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Infertility

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

Number: 0327

Least Cost Medically Necessary Brands

Note on least cost brands of follitropin: For Aetna commercial plans, Follistim AQ (follitropin beta) is more costly to Aetna than other brands of follicle-stimulating hormones (FSH) ("least cost brands"). There is a lack of reliable evidence that any one brand of FSH is superior to the least cost brands for medically necessary indications. Therefore, Aetna considers Follistim AQ to be medically necessary for members who have a documented contraindication or intolerance or allergy or failure of an adequate trial of one month of Gonal-F.

Policy

Note: REQUIRES PRECERTIFICATION

Precertification of Cetrotide (cetrorelix acetate), ganirelix acetate, Follistim AQ (follitropin beta), Gonal-F (follitropin alfa), Menopur (menotropins), Novarel (chorionic gonadotropin), Pregnyl (chorionic gonadotropin), Ovidrel (choriogonadotropin alfa), and chorionic gonadotropin is required of all Aetna participating providers and members in applicable plan designs. For precertification, call (866) 782-2779 (Commercial), or fax (860) 754-2515.

Policy History

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10/27/2020

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Next Review: 06/10/2021

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

Note: Medical/Pharmacy Benefit Alignment of Coverage for Infertility Drugs and Procedures:

Medical necessity review of infertility drugs by Aetna Specialty Pharmacy Guideline Management may be bypassed for infertility drugs that are for use with infertility medical procedures if the infertility procedure has been approved for coverage under the member's Aetna medical benefit plan. During precertification, a medical authorization number and confirmation of the approval of the infertility procedures will be required to bypass medical necessity review by Specialty Pharmacy Guideline Management. (**Note:** Some plans may require medical necessity review of all infertility drugs by Aetna Specialty Guideline Management. Members of these plans must undergo Specialty Pharmacy Guideline Management medical necessity review of all infertility drugs regardless of whether the drugs are for use with approved infertility medical procedures.)

Notes:

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 35 years of age or older. 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 35 years of age or older). However, this definition of infertility may vary due to state mandates and plan customization; please check plan documents.~~

3. According to the American Society for Reproductive Medicine (ASRM, 2013), for purposes of determining when evaluation and treatment for infertility or recurrent pregnancy loss are

appropriate, pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathologic examination.

4. 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. 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.

5. 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 follicle-stimulating hormone (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 in the prior 12 months if the woman is 35 years of age or younger. An unmedicated FSH level means that this blood test is drawn after the normal onset of menstruation, or after progesterone administration for women who do not reliably menstruate. 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 laboratory 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.

6. Infertility services for women with natural menopause age 40 years and older is not covered because it is not considered medically necessary treatment of disease; natural menopause is not considered a disease. For women age 40 and older, their unmedicated day 3 FSH must be less than 19 mIU/mL in all prior tests to document that they are not menopausal and eligible for

coverage of infertility treatment. Women with ovarian failure who are less than 40 years of age are considered to have the disease of premature ovarian failure (also known as premature ovarian insufficiency, primary ovarian insufficiency, or hypergonadotropic hypogonadism). For women with premature ovarian failure, advanced reproductive technology (ART) (in vitro fertilization) services are considered medically necessary until they reach 45 years of age, where criteria for ART below are met.

7. 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, basal body temperature
B. Laboratory studies:

1. Anti-adrenal antibodies for apparently spontaneous primary ovarian insufficiency (premature ovarian failure)
2. Anti-sperm antibodies (e.g., immunobead or mixed antiglobulin method)
3. Chlamydia trachomatis screening (see CPB 0433 - Chlamydia Trachomatis - Screening and Diagnosis (../400_499/0433.html))
4. Fasting and 2 hours post 75 gram glucose challenge levels
5. Lipid panel (total cholesterol, HDL cholesterol, triglycerides)
6. Post-coital testing (PCT) (Simms-Huhner test) of cervical mucus
7. Rubella serology
8. Testing for viral status (HIV, hepatitis B, hepatitis C)

9. 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. Anti-mullerian hormone (AMH), for the following indications: a) assessing menopausal status, including premature ovarian failure; b) assessing ovarian status, including ovarian reserve and ovarian responsiveness, as part of an evaluation for infertility and assisted reproduction protocols such as in vitro fertilization.
    c. 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 (AACE, 1999; NAMS, 2000; SOGC, 2002)
    d. Human chorionic gonadotrophin (hCG) (see Appendix for medical necessity limitations)
    e. Prolactin for women with an ovulatory disorder, galactorrhea, or a pituitary tumor
    f. Progestins (progesterone, 17-hydroxyprogesterone) (see Appendix for medical necessity limitations)
    g. Estrogens (estradiol) (see Appendix for medical necessity limitations)
    h. Thyroid stimulating hormone (TSH) for women with symptoms of thyroid disease
    i. Adrenocortitrophic hormone (ACTH) for ruling out Cushing's syndrome or Addison's disease in women who are amenorrheic
    j. Clomiphene citrate challenge test

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

11. The following laboratory studies are considered experimental and investigational for infertility:

    a. Anti-CarP (anti-carbamylated proteins) panel
    b. Antinuclear antibodies
    c. Antiovarian antibodies
    d. Antiphospholipid antibodies
    e. Antiphosphatidic acid antibodies
    f. Antiphosphatidylethanolamine antibodies
    g. Antiphosphatidylglycerol antibodies
    h. Antiphosphatidylinositol antibodies
    i. Antiphosphatidylserine antibodies
    j. Antiprothrombin antibodies (see CPB 0662 - Antiprothrombin Antibody Testing (../600_699/0662.html))
    k. Antithrombin III (ATIII) activity
    l. Antithrombin III (ATIII) antigen
    m. Antithyroglobulin antibodies
    n. Embryotoxicity assay (see CPB 0348 - Recurrent Pregnancy Loss (0348.html))
    o. Endometrial receptivity testing (e.g., endometrial receptivity array (ERA), integrin testing, beta-3 integrin test)
    p. Evaluation of telomere length
    q. Factor V Leiden coagulation
    r. Factor V Leiden mutation (see CPB 0140 - Genetic Testing (../100_199/0140.html))
    s. HLA genotyping (A, B, C, DR, DQ)
    t. Homocysteine (see CPB 0763 - Homocysteine Testing (../700_799/0763.html))
    u. Methylenetetrahydrofolate reductase (MTHFR)
    v. Oxidative Stress Adduct Test (OSA)
    w. Plasminogen Activator Inhibitor-I activity
    x. Plasminogen Activator Inhibitor-I (PAI-1) antigen
    y. Protein C activity
    z. Protein C antigen
    aa. Protein S activity
    ab. Protein S antigen (free or total)

ac. Prothrombin (Factor II) mutation (see CPB 0140 - Genetic Testing (../100_199/0140.html))

ad. Uterine and endometrial receptivity testing (Endometrial function test (EFT) (cyclin E and p27) and E-tegrity)

ae. Measurement of natural killer (NK) cell activity

af. Reproductive immunophenotyping

ag. Serum inhibin B measurement (value in assessing ovarian reserve is uncertain).

ah. Th1 (T Helper 1) and Th2 (T Helper 2) intracellular cytokine assay (Th1/Th2 ratio)

ai. uBiome SmartJane screen (see CPB 0650 - Polymerase Chain Reaction Testing: Selected Indications (../600_699/0650.html))

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 chromotubation (contrast dye) to assess tubal and other pelvic pathology, and to follow-up on hysterosalpingography abnormalities
6. Sonohysterography 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 %, Prochieve 8 %) or intramuscular progestins and progesterone vaginal suppositories (Endometrin), see CPB 0510 - Progestins (../500_599/0510.html))

8. Prolactin inhibitors (bromocriptine (Parlodel), cabergoline (Dostinex), peroglide (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:

- Acupuncture (see CPB 0135 - Acupuncture (../100_199/0135.html))
- Leukocyte immunization (immunizing the female partner with the male partner's leukocytes) (see CPB 0348 - Recurrent Pregnancy Loss (0348.html)); *and*
- Dehydroepiandrosterone (DHEA); *and*
- DuoStim IVF protocol; *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; *and*
- Stem cell therapy; *and*
- Vaginal sildenafil; *and*
- Vasodilators for women undergoing fertility treatment.

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 (0347.html))
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 (../100_199/0157.html)).
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_99/0020.html))

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 (../500_599/0501.html) 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) (Novarel, Pregnyl, Ovidrel)
- Human menopausal gonadotropin (hMG) (menotropins) (LH and FSH) (Menopur)
- Recombinant follitropin (recombinant FSH) (Follitropin alfa (Gonal-F); Follitropin beta (Follistim AQ))

Note: Brand names Bravelle, Fertinex, Follistim, and Repronex have been discontinued.

Gonadotropins are considered medically necessary for members undergoing ovulation induction or assisted reproductive technology (ART) who meet any of the following criteria:

- Clomiphene plus gonadotropins may be considered medically necessary in women who do not ovulate using clomiphene alone; *or*
- 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.); *or*
- 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); *or*
- 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)

Aetna considers continuation of therapy medically necessary in all members (including new members) requesting authorization for continuation of therapy who meet all initial authorization criteria.

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 (ganirelix acetate, cetrorelix 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.)

   See CPB 0501 - Gonadotropin-Releasing Hormone Analogs and Antagonists (../500_599/0501.html) for additional information and limitations.

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 (../100_199/0170.html).
5. Intravenous immunoglobulins are considered experimental and investigational for treatment of infertility. See CPB 0348 - Recurrent Pregnancy Loss (0348.html); and CPB 0206 - Parenteral Immunoglobulins (../200_299/0206.html).
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) - if initial testosterone level is low, a repeat measurement of total and free testosterone as well as serum luteinizing hormone (LH) and prolactin levels is medically necessary
   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 azoospermia (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 azoospermia (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. Spern 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 (0348.html)) 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)
15. Genetic testing of CFTR mutations for a man and his female partner if the man has congenital absence of the vas deferens (CAVD).

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 (../500_599/0532.html))
4. Testicular biopsy
5. Transrectal ultrasound (See CPB 0001 - Transrectal Ultrasound (../1_99/0001.html))
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) 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 (http://www.aetna.com/cpb/medical/data/500_599/0501.html) for additional information and limitations)
d. Recombinant follitropin products (recombinant FSH) (follitropin alfa (Gonal-F, Gonal-F RFF); follitropin beta (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.

Aetna considers continuation of therapy medically necessary in all members (including new members) requesting authorization for continuation of therapy who meet all initial authorization criteria.

Human chorionic gonadotropin (hCG) (Novarel, Pregnyl), human menopausal gonadotropin (hMG) (Menopur), and recombinant follitropins (Gonal-F, Gonal-F RFF, 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 (ganerelix 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 - Varicocele: Selected Treatments (../400_499/0413.html))
5. Spermatocelectomy 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 (../1_99/0007.html).

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. For purposes of this policy, mild male-factor infertility is defined as when 2 or more semen analyses, measured at least two weeks apart, have 1 or more variables below the 5th percentile (NICE, 2013).
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.

B. 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.

C. 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.

D. 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 any of the following criteria:

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

    1. For women 37 years of age or younger, three cycles of ovarian stimulation (with or without intrauterine insemination); *or*
    2. For women 38 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:

        a. Bilateral tubal disease (e.g., salpingitis isthmica nodosum, tubal obstruction, absence, or hydrosalpinges).
        b. Endometriosis stage 3 or 4 (see appendix).
        c. Failure to conceive after pelvic surgery with restoration of normal pelvic anatomy (e.g., myomectomy of cavitary-obscuring myomata, resection of intrauterine adhesions or uterine septum, or surgical reconstruction of tubal disease):

            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 cycle in women less than 38 years of age.

4. Women who have had a hysterectomy, or who have a medical contraindication to pregnancy such as severe cardiac disease, or have a medical condition that requires the mother to ingest a fetotoxic agent. Note: Some plans limit and/or exclude coverage for gestational surrogacy; please check benefit plan descriptions.

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 (0358.html) . However, under plans that limit coverage of ART to persons who are infertile, the in-vitro fertilization (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 a fresh ART cycle, previously frozen oocytes must be used (i.e. fertilized and transferred). Similarly, Before proceeding to the next fresh ART cycle, FET using cryopreserved embryos must be used if there are reasonable quality (grade B or its equivalent) cryopreserved embryo(s) available.
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), to fertilize frozen oocytes for in vitro fertilization, or for couples where a previous IVF treatment cycle has resulted in failed or poor (see Appendix) fertilization. **Note**: ICSI is considered not medically necessary in men whose abnormal sperm quality or quantity had been rectified by varicocelectomy. (For use of ICSI in preimplantation genetic diagnosis, see CPB 0358 - Invasive Prenatal Diagnosis of Genetic Diseases (0358.html)).
7. Assisted hatching is considered medically necessary when the plan in the cycle is to transfer the embryos into the uterus and the member meets any of the following criteria:

    a. Age is 38 years or older; *or*

b. Multiple (2 or more) failed embryo transfer attempts; *or*
c. Thickened zona pellucida.

Note: Assisted hatching is a process to assist in the implantation of the embryo; unless the cycle involves that transfer of the embryo assisted hatching is considered not medically necessary.

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.

9. **Note on oocytes used in ART cycles**: IVF cycles using either fresh or previously frozen oocytes are considered medically necessary when the ART cycle is considered medically necessary.

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. The IVF procedure to cryopreserve mature gametes (oocytes or sperm) or embryos is considered medically necessary for use in persons facing iatrogenic infertility due to chemotherapy, pelvic radiotherapy, other gonadotoxic therapies, or ovary or testicle removal for treatment of disease. Routine use of gamete cryopreservation in lieu of embryo cryopreservation, gamete cryopreservation to circumvent reproductive aging in healthy persons, cryopreservation of immature gametes, 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 gametes (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 mature gametes in persons facing infertility due to chemotherapy or other gonadotoxic therapies or gonad removal) is not considered treatment of disease and is not covered.

G. Cryopreservation of sperm is considered medically necessary in men facing iatrogenic infertility due to chemotherapy, pelvic radiotherapy, other gonadotoxic therapies, or testicular removal for treatment of disease. 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 or gonad removal) is not considered treatment of disease and is not covered.

H. The following procedures are considered experimental and investigational:

1. Determination of CAG-repeat polymorphisms in the polymerase γ (POLG) gene for evaluation of male infertility
2. Early Embryo Viability Assessment (Eeva) test
3. EmbryoGlue
4. Evaluation of CYP1A1 rs4646903 T > C genetic variations for risk of male infertility
5. Evaluation of *FAS/FASL* genetic variations for risk of male infertility
6. Evaluation of telomere length
7. Germ cell transplantation or cultured testicular stem cells
8. Hyperbaric oxygen therapy for the treatment of male infertility
9. Partial zonal dissection (PZD)
10. Preimplantation genetic testing for aneuploidy (PGT-A) (formerly called preimplantation genetic screening (PGS)) for IVF optimization (see CPB 0358 - Invasive Prenatal Diagnosis of Genetic Diseases (0358.html))
11. 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 (../100_199/0189.html), and CPB 0323 - Preconceptional Sex Selection Techniques (0323.html).

Appendix

Laboratory Services

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

Table: Laboratory Services per Cycle

	Natural monitoring	Clomid monitoring	Clomid IUI	Inj Mon Cycle	Inj IUI	IVF	GIFT	FET Code	PM
Transvaginal ultrasound	2	6	6	8	10				
Estradiol	2	6	6	8	10	10	10	10	
FSH	2	6	6	8	10	10	10	10	
LH	2	6	6	8	10	10	10	10	
Progesterone	2*	2*	2*	8	10	10	10	10	3
hCG	2	2	2	2	2	2	2	2	3

Key: IUI: intra-uterine insemination; Inj: injection; Mon: monthly; IVF: in-vitro fertilization; GIFT: gamete intra-fallopian transfer; FET: frozen embryo transfer; PM: pregnancy monitoring; FSH: follicle stimulating hormone; LH: luteinizing hormone; hCG: human chorionic gonadotropin.

*__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

Brand Names	Strength	Insemination Quantity†	ART Quantity‡
Gonadotropins/Menotropins (Initial Cycle*)			

Examples: Gonal F, Bravelle, etc.	75 IU	Less than age 35 years: 20 ampules (up to 35 ampules if FSH level is greater than 12 and less than 19) Age 35 to 39 years: 20 to 30 ampules (up to 40 ampules if FSH level is greater than 12 and less than 19) Age 40 years and older: 40 ampules (up to 50 ampules if FSH level is greater than 12 and less than 19)	Less than age 35 years: 30 to 40 ampules (up to 50 ampules if FSH level is greater than 12 and less than 19) Age 35 to 39 years: 35 to 45 ampules (up to 55 ampules if FSH is greater than 12 and less than 19) Age 40 years and older: 45 to 60 ampules (requests for more than 60 ampules are subject to clinical review; if FSH level is greater than 12 and less than 19, request medication protocol and clinical review (BMI, PCOS)) Donor eggs** (all ages): 30 to 40 ampules (up to 50 ampules if FSH level is greater than 12 and less than 19)
Examples: Follistim AQ, Gonal F, Bravelle, etc. §	150 IU, 300 IU, 450 IU, 600 IU, 900 IU, 450 IU MDV	10 ampules	15 ampules
Luteinizing Hormone (Initial Cycle*)			

Examples: Luveris, Menopur	75 IU	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	Less than age 35 years: 10 ampules Age 35 to 39 years: 10 to 20 ampules Age 40 years and older: 20 to 30 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 10 IU vial	1 vial	1 vial
Examples: Pregnyl, Novarel, HCG	5000 U 10,000 U	1 vial	1 vial
GnRH Antagonists (Initial Cycle*)			
Ganirelix acetate (prefilled syringe)	250 ug/0.5 ml	3 PFS	4 PFS
Cetrotide	0.25 mg	1 to 7 PFS	1 to 7 PFS
Cetrotide	3.0 mg	1 PFS	1 PFS

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:

Brand Names	Strength	Dose	Length of approval
Follitropins*			

Gonal-F Follistim AQ	450 unit MDV, 1050 unit MDV 150 unit SDV 150, 300, 600, 900 unit multi dose cartridges	After normalization of serum testosterone levels, use Gonal F concomitantly with hCG: 150 units three times a week; maximum dose 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).	6 months 6 months
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 Quality in ART Cycles:

An embryo is considered to be of reasonable quality (grade B or its equivalent) if it has less than 50 % fragmentation (see, e.g., Ebner, et al., 2001; Rhenman, et al., 2015; Shaw-Jackson, et al., 2013)..

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. In men who have met the definition of severe male factor infertility with

abnormal sperm quality or quantity more than 2 weeks apart in the past; and then had a successful varicocelectomy resulting in normal sperm quality or quantity, ICSI is considered not medically necessary.

Semen Analysis: World Health Organization Reference Values

- pH: 7.2 or more
- Sperm concentration: 15 million spermatozoa per ml or more
- Sperm morphology (percentage of normal forms): 4 % or more
- Semen volume: 1.5 ml or more
- Total motility (percentage of progressive motility and non-progressive motility): 40 % or more motile or 32 % or more with progressive motility
- Total sperm number: 39 million spermatozoa per ejaculate or more
- Vitality: 58 % or more live spermatozoa

Stages of Endometriosis

Surgically, endometriosis can be staged I–IV (Revised Classification of the American Society of Reproductive Medicine). The various stages show these findings:

Stage I (Minimal) -

Findings restricted to only superficial lesions and possibly a few filmy adhesions

Stage II (Mild) -

In addition, some deep lesions are present in the cul-de-sac

Stage III (Moderate) -

As above, plus presence of endometriomas on the ovary and more adhesions.

Stage IV (Severe) -

As above, plus large endometriomas, extensive adhesions.

Source: Adapted from ASRM, 1997.

Background

Infertility is a condition that is defined by the failure to achieve successful pregnancy after 12 months or more of unprotected heterosexual intercourse (after six months in women over 35 years of age) OR in those women, without a male partner, who are unable to conceive after at least 12 cycles of donor insemination (six cycles for women over 35 years of age).

The term primary infertility is applied to a couple who has never achieved a pregnancy; secondary infertility implies that at least one previous conception has taken place. This condition may be present in one or both sexual partners and may be reversible.

Diagnostic investigation of infertility includes complete physical examinations and certain testing for both partners. Infertility treatment may involve a series of procedures in an attempt to correct the cause of infertility.

Recurrent pregnancy loss is distinct from infertility is defined by two or more pregnancy losses. For purposes of determining when evaluation and treatment for infertility or recurrent pregnancy loss are appropriate, pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathologic examination.

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 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 a., 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 American College of Obstetricians and Gynecologists (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."

More recently, the ASRM (2015) concluded: "AMH is a promising screening test and is likely to be more useful in the general ICVF population or in women at high risk for DOR than in women at low risk for DOR. Low AMH cutpoints are fairly specific for poor ovarian reserve, but not for pregnancy. Future studies of AHM as a screening test should incorporate larger numbers of subjects in a high-risk or general risk IVF population. The use of AMH as a routine screening tool for DOR in a low-risk population is not recommended."

The American College of Obstetricians and Gynecologists (ACOG, 2015) concluded: "For general obstetrician-gynecologists, the most appropriate ovarian reserve screening tests to use in practice are basal follicle-stimulating hormone (FSH) plus estradiol levels or antimullerian hormone (commonly known as AHM) levels. An antral follicle count, commonly known as AFC, also may be useful if there is an indication to perform transvaginal ultrasonography." The guidelines state that antimullerian hormone level testing is a useful test in women at high risk of diminished ovarian reserve and in women undergoing IVF but has limited benefits in someone at low risk of diminished ovarian reserve.

Current Endocrine Society guidelines on polycystic ovarian syndrome (PCOS) (Lego, et al., 2013) have no recommendation for antimullerian hormone. The guidelines note that "it is possible" that antimullerian hormone may serve as a noninvasive screening or diagnostic test for PCOS in the adolescent population, although there are no well-defined cutoffs. In discussing PCOS in the perimenopausal and menopausal population, the guidelines note that AMH levels decrease with normal aging in women with and without PCOS, but the guidelines make no recommendation for AMH testing in this population.

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-Mullerian 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 gonadotrophin 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 then 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-Mullerian hormone prediction of ovarian response was independent of age and polycystic ovarian syndrome (PCOS). Anti-Mullerian 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 reliabe 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 intra-uterine 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.

Guercini 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(+) (NKT), TNFα/IL-10, IFNγ/IL-10, CD4(+) CD25(-) Foxp3(+), total CD4(+) Foxp3(+) (CD4(+) CD25(+) Foxp3 plus CD25(-) Foxp3(+)), and CD4(+) CD25(+) Foxp3(+) levels. Patients with successful ongoing pregnancies experienced a 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 cytotoxicity (p = 0.63), CD56(+) 16(+) 3(+) NK cells (p = 0.63), CD56(+) 3(+) NKT (p = 0.30), TNFα(+) IL-10(+) (p = 0.13), IFNg(+) 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 secretory 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 (SMD), 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 SMD 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 controlled 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”.

ICSI has become standard of care for fertilization of frozen oocytes in in vitro cycles despite a lack of controlled studies (see, e.g., Kazem, et al., 1995; Gook, et al., 2005; Li, et al., 2005). Gook and Edgar (2007) explained that: "In contrast to the low normal fertilization rates observed in cryopreserved mouse oocytes, higher normal fertilization rates (~50%) were observed following insemination of human oocytes cryopreserved using the DMSO [citing Al-Hasani et al., 1987; Siebzehnruebl et al., 1989; Hunter et al., 1991; Bernard et al., 1992] and the PROH procedures [citing Al-Hasani et al., 1987; Gook et al., 1994; Serafini et al., 1995]. Further evidence that cryopreservation using the PROH procedure had no adverse affect on fertilization was demonstrated by the observation of equivalent fertilization rates (~50%) following

insemination and ICSI [citing Gook et al., 1995; Li et al., 2005]. In contrast, Kazem et al. (1995) reported a lower rate with insemination (3%) relative to ICSI (43%). Despite the fact that there is no evidence from controlled comparisons of insemination techniques to suggest that ICSI is required to fertilize human cryopreserved oocytes, it has been adopted as the method of choice in subsequent clinical studies."

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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” (Swerdloff 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”.

Cryopreservation of immature oocytes and in vitro maturation are considered experimental procedures. The term in vitro maturation refers to the maturation in culture of immature oocytes after their recovery from follicles that may or may not have been exposed to exogenous FSH but were not exposed to either exogenous LH or hCG prior to retrieval to induce meiotic resumption. Guidelines from the American Society for Reproductive Medicine (2013) state that in vitro maturation should only be performed as an experimental procedure in specialized centers for carefully selected patients evaluatinb both efficacy and safety. The guidlines state that the intitial results of in vitro maturation suggest the potential for clinical application. However, at this time, patients must be made aware that the implantation and pregnancy rates are significantly lower than with standard IVF, limiting more universal utilization.

Chighizola and de Jesus (2014) noted that since the late 1980s some publications have proposed that antiphospholipid antibodies (aPL) may have some relationship with infertility, considering reported deleterious effects that aPL exert on trophoblast proliferation and growth. Although not included in current classification criteria for antiphospholipid syndrome, many physicians investigated for aPL in patients with a history of infertility, including antibodies not listed in classification criteria, and most of those patients will receive anticoagulant therapy if any of those antibodies have a result considered positive. These investigators performed a review of literature searching for studies that investigated the association of aPL and infertility and if aPL positivity alters IVF outcome. The definition of infertility, routine work-up to exclude other causes of infertility, definition of IVF failure as inclusion criteria and control populations were heterogeneous among studies. Most of them enrolled women over 40 years of age, and exclusion of other confounding factors was also inconsistent. Of 29 studies that assessed aPL positivity rates in infertile women, the majority had small sample sizes, implying a lack of power, and 13 (44.8 %) reported higher frequency of aPL in infertile patients compared to controls, but most of them investigated a panel of non-criteria aPL tests, whose clinical significance is highly controversial. Only 2 studies investigated all 3 criteria tests, and medium-high titer of anticardiolipin cut-off conforming to international guidelines was used in 1 study. Considering IVF outcome, there was also disparity in this definition: few studies assessed the live birth rate, others the implantation rate. Of 14 publications that addressed the relationship between aPL and IVF outcome, only 2 described a detrimental effect of these autoantibodies. The authors concluded that available data do not support an association between aPL and infertility, and aPL positivity does not seem to influence IVF outcome. They stated that well-designed clinical studies recruiting women with a clear diagnosis of infertility and a high-risk aPL profile should be performed to test whether clinically relevant aPL do-or not-exert an effect on human fertility.

Furthermore, an UpToDate review on “Evaluation of female infertility” (Kuohung and Hornstein, 2015b) states that “Testing for antibodies – Routine testing for antiphospholipid, antisperm, antinuclear, and antithyroid antibodies is not supported by existing data. Although an

association between antiphospholipid antibodies and recurrent pregnancy loss has been established, the other autoimmune factors remain under investigation as markers of fertility treatment failure".

In a Cochrane review, McDonnell et al (2014) examined the effectiveness and safety of functional ovarian cyst aspiration prior to ovarian stimulation versus a conservative approach in women with an ovarian cyst who were undergoing IVF or ICSI. These investigators searched the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO, CINAHL, ClinicalTrials.gov, Google Scholar and PubMed. The evidence was current to April 2014 and no language restrictions were applied. These researchers included all RCTs comparing functional ovarian cyst aspiration versus conservative management of ovarian cysts that have been seen on transvaginal ultrasound (TVS) prior to COH for IVF or ICSI. Ovarian cysts were defined as simple, functional ovarian cysts greater than 20 mm in diameter. Oocyte donors and women undergoing donor oocyte cycles were excluded. Study selection, data extraction and risk of bias assessments were conducted independently by 2 review authors. The primary outcome measures were live birth rate and adverse events. The overall quality of the evidence for each comparison was rated using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group methods. A total of 3 studies were eligible for inclusion (n = 339), all of which used agonist protocols. Neither live birth rate nor adverse events were reported by any of the included studies. There was no conclusive evidence of a difference between the group who underwent ovarian cyst aspiration and the conservatively managed group in the clinical pregnancy rate (OR 1.40, 95 % CI: 0.67 to 2.94, 3 studies, 339 women, I(2) = 0 %, low-quality evidence). This suggested that if the clinical pregnancy rate in women with conservative management was assumed to be 5 %, the chance following cyst aspiration would be between 4 % and 14 %. There was no evidence of a difference between the groups in the mean number of follicles recruited (0.55 follicles, 95 % CI: -0.48 to 1.59, 2 studies, 159 women, I(2) = 0 %, low-quality evidence) or mean number of oocytes collected (0.41 oocytes, 95 % CI: -0.04 to 0.85, 3 studies, 339 women, I(2) = 0 %, low-quality evidence). Findings for the cancellation rate (2 studies) were inconsistent but neither study reported a benefit for the aspiration group. The main limitations of the evidence were imprecision,

inconsistency, questionable applicability, and poor reporting of study methods. The authors concluded that there is insufficient evidence to determine whether drainage of functional ovarian cysts prior to controlled ovarian hyperstimulation influences live birth rate, clinical pregnancy rate, number of follicles recruited, or oocytes collected in women with a functional ovarian cyst. They stated that the findings of this review do not provide supportive evidence for this approach, particularly in view of the requirement for anesthesia, extra cost, psychological stress and risk of surgical complications.

Gleicher et al (2014) noted that a few years ago the ASRM, the European Society for Human Reproduction and Embryology (ESHRE) and the British Fertility Society declared preimplantation genetic screening (PGS#1) ineffective in improving IVF pregnancy rates and in reducing miscarriage rates. These investigators reviewed a presumably upgraded form of the procedure (PGS#2) that has recently been re-introduced. PGS#2 in comparison to PGS#1 is characterized by: (i) trophectoderm biopsy on day 5/6 embryos in place of day-3 embryo biopsy; and (ii) fluorescence in-situ hybridization (FISH) of limited chromosome numbers is replaced by techniques, allowing aneuploidy assessments of all 24 chromosome pairs. Reviewing the literature, the authors were unable to identify properly conducted prospective clinical trials in which IVF outcomes were assessed based on "intent-to-treat". Whether PGS#2 improves IVF outcomes can, therefore, not be determined. Re-assessments of data, alleged to support the effectiveness of PGS#2, indeed, suggested the opposite. Like with PGS#1, the introduction of PGS#2 into unrestricted IVF practice again appears premature, and threatens to repeat the PGS#1 experience, when thousands of women experienced reductions in IVF pregnancy chances, while expecting improvements. The authors concluded that PGS#2 is an unproven and still experimental procedure, which, until evidence suggests otherwise, should only be offered under study conditions, and with appropriate informed consents.

Lee et al (2015) examined if preimplantation genetic diagnosis for aneuploidy (PGD-A) with analysis of all chromosomes during ART is clinically and cost effective? These investigators performed a systematic review of the literature for full text English language articles using MEDLINE, EMBASE, SCOPUS, Cochrane Library databases, NHS

Economic Evaluation Database and EconLit. The Downs and Black scoring check-list was used to assess the quality of studies. Clinical effectiveness was measured in terms of pregnancy, live birth and miscarriage rates. A total of 19 articles meeting the inclusion criteria, comprising 3 RCTs in young and good prognosis patients and 16 observation studies were identified; 5 of the observational studies included a control group of patients where embryos were selected based on morphological criteria (matched cohort studies). Of the 5 studies that included a control group and reported implantation rates, 4 studies (including 2 RCTs) demonstrated improved implantation rates in the PGD-A group. Of the 8 studies that included a control group, 6 studies (including 2 RCTs) reported significantly higher pregnancy rates in the PGD-A group, and in the remaining 2 studies, equivalent pregnancies rates were reported despite fewer embryos being transferred in the PGD-A group. The 3 RCTs demonstrated benefit in young and good prognosis patients in terms of clinical pregnancy rates and the use of single embryo transfer. However, studies relating to patients of advanced maternal age, recurrent miscarriage and implantation failure were restricted to matched cohort studies, limiting the ability to draw meaningful conclusions. The authors concluded that given the uncertain role of PGD-A techniques, high-quality experimental studies using intention-to-treat analysis and cumulative live birth rates including the comparative outcomes from remaining cryopreserved embryos are needed to evaluate the overall role of PGD-A in the clinical setting. It is only in this way that the true contribution of PGD-A to ART can be understood.

There is some evidence that in women with high T-helper 1/T-helper 2 (Th1/Th2) ratios, there is an increased incidence of pregnancy loss and infertility. Thus, this test has been used by infertility specialists. However, there are no studies demonstrating the clinical utility of these measurements. A review by Ly et al (2010) stated: “Th1 dominance may well be a result of the miscarriage rather than a cause, and much more basic knowledge is needed about the complex cytokine networks in pregnancy and the correlation between cytokine production in peripheral mononuclear cells and decidual lymphocytes before tests measuring cytokines can be introduced in clinical practice”.

Ozkan et al (2014) noted that implantation necessitates complex interactions among the developing embryo, decidualizing endometrium, and developing maternal immune tolerance and/or alterations in cellular and humoral immune responses. Over-stimulation of Th1 or Th2 cytokines in systemic and local environments, alterations of the prevalence of interleukin-17 (IL-17) and regulatory T cell (Treg) cytokines have also been suggested to contribute to the pathogenesis of implantation failure. These researchers investigated the plasma levels of IL-4, IL-6, IL-10, tumor necrosis factor-alpha (TNFα), gamma interferon (IFNγ), transforming growth factor-beta (TGFβ), IL-17, IL-35, and suppressors of cytokine signaling 3 (SOCS3) in infertile and fertile women. This case-control study was conducted with 80 women suffering from unexplained infertility and 40 fertile women. Peripheral venous blood samples were drawn on day 21 of the menstrual cycle. The extracted plasma samples were assayed by an enzyme linked immunosorbent assay (ELISA). Statistical analysis was performed using SPSS version 16.0. The main findings were as follows: despite the significantly high IL-17 and IL-35 plasma levels of infertile women, IL-35/IL-17 ratio was significantly lower in the infertile group compared with that in the fertile group; SOCS3 plasma levels showed an inverse relation with plasma levels of all cytokines except IL-35; increased plasma IL-17 levels (greater than 3.42 pg/ml) have a negative impact on fertility; TNFα/IL-10, IFNγ/IL-10, IFNγ/IL-6, and IFNγ/IL-4 ratios were significantly higher in infertile group compared with those in the fertile group. The authors concluded that it is not possible to show the major immunological factor(s) of unexplained infertility, but these findings pointed out that the decreased suppressor activity of the immune system may play a role in implantation failure.

Furthermore, UpToDate reviews on “Overview of infertility” (Kuohung and Hornstein, 2015a) and “Evaluation of female infertility” (Kuohung and Hornstein, 2015b) do not mention the use of Th1/Th2 ratio or intracellular cytokine assay as a management tool.

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a hormone that is produced by the pituitary gland and exerts its effects primarily on the ovaries and testes. In females, hCG works with follicle-stimulating hormone to

produce mature ovum and progesterone. In males, it stimulates the production of androgen which leads to the development of male secondary sex characteristics. It may also stimulate testicular descent in the absence of anatomical abnormalities.

In general, hCG is thought to induce testicular descent in situations when descent would have occurred at puberty. hCG thus may help to predict whether or not orchiopexy will be needed in the future. Although, in some cases, descent following hCG administration is permanent, in most cases the response is temporary. Therapy is usually instituted between the ages of 4 and 9 years.

Commercially available hCG products are collected from human pregnancy urine.

Human chorionic gonadotropin is indicated for the following: prepubertal cryptorchidism not due to anatomic obstruction; selected cases of hypogonadotropic hypogonadism (hypogonadism secondary to a pituitary deficiency) in males; induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure, and who has been appropriately pretreated with human menotropins.

Human chorionic gonadotropin is available as Novarel, Pregnyl, and as a generic product in vials containing 10,000 units USP.

Human chorionic gonadotropin has not been proven effective for: obesity treatment; erectile dysfunction; precocious puberty treatment; and prostatic carcinoma or other androgen-dependent neoplasm treatment..

Human chorionic gonadotropin has not been demonstrated to be effective adjunctive therapy in the treatment of obesity. There is no substantial evidence that it increases weight loss beyond that resulting from caloric restriction, that it causes a more attractive or “normal” distribution of fat, or that it decreases the hunger and discomfort associated with calorie-restricted diets.

Early Embryo Viability Assessment (Eeva) Test

In a prospective, multi-center, cohort study, Conaghan et al (2013) evaluated the first computer-automated platform for time-lapse image analysis and blastocyst prediction and determined how the screening information may assist embryologists in day 3 (D3) embryo selection. A total of 160 women aged 18 years or older undergoing fresh IVF treatment with basal antral follicle count greater than or equal to 8, basal FSH less than 10 IU/ml, and greater than or equal to 8 normally fertilized oocytes were included in this study. A non-invasive test combining time-lapse image analysis with the cell-tracking software, Eeva (Early Embryo Viability Assessment), was used to measure early embryo development and generate usable blastocyst predictions by D3. Main outcome measure was improvement in the ability of experienced embryologists to select which embryos are likely to develop to usable blastocysts using D3 morphology alone, compared with morphology plus Eeva. Experienced embryologists using Eeva in combination with D3 morphology significantly improved their ability to identify embryos that would reach the usable blastocyst stage (specificity for each of 3 embryologists using morphology versus morphology plus Eeva: 59.7 % versus 86.3 %, 41.9 % versus 84.0 %, 79.5 % versus 86.6 %). Adjunctive use of morphology plus Eeva improved embryo selection by enabling embryologists to better discriminate which embryos would be unlikely to develop to blastocyst and was particularly beneficial for improving selection among good-morphology embryos. Adjunctive use of morphology plus Eeva also reduced inter-individual variability in embryo selection. The authors concluded that previous studies have shown improved implantation rates for blastocyst transfer compared with cleavage-stage transfer; addition of Eeva to the current embryo grading process may improve the success rates of cleavage-stage ETs.

VerMilyea et al (2014) noted that computer-automated time-lapse analysis has been shown to improve embryo selection by providing quantitative and objective information to supplement traditional morphology. In a blinded, multi-center study, these researchers examined relationship between such computer-derived outputs (High, Medium, Low scores), embryo implantation and clinical pregnancy. Data were collected from 6 clinics, including 205 patients whose embryos were imaged by the Eeva(TM) System. The Eeva scores were blinded and not considered during embryo selection. Embryos with high and medium scores had significantly higher implantation rates than those with low

scores (37 % and 35 % versus 15 %; p < 0.0001; p = 0.0004). Similar trends in implantation rates were observed in different IVF centers each using their own protocols. Further analysis revealed that patients with at least 1 high embryo transferred had significantly higher clinical pregnancy rates than those with only low embryos transferred (51 % versus 34 %; p = 0.02), although patients' clinical characteristics across groups were comparable. The authors concluded that these data, together with previous research and clinical studies, confirmed that computer-automated Eeva scores provided valuable information, which may improve the clinical outcome of IVF procedures and ultimately facilitate the trend of single embryo selection.

In summary, there is currently insufficient evidence to support the use of the EEVA test for improving embryo selection.

CAG-Repeat Polymorphisms in the Polymerase γ Gene (POLG) and Male Infertility

Zhang et al (2015) stated that CAG-repeat in the polymerase γ (POLG) gene encoding polymerase γ for mitochondria is important to spermatogenesis. Compared with a few researchers who raised alteration of CAG-repeat-affected male reproductive ability, others did not find the association between CAG-repeat polymorphisms and male infertility. These researchers performed a comprehensive meta-analysis to determine the association; 13 case-control studies were screened out using keywords search. From these studies, characteristics were extracted for conducting meta-analysis. Odds ratio (OR) and 95 % CI were used to describe the results; the results indicated that CAG-repeat allele was not a risk factor to male infertility (pooled OR = 1.03, 95 % CI: 0.79 to 1.34, p = 0.828). Four different genetic comparisons also demonstrated a negative result: heterozygote comparison (not 10/10 versus 10/10; pooled OR = 0.99, 95 % CI: 0.77 to 1.27, p = 0.948), homozygote comparison (not 10/not 10 versus 10/10; pooled OR = 1.08, 95 % CI: 0.56 to 2.06, p = 0.816), the recessive genetic comparison (not 10/not 10 versus not 10/10 + 10/10; pooled OR = 1.07, 95 % CI: 0.58 to 1.95, p = 0.829) and the dominant genetic comparison (not 10/not 10 + not 10/10 versus 10/10; pooled OR = 0.97, 95 % CI: 0.72 to 1.29, p = 0.804). The authors concluded that based on current researches, this

meta-analysis demonstrated no apparent association between POLG-CAG-repeat and male infertility. Similarly, CAG-repeat was not a sensitive site to male infertility.

Hyperbaric Oxygen Therapy

Metelev et al (2015) examined the potential of hyperbaric oxygen (HBO) for reduction of sperm DNA fragmentation level and reactive oxygen species (ROS) in semen. The study included 90 men with idiopathic infertility. Patients of the treatment group (n = 60) underwent HBO before IVF. In the control group (n = 30) IVF was carried out without prior course of HBO. Sperm DNA fragmentation analysis was carried out using the TUNEL assay, the level of ROS in the ejaculate was measured by chemiluminescence. Hyperbaric oxygen therapy resulted in a significant decrease in the mean level of sperm DNA fragmentation from 33.2 ± 7.5 to 11.9 ± 5.9 %, and the median ROS in sperm from 0.89 to 0.39 mV/s ($p < 0.05$). In the control group these changes were not statistically significant. Pregnancy after IVF occurred in 63.3 % (38/60) of sexual partners of the treatment group men and in 36.7 % (11/30) of the control group ($p < 0.05$). The authors concluded that the high efficiency of HBO in overcoming the adverse effects of oxidative stress on sperm parameters suggested that it is a promising method for the treatment of men with idiopathic infertility.

Genetic Testing of CFTR Mutations for a Man with Congenital Absence of the Vas Deferens

Yu and associates (2012) stated that numerous studies have reported cystic fibrosis transmembrane conductance regulator (CFTR) mutations in congenital bilateral absence of the vas deferens (CBAVD) patients, but their results are not completely consistent. These investigators performed a systemic review and meta-analysis with emphasis on clarifying further the genetic association of CFTR mutations with CBAVD. They searched the Medline database until March, 2011 for eligible articles reporting CFTR mutations in CBAVD. Relevant data from each included study were abstracted by 2 independent reviewers. The overall frequency of CFTR mutations in CBAVD and OR for common specific alleles were pooled under random-effect or fixed-effect model as appropriate. Subgroup analysis was performed by ethnicity, and potential

heterogeneity and bias were both assessed. Among CBAVD patients, 78 % had at least 1 CFTR mutation, 46 % having 2 and 28 % only 1. Moreover, the common heterozygous F508del/5T and F508del/R117H were observed in 17 % and 4 % of CBAVD cases, respectively, and the allele frequency in CBAVD was 17 % for F508del, 25 % for 5T and 3 % for R117H. Subgroup analysis indicated an increased frequency of cases with 2 mutations in Caucasian patients than in non-Caucasian (68 % versus 50 %, p = 0.012), but no differences for cases with at least 1 mutation (88 % versus 77 %, p = 0.163) or with only 1 mutation (17 % versus 25 %, p = 0.115). Caucasian patients had higher F508del frequency, but lower 5T frequency, than non-Caucasian (22 % versus 8 %, p = 0.001; 20 % versus 31 %, p = 0.009). Summary OR was 9.25 for 5T [95 % CI: 7.07 to 12.11, p = 0.000], with moderate heterogeneity (I(2)= 49.20 %, p= 0.019) and evident bias (Egger's test, p = 0.005), and it was 19.43 for 5T/(TG)12_13 (95 % CI: 10.48 to 30.03, p = 0.000) without any evidence of heterogeneity (I(2)= 0.1 %, p = 0.391) and bias (Egger's test, p = 0.160). The OR for 5T/(TG)12_13 was significantly higher than that for 5T allele (p = 0.000). The authors concluded that these findings demonstrated a high frequency of CFTR mutations in CBAVD patients, and these exhibited evident ethnic differences. In addition, 5T allele and 5T/(TG)12_13 may contribute to the increased risk for CBAVD, with the 5T penetrance probably being modulated by adjacent (TG)12_13.

The European Association of Urology’s guidelines on “Male infertility” (Jungwirth et al, 2012) stated that “Men with congenital bilateral absence of the vas deferens [CBAVD] often have mild clinical stigmata of cystic fibrosis (CF) (e.g., history of chest infections). Children born after intracytoplasmic sperm injection (ICSI), where the father has CBAVD and is either heterozygous or homozygous, must be followed-up. When a man has CBAVD, it is important to test him and his partner for CF mutations. If the female partner is found to be a carrier of cystic fibrosis transmembrane conductance regulator (CFTR), the couple must consider very carefully whether to proceed with ICSI using the husband's sperm, as the risk of having a baby with CF will be 25 % if the man is heterozygous and 50 % if the man is homozygous. If the female partner is negative for known mutations, the risk of being a carrier of unknown mutations is about 0.4 %”.

Sharma and co-workers (2014) noted that CF is usually considered a rare disease in the Indian population; 2 studies have reported on the frequency of CFTR gene mutations in Indian males with CAVD. However, data on the spectrum of CFTR gene mutations are still lacking. These researchers identified the spectrum of CFTR gene mutations and investigated an association of CF genetic modifiers in the penetrance of CAVD in infertile Indian men. A total of 60 consecutive infertile males with a diagnosis of CAVD were subjected to CFTR gene analysis that revealed 13 different CFTR gene mutations and 1 intronic variant that led to aberrant splicing. p.Phe508del (n = 16) and p.Arg117His (n = 4) were among the most common severe forms of CFTR mutations identified. The IVS8-T5 allele, which is considered as a mild form of CFTR mutation, was found with an allelic frequency of 28.3 %; 8 novel mutations were also identified in the CFTR gene from this patient cohort. It was noteworthy that the spectrum of CFTR gene mutation was heterogeneous, with exon 4 and exon 11 as hot spot regions. Moreover, these investigators also found an association of the CF genetic modifiers, viz., transforming growth factor (TGF)-β1 and endothelial receptor type-A (EDNRA) genes with the CAVD phenotype. The findings were of considerable clinical significance because men suffering from infertility due to CAVD can decide to use artificial reproduction technology. The children of men with CAVD are at risk of carrying CFTR mutations; therefore, genetic counseling is a crucial step for such patients. With special reference to developing countries, such as India, where whole gene sequencing is not feasible, the outcome of this study will make the screening procedure for CFTR gene simpler and more cost-effective as these researchers have identified hot spot regions of the CFTR gene that are more prone to mutation in Indian males with CAVD. Moreover, this was the first study from the Indian population to investigate the association of CF genetic modifiers with penetrance of the CAVD phenotype. They stated that the observed association of the genetic modifiers TGF-β1 and EDNRA in the penetrance of CAVD further supports their involvement in genesis of the vas deferens.

Yang and colleagues (2015) discussed the findings and significance of the detection of the CFTR gene mutation in azoospermia patients with congenital unilateral absence of the vas deferens (CUAVD). These researchers collected peripheral blood samples from 6 azoospermia patients with CUAVD for detection of the CFTR gene mutations and

single nucleotide polymorphisms (SNPs). They analyzed the genome sequences of the CFTR gene in comparison with the website of the UCSC Genome Browser on Human December 2013 Assembly. Missense mutation of c. 592G > C in exon 6 was found in 1 of the 6 azoospermia patients with CUAVD and splicing mutation of c. 1210-12T[5] was observed in the non-coding region before exon 10 in 2 of the patients, both with the V470 haplotype in exon 11. The authors concluded that mutations of the CFTR gene can be detected in azoospermia patients with CUAVD and the detection of the CFTR gene mutation is necessary for these patients.

Furthermore, an UpToDate review on "Evaluation of male infertility" (Swerdloff and Wang, 2017) states that "Absence of the vas deferens on physical examination, together with low seminal fluid volume and acidic pH, suggest congenital absence of vas deferens. Low or absent semen fructose will help to confirm the diagnosis of this condition, because the seminal vesicles are usually also absent. These patients should be tested for the CFTR gene mutations and, if positive in either the man or the female partner, genetic counseling is necessary before IVF and ICSI".

Vaginal Sildenafil for the Treatment of Female Infertility

Check et al (2004) examined if sildenafil improves endometrial thickness better than vaginal estradiol (E2) in women with a history of thin endometria. Women failing to attain an 8 mm endometrial thickness on either the oocyte retrieval cycle or their 1st frozen embryo transfer (ET) despite an oral graduated E2 regimen were treated again with graduated oral E2 and were also randomly assigned to vaginal sildenafil or vaginal E2 therapy. Endometrial thickness was compared between the groups. Neither vaginal E2 nor sildenafil significantly improved endometrial thickness or blood flow in the subsequent frozen ET-cycle. The authors concluded that these data failed to corroborate previous claims that 25-mg sildenafil 4 times daily intra-vaginally can improve endometrial thickness.

Zinger et al (2006) stated that vaginal sildenafil citrate has been shown to be useful in increasing endometrial thickness and achieving pregnancy in women with varied uterine disorders. However, it failed to demonstrate favorable results in the setting of Asherman's syndrome, a condition

characterized by the presence of uterine synechiae. These investigators have successfully applied this treatment in 2 women noted to have inadequate endometrium after surgical resection of uterine synechiae. Both patients had a history of a post-partum uterine curettage with subsequent secondary infertility. Asherman's syndrome was surgically demonstrated and treated in both patients. Post-operatively, both patients were noted to have a thin endometrium and failed to conceive despite fertility treatment. Subsequently, these women achieved pregnancy in the 1st treatment cycle with vaginal sildenafil citrate. Using trans-vaginal ultrasound, endometrial thickness was noted to improve when sildenafil citrate was administered. It is suspected that this medication causes selective vasodilatation, resulting in improved endometrial development.

Malinova et al (2013) noted that evaluation of endometrial receptivity remains a challenge in clinical practice. Ultrasound evaluation of endometrial thickness and texture and measurement of uterine artery blood flow has been used for endometrial assessment. These researchers investigated the role of combination of sildenafil citrate and serophene on endometrial thickness, endometrial volume, endometrial FI and VFI on angiohistogram, RI and PI to a. uterine on the day of hCG, in prediction of IUI outcome in infertile women. A total of 42 patients were selected randomly who had anovulatory infertility. In the sildenafil citrate plus serophene group (Group I), patients got 25 mg sildenafil citrate (Silden) vaginally and serophene 100 to 150 mg orally, and in serophene group (Group II), 100 to 150 mg of serophene was given orally. Mean endometrial thickness and endometrial volume was 11.8 +/- 2.6 v/s 10.2 +/- 2.8 and 5.2 +/- 1.4 v/s 3.6 +/- 1.8, respectively in group I and in group II ($p < 0.05$). There was significant decrease in PI and RI to a. uterina in group I. The authors concluded that combination of sildenafil citrate and serophene is an effective agent as a first-line of treatment for ovulation induction. This was a relatively small study, and its findings were confounded by the combined use of sildenafil and serophene.

Soliman and colleagues (2017) developed and characterized in-situ thermos-sensitive gels for the vaginal administration of sildenafil as a potential treatment of endometrial thinning occurring as a result of using clomiphene citrate for ovulation induction in women with type II eugonadotrophic anovulation. While sildenafil has shown promising

results in the treatment of infertility in women, the lack of vaginal pharmaceutical preparation and the side effects associated with oral sildenafil limit its clinical effectiveness. Sildenafil citrate in-situ forming gels were prepared using different grades of Pluronic (PF-68 and PF-127). Muco-adhesive polymers as sodium alginate and hydroxyethyl cellulose were added to the gels in different concentrations and the effect on gel properties was studied. The formulations were evaluated in terms of viscosity, gelation temperature (Tsol-gel), muco-adhesion properties, and in-vitro drug release characteristics. Selected formulations were evaluated in women with clomiphene citrate failure due to thin endometrium (Clinicaltrial.gov identifier NCT02766725). The Tsol-gel decreased with increasing PF-127 concentration and it was modulated by addition of PF-68 to be within the acceptable range of 28 to 37 °C. Increasing Pluronic concentration increased gel viscosity and muco-adhesive force but decreased drug release rate. Clinical results showed that the in-situ sildenafil vaginal gel significantly increased endometrial thickness and uterine blood flow with no reported side effects. Further, these results were achieved at lower frequency and duration of drug administration. The authors concluded that sildenafil thermos-sensitive vaginal gels might result in improved potential of pregnancy in anovulatory patients with clomiphene citrate failure due to thin endometrium. These preliminary findings need to be validated by well-designed studies.

Furthermore, an UpToDate review on “Overview of treatment of female infertility” (Kuohung and Hornstein, 2017) does not mention sildenafil as a management tool.

Germ Cell Transplantation or Cultured Testicular Stem Cells for the Treatment of Male Infertility

An UpToDate review on “Treatment of male infertility” (Wang and Swerdloff, 2017) states that “Mammalian (mouse) germ cells undergo self-renewal, can be maintained in vitro for several hours, can initiate organized, normal spermatogenesis when transplanted to mice depleted of germ cells due to genetic mutation or after chemotherapy, and can result in normal progeny after successful mating with females. Successful germ cell transplants can be achieved from mouse to mouse, rat to rat, and rat to immune-compromised mouse. Recently, successful

ectopic xenografts of testis from a number of species including primates into mice have allowed studies of drugs and toxicants on spermatogenesis without having to administer the agent to the species. These observations suggest that germ cell transplantation or cultured testicular stem cells may become a treatment for male infertility and for genetic diseases in men that can be corrected and eradicated in germ cell lines. This possibility raises serious ethical, social, and moral issues".

Intrauterine Administration of Human Chorionic Gonadotropin (hCG) for Subfertile Women Undergoing Assisted Reproduction

Craciunas and colleagues (2018) examined if intra-uterine (intra-cavity) administration of hCG (IC-hCG) around the time of ET improves clinical outcomes in sub-fertile women undergoing assisted reproduction. These investigators performed searches on January 9, 2018 using Cochrane methods. They looked for RCTs evaluating IC-hCG around the time of ET, irrespective of language and country of origin. Two review authors independently selected studies, assessed risk of bias, extracted data from studies, and attempted to contact study authors when data were missing. They performed statistical analysis using Review Manager 5. These researchers assessed evidence quality using GRADE methods. Primary outcomes were live-birth and miscarriage; secondary outcomes were clinical pregnancy rate and complications. A total of 17 RCTs examined the effects of IC-hCG administration for 4,751 sub-fertile women undergoing assisted reproduction; IC-hCG was administered in variable doses at different times before the ET; hCG was obtained from the urine of pregnant women or from cell cultures using recombinant DNA technology. Most studies (12/17) were at high risk of bias in at least 1 of the 7 domains assessed. Common problems were unclear reporting of study methods and lack of blinding. The main limitations for evidence quality were high risk of bias and serious imprecision. For analyses of live-birth and clinical pregnancy, there was considerable heterogeneity (I^2 > 75 %) and therefore these researchers presented subgroups for dosage and stage of ET. Exploration for sources of heterogeneity revealed 2 key pre-specified variables as important determinants: stage of ET (cleavage versus blastocyst stage) and dose of IC-hCG (less than 500 international units (IU) versus greater than or equal to 500 IU). They performed meta-analyses within subgroups defined by stage of embryo and dose of IC-hCG. Live-birth rates among women having cleavage-stage ET with an

IC-hCG dose of less than 500 IU compared to women having cleavage-stage ET without IC-hCG showed no benefit of the intervention and would be consistent with no substantive difference or disadvantage of indeterminate magnitude (risk ratio (RR) 0.76, 95 % CI: 0.58 to 1.01; 1 RCT; 280 participants; I^2 = 0 %; very low-quality evidence). In a clinic with a live-birth rate of 49 % per cycle, use of IC-hCG of less than 500 IU would be associated with a live-birth rate ranging from 28 % to 50 %. Results showed an increase in live-birth rate in the subgroup of women undergoing cleavage-stage ET with an IC-hCG dose of greater than or equal to 500 IU compared to women having cleavage-stage ET without IC-hCG (RR 1.57, 95 % CI: 1.32 to 1.87; 3 RCTs; 914 participants; I^2 = 0 %; moderate-quality evidence). At a clinic with a live-birth rate of 27 % per cycle, use of IC-hCG of greater than or equal to 500 IU would be associated with a live-birth rate ranging from 36 % to 51 %. Results showed no substantive differences in live-birth among women having blastocyst-stage ET with an IC-hCG dose of greater than or equal to 500 IU compared to women having blastocyst-stage ET without IC-hCG (RR 0.92, 95 % CI: 0.80 to 1.04; 2 RCTs; 1,666 participants; I^2 = 0 %; moderate-quality evidence). At a clinic with a live-birth rate of 36 % per cycle, use of IC-hCG of greater than or equal to 500 IU would be associated with a live-birth rate ranging from 29 % to 38 %. Evidence for clinical pregnancy among women having cleavage-stage ET with an IC-hCG dose of less than 500 IU showed no benefit of the intervention and would be consistent with no substantive difference or disadvantage of indeterminate magnitude (RR 0.88, 95 % CI: 0.70 to 1.10; 1 RCT; 280 participants; I^2 = 0 %; very low-quality evidence). Results showed an increase in clinical pregnancy rate in the subgroup of women having cleavage-stage ET with an IC-hCG dose of greater than or equal to 500 IU compared to women having cleavage-stage ET without IC-hCG (RR 1.49, 95 % CI: 1.32 to 1.68; 12 RCTs; 2,186 participants; I^2 = 18 %; moderate-quality evidence). Results showed no substantive differences in clinical pregnancy among women having blastocyst-stage ET with an IC-hCG dose of greater than or equal to 500 IU (RR 0.99, 95 % CI: 0.85 to 1.15; 4 RCTs; 2,091 participants; I^2 = 42 %; moderate-quality evidence) compared to women having blastocyst-stage ET with no IC-hCG. No RCTs examined blastocyst-stage ET with an IC-hCG dose of less than 500 IU. These researchers were uncertain whether miscarriage was influenced by intra-uterine hCG administration (RR 1.04, 95 % CI: 0.81 to 1.35; 11 RCTs; 3,927 participants; I^2 = 0 %; very low-quality evidence).

Reported complications were ectopic pregnancy (4r RCTs; 1,073 participants; 4 events overall), heterotopic pregnancy (1 RCT; 495 participants; 1 event), intra-uterine death (3 RCTs; 1,078 participants; 22 events), and triplets (1 RCT; 48 participants; 3 events). Events were few, and very low-quality evidence was insufficient to permit conclusions to be drawn. The authors concluded that there was moderate quality evidence that women undergoing cleavage-stage transfer using an IC-hCG dose of greater than or equal to 500 IU had an improved live-birth rate. There was insufficient evidence for IC-hCG treatment for blastocyst transfer. There should be further trials with live-birth as the primary outcome to identify the groups of women who would benefit the most from this intervention. There was no evidence that miscarriage was reduced following IC-hCG administration, irrespective of embryo stage at transfer or dose of IC-hCG. Events were too few to allow conclusions to be drawn with regard to other complications.

DuoStim IVF Protocol

DuoStim IVF cycles are IVF cycles for women with poor response to prior IVF cycles or diminished ovarian reserve. DuoStim has two steps. Step one includes stimulation, aspiration, fertilization and freeze of the embryos. Step two occurs after aspiration in step one and involves stimulation of any follicles that were too small to aspirate in step one. This second crop of follicles go to aspiration and fertilization.

Massin (2017) noted that the advent of embryo and oocyte vitrification today gives reproductive specialists an opportunity to consider new strategies for improving the practice and results of in-vitro fertilization (IVF) attempts. As the freezing of entire cohorts does not compromise, and may even improve, the results of IVF attempts, it is possible to break away from the standard sequence of stimulation-retrieval-transfer. The constraints associated with ovarian stimulation in relation to the potential harmful effects of the hormonal environment on endometrial receptivity can be avoided. This review examined the new stimulation protocols where progesterone is used to block the LH surge. Thanks to 'freeze all' strategies, the increase in progesterone could actually be no longer a cause for concern. There are 2 ways of using progesterone, whether it be endogenous, as in luteal phase stimulation, or exogenous, as in the use of progesterone in the follicular phase i.e., progestin-primed ovarian

stimulation. These investigators performed a literature search (until September 2016) on Medline. The following text words were utilized to generate the list of citations: progestin primed ovarian stimulation, luteal phase stimulation, luteal stimulation, DuoStim, double stimulation, random start. Articles and their references were then examined in order to identify other potential studies. All of the articles were reported in this review. The use of progesterone during ovarian stimulation is effective in blocking the LH surge, whether endogenous or exogenous, and it does not affect the number of oocytes collected or the quality of the embryos obtained. Its main constraint is that it requires total freezing and delayed transfer. A variety of stimulation protocols can be derived from these 2 methods, and their implications were discussed, from fertility preservation to ovarian response profiles to organization for the patients and clinics. These new regimens enable more flexibility and are of emerging interest in daily practice. However, their medical and economic significance remains to be demonstrated. The authors concluded that the use of luteal phase or follicular phase protocols with progestins could rapidly develop in the context of oocyte donation and fertility preservation not related to oncology. Their place could develop even more in the general population of patients in IVF programs. The strategy of total freezing continues to develop, thanks to technical improvements, in particular vitrification and PGS on blastocysts, and thanks to studies showing improvements in embryo implantation when the transfer take place far removed from the hormonal changes caused by ovarian stimulation.

Vaiarelli et al (2018) stated that the management and treatment of patients with poor ovarian response is still a controversial issue in IVF. Increasing evidences demonstrate that the number of oocytes retrieved after a controlled ovarian stimulation (COS) greatly influences the clinical outcome in terms of cumulative live-birth per started cycle. For this reason, any COS should aim to optimize the number of oocytes according to the ovarian reserve of the patient. These investigators provided an overview of new strategies proposed to manage poor responders according to the novel POSEIDON classification. Gonadotrophins cannot compensate for the absence of follicles in the ovary, therefore, COS in poor responders may benefit from the exploitation of multiple follicular waves within a single ovarian cycle, for instance, through luteal phase stimulation or double stimulation (follicular plus luteal) in the same ovarian cycle (DuoStim) protocols. The authors concluded that many strategies

have been proposed to manage poor responder patients, however, a consensus upon which is the most beneficial has not been yet reached; and DuoStim is the most promising approach to increase the number of oocytes collected in a single ovarian cycle; however, more embryological and clinical data is needed, as well as an analysis of its cost-effectiveness.

Cimadomo et al (2018) noted that 3 theories of follicle recruitment have been postulated to date: (i) the “continuous recruitment” theory, (ii) the “single recruitment episode” theory, and (iii) the “wave” theory. Yet, a clear characterization of this crucial biological process for human reproduction is missing. Recent advances implemented in IVF, such as blastocyst culture, aneuploidy testing and vitrification, have encouraged clinicians to maximize the exploitation of the ovarian reserve through tailored stimulation protocols, which is crucial especially for poor prognosis patients aiming to conceive after IVF. Luteal phase stimulations (LPS) has been already successfully adopted to treat poor prognosis or oncological patients through DuoStim, LPS-only or random-start ovarian stimulation approaches. Nevertheless, little, and mainly retrospective, evidence has been produced to support the safety of LPS in general. Feasibility of the LPS approach would severely question the classic “single recruitment episode” theory of follicular development. In a case-control study, these researchers determined if the mean numbers of blastocysts obtained from sibling cohorts of oocytes recruited after follicular phase stimulation (FPS) and LPS in the same ovarian cycle are similar. This trial was carried out with paired follicular phase- and luteal phase-derived cohorts of oocytes collected after stimulations in the same ovarian cycle (DuoStim) at 2 private IVF clinics between October 2015 and December 2017. This study included 188 poor prognosis patients undergoing DuoStim with pre-implantation genetic testing for aneuploidies (PGT-A); FPS and LPS were performed with the same daily dose of recombinant-gonadotrophins in an antagonist protocol. Blastocyst culture, trophectoderm biopsy, vitrification and frozen-warmed euploid single blastocyst transfers were performed. The primary outcome was the mean number of blastocysts obtained per oocyte retrieval from paired-FPS- and LPS-derived cohorts (required sample size = 165 patients; power = 90 %). Mean blastulation and euploidy rates were monitored, along with the number of oocytes, euploid blastocysts and clinical outcomes. Significantly fewer blastocysts were obtained after

FPS than LPS (1.2 ± 1.1 versus 1.6 ± 1.6, p < 0.01), due to fewer oocytes collected (3.6 ± 2.1 versus 4.3 ± 2.8, p < 0.01) and a similar mean blastocyst rates per retrieval (33.1 % ± 30.3 % versus 37.4 % ± 30.8 %, p = NS). The number of oocytes collected were correlated (R = 0.5, p < 0.01), while the blastocyst rates were uncorrelated among paired-FPS- and LPS-derived cohorts. Overall, a significantly lower chance of producing blastocyst(s) was reported after FPS than after LPS: 67.6 % (n = 127/188, 95 % confidence interval [CI]: 60.3 to 74.1) versus 77.1 % (n = 145/188, 95 % CI: 70.3 to 82.8; p = 0.05). The mean euploidy rates per retrieval were similar between FPS- and LPS-derived cohorts of oocytes (13.6 % ± 22.8 % versus 16.3 % ± 23.4 %, p = NS). Thus, on average fewer euploid blastocysts (0.5 ± 0.8 versus 0.7 ± 1.0, p = 0.02) resulted from FPS. Similar ongoing-pregnancy/delivery rates were reported, to-date, after FPS- and LPS-derived euploid single blastocyst transfers: 42.4 % (n = 28/66, 95 % CI: 30.5 to 55.2) versus 53.8 % (n = 35/65, 95 % CI: 41.1 to 66.1; p = NS). The authors concluded that this study provided evidence that the follicles recruited during the anovulatory phase of the ovarian cycle may be rescued through LPS. Of note, LPS-derived cohorts of oocytes were also larger than paired-FPS-derived cohorts and the oocytes showed comparable competence. These data supported the putative benefits of LPS in poor prognosis and oncological patients. Furthermore, they encourage additional clinical and basic research studies on this topic, which may revolutionize the basics of human folliculogenesis, as well as the future concept of approaches to ovarian stimulation in IVF.

The authors stated that more studies need to be conducted in the future to confirm the safety of LPS, especially in terms of ovarian and follicular environment, as well as the clinical, peri-natal and post-natal outcomes. The findings of this study showed preliminary data suggesting a similar ongoing implantation/delivery rate (greater than 22 weeks) between FPS- and LPS-derived euploid blastocysts, that need to be extended in the future, to populations other than poor prognosis patients and using approaches other than DuoStim together with a constant monitoring of the related peri-natal and post-natal outcomes.

Vaiarelli et al (2018) stated that a panel of experts known as the POSEIDON group has recently re-defined the spectrum of poor responder patients and introduced the concept of sub-optimal response.

Since an ideal management for these patients is still missing, they highlighted the importance of tailoring the ovarian stimulation based on the chance of each woman to obtain an euploid blastocyst. Interestingly, a novel pattern of follicle recruitment has been defined: multiple waves may arise during a single ovarian cycle. This evidence opened important clinical implications for the treatment of poor responders. For instance, double stimulation in the follicular (FPS) and luteal phase (LPS) of the same ovarian cycle (DuoStim) is an intriguing option to perform 2 oocyte retrievals in the shortest possible time. These investigators reported their 2-year experience of DuoStim application in 4 private IVF centers. To-date, 310 poor prognosis patients completed a DuoStim protocol and underwent IVF with blastocyst-stage pre-implantation-genetic-testing. LPS resulted into a higher mean number of oocytes collected than FPS; however, their competence (i.e., fertilization, blastocyst, euploidy rates, and clinical outcomes after euploid single-embryo-transfer) was comparable. Importantly, the rate of patients obtaining at least 1 euploid blastocyst increased from 42.3 % (n = 131/310) after FPS to 65.5 % (n = 203/310) with the contribution of LPS. A summary of the putative advantages and disadvantages of DuoStim was reported here through a Strengths-Weaknesses-Opportunities-Threats analysis. The strengths of this approach made it very promising. Moreover, the authors concluded that DuoStim still needs a more extensive and wider validation to testify its safety. Interesting future perspectives to investigate its clinical efficacy/efficiency would entail (i) a RCT comparing double-FPS versus DuoStim; (ii) the application of DuoStim in cancer patients for fertility preservation; (iii) as well as in prospective analyses focused on patients clustered according to either the Bologna criteria or the Poseidon stratification. They stated that until such evidence would be produced, DuoStim should be clinically applied only to a population of patients of poor prognosis and/or to whom time represents a critical issue.

The authors stated that the weaknesses of DuoStim are: a higher number of stimulations appeared to be canceled in the LP than in the FP; no RCT or cost-effectiveness analysis has been performed to-date investigating the use of DuoStim; a freeze-all approach is mandatory; it has been applied only to poor prognosis patients. The opportunities are: a decrease in the time and increase in the chance to obtain at least 1 competent embryo in a single menstrual cycle; the DuoStim protocol

might be better-tolerated from the patients than consecutive FPS cycles; the drop-out rate might be reduced; the knowledge regarding the mechanisms of follicular recruitment and ovarian physiology might be increased. The threats are: an analysis of the cost-effectiveness is yet eagerly needed; the total dose of gonadotrophins to be administrated is substantial; few biological, gynecological, obstetrical, and neonatal evidence of safety have been produced to date. The strengths of this approach make it very promising. However, more studies are needed in the future to limit its weaknesses, shed light on its putative threats, and realize its opportunities.

There is a clinical trial on “DuoStim in Cases of PGT: Comparison of Embryo Quantity and Embryonic Quality Using MitoScore” that is currently recruiting participants (last updated September 3, 2018).

Furthermore, an UpToDate review on “In vitro fertilization” (Paulson, 2019) does not mention DuoStim / double stimulation as a management tool.

Vasodilators for Women Undergoing Fertility Treatment

Gutarra-Vilchez et al (2014) noted that since 1978, when Patrick Steptoe and Robert Edwards achieved the birth of the first test tube baby, ARTs have been refined and improved. However, the rate of successful pregnancies brought to term has barely increased. Thus, closer evaluation of the interventions is needed along with working towards improving uterus receptivity. Vasodilators have been proposed to increase endometrial receptivity, thicken the endometrium and favor uterine relaxation, all of which could improve uterine receptivity and enhance the chances for successful assisted pregnancies. In a Cochrane review, these investigators evaluated the safety and effectiveness of vasodilators in women undergoing fertility treatment. The authors concluded that (i) evidence was insufficient to show that vasodilators increased the live-birth rate in women undergoing fertility treatment; (ii) low-quality evidence suggested that vasodilators may increase clinical pregnancy rates in comparison with placebo or no treatment, and (iii) evidence was insufficient to show whether any particular vasodilator, administered alone or in combination with other active medications, was superior, and evidence was insufficient to allow the

review authors to reach any conclusions regarding adverse effects. They stated that adequately powered studies are needed so that each treatment can be evaluated more accurately.

In a Cochrane review, Gutarra-Vilchez and colleagues (2018) examined the safety and effectiveness of vasodilators in women undergoing fertility treatment. These investigators searched the following electronic databases, trial registers, and websites: the Cochrane Gynaecology and Fertility Group (CGF) Specialized Register of controlled trials, the Cochrane Central Register of Controlled Trials, via the Cochrane Register of Studies Online (CRSO), Medline, Embase, PsycINFO, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Knowledge, the Open System for Information on Grey Literature in Europe (OpenSIGLE), the Latin American and Caribbean Health Science Information Database (LILACS), clinical trial registries, and the reference lists of relevant articles. They conducted the search in October 2017 and applied no language restrictions; RCTs comparing vasodilators alone or in combination with other treatments versus placebo or no treatment or versus other agents in women undergoing fertility treatment were selected for analysis. Four review authors independently selected studies, assessed risk of bias, extracted data, and calculated RRs. They combined study data using a fixed-effect model and assessed evidence quality using GRADE methods. The primary outcomes were live-birth or ongoing pregnancy and vasodilator side effects. Secondary outcomes included clinical pregnancy, endometrial thickness, multiple pregnancy, miscarriage, and ectopic pregnancy. These investigators included 15 studies with a total of 1,326 women. All included studies compared a vasodilator versus placebo or no treatment. They judged most of these studies as having unclear risk of bias. Overall, the quality of evidence was low-to-moderate for most outcomes. The main limitations were imprecision due to low numbers of events and participants and risk of bias due to unclear methods of randomization. Vasodilators probably made little or no difference in rates of live-birth compared with placebo or no treatment (RR 1.18, 95 % CI 0.83 to 1.69; 3 RCTs; n = 350; I^2 = 0 %; moderate-quality evidence) but probably increase overall rates of side effects including headache and tachycardia (RR 2.35, 95 % CI: 1.51 to 3.66; 4 RCTs; n = 418; I^2 = 0 %; moderate-quality evidence). Evidence suggested that if 236 per 1,000 women achieved live-birth with placebo or

no treatment, then between 196 and 398 per 1,000 will do so with the use of vasodilators. Compared with placebo or no treatment, vasodilators may slightly improve clinical pregnancy rates (RR 1.45, 95 % CI: 1.19 to 1.77; 11 RCTs; n = 1,054; I^2 = 6 %; low-quality evidence). Vasodilators probably made little or no difference in rates of multiple gestation (RR 1.15, 95 % CI: 0.55 to 2.42; 3 RCTs; n = 370; I^2 = 0 %; low-quality evidence), miscarriage (RR 0.83, 95 % CI 0.37 to 1.86; 3 RCTs; n = 350; I^2 = 0 %; low-quality evidence), or ectopic pregnancy (RR 1.48, 95 % CI: 0.25 to 8.69; 2 RCTs; n = 250; I^2 = 5 %; low-quality evidence). All studies found benefit for endometrial thickening, but reported effects varied (I^2 = 92 %) and ranged from a MD of 0.80 higher (95 % CI: 0.18 to 1.42) to 3.57 higher (95 % CI: 3.01 to 4.13) with very low-quality evidence, so these researchers were uncertain how to interpret these results. The authors concluded that evidence was insufficient to show whether vasodilators increase the live-birth rate in women undergoing fertility treatment. However, low-quality evidence suggested that vasodilators may slightly increase clinical pregnancy rates. Moderate-quality evidence showed that vasodilators increased overall side effects in comparison with placebo or no treatment. These investigators stated that adequately powered studies are needed so that each treatment can be evaluated more accurately.

Evaluation of CYP1A1 rs4646903 T > C Genetic Variations for Risk of Male Infertility

Cao and colleagues (2019) stated that number of studies have been carried out to examine the relationship between the CYP1A1 rs4646903 polymorphism and male infertility risk, but the sample size was small and the results were conflicting. These researchers conducted a meta-analysis to examine these associations. They performed a systematic search to identify all relevant studies from Medline, Web of science, Embase, China biology medical literature database (CBM), China National Knowledge Infrastructure (CNKI), WanFang and Weipu (VIP) databases up to June 30, 2018. The ORs with 95 % CIs were calculated to assess the strength of associations. All of the statistical analyses were conducted using Revman 5.3 and Stata 14.0. A total of 10 studies entailing 3,028 cases and 3,258 controls were included in this analysis. Overall, significant association was observed between the CYP1A1 rs4646903 polymorphism and male infertility (C versus T: OR=1.42, 95 %

CI: 1.14 to 1.76; CC versus TT: OR =2.13, 95 % CI:1.36 to 3.34; CC versus CT+TT: OR=1.96, 95 % CI: 1.30 to 2.95; CC+CT versus TT: OR= 1.51, 95 % CI:1.16 to 1.97). In subgroup analysis by ethnic group, a statistically significant association was observed in Asians (C versus T: OR=1.59, 95 % CI:1.22 to 2.08), but not in non-Asians (C versus T: OR= 1.01, 95 % CI: 0.79 to 1.30). Furthermore, none of the individual studies significantly affected the association between CYP1A1 rs4646903 polymorphism and male infertility, according to sensitivity analysis. The authors concluded that the findings of this meta-analysis supported that the CYP1A1 rs4646903 polymorphism might contribute to individual susceptibility to male infertility in Asians. Moreover, these researchers stated that large sample size, well-designed, and population-based studies are needed to validate the association between CYP1A1 gene variant rs4646903 polymorphism and male infertility risk.

The authors stated that this study had several drawbacks. First, only 10 studies were incorporated in the meta-analysis, the sample size of included published articles was small. Second, sub-group analyses such as by infertility type and source of control group were not performed, due to the lack of information. Third, the effects of gene-gene and gene-environment interactions on male infertility susceptibility were not estimated, as the studies enrolled lacked of information. Finally, these findings were based on unadjusted estimates, due to the lack of data of smoking, age, and other environmental exposure factors.

Evaluation of FAS/FASL Genetic Variations for Risk of Male Infertility

Asgari and colleagues (2019) noted that studies suggested that FAS/FASL polymorphisms are associated with male infertility; however, their results are still inconclusive. In a systematic review and meta-analysis, these researchers examined the overall association of FAS/FASL polymorphisms and risk of male infertility. They carried out a search on the databases of Science Direct, PubMed and Google Scholar. For performing the meta-analysis, pooled OR values with 95 % CI were applied in order to analyze the strength of association between the FAS/FASL polymorphisms and risk of male infertility. A total of 7 relevant studies published up to September 2018 were considered. FASL-844C/T genotype results of 559 patients and 623 healthy individuals were included in this study. For FAS-670A/G genotype effect, 751 patients and

821 healthy individuals were examined. Results showed that all analysis models including dominant, recessive and allelic models of FASL-844C/T and FAS-670A/G polymorphism had no significant effect on infertility in men ($p > 0.05$ and $p > 0.05$, respectively). According to sensitivity analysis, these findings were stable. The authors demonstrated that FAS/FASL polymorphisms might not be an effective factor on male reproductive health. These researchers stated that for precise determination of FAS/FASL polymorphisms effects on male infertility, large-scale, case-control studies are needed.

Evaluation of Telomere Length for Female and Male Infertility

Vasilopoulos and colleagues (2019) noted that telomere length (TL) has long been associated with aging, as telomeres serve as protective caps of chromosomes, and are thus deeply involved in the preservation of genome integrity and are vital to cellular functions. Traditionally, a strong link connects aging and infertility in both sexes, with an earlier onset in females. Over the last 10 years, telomeres have attracted increasing attention due to the role they play in fertility. In this review, these investigators examined the potential positive or negative association between relative TL and different factors of female and male infertility. They carried out a systematic search of the PubMed database. A total of 206 studies were identified; 45 met the criteria of validity and relevance. Following an analysis and a comparison of the study outcomes, several clear trends were observed. The majority of female infertility factors were associated with a shorter TL, with the exception of endometriosis, premature ovarian failure and clear cell carcinoma that were associated with a longer TL and PCOS, which revealed conflicting results among several studies, leading to ambiguous conclusions. Male infertility factors were associated with a shorter TL. The authors concluded that although the findings of this review could provide an outline of general trends in the association of TL with infertility factors, further epidemiological and original research studies are needed to examine the basis of these varying lengths of telomeres. Moreover, these researchers stated that many questions must first be addressed before the use of TL as a marker for identification of reproductive capacity can be employed in a clinical setting. They stated that further studies are needed to understand the

bases of TL associations with biological aging and reproductive capacity, and to determine how this knowledge can be used in medical applications.

Hyaluronan-Selected Intracytoplasmic Sperm Injection for Infertility Treatment (HABSelect)

Miller and colleagues (2019) noted that sperm selection strategies aimed at improving success rates of ICSI include binding to hyaluronic acid (herein termed hyaluronan). Hyaluronan-selected sperm have reduced levels of DNA damage and aneuploidy. Use of hyaluronan-based sperm selection for ICSI (so-called physiological ICSI [PICSI]) has been reported to reduce the proportion of pregnancies that end in miscarriage. However, the effect of PICSI on live-birth rates is uncertain. In a parallel, 2-group, randomized trial, these investigators examined the efficacy of PICSI versus standard ICSI for improving live-birth rates among couples undergoing fertility treatment. This study included couples undergoing an ICSI procedure with fresh embryo transfer at 16 assisted conception units in the United Kingdom. Eligible women (aged 18 to 43 years) had a BMI of 19 to 35 kg/m2 and a FSH concentration of 3.0 to 20.0 mIU/ml or, if no FSH measurement was available, an AMH concentration of at least 1.5 pmol/L. Eligible men (aged 18 to 55 years) had not had a vasovasostomy or been treated for cancer in the 24 months before recruitment and were able, after at least 3 days of sexual abstinence, to produce freshly ejaculated sperm for the treatment cycle. Couples were randomly assigned (1:1) with an online system to receive either PICSI or a standard ICSI procedure. The primary outcome was full-term (greater than or equal to 37 weeks' gestational age [GA]) live-birth, which was assessed in all eligible couples who completed follow-up. Between February 1, 2014 and August 31, 2016, a total of 2,772 couples were randomly assigned to receive PICSI (n = 1,387) or ICSI (n = 1,385), of whom 2,752 (1,381 in the PICSI group and 1,371 in the ICSI group) were included in the primary analysis. The term live-birth rate did not differ significantly between PICSI (27.4 % [379/1,381]) and ICSI (25.2% [346/1,371]) groups (OR 1.12, 95 % CI: 0.95 to 1.34; p = 0.18). There were 56 serious adverse events (AEs) in total, including 31 in the PICSI group and 25 in the ICSI group; most were congenital abnormalities and none was attributed to treatment. The authors concluded that compared with ICSI,

PICSI did not significantly improve term live-birth rates. Thus, these researchers stated that the wider use of PICSI is not recommended at present.

Stem Cell Therapy for the Treatment of Female Infertility

In a systematic review, Ahmadian and colleagues (2019) examined the evidence on stem cell therapy for ovarian disorders. These researchers evaluated different published studies on stem cell-based therapy for the treatment of various types of ovarian insufficiency and disorders such as premature ovarian insufficiency (POI) in the affected female population in animal or human clinical studies. They monitored 5 databases, including PubMed, Cochrane, Embase, Scopus, and ProQuest. A comprehensive online search was carried out using including criteria targeting application of stem cells in animal models for menopause. Two independent reviewers carefully evaluated titles and abstracts of studies. The stem cell type, source, dosage, route of administration were high-lighted in various POI animals models. Non-relevant and review articles were excluded. A total of 648 published studies were identified during the initial comprehensive search process from which 41 were selected according to designed criteria. Based on this analysis, stem cells could accelerate ovarian tissues rejuvenation, regulate systemic sex-related hormones levels and eventually increase fertility rate. The authors concluded that the evidence suggested that stem cell-based therapies could be considered as an alternative modality to deal with women undergoing POI.

An UpToDate review on “Treatments for female infertility” (Kuohung and Hornstein, 2020) does not mention stem cell therapy as a therapeutic option.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
CPT codes covered if selection criteria are met:	

Code	Code Description
0058T	Cryopreservation; reproductive tissue, ovarian [covered for women facing infertility due to chemotherapy or other gonadotoxic therapies]
0167U	Gonadotropin, chorionic (hCG), immunoassay with direct optical observation, blood
49203	Excision or destruction, open, intra-abdominal tumors, cysts or endometriomas, 1 or more peritoneal, mesenteric, or retroperitoneal primary or secondary tumors; largest tumor 5 cm diameter or less
49204	largest tumor 5.1 - 10.0 cm diameter
49205	largest tumor greater than 10.0 cm diameter
49320	Laparoscopy, abdomen, peritoneum, and omentum, diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)
49321	Laparoscopy, surgical; with biopsy (single or multiple)
49322	with aspiration of cavity or cyst (eg, ovarian cyst) (single or multiple)
52402	Cystourethroscopy with transurethral resection or incision of ejaculatory ducts
54500	Biopsy of testis, needle (separate procedure)
54505	Biopsy of testis, incisional (separate procedure)
54640	Orchiopexy, inguinal approach, with or without hernia repair
54650	Orchiopexy, abdominal approach, for intra-abdominal testis (eg, Fowler-Stephens)
54692	Laparoscopy, surgical; orchiopexy for intra-abdominal testis
54800	Biopsy of epididymis, needle
54830	Excision of local lesion of epididymis
54840	Excision of spermatocele, with or without epididymectomy
54860	Epididymectomy; unilateral
54861	bilateral
54865	Exploration of epididymis, with or without biopsy

Code	Code Description
54900	Epididymovasostomy, anastamosis of epididymis to vas deferens; unilateral
54901	bilateral
55000	Puncture aspiration of hydrocele, tunica vaginalis, with or without injection of medication
55040	Excision of hydrocele; unilateral
55041	bilateral
55060	Repair of tunica vaginalis hydrocele (Bottle type)
55110	Scrotal exploration
55300	Vasotomy for vasograms, seminal vesiculograms, or epididymograms, unilateral or bilateral
55400	Vasovasostomy, vasovasorrhaphy
55500	Excision of hydrocele of spermatic cord, unilateral (separate procedure)
55530	Excision of varicocele or ligation of spermatic veins for varicocele; (separate procedure)
55535	abdominal approach
55540	with hernia repair
55870	Electroejaculation
57530	Trachelectomy (cervicectomy), amputation of cervix (separate procedure)
58100	Endometrial sampling (biopsy) with or without endocervical sampling (biopsy), without cervical dilation, any method (separate procedure)
58120	Dilation and curettage, diagnostic and/or therapeutic (nonobstetrical)
58140	Myomectomy, excision of fibroid tumor(s) of uterus, 1 to 4 intramural myoma(s) with total weight of 250 g or less and/or removal of surface myomas; abdominal approach
58145	vaginal approach

Code	Code Description
58146	Myomectomy, excision of fibroid tumor(s) of uterus, 5 or more intramural myomas and/or intramural myomas with total weight greater than 250 g, abdominal approach
58321	Artificial insemination; intra-cervical
58322	intra-uterine
58323	Sperm washing for artificial insemination
58340	Catheterization and introduction of saline or contrast material for saline infusion sonohysterography (SIS) or hysterosalpingography
58345	Transcervical introduction of fallopian tube catheter for diagnosis and/or re-establishing patency (any method), with or without hysterosalpingography
58350	Chromotubation of oviduct, including materials
58545	Laparoscopy, surgical, myomectomy, excision; 1 to 4 intramural myomas with total weight of 250 g or less and/or removal of surface myomas
58546	5 or more intramural myomas and/or intramural myomas with total weight greater than 250 g
58555	Hysteroscopy, diagnostic (separate procedure)
58558	Hysteroscopy, surgical; with sampling (biopsy) of endometrium and/or polypectomy, with or without D & C
58559	with lysis of intrauterine adhesions (any method)
58560	with division or resection of intrauterine septum (any method)
58561	with removal of leiomyomata
58562	with removal of impacted foreign body
58563	with endometrial ablation (eg, endometrial resection, electrosurgical ablation, thermoablation)
58600	Ligation or transection of fallopian tube(s), abdominal or vaginal approach, unilateral or bilateral
58660	Laparoscopy, surgical; with lysis of adhesions (salpingolysis, ovariolysis) (separate procedure)

Code	Code Description
58661	with removal of adnexal structures (partial or total oophorectomy and/or salpingectomy)
58662	with fulguration or excision of lesions of the ovary, pelvic viscera, or peritoneal surface by any method
58672	with fimbrioplasty
58673	with salpingostomy (salpingoneostomy)
58700	Salpingectomy, complete or partial, unilateral or bilateral (separate procedure)
58720	Salpingo-oophorectomy, complete or partial, unilateral or bilateral (separate procedure)
58740	Lysis of adhesions (salpingolysis, ovariolysis)
58750	Tubotubal anastomosis
58752	Tubouterine implantation
58760	Fimbrioplasty
58770	Salpingostomy (salpingoneostomy)
58800	Drainage of ovarian cyst(s), unilateral or bilateral (separate procedure); vaginal approach
58805	abdominal approach
58820	Drainage of ovarian abscess; vaginal approach, open
58822	abdominal approach
58825	Transposition, ovary(s)
58900	Biopsy of ovary, unilateral or bilateral (separate procedure)
58920	Wedge resection or bisection of ovary, unilateral or bilateral
58925	Ovarian cystectomy, unilateral or bilateral
58970	Follicle puncture for oocyte retrieval, any method
58974	Embryo transfer, intrauterine
58976	Gamete, zygote, or embryo intrafallopian transfer, any method
70480	Computed tomography, orbit, sella, or posterior fossa or outer, middle, or inner ear; without contrast material
70481	with contrast material(s)

Code	Code Description
70482	without contrast material, followed by contrast material(s) and further sections
70540	Magnetic resonance (eg, proton) imaging, orbit, face, and/or neck; without contrast material(s)
70542	with contrast material(s)
70543	without contrast material(s), followed by contrast material(s) and further sequences
74440	Vasography, vesiculography, or epididymography, radiological supervision and interpretation
74740	Hysterosalpingography, radiological supervision and interpretation
74742	Transcervical catheterization of fallopian tube, radiological supervision and interpretation
76830	Ultrasound, transvaginal
76831	Saline infusion sonohysterography(SIS), including color flow Doppler, when performed
76856	Ultrasound, pelvic (nonobstetric), real time with image documentation; complete
76857	limited or follow-up (e.g., for follicles)
76870	Ultrasound, scrotum and contents
76872	Ultrasound, transrectal
80400	ACTH stimulation panel; for adrenal insufficiency
80402	for 21 hydroxylase deficiency
80406	for 3 beta-hydroxydehydrogenase deficiency
80412	Corticotropic releasing hormone (CRH) stimulation panel
80414	Chorionic gonadotropin stimulation panel; testosterone response
80415	estradiol response
80418	Combined rapid anterior pituitary evaluation panel
80426	Gonadotropin releasing hormone stimulation panel
80428	Growth hormone stimulation panel (eg, arginine infusion, l-dopa administration)

Code	Code Description
80438	Thyrotropin releasing hormone (TRH) stimulation panel; one hour
80439	two hour
81224	Intron 8 poly-T analysis (eg,male infertility)
82024	Adrenocorticotropic hormone (ACTH)
82157	Androstenedione
82465	Cholesterol, serum or whole blood, total
82626	Dehydroepiandrosterone (DHEA)
82670	Estradiol
82671	Estrogens; fractionated
82672	total
82679	Estrone
82757	Fructose, semen
82951	Glucose: tolerance test (GTT), three specimens (includes glucose)
83001	Gonadotropin; follicle stimulating hormone (FSH) [not covered for urinary FSH CLIA waived test with modifier QW]
83002	luteinizing hormone (LH)
83003	Growth hormone, human (HGH) (somatotropin)
83498	Hydroxyprogesterone, 17-d
83499	Hydroxyprogesterone, 20-
83519	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (eg, RIA) [measurement of anti-adrenal antibodies]
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [covered for anti-mullerian hormone testing] [not covered for the Th1/Th2 ratio, or antiphosphatidic acid antibodies]
83718	Lipoprotein, direct measurement; high density cholesterol (HDL cholesterol)
84144	Progesterone

Code	Code Description
84146	Prolactin
84233	Receptor assay; estrogen
84234	progesterone
84270	Sex hormone binding globulin (SHBG)
84402	Testosterone; free
84403	total
84443	Thyroid stimulating hormone (TSH)
84478	Triglycerides
84702	Gonadotropin, chorionic (hCG); quantitative
84703	qualitative
86256	Fluorescent noninfectious agent antibody; titer, each antibody [measurement of anti-adrenal antibodies]
86277	Growth hormone, human (HGH), antibody
86631	Antibody; Chlamydia
86632	Chlamydia, IgM
86689	HTLV or HIV antibody, confirmatory test (eg, Western Blot)
86701	HIV-1
86702	HIV-2
86703	HIV-1 and HIV-2, single result
86704	Hepatitis B core antibody (HBcAb); total
86705	IgM antibody
86706	Hepatitis B surface antibody (HBsAb)
86762	Antibody; rubella
86803	Hepatitis C antibody;
86804	confirmatory test (eg, immunoblot)
87110	Culture, chlamydia, any source
87270	Chlamydia trachomatis

Code	Code Description
87340	Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; hepatitis B surface antigen (HBsAg)
87341	hepatitis B surface antigen (HBsAg) neutralization
87491	Chlamydia trachomatis, amplified probe technique
87492	Chlamydia trachomatis, quantification
87810	Infectious agent detection by immunoassay with direct optical observation; Chlamydia trachomatis
88245	Chromosome analysis for breakage syndromes; baseline Sister Chromatid Exchange (SCE), 20-25 cells
88248	baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (eg, for ataxia telangectasia, Fanconi anemia, fragile X)
88249	score 100 cells, clastogen stress (eg, diepoxybutane, mitomycin C, ionizing radiation, UV radiation)
88261	Chromosome analysis; count 5 cells, 1 karyotype, with banding
88262	count 15-20 cells, 2 karyotypes, with banding
88263	count 45 cells for mosaicism, 2 karyotypes, with banding
88264	analyze 20-25 cells
88271	Molecular cytogenetics: DNA probe, each (eg, FISH)
88272	chromosomal in situ hybridization, analyze 3-5 cells (eg, for derivatives and markers)
88273	chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
88274	interphase in situ hybridization, analyze 25-99 cells
88275	interphase in situ hybridization, analyze 100-300 cells
88280	Chromosome analysis; additional karyotypes, each study
88283	additional specialized banding technique (eg, NOR, C-banding)
88285	additional cells counted, each study

Code	Code Description
88289	additional high resolution study
88291	Cytogenics and molecular cytogenetics, interpretation and report
89250	Culture of oocyte(s)/embryo(s), less than 4 days;
89251	with co-culture of oocyte(s)/embryos
89253	Assisted embryo hatching, microtechniques (any method)
89254	Oocyte identification from follicular fluid
89255	Preparation of embryo for transfer (any method)
89257	Sperm identification from aspiration (other than seminal fluid)
89258	Cryopreservation; embryo(s) [for infertility due to pelvic radiotherapy or chemotherapy]
89259	sperm [for infertility due to pelvic radiotherapy or chemotherapy]
89260	Sperm isolation; simple prep (e.g., sperm wash and swim-up) for insemination or diagnosis with semen analysis
89261	complex prep (eg, Percoll gradient, albumin gradient) for insemination or diagnosis with semen analysis
89264	Sperm identification from testis tissue, fresh or cryopreserved
89268	Insemination of oocytes
89272	Extended culture of oocyte(s)/embryo(s), 4-7 days
89280	Assisted oocyte fertilization, microtechnique; less than or equal to 10 oocytes
89281	greater than 10 oocytes
89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos
89291	greater than 5 embryos
89300	Semen analysis; presence and/or motility of sperm including Huhner test (post coital)
89310	motility and count (not including Huhner test)
89320	volume, count, motility, and differential

Code	Code Description
89321	sperm presence and motility of sperm, if performed
89322	volume, count, motility, and differential using strict morphologic criteria (eg, Kruger)
89325	Sperm antibodies
89329	Sperm evaluation; hamster penetration test
89330	cervical mucus penetration test, with or without spinnbarkeit test
89331	Sperm evaluation, for retrograde ejaculation, urine (sperm concentration, motility, and morphology, as indicated)
89337	Cryopreservation, mature oocyte(s)
89352	Thawing of cryopreserved; embryo(s)
90739 - 90747	Hepatitis B vaccine
90748	Hepatitis B and Haemophilus influenzae type b vaccine (Hib-HepB), for intramuscular use
93975	Duplex scan of arterial inflow and venous outflow of abdominal, pelvic, scrotal contents and/or retroperitoneal organs; complete study
93976	limited study
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family
CPT codes not covered for Indications listed in the CPB:	
Evaluation of CYP1A1 rs4646903 T > C genetic variations for risk of male infertility, evaluation of FAS/FASL genetic variations for risk of male fertility, stem cell therapy for the treatment of female infertility- no specific code	
0087T	Sperm evaluation, Hyaluronan sperm binding test
0357T	Cryopreservation; immature oocyte(s)
10005	Fine needle aspiration biopsy, including ultrasound guidance first lesion
10006	Fine needle aspiration biopsy, including ultrasound guidance; each additional lesion (List separately in addition to code for primary procedure)
10021	Fine needle aspiration; without imaging guidance; first lesion

Code	Code Description
43631 - 43635 43644 - 43645 43770 - 43775 43842 - 43848 43886 - 43888	Bariatric surgery
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81291	MTHFR (5, 10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81370	HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1
81400	Molecular pathology procedure, Level 1(eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) [Plasminogen activator inhibitor-I (PAI-1) antigen]
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) [determination of CAG-repeat polymorphisms in the polymerase γ (POLG) gene for evaluation of male infertility]
83001 - QW	Gonadotropin; follicle stimulating hormone (FSH) [urinary FSH - CLIA waived test]
83090	Homocysteine
85300	Clotting inhibitors or anticoagulants; antithrombin III, activity
85301	Clotting inhibitors or anticoagulants; antithrombin III, antigen assay
85302	Clotting inhibitors or anticoagulants; protein C, antigen
85303	Clotting inhibitors or anticoagulants; protein C, activity
85305	Clotting inhibitors or anticoagulants; protein S, total

Code	Code Description
85306	Clotting inhibitors or anticoagulants; protein S, free
86038	Antinuclear antibodies
86039	Antinuclear antibodies (ANA); titer
86146	Beta 2 Glycoprotein I antibody, each
86147	Cardiolipin (phospholipid) antibody, each Ig class
86148	Anti-phosphatidylserine (phospholipid) antibody
86255	Fluorescent noninfectious agent antibody; screen, each [antiovarain antibodies]
86357	Natural killer (NK) cells, total count[not covered for female infertility]
88184 - 88185	Flow cytometry, cell surface,
88187 - 88189	Flow cytometry, interpretation
89290 - 89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than, equal to, or greater than 5 embryos [not covered for preimplantation genetic screening]
89335	Cryopreservation, reproductive tissue, testicular
89342	Storage (per year); embryo(s)
89343	sperm/semen
89344	reproductive tissue, testicular/ovarian
89346	oocyte(s)
89354	reproductive tissue, testicular/ovarian
89356	oocytes, each aliquot
97810 - 97814	Acupuncture
99183	Physician or other qualified health care professional attendance and supervision of hyperbaric oxygen therapy, per session
Other CPT codes related to the CPB:	
90460 - 90461	Immunization administration through 18 years of age via any route of administration, with counseling by physician or other qualified health care professional
90471 - 90472	Immunization administration (includes percutaneous intradermal, subcutaneous, or intramuscular injections

Code	Code Description
There are no specific CPT codes for the Laboratory Test listed below:	
Oxidative Stress Adduct Test (OSA), Plasminogen activator inhibitor-I, antiphosphatidylglycerol antibodies, antiphosphatidylinositol antibodies, antithyroglobulin antibodies, anti-CarP (anti-carbamylated proteins) panel, the DuoStim IVF protocol	
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
G0472	Hepatitis C antibody screening for individual at high risk and other covered indication(s)
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
J1071	Injection, testosterone cypionate, 1mg
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

Code	Code Description
J2675	Injection, progesterone, per 50 mg
J3120	Injection, testosterone enanthate, up to 100 mg
J3121	Injection, testosterone enanthate, 1mg
J3130	Injection, testosterone enanthate, up to 200 mg
J3140	Injection, testosterone suspension, up to 50 mg
J3145	Injection, testosterone undecanoate, 1 mg
J3150	Injection, testosterone propionate, up to 100 mg
J3355	Injection, urofollitropin, 75 IU
J7512	Prednisone, immediate release or delayed release, oral, 1 mg
J8515	Cabergoline, oral, 0.25 mg
J8540	Dexamethasone, oral, 0.25 mg
J9202	Goserelin acetate implant, per 3.6 mg
J9218	Leuprolide acetate, per 1 mg
P3000	Screening Papanicolaou smear, cervical or vaginal, up to three smears, by technician under physician supervision
P3001	Screening Papanicolaou smear, cervical or vaginal, up to three smears, requiring interpretation by physician
Q0115	Post-coital direct, qualitative examinations of vaginal or cervical mucous
S0122	Injection, menotropins, 75 IU
S0126	Injection, follitropin alfa, 75 IU
S0128	Injection, follitropin beta, 75 IU
S0132	Injection, ganirelix acetate, 250 mcg [not covered for men]
S0187	Tamoxifen citrate, oral, 10 mg
S0265	Genetic counseling, under physician supervision, each 15 minutes
S2078	Laparoscopic supracervical hysterectomy (subtotal hysterectomy), with or without removal of tube(s), with or without removal of ovary(s)

Code	Code Description
S4011	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
S4013	Complete cycle, gamete intrafallopian transfer (GIFT), case rate
S4014	Complete cycle, zygote intrafallopian transfer (ZIFT), case rate
S4015	Compete in vitro fertilization cycle, not otherwise specified, case rate
S4016	Frozen in vitro fertilization cycle, case rate
S4017	Incomplete cycle, treatment canceled prior to stimulation, case rate
S4018	Frozen embryo transfer procedure canceled before transfer, case rate
S4020	In vitro fertilization procedure canceled before aspiration, case rate
S4021	In vitro fertilization procedure canceled after aspiration, case rate
S4022	Assisted oocyte fertilization, case rate
S4023	Donor egg cycle, incomplete, case rate
S4025	Donor services for in vitro fertilization (sperm or embryo), case rate
S4026	Procurement of donor sperm from sperm bank
S4028	Microsurgical epididymal sperm aspiration (MESA)
S4035	Stimulated intrauterine insemination (IUI), case rate
S4037	Cryopreserved embryo transfer, case rate
S4993	Contraceptive pills for birth control
S9560	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:	
Vasodilators for women undergoing fertility treatment - no specific code:	

Code	Code Description
A4575	Topical hyperbaric oxygen chamber, disposable
B4185	Parenteral nutrition solution, per 10 grams lipids
G0277	Hyperbaric oxygen under pressure, full body chamber, per 30 minute
J1561	Injection, immune globulin, (Gamunex-C/Gammaked), nonlyophilized (e.g. liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwised specified, 500 mg
J1568	Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard liquid), nonlyophilized (e.g. liquid), 500 mg
J2940	Injection, somatrem, 1 mg
J2941	Injection, somatropin, 1 mg
Q0515	Injection, sermorelin acetate, 1 mcg
S0090	Sildenafil citrate, 25 mg [phosphodiesterase 5 inhibitor] [vaginal Sildenafil]
S4027	Storage of previously frozen embryos
S4030	Sperm procurement and cryopreservation services; initial visit
S4031	Sperm procurement and cryopreservation services; subsequent visit
S4040	Monitoring and storage of cryopreserved embryos, per 30 days
S4042	Management of ovulation induction (interpretation of diagnostic tests and studies, non-face-to-face medical management of the patient), per cycle
S8930	Electrical stimulation of auricular acupuncture points; each 15 minutes of personal one-on-one contact with the patient
S9558	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-10 codes covered if selection criteria are met (not all-inclusive):	

Code	Code Description
B20	Human immunodeficiency virus [HIV] disease [HIV positive male undergoing sperm washing]
C00.0 - C69.92, C81.00 - C96.9	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
C4A.4- C4A.9	Merkel cell carcinoma, scalp, neck, trunk, upper limb including shoulder, lower limb including hip, overlapping sites and unspecified
C7A.00 - C7A.098	Malignant carcinoid tumors, small intestine, appendix, large intestine, rectum, and other sites
C7A.1	Malignant poorly differentiated neuroendocrine tumors
C7B.1	Secondary Merkel cell carcinoma
D25.0 - D25.9	Leiomyoma of uterus
D27.0 - D27.9	Benign neoplasm of ovary
D29.30 - D29.32	Benign neoplasm of epididymis
D35.2 - D35.3	Benign neoplasm of pituitary gland and craniopharyngeal duct
D39.0 - D39.2	Neoplasm of uncertain behavior of female genital organs
D40.8 - D40.9	Neoplasm of uncertain behavior of other and unspecified male genital organs
D44.3 - D44.4	Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct
E01.8	Other iodine-deficiency related thyroid disorders and allied conditions
E02	Subclinical iodine-deficiency hypothyroidism
E03.0 - E03.8	Other hypothyroidism
E22.8 - E22.9	Other and unspecified hyperfunction of pituitary gland
E22.1	Hyperprolactinemia
E23.0	Hypopituitarism
E23.6	Other disorders of pituitary gland
E25.0 - E25.9	Adrenogenital disorders

Code	Code Description
E28.1	Androgen excess
E28.2	Polycystic ovarian syndrome
E28.310 - E28.319	Premature menopause [poor ovarian reserve, spontaneous primary ovarian insufficiency]
E28.39	Other primary ovarian failure [poor ovarian reserve, spontaneous primary ovarian insufficiency]
E29.1	Testicular hypofunction
E89.0	Postprocedural hypothyroidism
E89.40 - E89.41	Postprocedural ovarian failure
I00 - I99.9	Diseases of the circulatory system
I86.1	Scrotal varices
L68.0	Hirsutism
N43.0 - N43.42	Hydrocele and spermatocele
N44.00 - N44.8	Noninflammatory disorders of testis
N46.01 - N46.9	Male infertility
N49.0 - N49.9	Inflammatory disorders of male genital disorders, not elsewhere classified
N50.0 - N50.9	Other and unspecified disorders of male genital organs
N51	Disorders of male genital organs in diseases classified elsewhere
N52.0 - N52.9	Male erectile dysfunction
N53.11 - N53.9	Other male sexual dysfunction
N64.3	Galactorrhea not associated with childbirth
N70.01 - N70.93	Salpingitis and oophoritis
N73.0 - N73.9	Other female pelvic inflammatory diseases
N80.0 - N80.9	Endometriosis

Code	Code Description
N83.00 - N83.9	Noninflammatory disorders of ovary, fallopian tube and broad ligament
N84.0	Polyp of corpus uteri
N84.8	Polyp of female genital tract, unspecified [fallopian tube]
N85.6	Intrauterine synechiae
N91.0 - N91.2	Amenorrhea
N92.4	Excessive bleeding in the premenopausal period
N92.5 - N92.6	Other and unspecified irregular menstruation
N94.2	Vaginismus
N95.0 - N95.9	Menopausal and other perimenopausal disorders
N97.0 - N97.9	Female infertility
N98.1	Hyperstimulation of ovaries
N99.83	Residual ovary syndrome
Q50.01 - Q50.6	Congenital malformations of ovaries, fallopian tubes and broad ligaments
Q51.0, Q51.20 - Q51.28 Q51.5 - Q51.7 Q51.820 - Q51.9	Congenital malformations of uterus and cervix
Q52.0 - Q52.9	Other congenital malformations of female genitalia
Q53.00 - Q53.9	Undescended and ectopic testicle
Q55.0 - Q55.21 Q55.29 - Q55.4 Q55.7 - Q55.8	Other congenital malformations of male genital organs
Q96.9	Turner's syndrome, unspecified
Q98.0 - Q98.4	Klinefelter syndrome
R36.1	Hematospermia
R39.83	Unilateral non-palpable testicle

Code	Code Description
R86.0 - R86.9	Abnormal findings in specimens from male genital organs
R93.811 - R93.9	Abnormal findings on diagnostic imaging of other specified body structures [follow-up on hysterosalpingography abnormalities]
T50.905+	Adverse effect of unspecified drugs, medicaments and biological substances
T66.xxx+	Radiation sickness, unspecified, initial encounter
Z11.3	Encounter for screening for infections with a predominantly sexual mode of transmission [Chlamydia trachomatis screening]
Z14.01 - Z14.02	Hemophilia A carrier
Z14.1	Cystic fibrosis carrier
Z14.8	Genetic carrier of other disease [high-risk of transmitting a genetic disorder from the female partner to the offspring]
Z20.828	Contact with and (suspected) exposure to other viral communicable diseases [partners of persons infected with hepatitis B]
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Z23	Encounter for immunization [rubella] [women susceptible to rubella]
Z31.41	Encounter for fertility testing
Z31.89	Encounter for other procreative management
Z52.810 - Z52.819	Egg (Oocyte) donor
Z78.0	Asymptomatic menopausal state
Z90.710 - Z90.712	Acquired absence of cervix and uterus
Z90.721 - Z90.722	Acquired absence of ovaries [for treatment of disease]
Z90.79	Acquired absence of other genital organ(s) [removal of testes for treatment of disease]
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	

Code	Code Description
N92.4 N95.0 - N95.9	Menopausal and other perimenopausal disorders
Z31.0	Encounter for reversal of previous sterilization
Z78.0	Asymptomatic menopausal state
Z79.890	Hormone replacement therapy
Z90.79	Acquired absence of other genital organ(s)
Z98.51 - Z98.52	Sterilization status

The above policy is based on the following references:

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