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Progestins

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

Number: 0510

(Replaces CPB 513)

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Policy History

Last Review
01/05/2023
Effective: 08/03/2001
Next Review: 04/27/2023

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

Policy

I. Etonogestrel Subdermal Implant

A. Aetna considers etonogestrel subdermal implant (Nexplanon) medically necessary for the prevention of pregnancy. **Note:** Many plans exclude coverage of contraceptives. Please check benefit plan descriptions for details.

Pl. Trial Ex. 055

B. Aetna considers etonogestrel subdermal implant experimental and investigational for all other indications because its effectiveness other than the one listed above has not been established.

II. Hydroxyprogesterone Caproate (Makena) Injection

Note: Requires Precertification:

Precertification of hydroxyprogesterone caproate (Makena) is required of all Aetna participating providers and members in applicable plan designs. For precertification of hydroxyprogesterone caproate (Makena), call (866) 752-7021, or fax (866) 267-3277.

A. *Criteria for Initial Approval*

Aetna considers hydroxyprogesterone caproate (Makena) injection medically necessary for prevention of preterm birth. Authorization of 21 weeks or through 36 weeks, 6 days of gestational age, whichever is less, may be granted when *all* of the following criteria are met (see Exclusion Criteria for Makena):

1. The current pregnancy is a singleton pregnancy (i.e., member is currently pregnant with only one baby); *and*
2. The member has a history of singleton spontaneous preterm birth, defined as delivery at less than 37 weeks gestation following preterm labor, preterm rupture of membranes, and cervical insufficiency; *and*
3. Makena will be initiated between 16 weeks, 0 days and 24 weeks, 6 days of gestation.

B. *Continuation of Therapy*

Aetna considers continuation of hydroxyprogesterone caproate (Makena) therapy medically necessary for all members (including new members) requesting authorization for

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continuation of therapy and meet all initial authorization criteria (see Exclusion Criteria for Makena).

C. *Exclusion Criteria for Makena*

The following are considered as exclusions for hydroxyprogesterone caproate (Makena):

1. Current or history of thrombosis or thromboembolic disorders;
2. Known or suspected breast cancer, other hormone-sensitive cancer, or a history of these conditions;
3. Undiagnosed abnormal vaginal bleeding unrelated to pregnancy;
4. Cholestatic jaundice of pregnancy;
5. Liver tumors, benign or malignant, or active liver disease; *and/or*
6. Uncontrolled hypertension.

D. Aetna considers hydroxyprogesterone caproate (Makena) injection experimental and investigational for all other indications including multiple gestation, known fetal anomaly, as a tocolytic agent for women with contractions, or other risk factors for preterm birth because its effectiveness for these indications has not been established.

III. Medroxyprogesterone Acetate Injection

A. Depo-Provera CI or generic formulation 150 mg/mL

Aetna considers Depo-Provera CI or generic formulation 150 mg/mL medically necessary for the following indications:

1. Prevention of pregnancy. **Note:** Many plans exclude coverage of contraceptives. Please check benefit plan descriptions for details.
2. Gender dysphoria when *all* of the following are met:

   a. The member is able to make an informed decision to engage in hormone therapy; *and*

b. The member has a diagnosis of gender dysphoria; *and*
c. The member's comorbid conditions are reasonably controlled; *and*
d. The member has been educated on any contraindications and side effects to therapy; *and*
e. This medication will be prescribed by or in consultation with a provider specialized in the care of transgender youth (e.g., pediatric endocrinologist, family or internal medicine physician, obstetrician-gynecologist), that has collaborated care with a mental health care provider for members less than 18 years of age.

B. Depo-Provera 400 mg/mL

Aetna considers Depo-Provera 400 mg/mL medically necessary as adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic endometrial or renal carcinoma. **Note**: Medroxyprogesterone acetate (Depo-Provera) injection, suspension 400 mg/mL was discontinued on October 27, 2020 (FDA, 2021).

C. Aetna considers intramuscular injection of medroxyprogesterone acetate as experimental and investigational for all other indications. **Note**: For medroxyprogesterone acetate oral formulation, refer to the pharmacy benefit plan.

IV. Progesterone Injection

A. Aetna considers progesterone intramuscular injection medically necessary for the treatment of amenorrhea or abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer.

B. Aetna considers progesterone intramuscular injection experimental and investigational for all other indications, including any of the following, because it has not been shown to be effective for these indications:

1. Prevention of pregnancy; *or*

2. Reduction of neonatal morbidity/prolongation of pregnancy in twin pregnancies; *or*
3. Treatment of endometrial hyperplasia; *or*
4. Treatment of premenstrual syndrome; *or*
5. Treatment of stroke.

Note: For progesterone intravaginal gel, insert or ring, and oral capsules, refer to the pharmacy benefit plan.

V. Progestin-Releasing Intrauterine Devices

A. Aetna considers progestin-releasing intrauterine devices (IUDs) (e.g., Kyleena levonorgestrel-releasing IUD; Mirena levonorgestrel-releasing IUD; Skyla levonorgestrel-releasing IUD; Liletta levonorgestrel-releasing IUD) medically necessary for contraception or for treatment of heavy menstrual bleeding. **Note:** Many plans exclude coverage of contraceptives. Please check benefit plan descriptions for details.

B. Aetna considers progestin-releasing IUDs experimental and investigational for all other indications (e.g., treatment of uterine fibroids) because its effectiveness for indications other than the ones listed above has not been established.

VI. Related Policies

For progesterone vaginal suppositories, refer to the pharmacy benefit plan.

For progestin/progesterone pellets, see CPB 0345 - Implantable Hormone Pellets (../300_399/0345.html).

See also:

- CPB 0327 - Infertility (../300_399/0327.html)
- CPB 0468 - Magnesium Sulfate/Terbutaline Pump for Preterm Labor (../400_499/0468.html)
- CPB 0501 - Gonadotropin-Releasing Hormone Analogs and Antagonists (0501.html)

- CPB 0512 - Premenstrual Syndrome and Premenstrual Dysphoric Disorder (0512.html).

Dosing Recommendations

Hydroxyprogesterone Caproate Injection

Hydroxyprogesterone caproate injection is available in generic formulation and as the brand name Makena.

Generic

- For intramuscular use: supplied as 250 mg/mL clear yellow solution in single-dose vials.
- The recommended dosing for hydroxyprogesterone caproate is as follows:

  - Administer intramuscularly at a dose of 250 mg (1 mL) once weekly, in the upper outer quadrant of the gluteus maximus.
  - Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation.
  - Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first.

Source: American Regent, 2019

Makena

- Makena is available for injection as:

  - Subcutaneous injection: 275 mg/1.1 mL clear yellow solution in single-use auto-injector
  - Intramuscular injection: 250 mg/mL clear yellow solution in single-dose vials
  - Intramuscular injection: 1250 mg/5 mL (250 mg/mL) clear yellow solution in multiple-dose vials.

- The recommended dosing for Makena is as follows:

- Makena auto-injector: Administer subcutaneously using auto-injector at a dose of 275 mg (1.1 mL) once weekly (every 7 days) in the back of either upper arm by a healthcare provider
- Makena (single- and multi-dose vials): Administer intramuscularly at a dose of 250 mg (1 mL) once weekly (every 7 days) in the upper outer quadrant of the gluteus maximus by a healthcare provider
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation
- Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first.

Source: AMAG Pharmaceuticals, 2018

Medroxyprogesterone Acetate Injection

Depo-Provera CI or generic formulation 150 mg/mL: For pregnancy prevention, the recommended dose is 150 mg every 3 months (13 weeks) administered by deep, intramuscular (IM) injection in the gluteal or deltoid muscle by a healthcare provider.

Source: Amphastar Pharmaceuticals, 2018; Pfizer, 2020

Depo-Provera 400 mg/mL: For endometrial or renal carcinoma, doses of 400 mg to 1000 mg of Depo-Provera Sterile Aqueous Suspension per week are recommended initially. If improvement is noted within a few weeks or months and the disease appears stabilized, it may be possible to maintain improvement with as little as 400 mg per month. Medroxyprogesterone acetate is not recommended as primary therapy, but as adjunctive and palliative treatment in advanced inoperable cases including those with recurrent or metastatic disease. The suspension is intended for intramuscular administration only.

Note: Medroxyprogesterone acetate (Depo-Provera) injection, suspension 400 mg/mL was discontinued on October 27, 2020 (FDA, 2021).

Source: Pfizer, 2017

Progesterone Injection

Progesterone injection is supplied as 50 mg/mL in a sterile solution of progesterone in a suitable vegetable oil available for intramuscular use.

For amenorrhea, the recommended dose is 5 to 10 mg given for six to eight consecutive days. If there has been sufficient ovarian activity to produce a proliferative endometrium, one can expect withdrawal bleeding forty-eight to seventy-two hours after the last injection. This may be followed by spontaneous normal cycles.

For abnormal uterine bleeding, the recommended dose is 5 to 10 mg given daily for six doses. Bleeding may be expected to cease within six days. When estrogen is given as well, the administration of progesterone is begun after two weeks of estrogen therapy. If menstrual flow begins during the course of injections of progesterone, they are discontinued.

Source: Watson Laboratories, 2007

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
Depo-Provera (injectable medroxyprogesterone acetate):	
Other CPT codes related to the CPB:	
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS codes covered if selection criteria are met:	
J1050	Injection, medroxyprogesterone acetate, 1 mg

Code	Code Description
ICD-10 codes covered if selection criteria are met:	
C50.011 - C50.019 C50.111 - C50.119 C50.211 - C50.219 C50.311 - C50.319 C50.411 - C50.419 C50.511 - C50.519 C50.611 - C50.619 C50.811 - C50.819 C50.911 - C50.919	Malignant neoplasm of female breast
C54.1	Malignant neoplasm of endometrium
C64.1 - C66.9 C68.0 - C68.9	Malignant neoplasm of kidney renal pelvis, ureter and other and unspecified urinary organs
E28.0 - E28.1	Estrogen and androgen excess
E28.2	Polycystic ovarian syndrome
E88.40 - E88.41	Unspecified mitochondrial metabolism disorder and MELAS syndrome
F64.0 - F64.9	Gender identity disorder
N80.00 - N80.03, N80.A0 - N80.D9	Endometriosis
N83.00 - N83.299	Follicular cyst, corpus luteum cyst and other and unspecified ovarian cysts
N89.7	Hematocolpos

Code	Code Description
N91.0 - N93.9	Absent, scanty, rare, excessive, frequent and irregular menstruation and other abnormal uterine and vaginal bleeding
N94.4 - N94.6	Dysmenorrhea
N95.0	Postmenopausal bleeding
N98.1	Hyperstimulation of ovaries
Z30.018	Encounter for initial prescription of other contraceptives
Z30.019	Encounter for initial prescription of contraceptives, unspecified
Z30.49	Encounter for surveillance of other contraceptives
Z30.8	Encounter for other contraceptive management
Z40.40	Encounter for surveillance of contraceptives, unspecified
Hydroxyprogesterone Caproate:	
HCPCS codes covered if selection criteria are met:	
J1726	Injection, hydroxyprogesterone caproate (Makena), 10 mg
J1729	Injection, hydroxyprogesterone caproate, not otherwise specified, 10 mg
ICD-10 codes covered if selection criteria are met:	
O09.211 - O09.219	Supervision of pregnancy with history of pre-term labor
O47.02	False labor before 37 completed weeks of gestation, second trimester
O47.03	False labor before 37 completed weeks of gestation, third trimester
Z87.51	Personal history of pre-term labor
ICD-10 codes not covered for indications listed in the CPB:	
C22.0 - C22.9	Malignant neoplasm of liver and intrahepatic bile ducts

Code	Code Description
C50.011 - C50.019, C50.111 - C50.119 C50.211 - C50.219, C50.311 - C50.319 C50.411 - C50.419, C50.511 - C50.519 C50.611 - C50.619. C50811 - C50.819 C50.911 - C50.919	Malignant neoplasm of female breast
C53.0 - C57.7	Malignant neoplasm of cervix uteri, corput uteri, ovary and other and unspecified female genital organs
D13.4 - D13.5	Benign neoplasm of liver and extrahepatic bile ducts
I10 - I16.2	Hypertensive disease
I26.01 - I26.99	Pulmonary embolism
I65.01 - I66.9	Occlusion and stenosis of precerebral and cereral arteries not resulting in cerebral infarction
I74.01 - I76	Arterial embolism and thrombosis and atheroembolism
I80.00 - I82.91	Phlebitis, thrombophlebitis, embolism and thrombosis, venous
K70.0 - K77	Diseases of liver
N88.3	Incompetence of cervix uteri [not pregnant]
N89.8	Other specified noninflammatory disorders of vagina [undiagnosed abnormal vaginal bleeding unrelated to pregnancy]

Code	Code Description
N93.8	Other specified abnormal uterine and vaginal bleeding [Dysfunctional or functional uterine or vaginal bleeding NOS] [undiagnosed abnormal vaginal bleeding unrelated to pregnancy]
N93.9	Abnormal uterine and vaginal bleeding, unspecified [undiagnosed abnormal vaginal bleeding unrelated to pregnancy]
O22.20 - O22.33	Superficial thrombophlebitis and deep phlebothrombosis in pregnancy
O22.50 - O22.53	Cerebral venous thrombosis in pregnancy
O26.611 - O26.63	Liver and biliary tract disorders in pregnancy, childbirth and the puerperium
O30.001 - O30.019 O30.031 - O30.93 O31.10x+ - O31.8x9+	Multiple gestation and complications specific to multiple gestation
O35.0xx+ - O35.9, O35.00X0 - O35.HXX9	Maternal care for known or suspected fetal abnormality and damage
O36.011+ - O36.93	Maternal care for other fetal problems
O87.0 - O87.1	Superficial thrombophlebitis and deep phlebothrombosis in the puerperium
O87.3	Cerebral venous thrombosis in the puerperium
O88.011 - O88.019	Obstectric air embolism in pregnancy
O99.89 [N88.3 also required]	Cervical incompetence, postpartum condition or complication [women with a cerclage in place]

Code	Code Description
Z85.3 - Z85.44	Personal history of malignant neoplasm of breast, cervix uteri, ovary, other parts of uterus and other and unspecified part of femail genital organs
Z86.711 - Z86.72	Personal history of venous thrombosis and embolism and thrombophlebitis
Progesterone injection:	
Other CPT codes related to the CPB:	
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS codes covered if selection criteria are met:	
J2675	Injection, progesterone acetate, per 50 mg
ICD-10 codes covered if selection criteria are met:	
E23.0	Hypopituitarism
E28.310 - E28.39	Premature menopause and other primary ovarian failure
N89.7	Hematocolpos
N91.0 - N92.3 N92.5 - N93.9	Absent, scanty, rare, excessive, frequent and irregular menstruation and other abnormal uterine and vaginal bleeding
N95.1	Menopausal and female climacteric states
N97.0 - N97.9	Female infertility
ICD-10 codes not covered for indications listed in the CPB:	
N85.00 - N85.02	Endometrial hyperplasia
N87.0 - N87.9	Dysplasia of cervix uteri
N94.3	Premenstrual tension syndrome
O30.001 - O30.099	Twin Pregnancy [not covered for reduction of neonatal morbidity/prolongation of pregnancy in twin pregnancies]
Z30.018	Encounter for initial prescription of other contraceptives
Z30.40	Encounter for surveillance of contraceptives, unspecified
Z30.49	Encounter for surveillance of other contraceptives
Z30.8	Encounter for other contraceptive management

Code	Code Description
Etonogestrol subdermal implant (Nexplanon):	
CPT codes covered if selection criteria are met:	
11976	Removal, implantable contraceptive capsules
HCPCS codes covered if selection criteria are met:	
J7307	Etonogestrel (contraceptive) implant system, including implant and supplies
ICD-10 codes covered if selection criteria are met:	
Z30.018	Encounter for initial prescription of other contraceptives
Z30.49	Encounter for surveillance of other contraceptives
Progestin-releasing intrauterine devices:	
CPT codes covered if selection criteria are met:	
58300	Insertion of intrauterine device (IUD)
58301	Removal of intrauterine device (IUD)
HCPCS codes covered if selection criteria are met:	
J7296	Levonorgestrel-releasing intrauterine contraceptive system (Kyleena), 19.5 mg
J7297	Levonorgestrel-releasing intrauterine contraceptive system (Lilleta), 52 mg
J7298	Levonorgestrel-releasing intrauterine contraceptive system (Mirena), 52 mg
J7301	Levonorgestrel-releasing intrauterine contraceptive system, 13.5 mg
S4981	Insertion of levonorgestrel-releasing intrauterine system
S4989	Contraceptive intrauterine device (e.g., Progestacert IUD), including implants and supplies
ICD-10 codes covered if selection criteria are met:	
N92.0	Excessive and frequent menstruation with regular cycle
N92.4	Excessive bleeding in the premenopausal period
Z30.430	Encounter for insertion of intrauterine contraceptive device
Z30.431	Encounter for routine checking of intrauterine contraceptive device
Z30.432	Encounter for removal of intrauterine contraceptive device

Code	Code Description
Z30.433	Encounter for removal and reinsertion of intrauterine contraceptive device
ICD-10 codes not covered for indications listed in the CPB:	
D25.0 - D25.9	Leiomyoma of uterus

Background

Etonogestrel Subdermal Implant and Progesterone Implants

Norplant (levonorgestrel) was an implantable, combined drug and delivery system that continuously releases a low-dose of the progestin levonorgestrel. Norplant was FDA approved for contraception and was surgically implanted in the physicians' office or clinic. A single implant provided contraception for up to 5 years. Norplant was useful for patients for whom compliance was an issue, and for patients for whom pregnancy posed an unacceptable medical risk. It was recommended that a trial of a progestin-only oral contraceptive be carried out prior to implantation, to assess patient tolerance to drug side effects. The distribution of Norplant was stopped in 2000 after questions surfaced about the strength of certain lots of the drug. In 2002, Wyeth Pharmaceuticals (Madison, NJ), the manufacture of Norplant, decided not to re-introduce Norplant to the U.S. market. Norplant (levonorgestrel subdermal implant) was discontinued globally in 2008.

On July 17, 2006, Implanon (Organon USA, Inc., Roseland, NJ), a single-rod progestogen-only (etonogestrel) contraceptive implant, received FDA approval. Implanon was a long-acting (up to 3 years), reversible, contraceptive method.

In a multi-center clinical study, Funk and colleagues (2005) evaluated the safety and effectiveness of Implanon. Sexually active American women (n = 330) with apparently normal menstrual cycles used the implant for up to 2 years. All subjects recorded bleeding and/or spotting daily in a diary.

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Safety was assessed through adverse experiences (AE), laboratory tests and physical and gynecological examinations. Total exposure was 474 woman-years (6,186 cycles), and 68 % of subjects had at least 1 year of exposure. No pregnancies occurred. The most common bleeding pattern observed throughout the study was infrequent bleeding, defined as less than 3 episodes of bleeding in a reference period (excluding amenorrhea). The least common pattern was frequent bleeding, defined as more than 5 episodes of bleeding in a reference period. Infrequent, prolonged and frequent bleeding patterns were most common early in the study and declined thereafter. During the 3-month reference periods 2 to 8 (months 4 to 24), the incidence of amenorrhea ranged from 14 to 20 %. A total of 43 subjects (13 %) withdrew from the study because of bleeding pattern changes and 76 subjects (23 %) discontinued because of other AE. Other common AE leading to discontinuation, besides bleeding irregularities, were emotional lability (6.1 %), weight increase (3.3 %), depression (2.4 %) and acne (1.5 %). Use of Implanon for up to 2 years had no clinically significant effects on laboratory parameters, physical and pelvic examinations, vital signs or body mass index. The average length of time required for Implanon insertion and that for removal were 0.5 and 3.5 mins, respectively, and all the procedures were uncomplicated. The return to normal menstrual cycles and fertility was rapid after removal. The authors concluded that Implanon is a safe, highly effective and rapidly reversible new method of contraception. This finding is in agreement with that of Croxatto (2000) as well as that of Zheng et al (1999).

Implanon was a single, thin, plastic, etonogestrel-releasing rod manufactured by Organon USA. "The improved design and composition made Implanon easier and faster to insert and remove than first generation implants. In 2010, the manufacturer replaced Implanon with Nexplanon, which is designed to be radiopaque (visible through x-ray) and has an improved insertion device. It is FDA-approved for use up to three years, although some research indicates effectiveness beyond that period" (KFF, 2019).

Nexplanon is a progestin indicated for use by women to prevent pregnancy. The contraceptive effect of Nexplanon is achieved by suppression of ovulation, increased viscosity of the cervical mucus, and alterations in the endometrium. One Nexplanon implant is administered

subdermally just under the skin at the inner side of the non-dominant upper arm. Nexplanon must be removed no later than by the end of the third year. Nexplanon is contraindicated in known or suspected pregnancy, liver tumors (beign or malignant), active liver disease, undiagnosed abnormal genital bleeding, known or suspected breast cancer, personal history of breast cancer, other progestin-sensitive cancer, and allergic reaction to any of the components of Nexplanon. The label carries warnings and precautions for insertion and removal complications such as pain, paresthesias, bleeding, hematoma, scarring, infection, or migration to vasculature, including pulmonary vessels, may occur. Symptoms associated with implants in pulmonary vessels include chest pain, dyspnea, cough, or hemoptysis. Other warnings and precautions include menstrual bleeding pattern, ectopic pregnancies, thrombotic and other vascular events, liver disease, elevated blood pressure and carbohydrate and lipid metabolic effects. The most common (≥10%) adverse reactions reported in clinical trials were change in menstrual bleeding pattern, headache, vaginitis, weight increase, acne, breast pain, abdominal pain, and pharyngitis (Organon USA, 2021).

Hydroxyprogesterone Caproate (Makena) Injection

U.S. Food and Drug Administration (FDA)-Approved Indications

- Makena is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

  Limitations of use:

  While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth.

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Hydroxyprogesterone caproate injection is available as Makena (AMAG Pharmaceuticals) or in generic formulation (American Regent). Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which hydroxyprogesterone caproate reduces the risk of recurrent preterm birth is not known.

Makena is contraindicated in current or history of thrombosis or thromboembolic disorders, known or suspected breast cancer, other hormone-sensitive cancer, undiagnosed abnormal vaginal bleeding unrelated to pregnancy, cholestatic jaundice of pregnancy, liver tumors (bening or malignant), activer liver disease, and uncontrolled hypertension. The label carries warnings and precautions for thromboembolic disorders, allergic reactions, decreased glucose tolerance, fluid retention, and depression. In a study where the Makena intramuscular injection was compared with placebo, the most common adverse reactions reported with Makena intramuscular injection (reported incidence in ≥ 2% of subjects and higher than in the control group) included injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%). In studies where the Makena subcutaneous injection using auto-injector was compared with Makena intramuscular injection, the most common adverse reaction reported with Makena auto-injector use (and higher than with Makena intramuscular injection) was injection site pain (10% in one study and 34% in another) (AMAG, 2018).

Preterm birth defined as less than 37 weeks gestation and very preterm birth defined as less than 34 weeks gestation. Preterm birth affects 12% of live births in US and preterm birth rate increased by 27% between 1982 and 2002. A history of spontaneous preterm birth is the strongest risk factor for preterm birth in later pregnancies. It is also the leading cause of infant mortality and disability.

17 Alpha-hydroxyprogesterone (17P) caproate has been used to prevent preterm birth. 17P is an oil-based, long-lasting formulation that allows for weekly IM dosing. Makena is a commercially available preparation containing 17P with benzoyl alcohol as a preservative. Makena is available as a 5 mL multidose vial (250 mg/mL) containing 1250 mg

hydroxyprogesterone caproate. Compounded versions of 17P may or may not contain a preservative. Compounded 17p can be available in single use preparations.

A study by Meis, et al. (2003) is often cited for use of 17P to prevent preterm birth. Meis et al (2003) reported the results of a multi-center randomized clinical study, involving over 450 high risk women, showed that weekly injections of 17-alpha-hydroxyprogesterone resulted in a significant reduction in recurrent preterm birth. The study involved 463 women with history of singleton preterm births (delivery of a liveborn singleton infant between 20 weeks gestation and 36 weeks 6 days of gestation) that received prenatal care within four months of pregnancy. The study compared weekly 17P injections to placebo (castor oil) beginning at week 16-20 and continuing until week 36. The 17P injections resulted in a 33% reduction in preterm birth before 37 weeks.

There were some limitations to the Meis, et al. study. It assumed a preterm birth rate of 37% but the placebo group had a 56% preterm rate. There were also higher than assumed preterm birth rate in the placebo group (56% vs. 37%) which are unexplained and makes the control group look much better. The results cannot be extrapolated to other populations since the inclusion criteria was strict and does not address other types of preterm birth. The study was not focused on perinatal morbidity and mortality like neonatal intensive care unit (NICU) days - it only examined decrease in preterm birth rates. Morbidity and mortality increases when birth occurs at less than 34 weeks compared to less than 37 week gestation.

In a randomized, double-blind, placebo-controlled trial, Rouse et al (2007) examined if 17 alpha-hydroxyprogesterone caproate (17P) would reduce the rate of preterm birth in twin gestations. Healthy women with twin gestations were assigned to weekly intramuscular injections of 250 mg of 17P or matching placebo, starting at 16 to 20 weeks of gestation and ending at 35 weeks. The primary study outcome was delivery or fetal death before 35 weeks of gestation. A total of 661 women were randomly assigned to treatment. Baseline demographic data were similar in the 2 study groups. Six women were lost to follow-up; data from 655 were analyzed (325 in the 17P group and 330 in the placebo group). Delivery or fetal death before 35 weeks occurred in 41.5 % of pregnancies in the

17P group and 37.3 % of those in the placebo group (relative risk, 1.1; 95 % confidence interval [CI]: 0.9 to 1.3). The rate of the pre-specified composite outcome of serious adverse fetal or neonatal events was 20.2 % in the 17P group and 18.0 % in the placebo group (relative risk, 1.1; 95 % CI: 0.9 to 1.5). Side effects of the injections were frequent in both groups, occurring in 65.9 % and 64.4 % of subjects, respectively (p = 0.69), but were generally mild and limited to the injection site. The authors concluded that treatment with 17P did not reduce the rate of preterm birth in women with twin gestations.

In a randomized study, Abu-Musa et al (2008) examined the effect of 17-alpha-hydroxyprogesterone caproate (HPC) before embryo transfer on the outcome of in-vitro fertilization and embryo transfer (IVF-ET). A total of 125 patients undergoing IVF-ET were randomly assigned into treatment and control groups. In the treatment group, 63 patients received 17-HPC (250 mg, i.m.), 1 day before ET. The control group consisted of 62 patients who did not receive any injections. Main outcome measures were pregnancy and multiple-pregnancy rates. The 2 groups were similar with respect to the age of patients, total dose of follicle-stimulating hormone, number of oocytes and embryos obtained, and number and quality of embryos transferred. There was no significant difference in the pregnancy rate (34.9 % versus 38.7 %) or in the rate of multiple gestation (15.9 % versus 9.7 %) between cases and controls, respectively. The authors concluded that the use of 17-HPC before ET does not appear to affect the outcome of IVF-ET.

In a multi-center, double-blind, placebo-controlled randomized trial, Lim et al (2011) estimated if administration of 17α-hydroxyprogesterone caproate can prevent neonatal morbidity in multiple pregnancies by reducing the preterm birth rate. Women with a multiple pregnancy were randomized to weekly injections of either 250 mg 17α-hydroxyprogesterone caproate or placebo, starting between 16 and 20 weeks of gestation and continuing until 36 weeks of gestation. The main outcome measure was adverse neonatal outcome. Secondary outcome measures were gestational age at delivery and delivery before 28, 32, and 37 weeks of gestation. A total of 671 women were randomized. A composite measure of adverse neonatal outcome was present in 110 children (16 %) born to mothers in the 17α-hydroxyprogesterone caproate group, and in 80 children (12 %) of mothers in the placebo group (relative

risk [RR] 1.34; 95 % CI: 0.95 to 1.89). The mean gestational age at delivery was 35.4 weeks for the 17α-hydroxyprogesterone caproate group and 35.7 weeks for the placebo group (p = 0.32). Treatment with 17α-hydroxyprogesterone caproate did not reduce the delivery rate before 28 weeks (6 % in the 17α-hydroxyprogesterone caproate group compared with 5 % in the placebo group, RR 1.04; 95 % CI: 0.56 to 1.94), 32 weeks (14 % compared with 10 %, RR 1.37; 95 % CI: 0.91 to 2.05), or 37 weeks of gestation (55 % compared with 50 %, RR 1.11; 95 % CI: 0.97 to 1.28). The authors concluded that 17α-hydroxyprogesterone caproate does not prevent neonatal morbidity or preterm birth in multiple pregnancies.

Rode et al (2009) provided an update on the preventive effect of progesterone on preterm birth in singleton pregnancies. A search in the PubMed, Embase, and Cochrane database was performed using the keywords: pregnancy, progesterone, preterm birth/preterm delivery, preterm labor, controlled trial, and randomized controlled trial. Studies on singleton pregnancies were selected. A meta-analysis was performed on randomized trials including singleton pregnancies with previous preterm birth. Two new randomized controlled trials of women with previous preterm birth were added to the 4 analyzed in the Cochrane review, and the meta-analysis of all 6 studies now showed that progesterone supplementation was associated with a significant reduction of delivery before 32 weeks and of perinatal mortality. Furthermore, a 3rd trial showed a positive effect on women with a short cervix at 23 weeks, and a 4th study showed that progesterone reduces the risk of preterm delivery in women with preterm labor. The authors concluded that in women with a singleton pregnancy and previous preterm delivery, progesterone reduces the rates of preterm delivery before 32 weeks, perinatal death, as well as respiratory distress syndrome and necrotizing enterocolitis in the newborn. Women with a short cervix or preterm labor may also benefit from progesterone, but further evidence is needed to support such a recommendation. Follow-up studies should focus on possible metabolic complications in the mother or the offspring.

In a double-blind, randomized, clinical trial, Combs et al (2011) examined if prophylactic treatment with 17-alpha-hydroxyprogesterone caproate (17Pc) in twin pregnancy will reduce neonatal morbidity (primary outcome) by prolonging pregnancy (secondary outcome). Mothers carrying dichorionic-diamniotic twins were randomly assigned (in a 2:1

ratio) to weekly injections of 250 mg of 17Pc or placebo, starting at 16 to 24 weeks and continued until 34 weeks. In all, 160 women were randomized to 17Pc and 80 to placebo. Composite neonatal morbidity occurred with similar frequency in the 17Pc and placebo groups (14 % versus 12 %, respectively, p = 0.62). Mean gestational age at delivery was not affected by 17Pc (35.3 versus 35.9 weeks, p = 0.10), but a 3-day difference in median gestational age favored placebo (p = 0 0.02). There were no perinatal deaths with 17Pc and 3 with placebo. The authors concluded that in twin pregnancy, prophylactic treatment with 17Pc did not prolong gestation or reduce neonatal morbidity.

The American College of Obstetricians and Gynecologists (ACOG) issued an opinion on the use of progesterone for prevention of preterm birth in response to the above studies in 2003. The Committee opinion supports use of 17P to decrease preterm birth in select high-risk groups. They were not sure if vaginal progesterone is as efficacious as 17P and needs to be studied in a larger population. They felt more studies were needed in patients with other high risk factors such as multiple gestations, short cervical length, or positive test for cervicovaginal fetal fibronectin. The opinion was to restrict use of 17P to those with documented history of previous spontaneous birth at less than 37 weeks gestation since unresolved issues remain such as best route of drug delivery and long term safety of drug.

The ACOG Committee also issued an opinion in January 2005 ahead of the release of a study sponsored by CDC, NICHD, March of Dimes entitled “stimated Effect of 17 Alphahydroxyprogesterone Caproate on Preterm Birth in the United States” The retrospective case study applied findings by Meis, et al to larger population based on 2002 birth certificate data and vital stats for two states. Taking this larger sample (n = 4,021,726), the authors found 30,000 women eligible for 17P with a 22.5% preterm birth rate. A statistical analysis for 10,000 subjects showed women could benefit from 17P (33% efficacy). The overall impact on US natality was real but modest: 2% (12.1% - 11.8%) and suggested 17P appears to be more valuable in reducing preterm birth in eligible women than the general population.

There is a limited overall effect in general population. Limitations of the study are that it is not known who used progesterone in previous gestations. The 33% efficacy found by Meis may not be generalized to the US population since the study population in their study was tightly managed. The expansion of use beyond October 2003 opinion should be guided by evidence based, controlled clinical studies to minimize unnecessary use of 17P and long term follow up of mothers and infants exposed to 17P is needed to assure safety. Future studies need to investigate clinical efficacy by race, ethnicity, maternal age, parity, prenatal care use, geography, and biologic parameters.

ACOG guidelines on prevention of preterm birth (ACOG, 2013) state that "[a] woman with a singleton gestation and a prior spontaneous preterm singleton birth should be offered progesterone supplementation starting at 16–24 weeks of gestation, regardless of transvaginal ultrasound cervical length, to reduce the risk of recurrent spontaneous preterm birth." The guideline state that "[v]aginal progesterone is recommended as a management option to reduce the risk of preterm birth in asymptomatic women with a singleton gestation without a prior preterm birth with an incidentally identified very short cervical length less than or equal to 20 mm before or at 24 weeks of gestation." The guidelines state that progesterone treatment does not reduce the incidence of preterm birth in women with twin or triplet gestations and, therefore, is not recommended as an intervention to prevent preterm birth in women with multiple gestations. The guidelines state that insufficient evidence exists to assess if progesterone and cerclage together have an additive effect in reducing the risk of preterm birth in women at high risk for preterm birth.

The Society for Maternal-Fetal Medicine Publications Committee (2012) sought to provide evidence-based guidelines for using progestogens for the prevention of preterm birth (PTB). Relevant documents, in particular randomized trials, were identified using PubMed (U.S. National Library of Medicine, 1983 through February 2012) publications, written in English, which evaluate the effectiveness of progestogens for prevention of PTB. Progestogens evaluated were, in particular, vaginal progesterone and 17Pc. Additionally, the Cochrane Library, organizational guidelines, and studies identified through review of the above were utilized to identify relevant articles. Data were evaluated according to population studied, with separate analyses for singleton versus multiple gestations, prior

PTB, or short trans-vaginal ultrasound cervical length (CL), and combinations of these factors. Consistent with U.S. Preventive Task Force suggestions, references were evaluated for quality based on the highest level of evidence, and recommendations were graded. Summary of randomized studies indicates that in women with singleton gestations, no prior PTB, and short CL less than or equal to 20 mm at less than or equal to 24 weeks, vaginal progesterone, either 90-mg gel or 200-mg suppository, is associated with reduction in PTB and perinatal morbidity and mortality, and can be offered in these cases. The issue of universal CL screening of singleton gestations without prior PTB for the prevention of PTB remains an object of debate. CL screening in singleton gestations without prior PTB can not yet be universally mandated. Nonetheless, implementation of such a screening strategy can be viewed as reasonable, and can be considered by individual practitioners, following strict guidelines. In singleton gestations with prior PTB 20 to 36 6/7 weeks, 17Pc 250 mg intra-muscularly weekly, preferably starting at 16 to 20 weeks until 36 weeks, is recommended. In these women with prior PTB, if the trans-vaginal ultrasound CL shortens to less than 25 mm at less than 24 weeks, cervical cerclage may be offered. Progestogens have not been associated with prevention of PTB in women who have in the current pregnancy multiple gestations, preterm labor, or preterm premature rupture of membranes. There is insufficient evidence to recommend the use of progestogens in women with any of these risk factors, with or without a short CL.

In a prospective, RCT, Elimian and associates (2016) compared the effectiveness of i.m. 17-OHPC with that of vaginal progesterone for prevention of recurrent preterm birth. Women with singleton pregnancies (16 to 20 weeks) and a history of spontaneous preterm birth (SPTB) were randomly allocated using a computer-generated randomization sequence to receive either a weekly intramuscular injection of 17-OHPC (250 mg) or a daily vaginal progesterone suppository (100 mg). Participants, investigators, and assessors were not masked to group assignment. The primary outcome was birth before 37 weeks of pregnancy. Per-protocol analyses were performed: participants who completed follow-up were included. Analyses included 66 women given intramuscular progesterone and 79 given vaginal progesterone. Delivery before 37 weeks was recorded among 29 (43.9 %) women in the intramuscular progesterone group and 30 (37.9 %) in the vaginal progesterone group (p = 0.50). The

authors concluded that weekly intramuscular administration of 17-OHPC and daily vaginal administration of a progesterone suppository exhibited similar efficacy in reducing the rate of recurrent preterm birth.

Manuck and co-workers (2016) noted that SPTB remains a leading cause of neonatal morbidity and mortality among non-anomalous neonates in the United States; SPTB tends to recur at similar gestational ages. Intramuscular 17-OHPC reduces the risk of recurrent SPTB. Unfortunately, 1/3 of high-risk women will have a recurrent SPTB despite 17-OHPC therapy; the reasons for this variability in response are unknown. These researchers hypothesized that clinical factors among women treated with 17-OHPC who suffer recurrent SPTB at a similar gestational age differ from women who deliver later, and that these associations could be used to generate a clinical scoring system to predict 17-OHPC response. Secondary analysis of a prospective, multi-center, RCT enrolling women with greater than or equal to 1 previous singleton SPTB of less than 37 weeks' gestation. Participants received daily omega-3 supplementation or placebo for the prevention of recurrent preterm birth; all were provided 17-OHPC. Women were classified as a 17-OHPC responder or non-responder by calculating the difference in delivery gestational age between the 17-OHPC-treated pregnancy and her earliest previous SPTB. Responders were women with pregnancy extending greater than or equal to 3 weeks later compared with the delivery gestational age of their earliest previous preterm birth; non-responders delivered earlier or within 3 weeks of the gestational age of their earliest previous preterm birth. A risk score for non-response to 17-OHPC was generated from regression models via the use of clinical predictors and was validated in an independent population. Data were analyzed with multivariable logistic regression. A total of 754 women met inclusion criteria; 159 (21 %) were non-responders. Responders delivered later on average (37.7 ± 2.5 weeks) than non-responders (31.5 ± 5.3 weeks), $p < 0.001$. Among responders, 27 % had a recurrent SPTB (versus 100 % of non-responders). Demographic characteristics were similar between responders and non-responders. In a multivariable logistic regression model, independent risk factors for non-response to 17-OHPC were each additional week of gestation of the earliest previous preterm birth (odds ratio [OR], 1.23; 95 % CI: 1.17 to 1.30, $p < 0.001$), placental abruption or significant vaginal bleeding (OR, 5.60; 95 % CI: 2.46 to 12.71, $p < 0.001$), gonorrhea and/or chlamydia in the current

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pregnancy (OR, 3.59; 95 % CI: 1.36 to 9.48, p = 0.010), carriage of a male fetus (OR, 1.51; 95 % CI: 1.02 to 2.24, p = 0.040), and a penultimate preterm birth (OR, 2.10; 95 % CI: 1.03 to 4.25, p = 0.041). These clinical factors were used to generate a risk score for nonresponse to 17-OHPC as follows: black +1, male fetus +1, penultimate preterm birth +2, gonorrhea/chlamydia +4, placental abruption +5, earliest previous preterm birth was 32 to 36 weeks +5. A total risk score greater than 6 was 78 % sensitive and 60 % specific for predicting non-response to 17-OHPC (area under the curve = 0.69). This scoring system was validated in an independent population of 287 women; in the validation set, a total risk score greater than 6 performed similarly with a 65 % sensitivity, 67 % specificity and area under the curve of 0.66. The authors concluded that several clinical characteristics define women at risk for recurrent preterm birth at a similar gestational age despite 17-OHPC therapy and can be used to generate a clinical risk predictor score. These data should be refined and confirmed in other cohorts, and women at high risk for non-response should be targets for novel therapeutic intervention studies.

In a systematic review and meta-analysis, Saccone and colleagues (2017) evaluated the effectiveness of vaginal progesterone compared with 17-OHPC in prevention of SPTB in singleton gestations with prior SPTB. Searches were performed in electronic databases. No restrictions for language or geographic location were applied. These researchers included all RCTs of asymptomatic singleton gestations with prior SPTB who were randomized to prophylactic treatment with either vaginal progesterone (i.e., intervention group) or intramuscular 17-OHPC (i.e., comparison group). The primary outcome was SPTB less than 34 weeks. Secondary outcomes were SPTB less than 37 weeks, less than 32 weeks, less than 28 weeks and less than 24 weeks, maternal adverse drug reaction and neonatal outcomes. The summary measures were reported as relative risk (RR) with 95 % confidence interval (CI). A total of 3 RCTs (680 women) were included. The mean gestational age at randomization was about 16 weeks. Women were given progesterone until 36 weeks or delivery. Regarding vaginal progesterone, 1 study used 90-mg gel daily; 1 used 100-mg suppository daily; and the other used one 200-mg suppository daily. All the included trials used 250-mg 17-OHPC weekly as comparison group. Women who received vaginal progesterone had a significantly lower rate of SPTB less than 34 weeks (17.5 % versus 25.0 %; RR 0.71, 95 % CI: 0.53 to 0.95; low quality of

evidence) and SPTB less than 32 weeks (8.9 % versus 14.5 %; RR 0.62, 95 % CI: 0.40 to 0.94; low quality of evidence) compared to women who received 17-OHPC. There were no significant differences in the rate of SPTB less than 37 weeks, SPTB less than 28 weeks and SPTB less than 24 weeks. The rate of women who reported adverse drug reactions was significantly lower in the vaginal compared to 17-OHPC group (7.1 % versus 13.2 %; RR 0.53, 95 % CI: 0.31 to 0.91; very low quality of evidence). Regarding neonatal outcomes, vaginal progesterone was associated with a lower rate of neonatal intensive care unit (ICU) admission compared to 17-OHPC (18.7 % versus 23.5 %; RR 0.63, 95 % CI: 0.47 to 0.83; low quality of evidence). For comparison of 17-OHPC versus vaginal progesterone, the quality of evidence was down-graded for all outcomes by at least 1 degree due to imprecision (the optimal information size was reached) and by at least 1 degree due to indirectness (different interventions). The authors concluded that daily vaginal progesterone started at about 16 weeks (either suppository or gel) is a reasonable, if not better, alternative to weekly 17-OHPC for prevention of SPTB in women with singleton gestations and prior SPTB. However, the quality level of the summary estimates was low/very low as assed by GRADE, indicating that the true effect may, or is even likely to, be substantially different from the estimate of the effect.

Furthermore, an UpToDate review on "Progesterone supplementation to reduce the risk of spontaneous preterm birth" (Norwitz, 2017) stated that "In women with a prior preterm birth, continuing hydroxyprogesterone caproate supplementation after placement of a cerclage has not been proven to be useful, but available data are limited to secondary analysis of one underpowered trial; and provided the following recommendations:

- For women with a singleton pregnancy who have had a previous spontaneous singleton preterm birth, we suggest progesterone treatment (Grade 2B). We suggest intramuscular injections of hydroxyprogesterone caproate rather than vaginal progesterone (Grade 2C), beginning in the second trimester (16 to 20 weeks) and continuing through the 36th week of gestation. We prescribe 250 mg weekly. Natural progesterone administered vaginally is a reasonable alternative.
- For women with twin pregnancies and a previous spontaneous preterm birth, the author prescribes hydroxyprogesterone

caproate. Not prescribing progesterone supplementation or prescribing natural progesterone vaginally is also reasonable.

- Routine progesterone supplementation does not appear to be useful for preventing preterm birth in the setting of preterm premature rupture of membranes or after an episode of arrested preterm labor. There is no information on efficacy in women with a positive fetal fibronectin test. The effect in women with a cerclage is unclear.

Progesterone containing products are classified as pregnancy category D: teratogenic properties demand evaluation of risk versus benefit.

In October 2020, the Center for Drug Evaluation and Research (CDER) of the FDA proposed withdrawal of approval of Makena (hydroxyprogesterone caproate injection). "In Makena's required postapproval confirmatory trial (Trial 003), 1708 women from nine countries were randomly assigned to receive Makena or placebo". The eligibility criteria were the same as those in the trial that was used as the basis for FDA-approval (Trial 002; Meis et al. (2003)). The trial included a co-primary efficacy end point, "the proportion of women delivering before 35 weeks' gestation and the proportion of neonates having at least one of six adverse health outcomes related to prematurity (neonatal death, grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and sepsis). The neonatal outcomes end point was included to verify clinical benefit to the neonate". According to CDER, Trial 003 did not demonstrate an effect of Makena on the surrogate end point of preterm birth, contradicting the findings from Trial 002, nor did it show an effect on neonatal outcomes. "The FDA's statutory authority and regulations state that the agency may withdraw an accelerated approval when the postapproval trial fails to confirm clinical benefit or when the drug is not shown to be safe or effective. Both conditions have been met for Makena. Trial 003 failed both to verify clinical benefit to neonates and to substantiate a reduction in preterm birth. For now, Makena remains available. When CDER determines that a drug should be withdrawn, the company can agree to withdraw it or request a public hearing. In this case, the company has requested a hearing. The FDA commissioner will decide whether to grant the request and, if it is granted, will then determine whether to withdraw approval" (Chang et al., 2020).

Medroxyprogesterone Acetate Injection

U.S. Food and Drug Administration (FDA)-Approved Indications

- Medroxyprogesterone acetate injection (Depo-Provera CI (Contraceptive Injection) (Pfizer Inc); generic (Amphastar Pharmaceuticals Inc) is indicated for use by females of reproductive potential to prevent pregnancy.

  Limitations of Use:

  The use of Depo-Provera CI is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate.

Compendial Uses

- Gender dysphoria

Medroxyprogesterone acetate, when administered at the recommended dose to women every 3 months, inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and results in endometrial thinning (Amphastar Pharmaceuticals, 2018). Depo-Provera CI (medroxyprogesterone acetate [MPA]) inhibits the secretion of gonadotropins which primarily prevents follicular maturation and ovulation and causes thickening of cervical mucus (Pfizer, 2020). These actions contribute to its contraceptive effect.

Medroxyprogesterone acetate carries a black box warning for risk of loss of bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of medroxyprogesterone acetate contraceptive injection during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. Medroxyprogesterone acetate contraceptive injection should not be used as a long-term birth control method (i.e., longer than 2 years) unless other birth control methods are considered inadequate.

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Medroxyprogesterone acetate is contraindicated for the following indications:

- Known or suspected pregnancy or as a diagnostic test for pregnancy
- Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease
- Known or suspected malignancy of breast
- Known hypersensitivity to medroxyprogesterone acetate or any of its other ingredients
- Significant liver disease
- Undiagnosed vaginal bleeding.

The label carries the following warnings and precautions:

- Thromboembolic Disorders: Discontinue Medroxyprogesterone acetate in patients who develop thrombosis
- Cancer Risks: Monitor women with a strong family history of breast cancer carefully
- Ectopic Pregnancy: Consider ectopic pregnancy if a woman using Medroxyprogesterone acetate becomes pregnant or complains of severe abdominal pain
- Anaphylaxis and Anaphylactoid Reactions: Provide emergency medical treatment
- Liver Function: Discontinue Medroxyprogesterone acetate if jaundice or disturbances of liver function develop
- Carbohydrate Metabolism: Monitor diabetic patients carefully.

The most common adverse reactions (incidence 5% or more) include menstrual irregularities (bleeding or spotting) 57% at 12 months, 32% at 24 months, abdominal pain/discomfort 11%, weight gain > 10 lbs at 24 months 38%, dizziness 6%, headache 17%, nervousness 11%, decreased libido 6%.

Medroxyprogesterone acetate is available as an oral tablet, subuctaneous suspension, and intramuscular suspension.

Intramuscular Injection

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Medroxyprogesterone acetate, a derivative of progesterone, as an intramuscular injection administered every 3 months, has been shown to be highly effective in the prevention of pregnancy (less than 1 % failure rate in the first year). Other formulations of medroxyprogesterone acetate (i.e. oral tablets) are indicated for the treatment of secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. They are also indicated for use in the prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving daily oral conjugated estrogens 0.625 mg tablets (Pfizer, 2018). Oral medroxyprogesterone acetate also has a Category 2A recommendation by the National Comprehensive Cancer Network (NCCN, 2021) for treatment of endometrial adenocarcinoma.

Intramuscular (IM) medroxyprogesterone has been used for the treatment of menorrhagia/abnormal uterine bleeding, as an alternative to oral progestogen therapy. However, since progestogen therapy for menorrhagia/abnormal uterine bleeding must be cyclical in nature, experts usually prescribe oral, rather than intramuscular medroxyprogesterone for these indications.

When being used as a contraceptive, medroxyprogesterone acetate (Depo-Provera CI) is only covered under plans that specifically cover contraceptive drugs, contraceptive devices, or contraceptive drug implants.

Parenteral medroxyprogesterone was used in the past as a treatment for precocious puberty, but has been replaced by other modalities.

Injectable medroxyprogesterone acetate has an off-label use for gender dysphoria. Cited by Coleman et al. (2012), gender dysphoria refers to discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics). Per "Standards of care for health of transsexual, transgender, and gender-nonconforming people, version 7", for individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered, such as hormone therapy to feminize or masculinize the body. For puberty suppression, adolescents with male

genitalia should be treated with GnRH analogues, which stop luteinizing hormone secretion and therefore testosterone secretion. Alternatively, they may be treated with progestins (such as medroxyprogesterone) or with other medications that block testosterone secretion and/or neutralize testosterone action. Adolescents with female genitalia should be treated with GnRH analogues, which stop the production of estrogens and progesterone. Alternatively, they may be treated with progestins (such as medroxyprogesterone). Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses. In both groups of adolescents, use of GnRH analogues is the preferred treatment.

Hembree et al. (2017) state that medroxyprogesterone is not as effective as GnRH analogs in lowering endogenous sex hormones, and may be associated with other side effects. Progestin preparations may be an acceptable treatment for persons without access to GnRH analogs or with a needle phobia. In transgender males, clinicians may also administer GnRH analogs or depot medroxyprogesterone to stop menses prior to testosterone treatment.

Medroxyprogesterone acetate (Depo-Provera) injection, suspension 400 mg/mL was discontinued on October 27, 2020 (FDA, 2021).

Lunelle (combination estrogen and medroxyprogesterone injection) was approved by the Food and Drug Administration (FDA) as a once per month injectable contraceptive in October 1999. Lunelle was not approved by the FDA for any indication other than the prevention of pregnancy. However, the Lunelle syringes were voluntarily recalled in 2002 due to concern over potency and possible risk of contraceptive failure. In October 2003, Pfizer stopped making Lunelle, so it is no longer available in the United States (American Pregnancy Association, 2013).

Progesterone Injection

Progesterone is available in different formuations such as intravaginal gel, insert or ring, oral capsules, and intramuscular oil.

Progesterone injection, a progestin, is a sterile solution of progesterone in a suitable vegetable oil available for intramuscular use is FDA-approved for treatment of amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer (Watson Laboratories, 2007).

The U.S. Pharmacopoeia states that progesterone or hydroxyprogesterone injection can be used to test for endogenous estrogen production and can be used to determine whether low levels of estrogen are present if withdrawal bleeding does not occur after a progestin challenge in menopausal women before estrogen-progestin ovarian hormone therapy is considered. The U.S. Pharmacopoeia notes, however, that determination that serum gonadotropins are elevated is the standard way to confirm menopause. The U.S. Pharmacopoeial Convention has concluded that injectable progesterone and hydroxyprogesterone has not been shown to be an effective treatment for premenstrual syndrome. Injectable progesterone or hydroxyprogesterone is not indicated for prevention of pregnancy.

Wong et al (2013) stated that pre-clinical studies suggested progesterone is neuroprotective after cerebral ischemia. The gold standard for assessing intervention effects across studies within and between subgroups is to use meta-analysis based on individual animal data (IAD). Pre-clinical studies of progesterone in experimental stroke were identified from searches of electronic databases and reference lists. Corresponding authors of papers of interest were contacted to obtain IAD and, if unavailable, summary data were obtained from the publication. Data were given as standardized mean differences (SMDs, continuous data) or odds ratios (binary data), with 95 % CIs. In an unadjusted analysis of IAD and summary data, progesterone reduced standardized lesion volume (SMD -0.766, 95 % CI: -1.173 to -0.358, $p < 0.001$). Publication bias was apparent on visual inspection of a Begg's funnel plot on lesion volume and statistically using Egger's test ($p = 0.001$). The authors concluded that using individual animal data alone, progesterone was associated with an increase in death in adjusted analysis (odds ratio 2.64, 95 % CI: 1.17 to 5.97, $p = 0.020$). Moreover, they stated that although progesterone significantly reduced lesion volume, it also appeared to increase the incidence of death after experimental stroke,

particularly in young ovariectomized female animals. Experimental studies must report the effect of interactions on death and on modifiers, such as age and sex.

Progesterone Vaginal Suppositories

Progesterone suppositories have been used to prevent preterm birth, habitual abortion and luteal phase defects. Progesterone suppositories must be compounded and are applied daily.

A study by de Fonesca et al (2003) is a major study supporting the use of progesterone vaginal suppositories for prevention of preterm birth. de Fonseca et al (2003) reported on the results of a randomized, placebo-controlled trial of progestin vaginal suppositories in high-risk women, and found that the incidence of preterm birth was significantly reduced, from 28.5 % to 13.8 % for births before 37 weeks, and from 18.6 % to 2.8 % for births before 34 weeks in the placebo versus the progesterone groups, respectively. The study involved 142 women deemed high risk due to a history of preterm birth, prophylactic cervical cerclage, or uterine malformation. The study found a 13.8 % reduction in preterm birth before 37 weeks in subjects assigned to progesterone vaginal suppositories compared to placebo.

In a randomized, double-blind, placebo-controlled study and meta-analysis, Norman et al (2009) examined the use of progesterone for prevention of preterm birth in twin pregnancy. A total of 500 women with twin pregnancy were recruited from 9 United Kingdom National Health Service clinics specializing in the management of twin pregnancy. Women were randomized, by permuted blocks of randomly mixed sizes, either to daily vaginal progesterone gel 90 mg (n = 250) or to placebo gel (n = 250) for 10 weeks from 24 weeks' gestation. All study personnel and participants were masked to treatment assignment for the duration of the study. The primary outcome was delivery or intra-uterine death before 34 weeks' gestation. Analysis was by intention-to-treat. Additionally these investigators undertook a meta-analysis of published and unpublished data to establish the efficacy of progesterone in prevention of early (less than 34 weeks' gestation) preterm birth or intra-uterine death in women with twin pregnancy. Three participants in each group were lost to follow-up, leaving 247 analysed per group. The combined proportion of intra-

uterine death or delivery before 34 weeks of pregnancy was 24.7 % (61/247) in the progesterone group and 19.4 % (48/247) in the placebo group (odds ratio [OR] 1.36, 95 % CI: 0.89 to 2.09; p = 0.16). The rate of adverse events did not differ between the 2 groups. The meta-analysis confirmed that progesterone does not prevent early preterm birth in women with twin pregnancy (pooled OR 1.16, 95 % CI: 0.89 to 1.51). The authors concluded that progesterone, administered vaginally, does not prevent preterm birth in women with twin pregnancy.

A number of double-blind clinical trials have failed to show that progesterone suppositories are more effective than placebo in treating premenstrual syndrome. Although proponents of progesterone therapy for PMS have agreed that many of the clinical trials have been done inappropriately with respect to selection criteria, study size, treatment duration and/or blinding method, at least one study has controlled these variables quite well (Maddocks, 1986). This study indicated that the response to progesterone vaginal suppositories is, at best, marginal and not significantly different from response to placebo. Freeman (2004) stated that progesterone has consistently failed to show efficacy for severe PMS/premenstrual dysphoric disorder in large, randomized, placebo-controlled trials.

In a Cochrane review on prenatal administration of progesterone for preventing preterm birth, Dodd et al (2006) noted that intramuscular progesterone is associated with a reduction in the risk of preterm birth of less than 37 weeks' gestation, and infant birth weight of less than 2500 grams. However, other important maternal and infant outcomes have been poorly reported to date, with most outcomes reported from a single trial only. It is unclear if the prolongation of gestation translates into improved maternal and longer-term infant health outcomes. Similarly, information regarding the potential harms of progesterone therapy to prevent preterm birth is limited. The authors concluded that further information is needed to ascertain the clinical value of the use of vaginal progesterone in the prevention of preterm birth. Guidelines from the American College of Obstetricians and Gynecologists (2003) have stated that whether vaginal progestins are as effective as intramuscular progestins in preventing preterm birth “remains to be proved in a larger population.”

Cahill et al (2010) estimated which strategy is the most cost-effective for the prevention of preterm birth and associated morbidity. These investigators used decision-analytic and cost-effectiveness analyses to estimate which of 4 strategies was superior based on quality-adjusted life-years, cost in US dollars, and number of preterm births prevented. Universal sonographic screening for cervical length and treatment with vaginal progesterone was the most cost-effective strategy and was the dominant choice over the 3 alternatives: cervical length screening for women at increased risk for preterm birth and treatment with vaginal progesterone; risk-based treatment with 17 alpha-hydroxyprogesterone caproate (17-OHP-C) without screening; no screening or treatment. Universal screening represented savings of $1,339 ($8,325 versus $9,664), when compared with treatment with 17-OHP-C, and led to a reduction of 95,920 preterm births annually in the United States. The authors concluded that universal sonographic screening for short cervical length and treatment with vaginal progesterone appears to be cost-effective and yields the greatest reduction in preterm birth at less than 34 weeks' gestation.

In a multi-center, randomized, double-blind, placebo-controlled study, Hassan and associates (2011) examined the safety and effectiveness of using micronized vaginal progesterone gel to reduce the risk of preterm birth and associated neonatal complications in women with a sonographic short cervix. Asymptomatic women with a singleton pregnancy and a sonographic short cervix (10 to 20 mm) at 19 + 0 to 23 + 6 weeks of gestation were enrolled in this study. They were allocated randomly to receive vaginal progesterone gel or placebo daily starting from 20 to 23 + 6 weeks until 36 + 6 weeks, rupture of membranes or delivery, whichever occurred first. Randomization sequence was stratified by center and history of a previous preterm birth. The primary endpoint was preterm birth before 33 weeks of gestation. Analysis was by intention- to-treat. Of 465 women randomized, 7 were lost to follow-up and 458 (vaginal progesterone gel, n = 235; placebo, n = 223) were included in the analysis. Women allocated to receive vaginal progesterone had a lower rate of preterm birth before 33 weeks than did those allocated to placebo (8.9 % (n = 21) versus 16.1 % (n = 36); RR, 0.55; 95 % CI: 0.33 to 0.92; p = 0.02). The effect remained significant after adjustment for co-variables (adjusted RR, 0.52; 95 % CI: 0.31 to 0.91; p = 0.02). Vaginal progesterone was also associated with a significant reduction in the rate

of preterm birth before 28 weeks (5.1 % versus 10.3 %; RR, 0.50; 95 % CI: 0.25 to 0.97; p = 0.04) and 35 weeks (14.5 % versus 23.3 %; RR, 0.62; 95 % CI: 0.42 to 0.92; p = 0.02), respiratory distress syndrome (3.0 % versus 7.6 %; RR, 0.39; 95 % CI: 0.17 to 0.92; p = 0.03), any neonatal morbidity or mortality event (7.7 % versus 13.5 %; RR, 0.57; 95 % CI: 0.33 to 0.99; p = 0.04) and birth weight less than 1,500 g (6.4 % (15/234) versus 13.6 % (30/220); RR, 0.47; 95 % CI: 0.26 to 0.85; p = 0.01). There were no differences in the incidence of treatment-related adverse events between the groups. The authors concluded that administration of vaginal progesterone gel to women with a sonographic short cervix in the mid-trimester is associated with a 45 % reduction in the rate of preterm birth before 33 weeks of gestation and with improved neonatal outcome.

Klein and colleagues (2011) noted that progesterone treatment reduces the risk of preterm delivery in high-risk singleton pregnancies. These researchers evaluated the preventive effect of vaginal progesterone in high-risk twins. This was a sub-analysis of a Danish-Austrian, double-blind, placebo-controlled, randomized trial (PREDICT study), in which women with twin pregnancies were randomized to daily treatment with progesterone or placebo pessaries from 20 to 24 weeks until 34 weeks' gestation. This subpopulation consisted of high-risk pregnancies, defined by the finding of cervical length less than or equal to 10th centile at 20 to 24 weeks' gestation or history of either spontaneous delivery before 34 weeks or miscarriage after 12 weeks. Primary outcome was delivery before 34 weeks. Secondary outcomes were complications for infants including long-term follow-up by Ages and Stages Questionnaire (ASQ) at 6 and 18 months of age. In 72 (10.6 %) of the 677 women participating in the PREDICT study, the pregnancy was considered to be high-risk, including 47 with cervical length less than or equal to 10th centile, 28 with a history of preterm delivery or late miscarriage and 3 fulfilling both criteria. Baseline characteristics for progesterone and placebo groups were similar. Mean gestational age at delivery did not differ significantly between the 2 groups either in patients with a short cervix (34.3 +/- 4.1 versus 34.5 +/- 3.0 weeks, p = 0.87) or in those with a history of preterm delivery or late miscarriage (34.6 +/- 4.2 versus 35.2 +/- 2.7 weeks, p = 0.62). Similarly, there were no significant differences between the treatment groups in maternal or neonatal complications and mean ASQ

score at 6 and 18 months of age. The authors concluded that in high-risk twin pregnancies, progesterone treatment does not significantly improve outcome.

Fonseca and colleagues (2007) noted that previous randomized trials have shown that progesterone administration in women who previously delivered prematurely reduces the risk of recurrent premature delivery. Asymptomatic women found at mid-gestation to have a short cervix are at greatly increased risk for spontaneous early preterm delivery. These investigators examined if progesterone reduces this risk in such women. Cervical length was measured by transvaginal ultrasonography at a median of 22 weeks of gestation (range of 20 to 25 weeks) in 24,620 pregnant women seen for routine prenatal care. Cervical length was 15 mm or less in 413 of the women (1.7 %), and 250 (60.5 %) of these 413 women were randomly assigned to receive vaginal progesterone (200 mg each night) or placebo from 24 to 34 weeks of gestation. The primary outcome was spontaneous delivery before 34 weeks. Spontaneous delivery before 34 weeks of gestation was less frequent in the progesterone group than in the placebo group (19.2 % versus 34.4 %; relative risk, 0.56; 95 % CI: 0.36 to 0.86). Progesterone was associated with a non-significant reduction in neonatal morbidity (8.1 % versus 13.8 %; relative risk, 0.59; 95 % CI: 0.26 to 1.25; p = 0.17). There were no serious adverse events associated with the use of progesterone. The authors concluded that in women with a short cervix, treatment with progesterone reduces the rate of spontaneous early preterm delivery.

Simhan and Caritis (2007) stated that although the use of progestational agents to prevent preterm birth among high-risk women is promising, the results of afore-mentioned trials highlight the gaps in the current knowledge of the biologic contribution of various risk factors to preterm birth. Unanswered questions regarding the possible mechanisms of action of the various progestins in preventing preterm birth have led to uncertainty with respect to choice of agent, route of administration, dose regimen, and clinical indication. The authors stated that further research on progestational agents is needed.

In an editorial that accompanied the studies by Rouse et al and Fonseca et al, Thornton (2007) stated that there are at least 14 ongoing trials involving women with high-risk pregnancies (both singleton and twin) that

aim to recruit a total of more than 5,000 women and the author was aware of at least 2 more currently awaiting funding decisions. These studies should have ample power to test the effect of progesterone on important fetal outcomes as well as any differential effect in twin gestations, and long-term follow-up of the surviving children will provide important additional information. In the meantime, the remaining uncertainties about both efficacy and fetal safety mean that even women at high-risk for preterm delivery should join one of the ongoing randomized trials, rather than take a treatment for which the efficacy and safety have not been proved.

In a Cochrane review, Su and colleagues (2010) examined if the use of progestational agents is effective as a form of treatment or co-treatment for women with threatened or established preterm labor with intact membranes. These investigators searched the Cochrane Pregnancy and Childbirth Group's Trials Register (March 2009), CENTRAL (The Cochrane Library 2009, Issue 1), MEDLINE (1966 to January 2009) and EMBASE (1974 to January 2009). They checked references of articles and communicated with authors and pharmaceutical industry. Randomized controlled trials that compared progestational agents, given either alone or in combination with other tocolytics, with a control group receiving another tocolytic, placebo or no treatment, for the treatment of preterm labor were selected. Two review authors independently extracted data and assessed trial quality. There were some data suggesting that the use of progestational agent resulted in a reduction of preterm deliveries at less than 37 weeks of gestation. The use of progestational agent may also attenuate the shortening of cervical length and reduce the frequency of uterine contractions. However, the analysis was limited by the small number of available studies. This review included 4 studies; however, the number of participants in each included study ranged from 35 to 60, which limits the power of the meta-analysis. The authors concluded that there is currently insufficient evidence to advocate progestational agents as a tocolytic agents for women presenting with preterm labor.

Although not proven effective, progesterone has also been used during first few months of pregnancy to prevent habitual or threatened abortion due to hormonal imbalance but may also delay expulsion of a defective ovum. Potter and Scott (2005) stated that inadequate progesterone

production has been proposed a cause of recurrent pregnancy loss and progesterone is given to prevent miscarriage, despite a lack of supportive evidence.

The American College of Obstetricians and Gynecologists (2008) has stated that "progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes. ... Progesterone supplementation for asymptomatic women with an incidentally identified very short cervical length (less than 15 mm) may be considered; however, routine cervical length screening is not recommended."

In a prospective RCT, Pirjani and colleagues (2017) compared 17OHP-C with vaginal progesterone suppository for the prevention of preterm birth in women with a sonographically short cervix and evaluated the changes of the CL over time. Eligible patients were asymptomatic pregnant women with a sonographically short cervix. The participants in group 1 (n = 147) received vaginal progesterone suppositories at a dose of 400 mg daily and the women in group 2 (n = 150) received an i.m. dose of 250 mg 17OHP-C once-weekly. Transvaginal sonography was repeated every 3 weeks until 36 gestational weeks or the occurrence of preterm labor. A total of 304 singleton pregnant women between 16 and 24 gestational weeks with CL less than 25 mm were enrolled in this study. The rates of preterm birth were 10.4 % in the progesterone group and 14 % in the 17OHP-C group: a difference that was not statistically significant ($p = 0.416$). Moreover, 264 participants underwent ultrasound examination 5 times and CL changes were studied for 15 weeks. The results showed that the CL changes over 15 weeks were statistically significant ($p < 0.001$), but the method of intervention (progesterone/17OHP-C) had no significant effect on CL change ($p = 0.64$). The authors concluded that these findings showed that vaginal progesterone and 17OHP-C had the same effect on the risk of preterm labor in asymptomatic women with a sonographically short cervix. These investigators detected no significant difference between the effect of 17OHP-C and vaginal progesterone on CL changes over time.

Progestin-Releasing IUDs

Progestin-releasing intrauterine systems (e.g., Kyleena levonorgestrel-releasing IUD; Mirena levonorgestrel-releasing intrauterine system; Progestasert progesterone-releasing intrauterine device) are safe, effective, long-term contraceptive devices. Progestasert offers pregnancy prevention for one year, and Mirena offers pregnancy prevention for 5 years. Progestin-releasing intrauterine systems have also been shown to decrease the volume of menstrual blood loss in women with normal periods and those with menorrhagia. Heavy menstrual bleeding markedly impairs the quality of life in many healthy women. Management of the condition usually depends on the degree of bleeding and discomfort found acceptable by the individual woman. Medical treatments include oral medications and a hormone-releasing intrauterine system (e.g., Mirena, Progestasert). Surgical options include conservative surgery (e.g., uterine resection or ablation) and hysterectomy. A Cochrane review (Marjoribanks et al, 2003) compared the safety, effectiveness, and acceptability of surgery versus medical therapy for heavy menstrual bleeding. The authors concluded that surgery reduces menstrual bleeding at one year more than medical treatments, but a hormone-releasing intrauterine system appears equally beneficial in improving quality of life and may control bleeding as effectively as conservative surgery over the long-term.

In June 2001, progesterone intrauterine insert, Progestasert (R), was discontinued.

Kuanitz et al (2009) compared the effects of the levonorgestrel intrauterine system and endometrial ablation in reducing heavy menstrual bleeding. This systematic review and meta-analysis was restricted to randomized controlled trials in which menstrual blood loss was reported using pictorial blood loss assessment chart scores. A total of 6 randomized controlled trials that included 390 women (levonorgestrel intrauterine system, n = 196; endometrial ablation, n = 194) were retrieved. Three studies pertained to 1st-generation endometrial ablation (manual hysteroscopy) and 3 to 2nd-generation endometrial ablation (thermal balloon). Study characteristics and quality were recorded for each study. Data on the effect of treatment on pictorial blood loss assessment chart scores were abstracted, integrated with meta-analysis

techniques, and presented as weighted mean differences. Both treatment modalities were associated with similar reductions in menstrual blood loss after 6 months (weighted mean difference, -31.96 pictorial blood loss assessment chart score [95 % CI: -65.96 to 2.04]), 12 months (weighted mean difference, 7.45 pictorial blood loss assessment chart score [95 % CI: -12.37 to 27.26]), and 24 months (weighted mean difference, -26.70 pictorial blood loss assessment chart score [95 % CI: -78.54 to 25.15]). In addition, both treatments were generally associated with similar improvements in quality of life in 5 studies that reported this as an outcome. No major complications occurred with either treatment modality in these small trials. The author concluded that based on the meta-analysis of 6 randomized clinical trials, the efficacy of the levonorgestrel intrauterine system in the management of heavy menstrual bleeding appears to have similar therapeutic effects to that of endometrial ablation up to 2 years after treatment.

On January 9, 2013, the FDA approved Skyla IUD, a levonorgestrel-releasing intrauterine system, for the prevention of pregnancy for up to 3 years. On February 27, 2015, the FDA approved Liletta levonorgestrel-releasing IUD system to prevent pregnancy for up to 3 years.

In a Cochrane review, Sangkomkamhang et al (2013) determined the effectiveness of progestogens or progestogen-releasing intrauterine systems in treating pre-menopausal women with uterine fibroids. These investigators searched the Menstrual Disorders and Subfertility Group Specialized Register (inception to August 17, 2012), CENTRAL (inception to August 17, 2012) and Database of Abstracts of Reviews of Effects (DARE) in The Cochrane Library, MEDLINE (inception to 1August 17, 2012), Ovid EMBASE (January 1, 2010 to August 17, 2012), Ovid PsycINFO (inception to August 17, 2012), CINAHL database, and trials registers for ongoing and registered trials. All identified published or unpublished randomized controlled trials (RCTs) assessing the effect of progestogens or progestogen-releasing intrauterine systems in treating pre-menopausal women with uterine fibroids. These researchers assessed all potentially eligible studies identified as a result of the search strategy. Two review authors extracted data from each included study using an agreed form and assessed the risk of bias. They resolved discrepancies through discussion. This review included 3 studies. However, data for progestogen-releasing intrauterine systems were

available from only 1 study that compared 29 women with a levonorgestrel (LNG)-IUS versus 29 women with a combined oral contraceptive (COC) for treating uterine fibroids. There was a significant reduction of menstrual blood loss (MBL) in women receiving the LNG-IUS compared to the COC using the alkaline hematin test (mean difference (MD) 77.5 %, 95 % CI: 71.3 % to 83.67 %, 58 women) and a pictorial assessment chart (PBAC) (MD 34.5 %, 95 % CI: 14.9 % to 54.1 %, 58 women). The reduction in uterine fibroid size was significantly greater in the leuprorelin group at 16 weeks compared to the progestogen lynestrenol group (MD -15.93 mm, 95 % CI: -18.02 to -13.84 mm, 46 women). There was no RCT evaluating the effect of DMPA on uterine fibroids. The authors concluded that progestogen-releasing intrauterine systems appear to reduce menstrual blood loss in pre-menopausal women with uterine fibroids. Oral progestogens did not reduce fibroid size or fibroid-related symptoms. However, there was a methodological limitation and the one included study with data had a small sample size. They stated that this evidence is insufficient to support the use of progestogens or progestogen-releasing intrauterine systems in treating pre-menopausal women with uterine fibroids.

The FDA approved Kyleena, Bayer AG's new low dose levonorgestrel-releasing intrauterine system (Bayer, 2016). Kyleena is a plastic T-shaped device containing 19.5mg of the progestin levonorgestrel. The size of the Kyleena T-body is 28mm x 30mm, and its placement tube has a diameter of 3.8mm. Once placed in the uterus, Kyleena continuously releases a low dose of the progestin directly into the uterus. Kyleena provides birth control for up to five years and also offers return to fertility after removal.

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Gender Affirming Surgery

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

Number: 0615

Table Of Contents

Policy History

Last Review
01/06/2023
Effective: 05/14/2002
Next Review: 06/22/2023

Review History

Definitions

Policy

Scope of Policy

This Clinical Policy Bulletin addresses gender affirming surgery.

Note: Some plans may cover gender affirming procedures in addition to the following policy. Please check the specific benefit plan documents.

Additional Information

Clinical Policy Bulletin Notes

State Information

California

Colorado

I. Medical Necessity

Aetna considers gender affirming surgery medically necessary when criteria for each of the following procedures is met:

Pl. Trial Ex. 056

A. *Requirements for Breast Removal* Washington

1. Signed letter from a qualified mental health professional (see Appendix) assessing the transgender/gender diverse individual's readiness for physical treatment; *and*
2. Documentation of marked and sustained gender dysphoria (see Appendix); *and*
3. Other possible causes of apparent gender incongruence have been excluded; *and*
4. Mental and physical health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed; *and*
5. Capacity to consent for the specific physical treatment; *and*
6. For members less than 18 years of age, completion of one year of testosterone treatment, unless hormone therapy is not desired or medically contraindicated; *and*
7. Risk factors associated with breast cancer have been assessed.

B. *Requirements for Breast Augmentation (Implants/Lipofilling)*

1. Signed letter from a qualified mental health professional (see Appendix) assessing the transgender/gender diverse individual's readiness for physical treatments; *and*
2. Documentation of marked and sustained gender dysphoria (see Appendix); *and*
3. Other possible causes of apparent gender incongruence have been excluded; *and*
4. Mental and physical health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed; *and*
5. Capacity to consent for the specific physical treatment; *and*
6. Completion of six months of feminizing hormone therapy (12 months for adolescents less than 18 years of age) prior to breast augmentation surgery, unless hormone therapy is not desired or medically contraindicated); *and*
7. Risk factors associated with breast cancer have been assessed.

C. *Requirements for Gonadectomy (Hysterectomy and Oophorectomy or Orchiectomy)*

1. Signed letter from a qualified mental health professional (see Appendix) assessing the transgender/gender diverse individual's readiness for physical treatments; *and*
2. Documentation of marked and sustained gender dysphoria (see Appendix); *and*
3. Other possible causes of apparent gender incongruence have been excluded; *and*
4. Mental and physical health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed; *and*
5. Capacity to consent for the specific physical treatment; *and*
6. Six months of continuous hormone therapy as appropriate to the member's gender goals (12 months for adolescents less than 18 years of age), unless hormone therapy is not desired or medically contraindicated.

D. *Requirements for Genital Reconstructive Surgery (i.e., vaginectomy, urethroplasty, metoidioplasty, phalloplasty, scrotoplasty, placement of a testicular prosthesis and erectile prosthesis, penectomy, vaginoplasty, labiaplasty, clitoroplasty and electrolysis or laser hair removal sessions for skin graft preparation for genital surgery)*

1. Signed letter from a qualified mental health professional (see Appendix) assessing the transgender/gender diverse individual's readiness for physical treatments; *and*
2. Documentation of marked and sustained gender dysphoria (see Appendix); *and*
3. Other possible causes of apparent gender incongruence have been excluded; *and*
4. Mental and physical health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed; *and*
5. Capacity to consent for the specific physical treatment; *and*

6. Six months of continuous hormone therapy as appropriate to the member's gender goals (12 months for adolescents less than 18 years of age), unless hormone therapy is not desired or medically contraindicated.

Note on gender specific services for the transgender community: Gender-specific services may be medically necessary for transgender persons appropriate to their anatomy. Examples include:

1. Breast cancer screening may be medically necessary for transmasculine persons who have not undergone chest masculinization surgery;
2. Prostate cancer screening may be medically necessary for transfeminine persons who have retained their prostate.

Aetna considers reversal of gender affirming surgery (performing surgical procedures to return anatomy to that of the sex assigned at birth) medically necessary for persons who regret their gender-related surgical intervention, where applicable requirements for gender affirming surgery listed above are met.

Aetna considers gonadotropin-releasing hormone medically necessary to suppress puberty in trans identified adolescents if they meet World Professional Association for Transgender Health (WPATH) criteria (see CPB 0501 - Gonadotropin-Releasing Hormone Analogs and Antagonists (../500_599/0501.html)).

II. Not Medically Necessary

Aetna considers more than one breast augmentation not medically necessary. This does not include the medically necessary replacement of breast implants (see CPB 0142 - Breast Implant Removal (../100_199/0142.html)).

Aetna considers the following procedures that may be performed as a component of a gender transition as not medically necessary and cosmetic (not an all-inclusive list) (see also CPB 0031 - Cosmetic Surgery (../1_99/0031.html)):

PLAINTIFFS003988

- Hair removal (e.g., electrolysis, laser hair removal) (Exception: A limited number of electrolysis or laser hair removal sessions are considered medically necessary for skin graft preparation for genital surgery)
- Tracheal shave (reduction thyroid chondroplasty)
- Facial Gender Affirming Procedures, including:

  - Brow (reduction, augmentation, lift)
  - Hair line advancement and/or hair transplant
  - Facelift/mid-face lift (following alteration of the underlying skeletal structures) (platysmaplasty)
  - Blepharoplasty (lipofilling)
  - Rhinoplasty (+/- fillers)
  - Cheek (implant, lipofilling)
  - Lip (upper lip shortening, lip augmentation)
  - Lower jaw (reduction of mandibular angle, augmentation)
  - Chin reshaping (osteoplastic, alloplastic (implant-based))
  - Chondrolaryngoplasty (vocal cord surgery)

- Body contouring gender affirming surgery, including (not an all-inclusive list):

  - Liposuction/lipofilling/implants (pectoral, hip, gluteal, calf).

III. Related Policies

- CPB 0031 - Cosmetic Surgery (../1_99/0031.html)
- CPB 0097 - External Breast Prosthesis (../1_99/0097.html)
- CPB 0501 - Gonadotropin-Releasing Hormone Analogs and Antagonists (../500_599/0501.html)
- CPB 0646 - Voice Therapy (0646.html)

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:	
13131	Repair, complex, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; 1.1 cm to 2.5 cm
13132	Repair, complex, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; 2.6 cm to 7.5 cm
13133	Repair, complex, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; each additional 5 cm or less
13160	Secondary closure of surgical wound or dehiscence, extensive or complicated
14021	Adjacent tissue transfer or rearrangement, scalp, arms and/or legs; defect 10.1 sq cm to 30.0 sq cm
14040	Adjacent tissue transfer or rearrangement, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; defect 10 sq cm or less
14041	Adjacent tissue transfer or rearrangement, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands and/or feet; defect 10.1 sq cm to 30.0 sq cm
14301	Adjacent tissue transfer or rearrangement, any area; defect 30.1 sq cm to 60.0 sq cm
14302	Adjacent tissue transfer or rearrangement, any area; each additional 30.0 sq cm, or part thereof
15002 -15003	Surgical preparation or creation of recipient site by excision of open wounds, burn eschar, or scar (including subcutaneous tissues), or incisional release of scar contracture, trunk, arms, legs; first 100 sq cm or 1% of body area of infants and children. + each additional

Code	Code Description
15004	Surgical preparation or creation of recipient site by excision of open wounds, burn eschar, or scar (including subcutaneous tissues), or incisional release of scar contracture, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet and/or multiple digits; first 100 sq cm or 1% of body area of infants and children
15100 - 15101	Split-thickness autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children + each additional 1%
15115	Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
15120	Split-thickness autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
15240 - 15241	Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet; 20 sq cm or less. + each additional
15273 -15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children + each additional 1%
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15277 - 15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children. + each additional 1%
15574	Formation of direct or tubed pedicle, with or without transfer; forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands or feet
15734	Muscle, myocutaneous, or fasciocutaneous flap; trunk

Code	Code Description
15738	Muscle, myocutaneous, or fasciocutaneous flap; lower extremity
15740	Flap; island pedicle requiring identification and dissection of an anatomically named axial vessel
15750	Flap; neurovascular pedicle
15757	Free skin flap with microvascular anastomosis
15771	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; 50 cc or less injectate [covered for breast augmentation only]
15772	Grafting of autologous fat harvested by liposuction technique to trunk, breasts, scalp, arms, and/or legs; each additional 50 cc injectate, or part thereof (List separately in addition to code for primary procedure) [covered for breast augmentation only]
15773	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; 25 cc or less injectate
15860	Intravenous injection of agent (eg, fluorescein) to test vascular flow in flap or graft
17380	Electrolysis epilation, each 30 minutes [Check benefits]
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue [laser hair removal] [Check benefits]
19318	Reduction mammaplasty
19325	Breast augmentation with implant
19350	Nipple/areola reconstruction [only covered when not performed at time of original breast surgery]
19357	Tissue expander placement in breast reconstruction, including sub sequent expansion(s) can be authorized for gender affirmation coverage
40808	Biopsy, vestibule of mouth
40818	Excision of mucosa of vestibule of mouth as donor graft
49329	Unlisted laparoscopy procedure, abdomen, peritoneum and omentum [graft from colon for vaginoplasty]
51040	Cystostomy, cystotomy with drainage

Code	Code Description
51102	Aspiration of bladder; with insertion of suprapubic catheter
52005	Cystourethroscopy, with ureteral catheterization, with or without irrigation, instillation, or ureteropyelography, exclusive of radiologic service
53400	Urethroplasty; first stage, for fistula, diverticulum, or stricture (eg, Johannsen type)
53405	Urethroplasty; second stage (formation of urethra), including urinary diversion
53410	Urethroplasty, 1-stage reconstruction of male anterior urethra
53430	Urethroplasty, reconstruction of female urethra
53520	Closure of urethrostomy or urethrocutaneous fistula, male (separate procedure)
54120	Amputation of penis; partial
54125	Amputation of penis; complete
54235	Injection of corpora cavernosa with pharmacologic agent(s) (eg, papaverine, phentolamine)
54300	Plastic operation of penis for straightening of chordee (eg, hypospadias), with or without mobilization of urethra
54304	Plastic operation on penis for correction of chordee or for first stage hypospadias repair with or without transplantation of prepuce and/or skin flaps
54336	1-stage perineal hypospadias repair requiring extensive dissection to correct chordee and urethroplasty by use of skin graft tube and/or island flap
54400 - 54417	Penile prosthesis
54520	Orchiectomy, simple (including subcapsular), with or without testicular prosthesis, scrotal or inguinal approach
54660	Insertion of testicular prosthesis (separate procedure)
55150	Resection of scrotum
55175	Scrotoplasty; simple
55180	complicated

Code	Code Description
55970	Intersex surgery; male to female [a series of staged procedures that includes male genitalia removal, penile dissection, urethral transposition, creation of vagina and labia with stent placement]
55980	female to male [a series of staged procedures that include penis and scrotum formation by graft, and prostheses placement]
56625	Vulvectomy simple; complete
56800	Plastic repair of introitus
56805	Clitoroplasty for intersex state
56810	Perineoplasty, repair of perineum, nonobstetrical (separate procedure)
57106, 57110	Vaginectomy, partial removal of vaginal wall, or complete removal of vaginal wall
57282	Colpopexy, vaginal; extra-peritoneal approach (sacrospinous, iliococcygeus)
57291 - 57292	Construction of artificial vagina
57335	Vaginoplasty for intersex state
57425	Laparoscopy, surgical, colpopexy (suspension of vaginal apex)
58150, 58180, 58260 - 58262, 58275 - 58291, 58541 - 58544, 58550 - 58554	Hysterectomy
58570 - 58573	Laparoscopy, surgical, with total hysterectomy
58661	Laparoscopy, surgical; with removal of adnexal structures (partial or total oophorectomy and/or salpingectomy)
58720	Salpingo-oophorectomy, complete or partial, unilateral or bilateral
58999	Unlisted procedure, female genital system (nonobstetrical) [metoidioplasty]

Code	Code Description
64708	Neuroplasty, major peripheral nerve, arm or leg, open; other than specified
64856	Suture of major peripheral nerve, arm or leg, except sciatic; including transposition
64859	Suture of each additional major peripheral nerve
64874	Suture of nerve; requiring extensive mobilization, or transposition of nerve
64910	Nerve repair; with synthetic conduit or vein allograft (eg, nerve tube), each nerve
CPT codes not covered for indications listed in the CPB [considered not medically necessary and cosmetic]:	
11950 - 11954	Subcutaneous injection of filling material (e.g., collagen)
15200	Full thickness graft, free, including direct closure of donor site, trunk; 20 sq cm or less [nipple reconstruction]
15775	Punch graft for hair transplant; 1 to 15 punch grafts
15776	Punch graft for hair transplant; more than 15 punch grafts
15780 - 15787	Dermabrasion
15788 - 15793	Chemical peel
15820 - 15823	Blepharoplasty
15824 - 15828	Rhytidectomy [face-lifting]
15830 - 15839	Excision, excessive skin and subcutaneous tissue (includes lipectomy); abdomen, infraumbilical panniculectomy
15876 - 15879	Suction assisted lipectomy
17380	Electrolysis epilation, each 30 minutes
19301	Mastectomy, partial (eg, lumpectomy, tylectomy, quadrantectomy, segmentectomy)
19303	Mastectomy, simple, complete
19316	Mastopexy
19340	Immediate insertion of breast prosthesis following mastopexy, mastectomy or in reconstruction
19342	Delayed insertion of breast prosthesis following mastopexy, mastectomy or in reconstruction

Code	Code Description
20999	Unlisted procedure, musculoskeletal system, general [unlisted augmentation] [check benefits]
21087	Nasal prosthesis
21120 - 21123	Genioplasty
21125 - 21127	Augmentation, mandibular body or angle; prosthetic material or with bone graft, onlay or interpositional (includes obtaining autograft)
21193	Reconstruction of mandibular rami, horizontal, vertical, C, or L osteotomy; without bone graft
21194	with bone graft (includes obtaining graft)
21195	Reconstruction of mandibular rami and/or body, sagittal split; without internal rigid fixation
21196	with internal rigid fixation
21208	Osteoplasty, facial bones; augmentation (autograft, allograft, or prosthetic implant)
21210	Graft, bone; nasal, maxillary or malar areas (includes obtaining graft)
21270	Malar augmentation, prosthetic material
30400 - 30420	Rhinoplasty; primary
30430 - 30450	Rhinoplasty; secondary
31599	Unlisted procedure, larynx [thyroid chondroplasty and tracheal shave] [voice modification surgery] [check benefits]
31899	Unlisted procedure, trachea, bronchi [thyroid chondroplasty and tracheal shave] [augmentation thyroid chondroplasty (thyroid cartilage augmentation)] [check benefits]
40799	Unlisted procedure, lips [lip shortening] [check benefits]
67900	Repair of brow ptosis (supraciliary, mid-forehead or coronal approach)
92507	Treatment of speech, language, voice, communication, and/or auditory processing disorder; individual
92508	Treatment of speech, language, voice, communication, and/or auditory processing disorder; group, two or more individuals

Code	Code Description
Other CPT codes related to the CPB:	
11980	Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin)
+90785	Interactive complexity (List separately in addition to the code for primary procedure)
90832 - 90838	Psychotherapy
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance of drug); subcutaneous or intramuscular
HCPCS codes covered if selection criteria are met:	
C1789	Prosthesis, breast (implantable)
C1813	Prosthesis, penile, inflatable
C2622	Prosthesis, penile, non-inflatable
J1071	Injection, testosterone cypionate, 1 mg
J3121	Injection, testosterone enanthate, 1 mg
J3145	Injection, testosterone undecanoate, 1 mg
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg
J9202	Goserelin acetate implant, per 3.6 mg
J9217	Leuprolide acetate (for depot suspension), 7.5 mg
J9218	Leuprolide acetate, per 1 mg
J9219	Leuprolide acetate implant, 65 mg
L8600	Implantable breast prosthesis, silicone or equal
S0189	Testosterone pellet, 75 mg
HCPCS codes not covered for indications listed in the CPB:	
G0153	Services performed by a qualified speech-language pathologist in the home health or hospice setting, each 15 minutes
L8499	Unlisted procedure for miscellaneous prosthetic services [prosthetic implant] [check benefits]
L8699	Prosthetic implant, not otherwise specified [check benefits]
S9128	Speech therapy, in the home, per diem
ICD-10 codes covered if selection criteria are met:	
F64.0 - F64.1	Transexualism and dual role transvestism
F64.8	Other gender identity disorders

Code	Code Description
F64.9	Gender identity disorder, unspecified
Z87.890	Personal history of sex reassignment
ICD-10 codes not covered for indications listed in the CPB:	
F64.2	Gender identity disorder of childhood

Background

The International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, (DSM-5-TR) are the diagnostic classifications and criteria manuals used in the United States. Notwithstanding, the World Professional Association of Transgender Health Standard of Care 8th edition (WPATH SOC8) states: "While Gender Dysphoria (GD) is still considered a mental health condition in the Diagnostic and Statistical Manual of Mental Disorders, (DSM-5-TR) of the American Psychiatric Association. Gender incongruence is no longer seen as pathological or a mental disorder in the world health community. Gender Incongruence is recognized as a condition in the International Classification of Diseases and Related Health Problems, 11th Version of the World Health Organization (ICD-11). Because of historical and current stigma, TGD people can experience distress or dysphoria that may be addressed with various gender-affirming treatment options. While nomenclature is subject to change and new terminology and classifications may be adopted by various health organizations or administrative bodies, the medical necessity of treatment and care is clearly recognized for the many people who experience dissonance between their sex assigned at birth and their gender identity."

Gender dysphoria refers to discomfort or distress that is caused by a discrepancy between an individual's gender identity and the gender assigned at birth (and the associated gender role and/or primary and secondary sex characteristics). A diagnosis of gender dysphoria requires a marked difference between the individual's expressed/experienced

gender and the gender others would assign him or her, and it must continue for at least six months. This condition may cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

Gender affirming surgery is performed to change primary and/or secondary sex characteristics. For transfeminine (assigned male at birth) gender transition, surgical procedures may include genital reconstruction (vaginoplasty, penectomy, orchidectomy, clitoroplasty), breast augmentation (implants, lipofilling), and cosmetic surgery (facial reshaping, rhinoplasty, abdominoplasty, thyroid chondroplasty (laryngeal shaving), voice modification surgery (vocal cord shortening), hair transplants) (Day, 2002). For transmasculine (assigned female at birth) gender transition, surgical procedures may include mastectomy, genital reconstruction (phalloplasty, genitoplasty, hysterectomy, bilateral oophorectomy), mastectomy, and cosmetic procedures to enhance male features such as pectoral implants and chest wall recontouring (Day, 2002).

The criterion noted above for some types of genital surgeries is based on expert clinical consensus that this experience provides ample opportunity for patients to experience and socially adjust in their desired gender role, before undergoing irreversible surgery (Coleman, et al., 2022).

It is recommended that transfeminine persons undergo feminizing hormone therapy (minimum 6 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

In addition to hormone therapy and gender affirming surgery, psychological adjustments are necessary in affirming sex. Treatment should focus on psychological adjustment, with hormone therapy and gender affirming surgery being viewed as confirmatory procedures dependent on adequate psychological adjustment. Mental health care may need to be continued after gender affirming surgery. The overall success of treatment depends partly on the technical success of the surgery, but more crucially on the psychological adjustment of the trans identified person and the support from family, friends, employers and the medical profession.

Nakatsuka (2012) noted that the third versions of the guideline for treatment of people with gender dysphoria (GD) of the Japanese Society of Psychiatry and Neurology recommends that feminizing/masculinizing hormone therapy and genital surgery should not be carried out until 18 years old and 20 years old, respectively. On the other hand, the sixth (2001) and the seventh (2011) versions of the standards of care for the health of transsexual, transgender, and gender non-conforming people of World Professional Association for Transgender Health (WPATH) recommend that transgender adolescents (Tanner stage 2, [mainly 12 to 13 years of age]) are treated by the endocrinologists to suppress puberty with gonadotropin-releasing hormone (GnRH) agonists until age 16 years old, after which gender-affirming hormones may be given. A questionnaire on 181 people with GID diagnosed in the Okayama University Hospital (Japan) showed that female to male (FTM) trans identified individuals hoped to begin masculinizing hormone therapy at age of 15.6 +/- 4.0 (mean +/- S.D.) whereas male to female (MTF) trans identified individuals hoped to begin feminizing hormone therapy as early as age 12.5 +/- 4.0, before presenting secondary sex characters. After confirmation of strong and persistent trans gender identification, adolescents with GD should be treated with gender-affirming hormone or puberty-delaying hormone to prevent developing undesired sex characters. These treatments may prevent transgender adolescents from attempting suicide, suffering from depression, and refusing to attend school.

Spack (2013) stated that GD is poorly understood from both mechanistic and clinical standpoints. Awareness of the condition appears to be increasing, probably because of greater societal acceptance and available hormonal treatment. Therapeutic options include hormone and surgical treatments but may be limited by insurance coverage because costs are high. For patients seeking MTF affirmation, hormone treatment includes estrogens, finasteride, spironolactone, and GnRH analogs. Surgical options include feminizing genital and facial surgery, breast augmentation, and various fat transplantations. For patients seeking a FTM gender affirmation, medical therapy includes testosterone and GnRH analogs and surgical therapy includes mammoplasty and phalloplasty. Medical therapy for both FTM and MTF can be started in early puberty, although long-term effects are not known. All patients considering treatment need counseling and medical monitoring.

Leinung and colleagues (2013) noted that the Endocrine Society's recently published clinical practice guidelines for the treatment of transgender persons acknowledged the need for further information on transgender health. These investigators reported the experience of one provider with the endocrine treatment of transgender persons over the past 2 decades. Data on demographics, clinical response to treatment, and psychosocial status were collected on all transgender persons receiving gender-affirming hormone therapy since 1991 at the endocrinology clinic at Albany Medical Center, a tertiary care referral center serving upstate New York. Through 2009, a total 192 MTF and 50 FTM transgender persons were seen. These patients had a high prevalence of mental health and psychiatric problems (over 50 %), with low rates of employment and high levels of disability. Mental health and psychiatric problems were inversely correlated with age at presentation. The prevalence of gender affirming surgery was low (31 % for MTF). The number of persons seeking treatment has increased substantially in recent years. Gender-affirming hormone therapy achieves very good results in FTM persons and is most successful in MTF persons when initiated at younger ages. The authors concluded that transgender persons seeking hormonal therapy are being seen with increasing frequency. The dysphoria present in many transgender persons is associated with significant mood disorders that interfere with successful careers. They stated that starting therapy at an earlier age may lessen the negative impact on mental health and lead to improved social outcomes.

Meyer-Bahlburg (2013) summarized for the practicing endocrinologist the current literature on the psychobiology of the development of gender identity and its variants in individuals with disorders of sex development or with transgenderism. Gender reassignment remains the treatment of choice for strong and persistent gender dysphoria in both categories, but more research is needed on the short-term and long-term effects of puberty-suppressing medications and cross-sex hormones on brain and behavior.

Note on Breast Reduction/Mastectomy and Nipple Reconstruction

The CPT codes for mastectomy (CPT codes 19303) are for breast cancer, and are not appropriate to bill for reduction mammaplasty for female to male (transmasculine) gender affirmation surgery. CPT 2020 states that “Mastectomy procedures (with the exception of gynecomastia [19300]) are performed either for treatment or prevention of breast cancer.” CPT 2020 also states that "Code 19303 describes total removal of ipsilateral breast tissue with or without removal of skin and/or nipples (eg, nipple-sparing), for treatment or prevention of breast cancer.” There are important differences between a mastectomy for breast cancer and a mastectomy for gender reassignment. The former requires careful attention to removal of all breast tissue to reduce the risk of cancer. By contrast, careful removal of all breast tissue is not essential in mastectomy for gender reassignment. In mastectomy for gender reassignment, the nipple areola complex typically can be preserved.

Some have tried to justify routinely billing CPT code 19350 for nipple reconstruction at the time of mastectomy for gender reassignment based upon the frequent need to reduce the size of the areola to give it a male appearance. However, the nipple reconstruction as defined by CPT code 19350 describes a much more involved procedure than areola reduction. The typical patient vignette for CPT code 19350, according to the AMA, is as follows: “The patient is measured in the standing position to ensure even balanced position for a location of the nipple and areola graft on the right breast. Under local anesthesia, a Skate flap is elevated at the site selected for the nipple reconstruction and constructed. A full-thickness skin graft is taken from the right groin to reconstruct the areola. The right groin donor site is closed primarily in layers.”

The AMA vignette for CPT code 19318 (reduction mammaplasty) clarifies that this CPT code includes the work that is necessary to reposition and reshape the nipple to create an aesthetically pleasing result, as is necessary in female to male breast reduction. "The physician reduces the size of the breast, removing wedges of skin and breast tissue from a female patient. The physician makes a circular skin incision above the nipple, in the position to which the nipple will be elevated. Another skin incision is made around the circumference of the nipple. Two incisions are

made from the circular cut above the nipple to the fold beneath the breast, one on either side of the nipple, creating a keyhole shaped skin and breast incision. Wedges of skin and breast tissue are removed until the desired size is achieved. Bleeding vessels may be ligated or cauterized. The physician elevates the nipple and its pedicle of subcutaneous tissue to its new position and sutures the nipple pedicle with layered closure. The remaining incision is repaired with layered closure" (EncoderPro, 2019). CPT code 19350 does not describe the work that that is being done, because that code describes the actual construction of a new nipple. Code 19350 is a CCI "incidental to" edit to code 19318, and, accordingly, the services of code 19350 are included in code 19318. Similarly, graft codes, such as code 15200 (full thickness skin graft), are CCI "incidental to" edits to code 19318, and, accordingly, the services of graft codes, such as 15200, are included in code 19318.

Vulvoplasty Versus Vaginoplasty as Gender-Affirming Genital Surgery for Transgender Women

Jiang and colleagues (2018) noted that gender-affirming vaginoplasty aims to create the external female genitalia (vulva) as well as the internal vaginal canal; however, not all patients desire nor can safely undergo vaginal canal creation. These investigators described the factors influencing patient choice or surgeon recommendation of vulvoplasty (creation of the external appearance of female genitalia without creation of a neovaginal canal) and evaluated the patient's satisfaction with this choice. Gender-affirming genital surgery consults were reviewed from March 2015 until December 2017, and patients scheduled for or who had completed vulvoplasty were interviewed by telephone. These investigators reported demographic data and the reasons for choosing vulvoplasty as gender-affirming surgery for patients who either completed or were scheduled for surgery, in addition to patient reports of satisfaction with choice of surgery, satisfaction with the surgery itself, and sexual activity after surgery. A total of 486 patients were seen in consultation for trans-feminine gender-affirming genital surgery: 396 requested vaginoplasty and 39 patients requested vulvoplasty; 30 Patients either completed or are scheduled for vulvoplasty. Vulvoplasty patients were older and had higher body mass index (BMI) than those seeking vaginoplasty. The majority (63 %) of the patients seeking vulvoplasty chose this surgery despite no contraindications to vaginoplasty. The

remaining patients had risk factors leading the surgeon to recommend vulvoplasty. Of those who completed surgery, 93 % were satisfied with the surgery and their decision for vulvoplasty. The authors concluded that this was the first study of factors impacting a patient's choice of or a surgeon's recommendation for vulvoplasty over vaginoplasty as gender-affirming genital surgery; it also was the first reported series of patients undergoing vulvoplasty only.

Drawbacks of this study included its retrospective nature, non-validated questions, short-term follow-up, and selection bias in how vulvoplasty was offered. Vulvoplasty is a form of gender-affirming feminizing surgery that does not involve creation of a neovagina, and it is associated with high satisfaction and low decision regret.

Autologous Fibroblast-Seeded Amnion for Reconstruction of Neo-vagina in Transfeminine Reassignment Surgery

Seyed-Forootan and colleagues (2018) stated that plastic surgeons have used several methods for the construction of neo-vaginas, including the utilization of penile skin, free skin grafts, small bowel or recto-sigmoid grafts, an amnion graft, and cultured cells. These researchers compared the results of amnion grafts with amnion seeded with autograft fibroblasts. Over 8 years, these investigators compared the results of 24 male-to-female transsexual patients retrospectively based on their complications and levels of satisfaction; 16 patients in group A received amnion grafts with fibroblasts, and the patients in group B received only amnion grafts without any additional cellular lining. The depths, sizes, secretions, and sensations of the vaginas were evaluated. The patients were monitored for any complications, including over-secretion, stenosis, stricture, fistula formation, infection, and bleeding. The mean age of group A was 28 ± 4 years and group B was 32 ± 3 years. Patients were followed-up from 30 months to 8 years (mean of 36 ± 4) after surgery. The depth of the vaginas for group A was 14 to 16 and 13 to 16 cm for group B. There was no stenosis in neither group. The diameter of the vaginal opening was 34 to 38 mm in group A and 33 to 38 cm in group B. These researchers only had 2 cases of stricture in the neo-vagina in group B, but no stricture was recorded for group A. All of the patients had good and acceptable sensation in the neo-vagina; 75 % of patients had sexual experience and of those, 93.7 % in group A and 87.5% in group B

expressed satisfaction. The authors concluded that the creation of a neo-vaginal canal and its lining with allograft amnion and seeded autologous fibroblasts is an effective method for imitating a normal vagina. The size of neo-vagina, secretion, sensation, and orgasm was good and proper. More than 93.7 % of patients had satisfaction with sexual intercourse. They stated that amnion seeded with fibroblasts extracted from the patient's own cells will result in a vagina with the proper size and moisture that can eliminate the need for long-term dilatation. The constructed vagina has a 2-layer structure and is much more resistant to trauma and laceration. No cases of stenosis or stricture were recorded. Level of Evidence = IV. These preliminary findings need to be validated by well-designed studies.

Pitch-Raising Surgery in Transfeminine Persons

Van Damme and colleagues (2017) reviewed the evidence of the effectiveness of pitch-raising surgery performed in male-to-female transsexuals. These investigators carried out a search for studies in PubMed, Web of Science, Science Direct, EBSCOhost, Google Scholar, and the references in retrieved manuscripts, using as keywords "transsexual" or "transgender" combined with terms related to voice surgery. They included 8 studies using cricothyroid approximation, 6 studies using anterior glottal web formation, and 6 studies using other surgery types or a combination of surgical techniques, leading to 20 studies in total. Objectively, a substantial rise in post-operative fundamental frequency was identified. Perceptually, mainly laryngeal web formation appeared risky for decreasing voice quality. The majority of patients appeared satisfied with the outcome. However, none of the studies used a control group and randomization process. The authors concluded that future research needs to investigate long-term effects of pitch-raising surgery using a stronger study design.

Azul and associates (2017) evaluated the currently available discursive and empirical data relating to those aspects of trans-masculine people's vocal situations that are not primarily gender-related, and identified restrictions to voice function that have been observed in this population, and made suggestions for future voice research and clinical practice. These researchers conducted a comprehensive review of the voice literature. Publications were identified by searching 6 electronic

databases and bibliographies of relevant articles. A total of 22 publications met inclusion criteria. Discourses and empirical data were analyzed for factors and practices that impact on voice function and for indications of voice function-related problems in trans-masculine people. The quality of the evidence was appraised. The extent and quality of studies investigating trans-masculine people's voice function was found to be limited. There was mixed evidence to suggest that trans-masculine people might experience restrictions to a range of domains of voice function, including vocal power, vocal control/stability, glottal function, pitch range/variability, vocal endurance, and voice quality. The authors concluded that more research into the different factors and practices affecting trans-masculine people's voice function that took account of a range of parameters of voice function and considered participants' self-evaluations is needed to establish how functional voice production can be best supported in this population.

Facial Feminization Surgery

Raffaini and colleagues (2016) stated that gender dysphoria refers to the discomfort and distress that arise from a discrepancy between a person's gender identity and sex assigned at birth. The treatment plan for gender dysphoria varies and can include psychotherapy, hormone treatment, and gender affirmation surgery, which is, in part, an irreversible change of sexual identity. Procedures for transformation to the female sex include facial feminization surgery, vaginoplasty, clitoroplasty, and breast augmentation. Facial feminization surgery can include forehead re-modeling, rhinoplasty, mentoplasty, thyroid chondroplasty, and voice alteration procedures. These investigators reported patient satisfaction following facial feminization surgery, including outcome measurements after forehead slippage and chin re-modeling. A total of 33 patients between 19 and 40 years of age were referred for facial feminization surgery between January of 2003 and December of 2013, for a total of 180 procedures. Surgical outcome was analyzed both subjectively through questionnaires administered to patients and objectively by serial photographs. Most facial feminization surgery procedures could be safely completed in 6 months, barring complications. All patients showed excellent cosmetic results and were satisfied with their procedures. Both frontal and profile views achieved a loss of masculine features. The authors concluded that patient satisfaction following facial feminization

surgery was high; they stated that the reduction of gender dysphoria had psychological and social benefits and significantly affected patient outcome. The level of evidence of this study was IV.

Morrison and associates (2018) noted that facial feminization surgery encompasses a broad range of cranio-maxillofacial surgical procedures designed to change masculine facial features into feminine features. The surgical principles of facial feminization surgery could be applied to male-to-female transsexuals and anyone desiring feminization of the face. Although the prevalence of these procedures is difficult to quantify, because of the rising prevalence of transgenderism (approximately 1 in 14,000 men) along with improved insurance coverage for gender-confirming surgery, surgeons versed in techniques, outcomes, and challenges of facial feminization surgery are needed. These researchers appraised the current facial feminization surgery literature. They carried out a comprehensive literature search of the Medline, PubMed, and Embase databases was conducted for studies published through October 2014 with multiple search terms related to facial feminization. Data on techniques, outcomes, complications, and patient satisfaction were collected. A total of 15 articles were selected and reviewed from the 24 identified, all of which were either retrospective or case series/reports. Articles covered a variety of facial feminization procedures. A total of 1,121 patients underwent facial feminization surgery, with 7 complications reported, although many articles did not explicitly comment on complications. Satisfaction was high, although most studies did not use validated or quantified approaches to address satisfaction. The authors concluded that facial feminization surgery appeared to be safe and satisfactory for patients. These researchers stated that further studies are needed to better compare different techniques to more robustly establish best practices; prospective studies and patient-reported outcomes are needed to establish quality-of-life (QOL) outcomes for patients.

In a systematic review, Gorbea et al (2021) provided a portrait of gender affirmation surgery (GAS) insurance coverage across the U.S., with attention to procedures of the head and neck. State policies on transgender care for Medicaid insurance providers were collected for all 50 states. Each state's policy on GAS and facial gender affirmation surgery (FGAS) was examined. The largest medical insurance

companies in the U.S. were identified using the National Association of Insurance Commissioners Market Share report. Policies of the top 49 primary commercial medical insurance companies were examined. Medicaid policy reviews found that 18 states offer some level of gender-affirming coverage for their patients, but only 3 include FGAS (17 %); 13 states prohibit Medicaid coverage of all transgender surgery, and 19 states have no published gender-affirming medical care coverage policy; 92 % of commercial medical insurance providers had a published policy on GAS coverage. Genital reconstruction was described as a medically necessary aspect of transgender care in 100 % of the commercial policies reviewed; 93 % discussed coverage of FGAS, but 51 % considered these procedures cosmetic. Thyroid chondroplasty (20 %) was the most commonly covered FGAS procedure. Mandibular and frontal bone contouring, rhinoplasty, blepharoplasty, and facial rhytidectomy were each covered by 13 % of the medical policies reviewed. The authors concluded that while certain surgical aspects of gender-affirming medical care are nearly ubiquitously covered by commercial insurance providers, FGAS is considered cosmetic by most Medicaid and commercial insurance providers. Level of Evidence = V.

Hohman and Teixeira (2022) stated that with respect to gender affirmation procedures for the face, the majority of interventions will occur in patients transitioning from male to female, i.e., transgender women. While there are slightly more transgender women than transgender men in the population (33 % transgender women, 29 % transgender men, 35 % non-binary, 3 % cross-dressers, according to the USTS), the reason that more females require surgery than males is that testosterone therapy typically produces enough changes in secondary sex characteristics of the face (growth of facial hair, thickening of the skin, increase in frontal bossing, lowering of the voice, etc.) that surgery is not necessary . In some cases, placement of implants or fat transfer can increase volume in the lower 1/3 of the face and contribute to masculinization. Still, the primary area of focus for facial feminization is generally the upper 1/3. Feminization of the upper 1/3 of the face often requires several techniques to be applied in combination: The advancement of the hairline, hair transplantation, brow-lifting, and reduction of frontal bossing or "frontal cranioplasty". While the advancement of a scalp flap, hair transplant, and pretrichial brow-lifting are commonly employed cosmetic surgery interventions, frontal cranioplasty bears special consideration. Several methods of

reducing the brow's prominence are often described as type 1, 2, and 3 frontal cranioplasties. Type 1 cranioplasty reduces the supra-orbital ridge's protrusion, usually using a drill, including decreasing the thickness of the anterior table of the frontal sinus. This technique is the simplest, but it is only effective in patients with either a very thick anterior frontal sinus table or an absent pneumatized frontal sinus. Type 2 cranioplasty involves augmentation of the forehead's convexity using bone cement or methyl methacrylate in addition to a reduction of the supra-orbital ridge with a drill. Type 3 cranioplasty is advocated by many prominent facial feminization surgeons and consists of removal of the anterior table of the frontal sinus, thinning of the bone flap, and replacement of that bone onto the frontal sinus but in a more recessed position, in addition to a reduction of the remainder of the supra-orbital ridge. An alternative to removal and recession of the frontal sinus's anterior table is to thin the bone with a drill and then fracture it in a controlled fashion to produce the desired contour, which is also performed routinely by some authors.

Forehead Feminization Cranioplasty

Eggerstedt and colleagues (2020) stated that forehead feminization cranioplasty (FFC) is an important component of gender-affirming surgery and has become increasingly popular in recent years. However, there is little objective evidence for the procedure's safety and clinical impact via patient-reported outcome measures (PROMs). In a systematic review, these researchers determined what complications are observed following FFC, the relative frequency of complications by surgical technique, and what impact the procedure has on patient's QOL. They carried out database searches in PubMed/Medline, Scopus, CINAHL, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, and PsycINFO. The search terms included variations of forehead setback/FFC. Both controlled vocabularies (i.e., MeSH and CINAHL's Suggested Subject Terms) and keywords in the title or abstract fields were searched. Two independent reviewers screened the titles and abstracts of all articles; and 2 independent surgeon reviewers examined the full text of all included articles, and relevant data points were extracted. Main outcomes and measures included complications and complication rate observed following FFC. Additional outcome measures were the approach used, concurrent procedures carried out, and the use and findings of a PROM. A total of 10 articles describing FFC were included,

entailing 673 patients. The overall pooled complication rate was 1.3 %; PROMs were used in 50 % of studies, with no standardization among studies. The authors concluded that complications following FFC were rare and infrequently required reoperation. Moreover, these researchers stated that further studies into standardized and validated PROMs in facial feminization patients are needed. Level of Evidence = III.

Hand Feminization and Masculinization

Lee and colleagues (2021) noted that anatomical characteristics that are incongruent with an individual's gender identity can cause significant gender dysphoria. Hands exhibit prominent dimorphic sexual features, but despite their visibility, there are limited studies examining gender affirming procedures for the hands. These researchers examined the anatomical features that define feminine and masculine hands, the surgical and non-surgical approaches for feminization and masculinization of the hand; and adapted established aesthetic hand techniques for gender affirming care. They carried out a comprehensive database search of PubMed, Embase OVID and SCOPUS to identify articles on the characterization of feminine or masculine hands, hand treatments related to gender affirmation, and articles related to techniques for hand feminization and masculinization in the non-transgender population. From 656 possibly relevant articles, 42 met the inclusion criteria for the current literature search. There is currently no medical literature specifically examining the surgical or non-surgical options for hand gender affirmation. The available techniques for gender affirming procedures discussed in this paper were appropriated from those more commonly used for hand rejuvenation. The authors concluded that there is very little evidence addressing the options for transgender individuals seeking gender affirming procedures of the hand. These researchers stated that although established procedures used for hand rejuvenation may be employed in gender affirming care, further study is needed to determine relative salience of various hand features to gender dysphoria in transgender patients of various identities, as well as development of novel techniques to meet these needs. Level of Evidence = III.

Peritoneal Pull-Through Technique Vaginoplasty in Neovagina Construction in Gender-Affirming Surgery

Tay and Lo (2022) reviewed the application, effectiveness and outcomes of a novel surgical technique, peritoneal pull-through technique vaginoplasty, in gender-affirming surgery. Specific outcome parameters included healing time, depth of cavity achieved,) alleviation of dysphoria, and morbidity of the surgery. These researchers carried out a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and PROSPERO registration obtained before commencement. A search was performed in OVID Medline, Embase, Willey Online Library and PubMed. Specialty-related journals, grey literature and reference lists of relevant articles were manually searched. From 476 potentially relevant articles, 12 articles were analyzed; and the publications were all level 4 or level 5 evidence. Healing times were poorly reported or often not mentioned. A total of 8 authors reported neovagina cavity depth of at least 13 cm and good patient satisfaction. Alleviation of dysphoria was not discussed by any of the publications and only 6reported complications. Average follow-up ranged from 6 weeks to 14.8 months. The authors concluded that the use of peritoneal pull-through vaginoplasty in gender-affirming surgery is promising and novel; however, there is a paucity of data. These investigators stated that further research and longer-term data are needed to examine the safety and effectiveness of this technique including stabilization of vaginal depth, later morbidity and complications. Patients seeking this surgery overseas should be informed of the potential difficulties they may face.

Urethral Complications and Outcomes in Transgender Men

Hu et al (2022) noted that urologic problems, such as urethral fistulas and strictures, are among the most frequent complications following phalloplasty. Although many studies have reported successful phalloplasty and urethral reconstruction with reliable outcomes in transgender men; so far, no method has become standardized. These researchers examined the reports on urological complications and outcomes in transgender men with respect to various types of urethral reconstruction. They carried out a comprehensive literature search of PubMed, Scopus, and Google Scholar databases for studies related to

phalloplasty in transsexuals. Data on various phallic urethral techniques, urethral complications, and outcomes were collected and analyzed using the random-effects model. A total of 21 studies (1,566 patients) were included: 8 studies (1,061 patients) on "tube-in-tube", 9 studies (273 patients) on "prelaminated flap, and 6 studies (221 patients) on "second flap". Compared with the tube-in-tube technique, the pre-laminated flap was associated with a significantly higher urethral stricture/stenosis rate; however, there was no difference between the pre-laminated flap and the 2nd flap techniques. For all phalloplasty patients, the pooled rate of urethral fistula or stenosis was 48.9 %, the rate of the ability to void while standing was 91.5 %, occurrence rate of tactile or erogenous sensation was 88 %, the prosthesis complication rate was 27.9 %, and patient-reported satisfactory outcome rate was 90.5 %. The authors concluded that urethral reconstruction with a pre-laminated flap was associated with a significantly higher urethral stricture rate and increased need of revision surgery compared with that observed using a skin flap. Overall, most patients were able to void while standing and were satisfied with the outcomes.

Appendix

DSM 5 Criteria for Gender Dysphoria in Adults and Adolescents

I. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by two or more of the following:

A. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or, in young adolescents, the anticipated secondary sex characteristics)

B. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or, in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)

C. A strong desire for the primary and/or secondary sex characteristics of the other gender
D. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender)
E. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender)
F. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

II. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

There is no minimum duration of relationship required with mental health professional. It is the professional's judgment as to the appropriate length of time before a referral letter can appropriately be written. A common period of time is three months, but there is significant variation in both directions.

Evaluation of candidacy for gender affirmation surgery by a mental health professional is covered under the member's medical benefit, unless the services of a mental health professional are necessary to evaluate and treat a mental health problem, in which case the mental health professional's services are covered under the member's behavioral health benefit. Please check benefit plan descriptions.

Characteristics of a Qualified Health Professionals (From SOC-8)

Qualifications of Mental Health Professional for assessing transgender and gender diverse adults for physical treatments (from WPATH SOC-8):

1. Are licensed by their statutory body and hold, at a minimum, a master's degree or equivalent training in a clinical field relevant to this role and granted by a nationally accredited statutory institution.
2. Are able to identify co-existing mental health or other psychosocial concerns and distinguish these from gender dysphoria, incongruence, and diversity.
3. Are able to assess capacity to consent for treatment.

4. Have experience or be qualified to assess clinical aspects of gender dysphoria, incongruence, and diversity.
5. Undergo continuing education in health care relating to gender dysphoria, incongruence, and diversity.
6. Liaise with professionals from different disciplines within the field of transgender health for consultation and referral on behalf of gender diverse adults seeking gender-affirming treatment, if required.

Credentials of surgeons who perform gender-affirming surgical procedures (fromWPATH SOC-8):

1. Training and documented supervision in gender-affirming procedures;
2. Maintenance of an active practice in gender-affirming surgical procedures;
3. Knowledge about gender diverse identities and expressions;
4. Continuing education in the field of gender-affirmation surgery;
5. Tracking of surgical outcomes.

Characteristics of health care professionals working with gender diverse adolescents:

1. Are licensed by their statutory body and hold a postgraduate degree or its equivalent in a clinical field relevant to this role granted by a nationally accredited statutory institution.
2. Receive theoretical and evidenced-based training and develop expertise in general child, adolescent, and family mental health across the developmental spectrum.
3. Receive training and have expertise in gender identity development, gender diversity in children and adolescents, have the ability to assess capacity to assent/consent, and possess general knowledge of gender diversity across the life span.
4. Receive training and develop expertise in autism spectrum disorders and other neurodevelopmental presentations or collaborate with a developmental disability expert when working with autistic/neurodivergent gender diverse adolescents.
5. Continue engaging in professional development in all areas relevant to gender diverse children, adolescents, and families.

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