stimulation syndrome (OHSS) when hCG was used (Peto OR 3.62, 95 % CI: 1.85 to 7.06). There were 8 studies (875 women) in the second comparison, progesterone versus placebo or no treatment. The results suggested a significant effect in favor of progesterone for the live birth rate (Peto OR 2.95, 95 % CI: 1.02 to 8.56) based on one study. For clinical pregnancy (CPR) the results also suggested a significant result in favor of progesterone (Peto OR 1.83, 95 % CI: 1.29 to 2.61) based on seven studies. For the other outcomes the results indicated no difference in effect. The third comparison (15 studies, 2,117 women) investigated progesterone versus hCG regimens. The hCG regimens were subgrouped into comparisons of progesterone versus hCG and progesterone versus progesterone + hCG. The results did not indicate a difference of effect between the interventions,
except for OHSS. Subgroup analysis of progesterone versus progesterone + hCG showed a significant benefit from progesterone (Peto OR 0.45, 95% CI: 0.26 to 0.79). The fourth comparison (9 studies, 1,571 women) compared progesterone versus progesterone + estrogen. Outcomes were subgrouped by route of administration. The results for clinical pregnancy rate in the subgroup progesterone versus progesterone + transdermal oestrogen suggested a significant benefit from progesterone + estrogen. There was no evidence of a difference in effect for other outcomes. Six studies (1,646 women) investigated progesterone versus progesterone + GnRH agonist. These researchers subgrouped the studies for single-dose GnRH agonist and multiple-dose GnRH agonist. For the live birth, clinical pregnancy and ongoing pregnancy rate the results suggested a significant effect in favor of progesterone + GnRH agonist. The Peto OR for the live birth rate was 2.44 (95% CI: 1.62 to 3.67), for the clinical pregnancy rate was 1.36 (95% CI: 1.11 to 1.66) and for the ongoing pregnancy rate was 1.31 (95% CI: 1.03 to 1.67). The results for miscarriage and multiple pregnancies did not indicate a difference of effect. The last comparison (32 studies, 9,839 women) investigated different progesterone regimens: Intra-muscular (IM) versus oral administration, IM versus vaginal or rectal administration, vaginal or rectal versus oral administration, low-dose vaginal versus high-dose vaginal progesterone administration, short protocol versus long protocol and micronized progesterone versus synthetic progesterone. The main results of this comparison did not indicate a difference of effect except in some subgroup analyses. For the outcome clinical pregnancy, subgroup analysis of micronized progesterone versus synthetic progesterone showed a significant benefit from synthetic progesterone (Peto OR 0.79, 95% CI: 0.65 to 0.96). For the outcome multiple pregnancies, the subgroup analysis of IM progesterone versus oral progesterone suggested a significant benefit from oral progesterone (Peto OR 4.39, 95% CI: 1.28 to 15.01). The authors concluded that this review showed a significant effect in favor of progesterone for luteal phase support, favoring synthetic progesterone over micronized progesterone. Overall, the addition of other substances such as estrogen or hCG did not seem to improve outcomes. They also found no evidence favoring a specific route or duration of administration of progesterone. These investigators found that hCG, or hCG plus progesterone, was associated with a higher risk of OHSS. The use of hCG should therefore be avoided. There were significant results showing a benefit from addition of GnRH agonist to progesterone for the outcomes of live birth, clinical pregnancy and ongoing pregnancy. For now, progesterone seems to be the best option as luteal phase support, with better pregnancy results when synthetic progesterone is used.

Morley et al (2013) stated that recurrent miscarriage (RM) is defined as the loss of 3 or more consecutive pregnancies. Further research is required to understand the causes of RM, which remain unknown for many couples. Human chorionic gonadotropin is vital for maintaining the corpus luteum, but may have additional roles during implantation which support its use as a therapeutic agent for RM. In a Cochrane review, these investigators determined the efficacy of hCG in preventing further miscarriage in women with a history of unexplained RM. They searched the Cochrane Pregnancy and Childbirth Group's Trials Register (September 30, 2012) and reference lists of retrieved studies. Randomized controlled trials investigating the efficacy of hCG versus placebo or no treatment in preventing RM were included for analysis. Quasi-randomized trials were included. Cluster-randomized trials and trials with a cross-over design were excluded. Two review authors independently assessed trials for inclusion and assessed the methodological quality of each study. Date were extracted by 2 review authors and checked for accuracy. These investigators included 5 studies (involving 596 women). Meta-analysis suggested a statistically significant reduction in miscarriage rate using hCG. The number of women needed to treat to prevent subsequent pregnancy loss was 7. However, when 2 studies of weaker methodological quality were removed, there was no longer a statistically significant benefit (risk ratio 0.74; 95% CI: 0.44 to 1.23). There were no documented adverse effects of using hCG. The authors concluded that the evidence supporting hCG supplementation to prevent RM remains equivocal. A well-designed randomized controlled trial of adequate power and methodological quality is required to determine whether hCG is beneficial in RM.
Also, an UpToDate review on “Overview of treatment of female infertility” (Kuohung and Hornstein, 2014) does not mention the use of human chorionic gonadotropin as a management tool.

Current guidelines recommend hCG in men only for pituitary hypogonadism to address infertility issues. It is not recommended for long-term use outside of infertility treatment. The European Association of Urology’s guidelines on “Male hypogonadism” (Dohle et al, 2012) noted that “In patients with secondary hypogonadism and fertility issues, and in selected cases of primary hypogonadism, hCG treatment can be chosen to support endogenous testosterone production for the period of infertility treatment. The dosage has to be adjusted individually to prevent suppression of FSH serum levels. hCG treatment has higher costs than testosterone treatment. There is insufficient information about the therapeutic and adverse effects of long-term hCG treatment. This type of treatment can therefore not be recommended for male hypogonadism, except in patients in whom fertility treatment is an issue”.

In a Cochrane review, Siristatidis et al (2013) compared outcomes associated with in-vitro maturation (IVM) followed by IVF or ICSI versus conventional IVF or ICSI, among women with PCOS undergoing assisted reproductive technologies (ART). These searched the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of controlled trials to May 2013 for any relevant trials identified from the title, abstract, or keyword sections. This was followed by a search of the electronic database MEDLINE, EMBASE, LILACS and CINAHL, without language restriction. They also performed a manual search of the references of all retrieved articles; sought unpublished papers and abstracts submitted to international conferences, searched the clinicaltrials.gov and WHO portal registries for submitted protocols of clinical trials, and contacted experts. In addition, these researchers examined the National Institute of Clinical Excellence (NICE) fertility assessment and treatment guidelines and hand-searched reference lists of relevant articles (from 1970 to May 2013). All randomized trials (RCTs) on the intention to perform IVM before IVF or ICSI compared with conventional IVF or ICSI for subfertile women with PCOS. Three review authors independently assessed eligibility and quality of trials. Primary outcome measure was live birth rate per randomized woman. There were no RCTs suitable for inclusion in the review, although there are currently 3 ongoing trials that have not yet reported results. The authors concluded that although promising data on the IVM technique have been published, unfortunately there is still no evidence from RCTs upon which to base any practice recommendations regarding IVM before IVF or ICSI for women with PCOS.

Furthermore, an UpToDate review on “Fertility preservation in patients undergoing gonadotoxic treatment or gonadal resection” (Sonmezer and Oktay, 2014) states that “When embryo cryopreservation is not feasible, cryopreservation of oocytes matured in vivo is a reasonable option. In vitro maturation of oocytes is an investigational procedure; implantation and ongoing pregnancy rates are lower than with conventional in vitro fertilization (IVF) using in vivo matured oocytes”.

Chen et al (2013) stated that reactive oxygen species (ROS) are an array of molecules including oxygen-centered radicals, which are endowed with 1 or more unpaired electrons and non-radical oxygen derivatives such as hydrogen peroxide, which behave, to a large extent, like a double-edged sword in human sperm biology. These investigators reviewed the current knowledge of ROS in sperm physiology and pathology, as well as related therapies in spermatozoal dysfunction. They searched for keywords from PUBMED, including reactive oxygen species, oxidative stress, sperm function, and antioxidant therapy. Low levels of ROS exert critical function in normal sperm physiology, such as fertilizing ability (acrosome reaction, hyper-activation, capacitation, and chemotaxis) and sperm motility; while increased ROS generation and/or decreased antioxidant capacity leads to the imbalance between oxidation and reduction in living systems, which is called sperm oxidative stress. This condition was widely considered to be a significant contributory factor to sperm DNA damage/apoptosis, lipid peroxidation, and reduced motility, which in turn, increased risk of male factor infertility/subfertility and birth defects. Under the current status quo, numerous subsequent studies have concentrated on antioxidant therapy.
Although utility of such a therapeutic strategy significantly improved sperm function and motility in a myriad of experimental and clinical reports, the overall effectiveness still remains controversial mainly due to non-standardized assay to measure the level of ROS and sperm DNA damage, various antioxidant supplementation strategies, and inadequate fertilization and pregnancy data after clinical treatment. Therefore, standardized assessment and evaluation of ROS and total antioxidant capacity in semen should be established to keep ROS in a physiological level and prevent over-treatment of antioxidants toward reductive stress, which should be kept in mind, especially in assisted reproductive procedure. The authors noted that the significance of large sample size populations, double-blind randomized, placebo-controlled clinical trials of antioxidant therapies is emphasized in this review to achieve optimal ingredients and dosage of antioxidants for patients with reactive oxygen-induced male fertility/subfertility.

Also, an UpToDate review on “Evaluation of male infertility” (Swerdlow and Wang, 2014) states that “Generation of reactive oxygen species may be a cause of sperm dysfunction and a predictor of fertilization in vitro. Reactive oxygen species lead to lipid peroxidation of the sperm membrane and are also deleterious to sperm motility. This is still regarded as a research test and is not often used for diagnosis of a specific sperm defect”.

**CPT Codes / HCPCS Codes / ICD-9 Codes**

**CPT codes covered if selection criteria are met:**

- 0058T
- 0059T
- 49203
- 49204
- 49205
- 49320
- 49321
- 49322
- 52402
- 54500
- 54505
- 54640
- 54650
- 54692
- 54800
- 54830
CPT codes not covered for indications listed in the CPB:

0087T
10021
10022
43631 - 43635
43644 - 43645
43770 - 43775
43842 - 43848
43886 - 43888
81400
83001 - QW
86357
88184 - 88185
88187 - 88189
89280
89281
89335
89342
89343
89344
89346
89352
Other CPT codes related to the CPB:

90460 - 90461
90471 - 90472

HCPCS codes covered if selection criteria are met:

G0010  Administration of hepatitis B vaccine
G0027  Semen analysis; presence and/or motility of sperm excluding Huhner
G0123  Screening cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation, screening by cytotechnologist under physician supervision
G0124  Screening cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation, requiring interpretation by physician
G0141 - G0148  Screening cytopathology smears, cervical or vaginal
J0725  Injection, chorionic gonadotropin, per 1,000 USP units
J0900  Injection, testosterone enanthate and estradiol valerate, up to 1cc
J1000  Injection, depo-estradiol cypionate, up to 5 mg
J1060  Injection, testosterone cypionate and estradiol cypionate, up to 1 ml
J1094  Injection, dexamethasone acetate, 1 mg
J1100  Injection, dexamethasone sodium phosphate, 1 mg
J1380  Injection, estradiol valerate, up to 10 mg
J1410  Injection, estrogen conjugated, per 25 mg
J1620  Injection, gonadorelin HCl, per 100 mcg
J2370  Injection, phenylephrine HCl, up to 1 ml
J2675  Injection, progesterone, per 50 mg
J3120  Injection, testosterone enanthate, up to 100 mg
J3130  Injection, testosterone enanthate, up to 200 mg
J3140  Injection, testosterone suspension, up to 50 mg
J3150  Injection, testosterone propionate, up to 100 mg
J3355  Injection, urofollitropin, 75 IU
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7506</td>
<td>Prednisone, oral, per 5 mg</td>
</tr>
<tr>
<td>J8515</td>
<td>Cabergoline, oral, 0.25 mg</td>
</tr>
<tr>
<td>J8540</td>
<td>Dexamethasone, oral, 0.25 mg</td>
</tr>
<tr>
<td>J9202</td>
<td>Goserelin acetate implant, per 3.6 mg</td>
</tr>
<tr>
<td>J9218</td>
<td>Leuprolide acetate, per 1 mg</td>
</tr>
<tr>
<td>P3000</td>
<td>Screening Papanicolaou smear, cervical or vaginal, up to three smears, by technician under physician supervision</td>
</tr>
<tr>
<td>P3001</td>
<td>Screening Papanicolaou smear, cervical or vaginal, up to three smears, requiring interpretation by physician</td>
</tr>
<tr>
<td>Q0115</td>
<td>Post-coital direct, qualitative examinations of vaginal or cervical mucous</td>
</tr>
<tr>
<td>S0122</td>
<td>Injection, menotropins, 75 IU</td>
</tr>
<tr>
<td>S0126</td>
<td>Injection, follitropin alfa, 75 IU</td>
</tr>
<tr>
<td>S0128</td>
<td>Injection, follitropin beta, 75 IU</td>
</tr>
<tr>
<td>S0132</td>
<td>Injection, ganirelix acetate, 250 mcg [not covered for men]</td>
</tr>
<tr>
<td>S0187</td>
<td>Tamoxifen citrate, oral, 10 mg</td>
</tr>
<tr>
<td>S0265</td>
<td>Genetic counseling, under physician supervision, each 15 minutes</td>
</tr>
<tr>
<td>S2078</td>
<td>Laparoscopic supravaginal hysterectomy (subtotal hysterectomy), with or without removal of tube(s), with or without removal of ovary(s)</td>
</tr>
<tr>
<td>S4011</td>
<td>In vitro fertilization; including but not limited to identification and incubation of mature oocytes, fertilization with sperm, incubation of embryo(s), and subsequent visualization for determination of development</td>
</tr>
<tr>
<td>S4013</td>
<td>Complete cycle, gamete intrafallopian transfer (GIFT), case rate</td>
</tr>
<tr>
<td>S4014</td>
<td>Complete cycle, zygote intrafallopian transfer (ZIFT), case rate</td>
</tr>
<tr>
<td>S4015</td>
<td>Compete in vitro fertilization cycle, not otherwise specified, case rate</td>
</tr>
<tr>
<td>S4016</td>
<td>Frozen in vitro fertilization cycle, case rate</td>
</tr>
<tr>
<td>S4017</td>
<td>Incomplete cycle, treatment canceled prior to stimulation, case rate</td>
</tr>
<tr>
<td>S4018</td>
<td>Frozen embryo transfer procedure canceled before transfer, case rate</td>
</tr>
<tr>
<td>S4020</td>
<td>In vitro fertilization procedure canceled before aspiration, case rate</td>
</tr>
<tr>
<td>S4021</td>
<td>In vitro fertilization procedure canceled after aspiration, case rate</td>
</tr>
<tr>
<td>S4022</td>
<td>Assisted oocyte fertilization, case rate</td>
</tr>
<tr>
<td>S4023</td>
<td>Donor egg cycle, incomplete, case rate</td>
</tr>
</tbody>
</table>
Donor services for in vitro fertilization (sperm or embryo), case rate

Procurement of donor sperm from sperm bank

Microsurgical epididymal sperm aspiration (MESA)

Stimulated intrauterine insemination (IUI), case rate

Cryopreserved embryo transfer, case rate

Contraceptive pills for birth control

Home injectable therapy; hormonal therapy (e.g., leuprolide, goserelin), including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

HCPCS codes not covered for indications listed in the CPB:

Parenteral nutrition solution, per 10 grams lipids

Injection, immune globulin, (Gamunex/Gamunex-C/Gammaked), nonlyophilized (e.g., liquid), 500 mg

Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg

Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg

Injection, immune globulin, (Gammagard liquid), nonlyophilized, (e.g., liquid), 500 mg

Injection, somatrem, 1 mg

Injection, somatropin, 1 mg

Injection, sermorelin acetate, 1 mcg

Storage of previously frozen embryos

Sperm procurement and cryopreservation services; initial visit

Sperm procurement and cryopreservation services; subsequent visit

Monitoring and storage of cryopreserved embryos, per 30 days

Management of ovulation induction (interpretation of diagnostic tests and studies, non-face-to-face medical management of the patient), per cycle

Home injectable therapy; growth hormone, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-9 codes covered if selection criteria are met (not all-inclusive):

http://qawww.aetna.com/cpb/medical/data/300_399/0327_draft.html

11/03/2014
Human immunodeficiency virus [HIV] disease [HIV positive male undergoing sperm washing]

Malignant neoplasms, lip, oral cavity, and pharynx, digestive organs and peritoneum, respiratory and intrathoracic organs, bone, connective tissue, skin, and breast, genitourinary organs, other and unspecified sites, lymphatic and hematopoietic tissue

Neuroendocrine tumors, small intestines, appendix, large intestine, rectum, other and unspecified sites

Malignant poorly differentiated neuroendocrine tumors

Secondary merkel cell carcinoma

Uterine leiomyoma

Benign neoplasm of ovary

Benign neoplasm of epididymis

Benign neoplasm of pituitary gland and craniopharyngeal duct (pouch)

Neoplasm of uncertain behavior of genitourinary organs

Neoplasm of uncertain behavior of other and unspecified male genital organs

Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct

Congenital hypothyroidism

Acquired hypothyroidism

Other and unspecified anterior pituitary hyperfunction

Other anterior pituitary disorders

Adrenogenital disorders

Other ovarian hyperfunction [hypersecretion of ovarian androgens]

Postablative ovarian failure

Premature menopause [poor ovarian reserve]

Polycystic ovaries

Other testicular hypofunction

Scrotal varices

Hydrocele

Infertility, male

Impotence of organic origin
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>608.0 - 608.89</td>
<td>Other specified disorders of male genital organs</td>
</tr>
<tr>
<td>611.6</td>
<td>Galactorrhea not associated with childbirth</td>
</tr>
<tr>
<td>614.0 - 614.9</td>
<td>Inflammatory disease of ovary, fallopian tube, pelvic cellular tissue, and peritoneum</td>
</tr>
<tr>
<td>617.0 - 617.9</td>
<td>Endometriosis</td>
</tr>
<tr>
<td>620.0 - 620.9</td>
<td>Noninflammatory disorders of ovary, fallopian tube, and broad ligament</td>
</tr>
<tr>
<td>621.0</td>
<td>Polyp of corpus uteri</td>
</tr>
<tr>
<td>621.5</td>
<td>Intrauterine synechiae</td>
</tr>
<tr>
<td>625.1</td>
<td>Vagismus</td>
</tr>
<tr>
<td>626.0</td>
<td>Absence of menstruation</td>
</tr>
<tr>
<td>626.4</td>
<td>Irregular menstrual cycle</td>
</tr>
<tr>
<td>628.0 - 628.9</td>
<td>Infertility, female</td>
</tr>
<tr>
<td>704.1</td>
<td>Hirsutism</td>
</tr>
<tr>
<td>752.0</td>
<td>Anomalies of ovaries</td>
</tr>
<tr>
<td>752.10 - 752.19</td>
<td>Anomalies of fallopian tubes and broad ligaments</td>
</tr>
<tr>
<td>752.2</td>
<td>Doubling of uterus</td>
</tr>
<tr>
<td>752.40 - 752.49</td>
<td>Anomalies of cervix, vagina, and external female genitalia</td>
</tr>
<tr>
<td>752.51</td>
<td>Undescended testis</td>
</tr>
<tr>
<td>752.89</td>
<td>Other specified anomalies of genital organs</td>
</tr>
<tr>
<td>758.6</td>
<td>Gonadal dysgenesis</td>
</tr>
<tr>
<td>758.7</td>
<td>Klinefelter's syndrome</td>
</tr>
<tr>
<td>792.2</td>
<td>Nonspecific abnormal findings in semen</td>
</tr>
<tr>
<td>793.2</td>
<td>Nonspecific (abnormal) findings on radiological and other examination of other intrathoracic organs [follow-up on hystersalpingography abnormalities]</td>
</tr>
<tr>
<td>990</td>
<td>Effects of radiation, unspecified</td>
</tr>
<tr>
<td>995.20</td>
<td>Unspecified adverse effect of unspecified drug, medicinal and biological substance [chemotherapy]</td>
</tr>
<tr>
<td>V01.79</td>
<td>Contact with or exposure to other viral diseases [partners of persons infected with hepatitis B]</td>
</tr>
<tr>
<td>V04.3</td>
<td>Need for prophylactic vaccination and inoculation against rubella alone [women susceptible to rubella]</td>
</tr>
</tbody>
</table>
V08 Asymptomatic human immunodeficiency virus [HIV] infection status [HIV positive NOS]

V26.1 Artificial insemination

V26.21 Fertility testing

V59.70 - V59.74 Egg (oocyte) (ovum) donor

V74.5 Venereal disease [chlamydia trachomatis screening]

V83.01 - V83.02 Asymptomatic and symptomatic hemophilia A carrier

V83.81 Cystic fibrosis gene carrier

V83.89 Other genetic carrier status [high risk of transmitting a genetic disorder from the female partner to the offspring]

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

302.50 - 302.53 Trans-sexualism [persons with gender reassignment are considered to have elective sterilization]

627.0 - 627.9 Menopausal and postmenopausal disorders

752.64 Micropenis

V07.4 Hormone replacement therapy (postmenopausal)

V26.0 Tuboplasty or vasoplasty after previous sterilization

V26.51 Tubal ligation status

V26.52 Vasectomy status

V45.77 Acquired absence of genital organs

V49.81 Asymptomatic postmenopausal status (age-related) (natural)

Other ICD-9 codes related to the CPB:

001.0 - 139.8 Infectious and parasitic diseases

209.40 - 209.69 Benign carcinoid tumors, small intestine, appendix, large intestine, rectum, other and unspecified sites

209.70 - 209.74, Secondary neuroendocrine tumor, unspecified site, distant lymph nodes, liver, bone, peritoneum and other sites

209.79

210.0 - 239.9 Benign neoplasms, carcinomas in situ, neoplasms of uncertain nature, neoplasms of unspecified nature

240.0 - 246.9 Disorders of thyroid gland

250.60 - 250.63 Diabetes with neurological manifestations
256.39 Other ovarian failure [poor ovarian reserve]
357.2 Polyneuropathy in diabetes
611.6 Galactorrhea not associated with childbirth
614.1 Chronic salpingitis and oophoritis
614.2 Salpingitis and oophoritis not specified as acute, subacute, or chronic
626.0 Absence of menstruation
633.00 - 633.91 Ectopic pregnancy
640.00 - 648.94 Complications mainly related to pregnancy
704.1 Hirsutism
706.1 Other acne
752.0 - 752.19 Anomalies of ovaries, fallopian tubes and broad ligaments
758.0 - 758.5 Chromosomal anomalies
773.0 Hemolytic disease due to Rh isoimmunization
905.1 Late effect of fracture of spine and trunk without mention of spinal cord lesion
907.2 Late effect of spinal cord injury
952.00 - 952.9 Spinal cord injury without evidence of spinal bone injury
990 Effects of radiation, unspecified
E933.1 Adverse effects of antineoplastic and immunosuppressive drugs
V10.40 - V10.49 Personal history of malignant neoplasm of genital organs
V13.29 Personal history of other genital system and obstetric disorders
V22.0 - V22.1 Normal pregnancy
V23.0 - V23.9 Supervision of high-risk pregnancy
V26.31 - V26.33 Genetic counseling and testing
V26.81 Encounter for assisted reproductive fertility procedure cycle
V73.88 Special screening examination for other specified chlamydial diseases
V73.98 Special screening for unspecified chlamydial disease
V74.5 Special screening for venereal disease
V77.6 Special screening for cystic fibrosis
V81.6 Special screening for other and unspecified genitourinary conditions
V83.81 - V83.89 Genetic carrier status
V84.01 - V84.89 Genetic susceptibility to disease

The above policy is based on the following references:


http://qawww.aetna.com/cpb/medical/data/300_399/0327_draft.html 11/03/2014
216. Sonmez M, Oktay K. Fertility preservation in patients undergoing gonadotoxic treatment or gonadal resection. Last reviewed February 2014. UpToDate Inc., Waltham, MA.