Gonadotropin-Releasing Hormone Analogs and Antagonists AHM

Clinical Indications

- **Leuprolide** (Lupron, Viadur, Eligard) is considered medically necessary for **1 or more** of the following indications subject to the specified limitations:
    - Endometriosis (including adenomyosis, also known as endometriosis interna). Recommended duration of treatment with Lupron Depot 3.75 mg or Lupron Depot - 3 month 11.25 mg alone or in combination with norethindrone acetate -six months. If symptoms of endometriosis recur after the first course of therapy, a second treatment with a six-month course of Lupron Depot and norethindrone acetate 5 mg daily may be considered. Leuprolide Depot alone is not recommended for retreatment. Further treatment beyond two treatments (total of 12 months) is considered unproven. Up to 6 months per treatment -- because of lack of safety data with long-term use, and concerns in available peer-reviewed medical literature regarding effects on bone density. Lupron dosages greater than 3.75 mg per month or 11.25 mg per 3 months are subject to medical necessity review.
    - For the prevention of heavy uterine bleeding in pre-menopausal women during chemotherapy.
    - For the treatment of dysmenorrhea that is refractory to oral contraceptives.
    - For the treatment of members with prostate cancer -1 mg given subcutaneously daily. If receiving leuprolide acetate suspension (Lupron Depot), dosing is: Lupron Depot 7.5 mg for 1-month administration, given as a single intramuscular injection every 4 weeks. Lupron Depot 22.5 mg for 3-month administration, given as a single intramuscular injection every 12 weeks. Lupron Depot 30 mg for 4-month administration, given as a single intramuscular injection every 16 weeks. Lupron Depot 45 mg for 6-month administration, given as a single intramuscular injection every 24 weeks.
    - For the treatment of women with chronic refractory pelvic pain where attempts at medical therapy with analgesics and oral contraceptive have been unsuccessful.

- For the treatment of women with dysfunctional uterine bleeding when other pharmacotherapies (e.g., non-steroidal anti-inflammatory drugs and estrogen-progestin contraceptives) have failed.
- For the treatment of men and pre-menopausal women with hormone-receptor positive breast cancer. Recommended dose is 3.75 mg IM depot once monthly or 11.25 mg IM depot every three months although optimal dosing has not yet been clearly defined.
- For the treatment of relapsed granulosa cell tumors of the ovary for clinical relapse following initial treatment in persons with stage II to IV granulosa cell tumors
- For the treatment of recurrent epithelial ovarian cancer, primary peritoneal cancer, and fallopian tube cancer
- For the treatment-resistant paraphilias for individuals who have failed pharmacotherapies including medroxyprogesterone acetate (MPA) and/or selective serotonin reuptake inhibitors (SSRIs).
- For true (central) precocious puberty, which is defined as sexual maturation before age 8 in girls and age 10 in boys and diagnosis is confirmed with a bone age advanced one year or more beyond chronologic age and pubertal response to a GnRH stimulation test; and Intracranial tumor has been ruled out by CT, MRI, or ultrasound; and Baseline laboratory investigations have been performed, including: a) height and weight; b) sex steroid levels; c) adrenal steroid level to exclude congenital adrenal hyperplasia; d) beta human chorionic gonadotropin to rule out chorionic gonadotropin-secreting tumor; and e) pelvic/adrenal/testicular ultrasound to rule out a steroid-secreting tumor.
- Infertility (used in conjunction with urofollitropin or menotropins) to suppress luteinizing hormone (LH) production in members with documented premature LH surge, or used in "super-ovulation" regimens associated with in vitro fertilization
- Preservation (suppression) of ovarian function in premenopausal women with ER-negative breast cancer receiving chemotherapy
- To decrease endometrial thickness prior to endometrial ablation or surgery (recommended treatment is up to 2 months. Lupron dosages greater than 3.75 mg per month or 11.25 mg per 3 months are subject to medical necessity review.)
- To decrease fibroid size and reduce anemia prior to fibroid surgery (Recommended dose of Lupron Depot 3.75 mg is monthly. The recommended duration of therapy with Lupron Depot 3.75 mg is up to 3 months. The recommended dose of Lupron Depot -3 Month 11.25 mg is one injection. The symptoms associated with fibroids will recur following discontinuation of therapy. Under accepted guidelines, leuprolide does not prevent or replace the eventual need for surgery except in peri-menopausal women. Lupron dosages greater than 3.75 mg per month or 11.25 mg per 3 months are subject to medical necessity review. If additional treatment with Lupron Depot 3.75 mg or Lupron Depot - 3 months 11.25 mg is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.
- To suppress onset of puberty in cases where the adolescent meets medical necessity criteria for growth hormone supplementation and has early onset of puberty and is not within target growth range (within 1 standard deviation of mean height for age and sex)
- To suppress onset of puberty in transgender adolescents if they meet WPATH criteria
- For female to male transgender persons, to stop menses prior to testosterone treatment and to reduce estrogens to levels found in biological males.
- To reduce testosterone levels in male to female transgender persons.
- To treat severe refractory premenstrual syndrome for women who do not respond to or are unable to tolerate SSRIs and oral contraceptives

- **Leuprolide** is considered experimental and investigational for all other indications, including any of the following conditions, because limited information has been published and further research including randomized, controlled trials is required to determine its efficacy:
  - ACTH-dependent Cushing syndrome

- Alzheimer's disease
- Amenorrhea induction prior to bone marrow transplant
- Autoimmune progesterone dermatitis of pregnancy
- Benign prostatic hyperplasia
- Catamenial pneumothorax
- Endometrial cancer (including endometrial stromal sarcoma)
- Epilepsy
- Hyperandrogenism
- Irritable bowel syndrome
- Juvenile idiopathic arthritis
- Menorrhagia (metromenorrhagia, metrorrhagia, menometrorrhagia)
- Menstrual migraines
- Myeloma
- Osteosarcoma
- Parotid gland cancer
- Polycystic ovarian disease
- Poryhyria cutanea tarda
- Precocious pubarche alone, or pseudoprecocious puberty (gonadotropin independent precocious puberty)
- Premature ovarian failure
- Preservation (suppression) of ovarian function during chemotherapy
- Preservation (suppression) of testicular function during chemotherapy
- Salivary gland cancer
- Sickle cell anemia-associated priapism
- Stuttering
- Testicular cancer
- Uterine cancer

- **Goserelin** (Zoladex) is considered medically necessary for **1 or more** of the following indications:
  - Hormone-receptor positive breast cancer in men and pre-menopausal women
  - Prostatic carcinoma
  - Endometrial thinning prior to endometrial ablation or hysterectomy (preoperative adjunct) (short-term (less than 6 months) use) See Endometrial Ablation CPB
  - Endometriosis (including adenomyosis, also known as endometriosis interna). Recommended duration of treatment with Lupron Depot 3.75 mg or Lupron Depot - 3 month 11.25 mg alone or in combination with norethindrone acetate -six months. If symptoms of endometriosis recur after the first course of therapy, a second treatment with a six-month course of Lupron Depot and norethindrone acetate 5 mg daily may be considered. Leuprolide Depot alone is not recommended for retreatment. [A] If norethindrone acetate is contraindicated, then retreatment is not recommended. Bone density is recommended before retreatment begins to ensure that values are within normal limits. Further treatment beyond two treatments (total of 12 months) is considered unproven. Lupron dosages greater than 3.75 mg per month or 11.25 mg per 3 months are subject to medical necessity review.
  - Dysfunctional uterine bleeding when other pharmacotherapies (e.g., non-steroidal anti-inflammatory drugs and estrogen-progestin contraceptives) have failed
  - For true (central) precocious puberty, which is defined as sexual maturation before age 8 in girls and age 10 in boys and diagnosis is confirmed with a bone age advanced one year or more beyond chronologic age and pubertal response to a GnRH stimulation test; and Intracranial tumor has been ruled out by CT, MRI, or ultrasound; and Baseline laboratory investigations have been performed, including: a) height and weight; b) sex steroid levels; c) adrenal steroid level to exclude congenital adrenal hyperplasia; d) beta

human chorionic gonadotropin to rule out chorionic gonadotropin-secreting tumor; and e) pelvic/adrenal/testicular ultrasound to rule out a steroid-secreting tumor.
    - For female to male transgender persons, to stop menses prior to testosterone treatment and to reduce estrogens to levels found in biological males
    - To reduce testosterone levels in male to female transgender persons
    - Preservation (suppression) of ovarian function in premenopausal women with ER-negative breast cancer receiving chemotherapy
    - Uterine fibroids (leiomyoma uteri) (preoperative adjunct to surgical treatment) (short-term (less than 6 months) use).
- **Goserelin** is considered experimental and investigational for all other indications because its effectiveness for these indications has not been established. For use of goserelin in infertility, see the Infertility Guideline
    - Preservation of testicular function during chemotherapy
    - Chronic pelvic pain
    - Invasive ductal breast cancer
    - Pancreatic cancer
    - Premature ovarian failure secondary to chemotherapy
- **Histrelin** is considered medically necessary for **1 or more** of the following indications:
    - Vantas histrelin acetate subcutaneous implant is considered medically necessary for treatment of members with prostate cancer
    - Supprelin LA histrelin acetate subcutaneous implant is considered medically necessary for true (central) precocious puberty, which is defined as sexual maturation before age 8 in girls and age 10 in boys and tumor has been ruled out by lab tests, CT, MRI, or ultrasound
- **Histrelin acetate** implants is considered experimental and investigational for all other indications (e.g., precocious puberty due to adrenal hyperplasia) because there is insufficient evidence in the peer-reviewed literature
- **Triptorelin** (Trelstar) is considered medically necessary for **1 or more** of the following indications:
    - Treatment of men with advanced prostate cancer
    - For true (central) precocious puberty, defined as sexual maturation before age 8 in girls and age 10 in boys I. Child should be clinically diagnosed with central precocious puberty (idiopathic or neurogenic), defined as sexual maturation before age 8 in girls and age 10 in boys; and clinical diagnosis is confirmed with: a) bone age advanced one year or more beyond chronologic age; and b) pubertal response to a GnRH stimulation test; andintracranial tumor has been ruled out by CT, MRI, or ultrasound; and baseline laboratory investigations have been performed, including: a) height and weight; b) sex steroid levels; c) adrenal steroid level to exclude congenital adrenal hyperplasia; d) beta human chorionic gonadotropin to rule out chorionic gonadotropin-secreting tumor; and e) pelvic/adrenal/testicular ultrasound to rule out a steroid-secreting tumor.
    - Non-atypical endometrial hyperplasia
    - Endometriosis (including adenomyosis, also known as endometriosis interna). Recommended duration of treatment with Lupron Depot 3.75 mg or Lupron Depot - 3 month 11.25 mg alone or in combination with norethindrone acetate -six months. If symptoms of endometriosis recur after the first course of therapy, a second treatment with a six-month course of Lupron Depot and norethindrone acetate 5 mg daily may be considered. Leuprolide Depot alone is not recommended for retreatment. [A] If norethindrone acetate is contraindicated, then retreatment is not recommended. Bone density is recommended before retreatment begins to ensure that values are within normal limits. Further treatment beyond two treatments (total of 12 months) is considered

unproven. [K] Lupron dosages greater than 3.75 mg per month or 11.25 mg per 3 months are subject to medical necessity review.
    - Preservation (suppression) of ovarian function in premenopausal women with ER-negative breast cancer receiving chemotherapy
    - Uterine fibroids (leiomyoma uteri) (preoperative adjunct to surgical treatment)
- Triptorelin is considered experimental and investigational for fibrocystic breast disease and all other indications because of insufficient evidence in the peer-reviewed literature .
- **Degarelix** is considered medically necessary for **1 or more** of the following indications:
    - For the treatment of adult men with prostate cancer. [L]
- Degarelix is considered experimental and investigational for all other indications (e.g., benign prostatic hyperplasia and colon cancer) because of insufficient evidence in the peer-reviewed literature.
- **Lupaneta Pack** (leuprolide acetate and norethindrone acetate) is considered medically necessary for **1 or more** of the following indications:
    - For adult women 18 years of age and older with endometriosis who have had a previous treatment with or intolerance to both Lupron Depot (leuprolide acetate) and norethindrone oral tablets.
- Lupaneta Pack is considered experimental and investigational for all other indications, including abnormal uterine bleeding, and concomitant use with other LHRH agents.
- Lupaneta Pack is considered not medically necessary for persons with the following contraindications to its use:
    - Females who are pregnant or lactating
    - Persons with a known or history of breast oro ther hormone-sensitive cancer
    - Persons with thrombotic or thromboembolic disorders
    - Persons with liver tumors or liver disease
- **State Step Therapy Exception: For Fully Insured in states: CO, GA, IA, LA, NY, OH, OK, SD, VA, WA Turnaround time other than are standard: GA (urgent 24 hrs, non-urgent- 2 business days; LA (urgent -24 hrs from receipt of all info. or 72 hrs from request if no info received. Non urgent requests- 72 hrs of receipt of all info. or 15 calendar days from request if no info. was received); NY (72 hrs or 24 hrs for expedited-life threatening); OH (48 hrs -urgent or 10 calendar days for non-urgent); OK (Urgent 24 hrs. Non-urgent 72 hrs); TX (TAT's for TX- 24 hours); VA (Non- Urgent requests 2 business from rec. of info or 15 calendar days from request). WA (Urgent- 1 business day from receipt of info, or 48 hours from request whichever is earlier. Non urgent request- 3 business days of receipt of info or 5 calendar days from request whichever is earlier). Carriers must approve step therapy override exception requests if 1 or more of the following circumstances apply:**
    - **Cause an adverse reaction or is contraindicated based on the FDA prescribing information.**
    - **Decrease a covered person's ability to achieve or maintain reasonable functional ability in performing daily activities**
    - **Cause physical or mental harm to the covered person**
    - **Cause a significant barrier to the adherence to or compliance with the plan of care**
    - **It is expected to be ineffective based on the known clinical characteristics of the patient and the known characteristics of the prescription drug regimen such as 1 or more of the following scenarios:**
        - **The patient previously stopped taking the drug required under the step therapy protocol, or another drug in the same pharmacological class or with the same mechanism of action, because the drug was not effective, had a diminished effect, or because of an adverse event.**
        - **The drug that is subject to the step therapy protocol was previously prescribed for the patient's condition, the patient received benefits for the**

drug under a health benefit plan. The patient is stable on the drug, and the change in the patient's drug regimen required by the step therapy protocol is expected to be ineffective or cause harm to the patient (based on the known clinical characteristics of the patient and the known characteristics of the required drug regimen).

- **Arizona: the prescription drug required by the step therapy protocol is not in the best interest of the patient based on medical necessity because the patient's use of the prescription drug is expected to cause 1 or more of the following**
  - **A barrier to the patient's adherence to or compliance with the patient's plan of care.**
  - **A negative impact on the patient's comorbid conditions.**
  - **A clinically predictable negative drug interaction.**
  - **A decrease in the patient's ability to achieve or maintain a reasonably functional ability in performing daily activities for which the patient has experienced a positive therapeutic outcome.**
  - **The patient has experienced a positive therapeutic outcome on a prescribed drug selected by the patient's health care provider for the medical condition under consideration while on the patient's current or previous health care plan. A health care provider may not use a pharmaceutical sample for the purpose of qualifying for an exception to step therapy.**
- **South Dakota, Virginia-The patient is currently receiving a positive therapeutic outcome on a prescription drug recommended by his provider for the medical condition under consideration while on a current or the immediately preceding health benefit plan.**

- **State Step Therapy Exception: Oregon. Carriers must approve a request for an exception to step therapy if the entity determines that the evidence submitted by the prescribing practitioner is sufficient to establish 1 or more of the following**
  - **Cause an adverse reaction or is contraindicated based on the FDA prescribing information**
  - **The prescription drug required by the step therapy is expected to be ineffective based on the known clinical characteristics of the beneficiary and the known characteristics of the prescription drug regimen**
  - **The patient previously stopped taking the drug required under the step therapy protocol, or another drug in the same pharmacological class or with the same mechanism of action, because the drug was not effective, had a diminished effect, or because of an adverse event.**
  - **For a period of at least 90 days the beneficiary has experienced a positive therapeutic outcome from the drug for which the exception is requested while enrolled in the current or immediately preceding health care coverage and changing to the drug required by the step therapy may cause a clinically predictable adverse reaction or physical or mental harm to the beneficiary; or**
  - **The prescription drug required by the step therapy is not in the best interest of the beneficiary based on medical necessity.**

Background

- **Leuprolide (Lupron, Viadur, Eligard) is a gonadotropin-releasing hormone (Gn-RH) analog, which may be indicated for treatment of certain conditions, which are hormonally regulated. Lupron (leuprolide acetate) is a synthetic analog of luteinizing hormone**

releasing hormone (LHRH). It acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. In humans, administration of leuprolide results in an initial increase in circulating luteinizing hormone (LH) and follicle stimulating hormone (FSH) leading to transient increases in gonadal steroids. However, continuous administration of leuprolide results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In premenopausal females, estrogen levels are reduced to postmenopausal levels. These decreases occur within two-to-four weeks after initiation of therapy.

- **Approved uses of Lupron (leuprolide acetate) are advanced prostate cancer, endometriosis, uterine leiomyomata, and central precocious puberty. Lupron (leuprolide acetate) is available as an IM injection. There are two formulations of the drug -Lupron and Lupron-PED. The strengths available for Lupron are 7.5 mg dosed monthly, 22.5 mg dosed every three months, 30 mg dosed every four months and 45 mg dosed every six months. The PED form is used to treat central precocious puberty. Lupron-PED doses are weight based and generally given every 28 days. The strengths available for Lupron PED are 7.5 mg, 11.25 mg, and 15 mg.**
- **Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density. There is an increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving GnRH agonists for the treatment of prostate cancer.**
- **Lupron (leuprolide acetate) should not be utilized in the following: Females who are pregnant or lactating. Lupron (leuprolide acetate) is considered pregnancy category X and may lead to fetal harm. Known hypersensitivity to Lupron (leuprolide acetate), gonadotropin releasing hormone (GnRH), GnRH analogs, or any of the excipients in the formulations.**
- **Eligard (leuprolide acetate) is a synthetic analog of leutenizing hormone releasing hormone (LHRH).Eligard (leuprolide acetate) is indicated for the palliative treatment of advanced prostate cancer.Eligard (leuprolide acetate) is available as an injectable subcutaneous suspension: 7.5 mg once monthly; 22.5 mg every three months; 30 mg every four months; 45 mg every six months. The recommended dose of Eligard for prostate cancer is 7.5 mg SQ suspension once monthly OR 22.5 mg SQ every three months OR 30 mg SQ every four months or 45mg SQ every six months.**
- **Response to Eligard (leuprolide acetate) should be monitored by measuring serum concentrations of testosterone and prostate specific antigen periodically. Results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions. The recommended dose of Eligard for breast cancer is 7.5 mg SQ once monthly until disease progression although optimal dosing has not yet been clearly defined. The safety and efficacy of Eligard (leuprolide acetate) in pediatric patients <18 years old has not been established. Eligard (leuprolide acetate) is considered pregnancy category X and may lead to fetal harm. Eligard (leuprolide acetate) should not be used in known cases of hypersensitivity to leuprolide, gonadotropin releasing hormone (GnRH), GnRH analogs or any of the excipients in the formulation.**
- **A generic formulation of leuprolide acetate is available as a kit for subcutaneous injection. The kit is supplied as a 1 mg / 0.2 mL concentration and contains a vial of leuprolide, gauze, and syringes for 14 doses. Approved uses of leuprolide acetate are advanced prostate cancer and central precocious puberty. Recommended dose in prostate cancer is 1 mg subcutaneously once daily. Recommended dose of leuprolide acetate kit for central**

precocious puberty is 50 mcg/kg SC once daily. If response is not satisfactory, dosage may be titrated upward in 10 mcg/kg/day increments.

- **Leuprolide may be indicated in advanced cancer (palliative treatment) in patients who have inoperable prostate tumor, or refuse orchiectomy. The available literature suggests combined therapy with leuprolide and an anti-androgen (e.g., megestrol, flutamide) appears to produce additive effects and to be more effective than leuprolide therapy alone in the treatment of advanced prostate cancer. According to established guidelines, recommended dosing of leuprolide for palliative treatment of advanced prostate cancer is 1 mg given subcutaneously daily. According to established guidelines, if patient is receiving leuprolide acetate suspension (Lupron depot) dosing is 7.5 mg IM once-monthly.**
- **Leuprolide has been used in the treatment of true (central) precocious puberty, defined as sexual maturation less than age 8 in girls, and sexual maturation less than age 10 in boys. The available literature suggests tumors should be ruled out by lab tests, CT, MRI, or ultrasound. Leuprolide is not indicated for precocious pubarche alone or pseudoprecocious puberty (gonadotropin-independent precocious puberty). According to established guidelines, recommended starting doses are: Lupron Depot Ped: 0.3 mg/kg every 4 weeks (minimum 7.5 mg), or Lupron injection: 50 mcg/kg daily. Doses may be titrated upwards in order to achieve hormonal down-regulation.**
- **Studies of leuprolide for endometriosis indicate that 6 months is an appropriate length for therapy. Because of lack of safety data with long-term use, and because of concerns expressed in the available literature regarding effects on bone density, treatment after 6 months is typically not recommended. According to established guidelines, recommended dosing of leuprolide for endometriosis is 3.75 mg as a single monthly intra-muscular (IM) injection.**
- **Leuprolide has been studied for the treatment of uterine fibroids (leiomyoma uteri), as a pre-operative adjunct to surgical treatment. Clinical studies have demonstrated the benefit of leuprolide in reducing vascular and surgical complications secondary to obstructive fibroid size. In tests, gonadotropin-releasing hormone (GnRH) agonists have effectively reduced the fibroid size, but their use was accompanied by a rapid re-growth following discontinuation. The available literature states leuprolide therapy does not prevent or replace the eventual need for surgery. If used as a pre-operative adjunct, the available literature states short-term treatment only is recommended (i.e., 1 to 3 months).**
- **Leuprolide also has been shown to be an effective pre-operative adjunct to decrease endometrial thickness prior to endometrial ablation. If used as a pre-operative adjunct, short-term treatment only (i.e., 1 to 2 months) is indicated.Leuprolide is used in conjunction with urofollitropin or menotropins in patients with infertility. It has been used to suppress LH production in patients with documented premature leteinizing hormone (LH) surge. In addition, it has been used in "super-ovulation" regimens associated with in-vitro fertilization. Treatment of infertility may be subject to limitations under some benefit plans. Some HMO contracts, with or without a separate infertility benefit such as the Advanced Reproductive Technology (ART) Rider, specifically exclude injectable infertility drugs.**
- **Leuprolide has been shown to be useful in the treatment of metastatic breast cancer in pre-menopausal patients whose disease has progressed or recurred despite a 3 or more months trial of tamoxifen. Consensus guidelines from the National Comprehensive Cancer state that leuprolide may be an appropriate option for persons with stage II to IV granulosa cell tumors of the ovary that have relapsed after platinum-based chemotherapy (NCCN, 2007). Granulosa cell tumors are frequently hormonally active and often demonstrate estrogen receptor positivity. Thus, leuprolide been used as a method of reducing estrogen production in salvage therapy for recurrent, advanced stage granulosa cell tumors.**

- **Leuprolide has been used as treatment for various other conditions (e.g., polycystic ovarian disease, hypermenorrhea, pre-menstrual syndrome, paraphilias, and endometrial cancer). At this time limited information has been published to show efficacy for conditions other than those mentioned in the clinical criteria above. Further research with randomized, controlled trials is required to determine efficacy in these other conditions.**
- **The American Society of Clinical Oncology's recommendations on fertility preservation in cancer patients (Lee et al, 2006) stated that sperm and embryo cryo-preservation are considered standard practice. On the other hand, the use of GnRH analogs or antagonists for testicular or ovarian suppression is considered investigational. ASCO guidelines state: "At this time, since there is insufficient evidence regarding the safety and effectiveness of GnRH analogs and other means of ovarian suppression on female fertility preservation, women interested in ovarian suppression for this purpose are encouraged to participate in clinical trials." The guidelines also noted that there is insufficient evidence of the effectiveness of GnRH analogues in preventing chemotherapy-induced gonadal damage in men: "The efficacy of gonadoprotection through hormonal manipulations has only been evaluated in very small studies in cancer patients."**
- **In a review of the literature, Sonmezer and Oktay (2006) explained that there are a limited number of prospective studies of GnRH analogues in preventing chemotherapy-induced gonadal damage, "which are flawed because of short-term follow-up and/or because of lack of control subjects." The review notes that "[i]n addition to the lack of consistent support from clinical studies, there is currently no biological explanation for who GnRHa [GnRH analogues] can affect ovarian reserve." The authors concluded that "[i]n the absence of a prospective randomized study with sufficient power, we do not rely on ovarian suppression as an effective means of fertility preservation."**
- **Leuprolide has been employed as a therapeutic option for individuals with paraphilia who have failed pharamcotherapies such as cyproterone acetate (CPA), medroxyprogesterone acetate (MPA), and selective serotonin reuptake inhibitors (SSRIs). Leuprolide is thought to decrease sexual drive in men afflicted with paraphilas by decreasing testosterone production. Briken et al (2003) stated that in addition to psychotherapy, pharmacotherapy is an important treatment option for paraphilias, especially in sexual offenders. They noted that research has showed that LH-releasing hormone (LHRH) agonists may offer a new treatment option for treatment of paraphilic patients. These investigators performed a literature review on the use of LHRH agonist a new treatment option for treatment of paraphilic patients.**
- **They found 4 case reports, 1 case-control study, 7 open uncontrolled studies, and 1 study comparing patients receiving CPA with those receiving LHRH agonist treatment in forensic hospitals. In total, the studies reported on a sample of 118 treated patients with different forms of paraphilias --sadism, pedophilia, exhibitionism, voyeurism. Nearly all of the studies used self-reports to measure the effects of medication. Duration of follow-up was between 6 months and 7 years and revealed that there were no relapses if patients remained under treatment. Patients previously treated with other agents like CPA, MPA, or SSRIs reported better effects when taking LHRH agonists.**
- **The authors concluded that although there is a need for further research, LHRH agonists offer a treatment option for patients with severe paraphilia. Furthermore, in a review on medications that may alter behaviors of sex-offenders, Scober and colleagues (2006) stated that therapeutic drugs include LHRH inhibitors (e.g., leuprolide acetate, CPA, and triptorelin), synthetic estrogens (e.g., diethylstilbestrol), and progesterones (e.g., MPA).**
- **Leuprolide has also been tried for the treatment of seizures (Akaboshi and Takeshita, 2000) as well as Alzheimer's disease (Casadesus et al, 2006). However, there is currently insufficient evidence to support its use for thes indications.**

- **Available evidence on the effectiveness of leuprolide for the treatment of endometrial stromal sarcoma is limited to case reports. Guidelines on systemic therapy for uterine sarcoma from Cancer Care Ontario included no recommendation for the use of leuprolide in uterine stromal sarcomas (Kanjeekal et al, 2004). Furthermore, the National Cancer Institute's PDQ on uterine sarcoma (2008) did not include leuprolide or GnRH analogs as treatment options for uterine sarcoma.**
- **Quaas and Ginsburg (2007) provided a systematic review on prevention and treatment of uterine bleeding in the setting of hematologic malignancy. These researchers performed MEDLINE, PubMed, EMBASE and Cochrane searches with the terms uterine bleeding, uterine hemorrhage, hematologic malignancy. All identified literature sources were included in the review. The identified literature is largely comprised of case series and pilot studies. No evidence-based protocols for gynecologists and hematologists are available. The majority of the identified literature centers on menstrual suppression with GnRH agonists in hematologic malignancy, although no randomized trials could be identified. Review of the identified literature suggests that medical prevention with GnRH agonist therapy is highly effective for prevention of uterine bleeding in hematologic malignancy.**
- **With respect to treatment of acute uterine bleeding in the setting of hematologic malignancy, medical therapy can be used and is successful in the majority of patients, according to the identified studies. Surgical treatment should be used expeditiously if medical treatment options fail to control acute bleeding. Empiric prevention and treatment algorithms for the discussed clinical settings are proposed. The authors stated that more research is necessary on the topic, with the goal to develop evidence-based guidelines for gynecology and hematology-oncology care providers. Close cooperation between the specialties may improve morbidity and mortality associated with uterine bleeding in hematological malignancy in the future.**
- **Hembree and colleagues (2009) formulated practice guidelines for endocrine treatment of transsexual persons. This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low. Committees and members of the Endocrine Society, European Society of Endocrinology, European Society for Paediatric Endocrinology, Lawson Wilkins Pediatric Endocrine Society, and World Professional Association for Transgender Health commented on preliminary drafts of these guidelines. The authors concluded that transsexual persons seeking to develop the physical characteristics of the desired gender require a safe, effective hormone regimen that will (i) suppress endogenous hormone secretion determined by the person's genetic/biologic sex and (ii) maintain sex hormone levels within the normal range for the person's desired gender.**
- **A mental health professional (MHP) must recommend endocrine treatment and participate in ongoing care throughout the endocrine transition and decision for surgical sex re-assignment. The endocrinologist must confirm the diagnostic criteria the MHP used to make these recommendations. Because a diagnosis of transsexualism in a prepubertal child can not be made with certainty, the authors do not recommend endocrine treatment of prepubertal children. They recommended treating transsexual adolescents (Tanner stage 2) by suppressing puberty with GnRH analogs until age 16 years old, after which cross-sex hormones may be given. They suggested suppressing endogenous sex hormones, maintaining physiologic levels of gender-appropriate sex hormones and monitoring for known risks in adult transsexual persons.**
- **An UpToDate review on "Heavy or irregular uterine bleeding during chemotherapy"(Milbourne, 2013) states that "We suggest inducing amenorrhea with a**

GnRH agonist [e.g., leuprolide acetate] in premenopausal women at risk of chemotherapy induced thrombocytopenia"

- **UpToDate reviews on "Treatment of locally advanced, recurrent, or metastatic endometrial cancer"(Campos and Miller, 2013) and "Overview of endometrial carcinoma" (Plaxe and Mundt, 2013) do not mention leuprolide as a therapeutic option. Also, the 2013 NCCN's Drugs and Biologics Compendium does not list uterine cancer as an indication of leuprolide acetate. UpToDate reviews on "Malignant salivary gland tumors: Treatment of recurrent and metastatic disease" (Laurie, 2013) and "Salivary gland tumors: Treatment of locoregional disease" (Lydiatt and Quivey, 2013) do NOT mention the use of leuprolide as a therapeutic option. Also, the 2013 NCCN's Drugs and Biologics Compendium does not list parotid carcinoma as a recommended indication of leuprolide acetate. The NCCN Drugs & Biologics Compendium (2014) does not list salivary gland cancer as a recommended indication of leuprolide acetate; and it does not list pancreatic cancer as a recommended indication of goserelin acetate.**
- **Zoladex (goserelin) is a synthetic analog of luteinizing hormone releasing hormone (LHRH) also known as gonadotropin releasing hormone (GnRH). In males and premenopausal females, LHRH is released from the hypothalamus in intervals of approximately every 90 minutes. LHRH binds to the LHRH receptors on the pituitary gland resulting in the release of LH and Follicle Stimulating Hormone (FSH). In response to LH stimulation in males, the leydig cells of the testes produce testosterone.**
- **In response to LH stimulation in females, the ovaries secrete estrogens. Zoladex (goserelin) stimulates LH receptors continuously which results in a down regulation of LH receptors leading to decreased estrogen and testosterone secretion. Zoladex (goserelin) is indicated for the palliative treatment of advanced prostate cancer, adjuvant treatment of locally advanced prostate cancer, palliative treatment of advanced breast cancer, endometrial thinning and endometriosis. Goserelin (Zoladex) is a GnRH (also known as gonadorelin and LHRH) analog, which is indicated in certain conditions requiring suppression of estrogen or testosterone secretion. At this time it is available only in a continuous-release subcutaneous implant that releases drug over a period of about 28 days.**
- **Goserelin is approved by the Food and Drug Adminsitration (FDA) for treatment of advanced metastatic prostate cancer and advanced endometriosis. Goserelin has also been shown to be effective for treatment or palliation of breast cancer in pre-menopausal patients. Goserelin has been studied for the treatment of uterine fibroids. Clinical studies have demonstrated the benefit of leuprolide in reducing vascular and surgical complications secondary to obstructive fibroid size. In tests, GnRH agonists have effectively reduced the fibroid size, but their use was accompanied by a rapid reg-rowth following discontinuation. Therefore, the literature states that goserelin therapy does not prevent or replace the eventual need for surgery. If used as a pre-operative adjunct, the literature recommends short-term treatment (6 months or less).**
- **Goserelin has been shown to be effective for the short-term (less than 6 months) pre-operative adjunct to endometrial ablation or surgery for leiomyomata uteri (uterine fibroids). Goserelin is available as Zoladex in 3.6 mg SQ injection given every 28 days and 10.8 mg SQ injection given every 12 weeks. Recommended dose of Zoladex for prostate cancer 3.6 mg SC every 28 days or 10.8 mg SC every 12 weeks. Zoladex is indicated for long term treatment unless clinically inappropriate. When Zoladex (goserelin) is given in combination with radiotherapy and flutamide, treatment should begin eight weeks prior to initiation of radiotherapy and continue during radiation therapy. One treatment regimen is: 3.6 mg SC eight weeks prior to radiotherapy followed 28 days later by 10.8 mg SC every 12 weeks. Alternative therapy involves two 3.6 mg injections spaced 28 days apart prior to radiation. Two more injections occur during radiation therapy.**

- **Recommended dose of Zoladex for breast cancer is 3.6 mg SC every 28 days. Recommended dose of Zoladex for endometriosis is 3.6 mg SC every 28 days up to six months. Recommended dose of Zoladex for endometrial thinning is 3.6 mg SC four weeks prior to ablation OR two (2) 3.6 mg injections spaced four weeks apart with the second injection occurring two to four weeks prior to ablation. Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density.There is an increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving GnRH agonists for the treatment of prostate cancer. The 10.8 mg dose of Zoladex is contraindicated in females.**
- **Zoladex should not be utilized in persons with a known hypersensitivity to goserelin products, luteinizing hormone releasing hormone (LHRH), or LHRH analogues. Except for use in prostate cancer, Zoladex (goserelin) should not be continued or restarted after malignant disease progression (Exception = Prostate Cancer). Zoladex should not be used concomitantly with other LHRH agents. Zoladex should not be used in abnormal vaginal bleeding of unknown etiology. The safety and efficacy of Zoladex in pediatric patients <18 years old has not been established.**
- **Goserelin is under investigation as a method of prevention of chemotherapy-induced gonadal damage. In a prospective pilot study (n = 5), Franke et al (2005) explored the effects of goserelin acetate in women with Hodgkin's disease (HD) receiving chemotherapy while taking a continuous combined estrogen-progestin preparation as add-back on the prevention of premature ovarian failure (POF). Pre-menopausal women with HD received goserelin and add-back until polychemotherapy was completed. Every 4 weeks during treatment and thereafter, a hormonal profile (follicle-stimulating hormone (FSH), LH, 17beta-estradiol, progesterone and inhibin B) was measured until resumption of menstruation or the development of a hyper-gonadotropic state (2 x FSH greater than 30 U/l). All patients reached pre-pubertal status during treatment.**
- **Following cessation of goserelin therapy, 1 patient developed a hyper-gonadotropic state and 4 patients resumed menstruation. One of those patients became pregnant and delivered a healthy son. These investigators concluded that the effectiveness of GnRH agonist plus add-back on the prevention of POF during polychemotherapy in women with HD needs further elucidation in randomized controlled trials (RCTs).**
- **Del Mastro et al (2006) noted that standard methods to prevent chemotherapy-induced early menopause in young, breast cancer patients are unavailable to date. Pre-clinical data has suggested that LHRH analogs given during treatment can decrease the gonado-toxicity induced by chemotherapy. In a phase II clinical trial, these investigators evaluated the activity of such a method in young, breast cancer patients undergoing adjuvant chemotherapy. Pre-menopausal patients received goserelin 3.6 mg every 4 weeks before and during chemotherapy. According to 2-stage optimal phase II Simon design, treatment was considered clinically interesting if it was able to prevent menopause in 19 out of 29 patients of the study population. The resumption of ovarian function was defined by a resumption of menstrual activity or by a FSH value less than or equal to 40 IU/l within 12 months after the last cycle of chemotherapy.**
- **A total of 30 patients were enrolled and 29 were evaluable. Median age was 38 years (range of 29 to 47 years). All but 1 patient received CEF regimen (cyclophosphamide, epirubicin, 5-fluorouracil). Resumption of menstrual activity was observed in 21 patients (72 %; 95 % confidence interval [CI]: 52 to 87 %) and a FSH value less than or equal to 40 IU/l in 24 patients (83 %; 95 % CI: 63 to 93 %). Menses resumption was observed in 16 out of 17 patients (94 %) with age less than 40 years and in 5 out of 12 patients (42 %) with age 40 years or over. These researchers concluded that goserelin given before and during**

chemotherapy may prevent premature menopause in the majority of patients. However, the different success rate by age indicates the need of a prospective evidence of the effectiveness of such a strategy.

- **In a prospective RCT, Badawy et al (2009) examined if GnRHa administration before and during combination chemotherapy for breast cancer could preserve post-treatment ovarian function in young women or not. A total of 80 patients with unilateral adenocarcinoma of the breast and with no metastasis who had undergone modified radical mastectomy or breast-conserving surgery plus full axillary lymph node dissection were included in the study. Patients were assigned randomly to receive combined GnRHa and chemotherapy or chemotherapy alone. One woman in each group dropped out. Main outcome measures included return of spontaneous menstruation and ovulation as well as hormonal changes (FSH, LH, E(2), P) during and after the course of treatment. In the study group, 89.6 % resumed menses and 69.2 % resumed spontaneous ovulation within 3 to 8 months of termination of the GnRHa/chemotherapy co-treatment; 11.4 % experienced hyper-gonadotrophic amenorrhea and ovarian failure 8 months after treatment.**
- **In the control group (chemotherapy without GnRHa), 33.3 % resumed menses and 25.6 % resumed normal ovarian activity. The median FSH and LH concentrations, 6 months after completion of the GnRHa/chemotherapy cotreatment group, were significantly less than the control group. During the GnRHa/chemotherapy co-treatment the concentrations of FSH, LH, and P decreased to almost pre-pubertal levels. However, within 1 to 3 months after the last GnRHa injection, an increase in LH and FSH concentrations was detected, followed several weeks later in by an increase in P concentrations to within normal levels. The authors concluded that administration of GnRHa before and during combination chemotherapy for breast cancer may preserve post-treatment ovarian function in women less than 40 years. Moreover, they stated that long-term studies are needed.**
- **In a systematic review, Clowse et al (2009) examined if administration of GnRHa during chemotherapy is protective of ovarian function and fertility. These investigators searched the English language literature (1966 to April 2007) using Medline and meeting abstracts and included studies that reported an association between GnRHa and ovarian preservation in women receiving chemotherapy. Studies without a control group were excluded. Ovarian preservation was defined as the resumption of menstrual cycles and a pre-menopausal FSH after chemotherapy. Fertility was determined by a woman's ability to become pregnant. These researchers estimated the summary relative risk (RR) and associated 95 % CI using a random effects model. A total of 9 studies included 366 women -3 studies included women with autoimmune disease receiving cyclophosphamide; 6 studies included women with hematologic malignancy receiving combination chemotherapy.**
- **In total, 178 women were treated with GnRHa during chemotherapy, 93 % of whom maintained ovarian function. Of the 188 women not treated with GnRHa, 48 % maintained ovarian function. The use of a GnRHa during chemotherapy was associated with a 68 % increase in the rate of preserved ovarian function compared with women not receiving a GnRHa (summary RR = 1.68, 95 % CI: 1.34 to 2.1). Among the GnRHa-treated women, 22 % achieved pregnancy following treatment compared with 14 % of women without GnRHa therapy (summary RR = 1.65, CI: 1.03 to 2.6). The authors concluded that based on the available studies, GnRHa appear to improve ovarian function and the ability to achieve pregnancy following chemotherapy. Several RCTs are underway to define the role and mechanism of GnRHa in ovarian function preservation.**
- **Moore et al (2015) randomly assigned 257 premenopausal women with operable hormone-receptor-negative breast cancer to receive standard chemotherapy with the GnRH agonist goserelin (goserelin group) or standard chemotherapy without goserelin (chemotherapy alone group). For patients randomly assigned to the goserelin group, goserelin at a dose of 3.6 mg was administered subcutaneously every 4 weeks beginning 1 week before the**

initial chemotherapy dose and was continued to within 2 weeks before or after the final chemotherapy dose. The primary study end-point was the rate of ovarian failure at 2 years, with ovarian failure defined as the absence of menses in the preceding 6 months and levels of follicle stimulating hormone (FSH) in the post-menopausal range. Rates were compared with the use of conditional logistic regression.

- **Secondary end-points included pregnancy outcomes and disease-free and overall survival. At baseline, 218 patients were eligible and could be evaluated. Among 135 with complete primary endpoint data, the ovarian failure rate was 8 % in the goserelin group and 22 % in the chemotherapy alone group (odds ratio, 0.30; 95 % CI: 0.09 to 0.97; 2 sided p = 0.04). Owing to missing primary endpoint data, sensitivity analyses were performed, and the results were consistent with the main findings. Missing data did not differ according to treatment group or according to the stratification factors of age and planned chemotherapy regimen. Among the 218 patients who could be evaluated, pregnancy occurred in more women in the goserelin group than in the chemotherapy alone group (21 % versus 11 %, p = 0.03); women in the goserelin group also had improved disease-free survival (p = 0.04) and overall survival (p = 0.05).**
- **The investigators concluded that, although missing data weaken interpretation of the findings, administration of goserelin with chemotherapy appeared to protect against ovarian failure, reducing the risk of early menopause and improving prospects for fertility. Commenting on this study, Rebener (2015) stated that these findings are reassuring and suggest that a GnRH agonist could be provided to premenopausal women undergoing chemotherapy. The editorialist stated that, although the results should be reproducible in women treated for other cancers, no confirmatory data exist; also, the utility of this approach in young women with hormone-receptor-positive breast cancer remains to be shown.**
- **Rebener (2014) stated that, while the results of the study by Moore et al are encouraging and the only reported downside of goserelin (which is not FDA approved for ovarian suppression in breast cancer patients) was the development of menopausal symptoms (e.g., hot flashes, accelerated bone loss), it's worth noting that results of many prior studies have been inconsistent and in this study population, between group pregnancy rates were of borderline statistical significance. The author stated that only further studies will answer the questions of whether these findings persist in larger studies and whether they pertain only to women with receptor-negative breast cancer.**
- **The editorialist stated that the benefits of preventing ovarian failure with its consequent vasomotor symptoms, dyspareunia, and rapid bone loss are well established, and this study adds to the growing evidence supporting the efficacy of GnRH agonists during chemotherapy.**
- **Del Mastro et al (2014) conducted a systematic review and metaanalysis of randomized trials evaluating the efficacy of GnRH analogues (GnRHa), given before and during chemotherapy, in the prevention of POF in pre-menopausal cancer patients. Studies were retrieved by searching PubMed, Web of Knowledge database and the proceedings of major conferences. The investigators calculated Odds Ratios (OR) and 95 % CIs for POF from each trial and obtained pooled estimates through the random effects model as suggested by DerSimonian and Laird. A total of 9 studies were included in the meta-analysis with 225 events of POF occurring in 765 analyzed patients. The authors stated that pooled OR estimate indicates a highly significant reduction in the risk of POF (OR = 0.43; 95 % CI: 0.22 to 0.84; p = 0.013) in patients receiving GnRHa.**
- **There was statistically significant heterogeneity among studies (I(2) = 55.8 %; p = 0.012). The authors said that there was no evidence of publication bias. Subgroups analyses showed that the protective effect of GnRHa against POF was similar in subgroups of patients defined by age and timing of POF assessment, while it was present in breast**

cancer but unclear in ovarian cancer and lymphoma patients. The authors stated that their pooled analysis of randomized studies shows that the temporary ovarian suppression induced by GnRHa significantly reduces the risk of chemotherapy-induced POF in young cancer patients.

- **NCCN's clinical practice guideline on breast cancer (2015) states: "Randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea. Smaller historical experiences in patients with ER-positive disease have reported conflicting results with regards to the protective effect of GnRH therapy on fertility".**
- **In a Cochrane review, Cheong et al (2014) evaluated the safety and effectiveness of nonsurgical interventions for women with chronic pelvic pain. These investigators searched the Menstrual Disorders and Subfertility Group Specialised Register. They also searched (from inception to February 5, 2014) AMED, CENTRAL, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS; and hand-searched sources such as citation lists, trial registers and conference proceedings. Randomized controlled trials on non-surgical management of chronic pelvic pain were eligible for inclusion. These investigators included studies of women with a diagnosis of pelvic congestion syndrome or adhesions but excluded those with pain known to be caused by endometriosis, primary dysmenorrhea (period pain), active chronic pelvic inflammatory disease or irritable bowel syndrome.**
- **These researchers considered studies of any non-surgical intervention, including lifestyle, physical, medical and psychological treatments. Study selection, quality assessment and data extraction were performed independently by 2 review authors. Meta-analysis was performed using the Peto odds ratio (Peto OR) for dichotomous outcomes and the mean difference (MD) for continuous outcomes, with 95 % CIs. The primary outcome measure was pain relief, and secondary outcome measures were psychological outcomes, quality of life, requirement for analgesia and adverse effects. The quality of the evidence was assessed by using GRADE methods. A total of 21 RCTs were identified that involved non-surgical management of chronic pelvic pain: 13 trials were included in the review, and 8 were excluded.**
- **The studies included a total of 750 women -406 women in the intervention groups and 344 in the control groups. Included studies had high attrition rates, and investigators often did not blind adequately or did not clearly describe randomization procedures.Progestogen (medroxyprogesterone acetate (MPA)) was more effective than placebo at the end of treatment in terms of the number of women achieving a greater than 50 % reduction in visual analog scale (VAS) pain score immediately after treatment (Peto OR 3.00, 95 % CI: 1.70 to 5.31, 2 studies, n = 204, I(2) = 22 %, moderate-quality evidence). Evidence of benefit was maintained up to 9 months after treatment (Peto OR 2.09, 95 % CI: 1.18 to 3.71, 2 studies, n = 204, I(2) = 0 %, moderate-quality evidence). Women treated with progestogen reported more adverse effects (e.g., weight gain, bloatedness) than those given placebo (high-quality evidence).**
- **The estimated effect of lofexidine on pain outcomes when compared with placebo was compatible with benefit and harm (Peto OR 0.42, 95 % CI: 0.11 to 1.61, 1 study, 39 women, low-quality evidence). Women in the lofexidine group reported more adverse effects (including drowsiness and dry mouth) than women given placebo (moderate-quality evidence). Head-to-head comparisons showed that women taking goserelin had greater improvement in pelvic pain score (MD 3, 95 % CI: 2.08 to 3.92, 1 study, n = 47, moderate-quality evidence) at 1 year than those taking progestogen. Women taking gabapentin had a lower VAS pain score than those taking amytriptyline (MD -1.50, 95 % CI: -2.06 to -0.94, n = 40, low-quality evidence).**

- **Study authors reported that no statistically significant difference was observed in the rate of adverse effects among women taking gabapentin compared with women given amytriptyline. The study comparing goserelin versus progestogen did not report on adverse effects. Women who underwent reassurance ultrasound scans and received counseling were more likely to report improved pain than those treated with a standard "wait and see" policy (Peto OR 6.77, 95 % CI: 2.83 to 16.19, n = 90, low-quality evidence). Significantly more women who had writing therapy as a disclosure reported improvement in pain than those in the non-disclosure group (Peto OR 4.47, 95 % CI: 1.41 to 14.13, n = 48, very low-quality evidence). No difference between groups in pain outcomes was noted when other psychological therapies were compared with standard care or placebo (quality of evidence ranged from very low to low).**
- **Studies did not report on adverse effects. Distension of painful pelvic structures was more effective for pain when compared with counseling (MD 35.8, 95 % CI: 23.08 to 48.52 on a 0 to 100 scale, 1 study, n = 48, moderate-quality evidence). No difference in pain levels was observed when magnetic therapy was compared with use of a control magnet (very low-quality evidence). Studies did not report on adverse effects. The results of studies examining psychological and complementary therapies could not be combined to yield meaningful results. The authors concluded that evidence of moderate quality supported progestogen as an option for chronic pelvic pain, with efficacy reported during treatment. In practice, this option may be most acceptable among women unconcerned about progestogenic adverse effects (e.g., weight gain, bloatedness -- the most common adverse effects).**
- **Although some evidence suggested possible benefit of goserelin when compared with progestogen, gabapentin as compared with amytriptyline, ultrasound versus "wait and see" and writing therapy versus non-disclosure, the quality of evidence is generally low, and evidence is drawn from single studies. They stated that given the prevalence and healthcare costs associated with chronic pelvic pain in women, RCTs of other medical, lifestyle and psychological interventions are urgently needed.**
- **Histrelin, an LH-releasing hormone (LH-RH) agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. Continuous administration of histrelin causes a reversible down-regulation of the GnRH receptors in the pituitary gland and desensitization of the pituitary gonadotropes. These inhibitory effects result in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. These decreases occur within 2 to 4 weeks after initiation of treatment.**
- **The histrelin implant is designed to provide continuous subcutaneous release of histrelin at a rate of 50 to 60 mcg/day (Vantas) or approximately histrelin 65 mcg per day (Supprelin LA) over 12 months. Supprelin LA (histrelin acetate) is a luteinizing hormone-releasing hormone (LH-RH) agonist that inhibits gonadotropin secretion. Supprelin LA (histrelin acetate) is indicated for the treatment of children with central precocious puberty. Supprelin LA (histrelin acetate) is available as a 50 mg (12 month) SQ implant. The recommended dose for idiopathic or neurogenic central precocious puberty is 1 50 mg implant inserted SQ every 12 months to the inner aspect of upper arm. Supprelin (histrelin acetate) LA is not interchangeable with Vantas (histrelin acetate), which also contains 50mg of histrelin acetate per implant but is indicated for the palliative treatment of advanced prostate cancer.**
- **Children with central precocious puberty (neurogenic or idiopathic) have an early onset of secondary sexual characteristics (earlier than 8 years of age in females and 9 years of age in males). They also show a significantly advanced bone age, which can result in diminished adult height attainment. Supprelin LA was approved by the FDA for the treatment of children with central precocious puberty based on the results of a single-arm, open-label study involving 36 patients ranging in age from 4 to 11 years. The primary**

endpoint of the study was hormonal suppression below pubertal levels by month 3 with continued suppression upon GnRH challenge. All patients in the study were suppressed within the first month of treatment.

- **Prior to initiation of treatment, a clinical diagnosis of central precocious puberty should be confirmed by measurement of blood concentrations of total sex steroids, LH and FSH following stimulation with a GnRH analog, and assessment of bone age versus chronological age. Baseline evaluations should include height and weight measurements, diagnostic imaging of the brain (to rule out intra-cranial tumor), pelvic/testicular/adrenal ultrasound (to rule out steroid secreting tumors), human chorionic gonadotropin levels (to rule out chorionic gonadotropin secreting tumor), and adrenal steroids to exclude congenital adrenal hyperplasia. During treatment, LH, FSH and estradiol or testosterone should be monitored at 1 month post implantation then every six months thereafter. Additionally, height (for calculation of height velocity) and bone age should be assessed every six to 12 months.**
- **Supprelin LA should be removed after 12 months of therapy. At the time an implant is removed, another implant may be inserted to continue therapy. Discontinuation of Supprelin LA should be considered at the discretion of the physician and at the appropriate time point for the onset of puberty (approximately 11 years for females and 12 years for males). Supprelin LA (histrelin acetate) implants are sterile non-biodegradable, diffusion-controlled, HYDRON polymer reservoirs containing histrelin acetate, and designed to deliver approximately 65 mcg histrelin acetate per day over 12 months. The safety and effectiveness of Supprelin LA in persons less than two years old has not been established. Supprelin LA should not be used in women who are pregnant or lactating. Supprelin LA should not be used concomitantly with other LHRH agents.**
- **Vantas was approved by the FDA for the palliative treatment of advanced prostate cancer. The FDA approval was based upon an open-label, multi-center study evaluating 138 patients with advanced prostate cancer and mean baseline serum levels of 388.3 ng/dL for testosterone and 83.6 ng/mL for prostate-specific antigen (PSA). Patients were treated with a single histrelin acetate implant and were evaluated for at least 60 weeks. Of the 138 patients, 37 had Jewett stage C disease, 29 had stage D disease, and 72 had an elevated or rising serum PSA after definitive therapy for localized disease. Ninety percent of patients were 65 years of age or older. Efficacy was determined by the number of patients who attained the criterion level of chemical castration (defined as serum testosterone 50 ng/dL or less) at week 4 and maintained this level through week 52. The study found that all evaluable patients (n = 134) attained chemical castration after 4 weeks of treatment.**
- **A statistically significant low mean testosterone level of less than 16 ng/dL ($p < 0.0001$) was achieved by week 4, and testosterone levels maintained below 20 ng/dL through week 52 of the study. The investigators reported that all patients experienced a decrease in PSA levels after they began treatment with histrelin implant. By week 24, 93 % of patients (n = 103) experienced a decrease in serum PSA to within normal limits. Vantas may lead to fetal harm if given during pregnancy (category X). Known hypersensitivity to histrelin, gonadotropin releasing hormone (GnRH), GnRH analogs, or any of the excipients in the formulations. Histrelin acetate is available as Vantas in 50 mg SQ implant. The recommended dose of Vantas for prostated cancer is one implant inserted SQ every 12 months.**
- **Use of more than one implant at a time offers no additional proven benefit. The FDA labeling recommends that response to Vantas should be monitored by measuring serum concentrations of testosterone and PSA periodically, especially if the anticipated clinical or biochemical response to treatment has not been achieved. Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density.There is an increased risk of**

diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving GnRH agonists for the treatment of prostate cancer.

- **Abarelix (Plenaxis): Plenaxis (abarelix) is a GnRH antagonist approved by the FDA in November 2003. It is indicated for the treatment of the symptoms of men with advanced prostate cancer who can not take other hormone therapies and who have refused surgical castration. Plenaxis is marketed under a voluntary risk management program agreed to and administered by the sponsor that will restrict the use of Plenaxis to patients with advanced prostate cancer, who have no alternative therapy, because of an increased risk of serious, and potentially life-threatening, allergic reactions associated with its use.**
- **In a phase III clinical study (n = 269), McLeod and colleagues (2001) evaluated the levels of testosterone and other hormones in men with prostate cancer treated with abarelix versus leuprolide. The authors concluded that treatment with abarelix produced a higher percentage of patients who avoided a testosterone surge and had a more rapid time to testosterone suppression with a higher rate of medical castration 1 day after treatment and greater reductions in testosterone, LH, FSH, and dihydrotestosterone during the first 2 weeks of treatment compared with leuprolide. The achievement and maintenance of castration was comparable between the two groups.**
- **In another phase III clinical trial (n = 255), Trachtenberg et al (2002) reported that abarelix as monotherapy achieved medical castration significantly more rapidly than combination therapy (LHRH agonist and a non-steroidal anti-androgen) and avoided the testosterone surge characteristic of agonist therapy. Both treatments were equally effective in reducing serum PSA, and achieving and maintaining castrate levels of testosterone. Koch et al (2003) stated that abarelix provided a safe and effective medical alternative to surgical castration in symptomatic patients (n = 81) with advanced prostate cancer without the risk of the clinical flare associated with LHRH agonists. In June 2006, the manufacturer of abarelix voluntarily discontinued its sale and distribution due to a significantly reduced demand for the product. The drug was no longer be available after August 31, 2006.**
- **Degarelix (Firmagon): Firmagon (degarelix) is a GnRH receptor antagonist. Firmagon (degarelix) binds reversibly to the pituitary GnRH receptors, thereby reducing the release of gonadotropins (luteinizing hormone and follicle-stimulating hormone) and consequently testosterone. In men, the level of testosterone is reduced to a level typically seen in surgically castrated men. On December 29, 2008, the FDA approved degarelix, a GnRH receptor inhibitor, for the treatment of patients with advanced prostate cancer. The effectiveness of degarelix was established in a clinical trial in which patients with prostate cancer received either degarelix or leuprolide. Longterm androgen deprivation therapy prolongs the QT interval. Consider risks and benefits especially when used concomitantly with other medications known to prolong the QT interval. Do not administer degarelix intravenously.**
- **Degarelix should not be used with other LHRH agonists. Use with caution in patients with creatinine clearance (Clcr) <50 mL/minute. Hypersensitivity reactions, including anaphylaxis, urticaria and angioedema, have been reported post-marketing with Firmagon (degarelix). In case of a serious hypersensitivity reaction, discontinue Firmagon (degarelix) immediately if the injection has not been completed, and manage as clinically indicated. Patients with a known history of serious hypersensitivity reactions to Firmagon (degarelix) should not be re-challenged with Firmagon (degarelix). Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density.**
- **There is an increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving GnRH agonists for the treatment of prostate cancer. Firmagon (degarelix) should not be utilized in persons with known**

hypersensitivity to degarelix, mannitol, or any of the excipients in the formulations. Degarelix is not indicated in women and may lead to fetal harm if given during pregnancy (pregnancy category X). The safety and efficacy of degarelix in pediatric patients <18 years old has not been established.Degarelix is available as Firmagon in 80mg and 120mg vials.

- **The recommended dose of degarelix for prostate cancer is: Loading dose: 240 mg given as two subcutaneous injections of 120 mg at a concentration of 40 mg/mL. Maintenance dose - Administration every 28 days: 80 mg given as one subcutaneous injection at a concentration of 20 mg/mL - 28 days after the starting/loading dose.**
- **In a 12 month, comparative, randomized, open label, parallel group phase III study, Klotz et al (2008) assessed the safety and effectiveness of degarelix versus leuprolide for achieving and maintaining testosterone suppression in a 1 year phase III trial involving patients with prostate cancer. A total of 610 patients with adenocarcinoma of the prostate (any stage; median age of 72 years; median testosterone of 3.93 ng/ml, median PSA level of 19.0 ng/ml) were randomized and received study treatment. Androgen-deprivation therapy was indicated (neoadjuvant hormonal treatment was excluded) according to the investigator's assessment. Three dosing regimens were evaluated: a starting dose of 240 mg of degarelix subcutaneous (SC) for 1 month, followed by SC maintenance doses of 80 mg or 160 mg monthly, or IM leuprolide doses of 7.5 mg monthly.**
- **Therapy was maintained for the 12 month study. Both the intent-to-treat (ITT) and per protocol populations were analyzed. The primary endpoint of the trial was suppression of testosterone to less than or equal to 0.5 ng/ml at all monthly measurements from day 28 to day 364, thus defining the treatment response. This was achieved by 97.2 %, 98.3 % and 96.4 % of patients in the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively (ITT population). At 3 days after starting treatment, testosterone levels were less than or equal to 0.5 ng/ml in 96.1 % and 95.5 % of patients in the degarelix 240/80 mg and 240/160 mg groups, respectively, and in none in the leuprolide group. The median PSA levels at 14 and 28 days were significantly lower in the degarelix groups than in the leuprolide group ($p < 0.001$).**
- **The hormonal side effect profiles of the 3 treatment groups were similar to previously reported effects for androgen deprivation therapy. The SC degarelix injection was associated with a higher rate of injection site reactions than with the IM leuprolide injection (40 % versus less than 1 %; $p < 0.001$, respectively). There were additional differences between the degarelix and leuprolide groups for urinary tract infections (3 % versus 9 %. $p < 0.01$, respectively), arthralgia (4 % versus 9 %, $p < 0.05$, respectively) and chills (4 % versus 0 %, $p < 0.01$, respectively). There were no systemic allergic reactions. The authors concluded that degarelix was not inferior to leuprolide at maintaining low testosterone levels over a 1 year treatment period.**
- **Degarelix induced testosterone and PSA suppression significantly faster than leuprolide; PSA suppression was also maintained throughout the study. Degarelix represents an effective therapy for inducing and maintaining androgen deprivation for up to 1 year in patients with prostate cancer, and has a different mechanism of action from traditional GnRH agonists. Its immediate onset of action achieves a more rapid suppression of testosterone and PSA than leuprolide. Furthermore, there is no need for anti-androgen supplements to prevent the possibility of clinical "flare". The findings of Klotz et al (2008) are in agreement with those of Gittelman et al (2008) as well as Van Poppel et al (2008).**
- **In a phase 3, 1-year, multi-center, randomized, open-label study, Tombal et al (2010) compared the safety and effectiveness of degarelix at 240 mg for 1 month, and then 80 mg monthly (240/80mg); degarelix at 240 mg for 1 month, and then 160 mg monthly; and leuprolide at 7.5 mg/month. Overall, 610 patients with histologically confirmed prostate cancer (all stages), for whom androgen deprivation therapy was indicated, were included. The primary endpoint of this trial has been reported previously; the protocolled and**

exploratory subgroup analyses reported in this paper focus on degarelix at 240/80 mg (dose approved by the FDA and the European Medicine Evaluation Association for the treatment of patients with hormone-naive advanced prostate cancer).

- **Prostate-specific antigen progression-free survival (2 consecutive increases in PSA of 50 % compared with nadir and greater than or equal to 5 ng/ml on 2 consecutive measurements at least 2 weeks apart or death) and change in PSA were reviewed. Effects of baseline disease stage (localized, locally advanced, and metastatic) and PSA level (less than 10, 10 to 20, greater than 20 to 50, and greater than 50 ng/ml) were analysed. Patients receiving degarelix showed a significantly lower risk of PSA progression or death compared with leuprolide (p = 0.05). Prostate-specific antigen recurrences occurred mainly in patients with advanced disease and exclusively in those with baseline PSA greater than 20 ng/ml.**
- **Patients with PSA greater than 20 ng/ml had a significantly longer time to PSA recurrence with degarelix (p = 0.04). The relatively low number of patients in each subgroup is a limitation of this study. The authors concluded that these findings generate the hypothesis that degarelix at 240/80 mg offers improved PSA control compared with leuprolide. Prostate-specific antigen recurrences occurred almost exclusively in patients with metastatic prostate cancer or high baseline PSA during this 1-year study. The authors stated that further studies are needed to confirm these findings.**
- **Ghiringhelli and colleagues (2013) noted that FSH receptor was recently found to be selectively expressed by endothelial cells on tumor-associated blood vessels in a wide range of human cancers. In this context, these researchers hypothesized that degarelix may have anti-angiogenic effects via its capacity to block FSH production. These investigators reported the case of a patient with metastatic colon cancer exhibiting tumor progression after failure of all conventional chemotherapeutic regimens. The addition of degarelix to the last chemotherapeutic regimen was proposed as compassionate treatment. Degarelix induced a rapid decrease in FSH level. This treatment induced radiological stabilization and carcino-embryonic antigen stabilization during 1 year.**
- **Contrast-enhanced ultrasonography demonstrated reduction of tumor vasculature. The authors stated that this case represented the first report of an anti-tumoral effect of degarelix in metastatic colon cancer and suggested an anti-angiogenic property of this drug. The clinical value of degarelix in the treatment of colon cancer needs to be ascertained in well-designed RCTs.**
- **Benign Prostatic Hyperplasia: Sakai et al (2015) noted that degarelix is a GnRH receptor (GnRHR) antagonist approved for use in patients with prostate cancer (PCa) who need androgen deprivation therapy. The slowing of prostate cell growth is a common goal shared by PCa and benign prostatic hyperplasia (BPH) patients, and the effect of degarelix on BPH cells has not yet been investigated. These researchers evaluated the direct effect of degarelix on human BPH primary cell growth. Gene expression studies performed with BPH (n = 11), stage 0 (n = 15), and PCa (n = 65) human specimens demonstrated the presence of GNRHR1 and GNRHR2 and their respective endogenous peptide ligands. BPH-isolated epithelial and stromal cells were either cultured alone or co-cultured (1:4 or 4:1 ratio of epithelial to stromal cells) and subsequently treated with increasing concentrations of degarelix.**
- **Degarelix treatment induced a decrease in cell viability and cell proliferation rates, which occurred in parallel to an increase in apoptosis. Both epithelial and stromal BPH cells were sensitive to degarelix treatment and, interestingly, degarelix was also effective when the cells were growing in a co-culture microenvironment. In contrast to degarelix, the GnRHR agonists, leuprolide and goserelin, exerted no effect on the viability of BPH epithelial or stromal cells. The authors concluded that (i) prostate tissues express GNRHR and are a potential target for degarelix; and (ii) degarelix directly inhibits BPH cell growth**

through a decrease in cell proliferation and an increase in apoptosis. Furthermore, an UpToDate review on "Medical treatment of benign prostatic hyperplasia" (Cunningham and Kadmon, 2016) does not mention degarelix as a therapeutic option.

- **Triptorelin (Trelstar): Trelstar (triptorelin) is a synthetic analog of luteinizing hormone releasing hormone (LHRH). Trelstar (triptorelin) is a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Trelstar, Trelstar Depot and Trelstar LA were approved by the FDA for the palliative treatment of advanced prostate cancer. It offers an alternative treatment for prostate cancer when orchiectomy or estrogen administration is either not indicated or unacceptable to the patient. Triptorelin is available as Trelstar in 3.75 mg IM injection given every 28 days and 11.25 mg IM injection given every 84 days and 22.5 mg IM injection given every 168 days.**
- **The recommended dose of the depot version of triptorelin (Trelstar Depot) is 3.75 mg once-monthly. The recommended dose of the long-acting version of triptorelin (Trelstar LA) is 11.25 mg every 84 days. Trelstar received approval on March 10, 2010 under NDA 022437 for a recommended dose of a single 22.5-mg IM injection every 24 weeks. Trelstar (triptorelin) is given as an IM injection and must be administered under physician supervision. Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density. There is an increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving GnRH agonists for the treatment of prostate cancer.**
- **Trelstar is pregnancy category X and may lead to fetal harm. The safety and effectiveness of Trelstar in pediatric patients <18 years old has not been established. Trelstar should not be used in known cases of hypersensitivity to triptorelin, gonadotropin releasing hormone (GnRH), GnRH analogs, or any of the excipients in the formulations. Trelstar should not be used concomitantly with other LHRH agents.**
- **Arriagada et al (2005) evaluated the role of ovarian suppression in patients with early breast cancer previously treated with local surgery and adjuvant chemotherapy. A total of 926 pre-menopausal patients with completely resected breast cancer and either axillary node involvement or histological grade 2 or 3 tumors were randomized after surgery to adjuvant chemotherapy alone (control arm) or adjuvant chemotherapy plus ovarian suppression (ovarian suppression arm). Ovarian suppression was obtained by either radiation-induced ovarian ablation or triptorelin for 3 years. The analyses were performed with Cox models stratified by center. Median follow-up was 9.5 years. Mean age was 43 years. Ninety per cent of patients had histologically proven positive axillary nodes, 63 % positive hormonal receptors and 77 % had received an anthracycline-based chemotherapy regimen.**
- **Ovarian suppression was by radiation-induced ovarian ablation (45 % of patients) or with triptorelin (48 %). At the time of randomization, all patients had regular menses or their FSH and estradiol levels indicated a pre-menopausal status. The 10-year disease-free survival rates were 49 % (95 % CI: 44 % to 54 %) in both arms (p = 0.51). The 10-year overall survival rates were 66 % (95 % CI: 61 % to 70 %) for the ovarian suppression arm and 68 % (95 % CI: 63 % to 73 %) for the control arm (p = 0.19). There were no variations in the treatment effect according to age, hormonal receptor status or ovarian suppression modality. However, in patients less than 40 years of age and with estrogen receptor-positive tumors, ovarian suppression significantly decreased the risk of recurrence (p = 0.01).**
- **The authors concluded that the results of this trial, after at least 10 years of follow-up, do not favor the use of ovarian suppression after adjuvant chemotherapy. They stated that**

the potential beneficial effect in younger women with hormone-dependent tumors should be further assessed.

- **Jannuzzo et al (2009) noted that LHRH agonists (e.g., triptorelin) reduce ovarian estrogen production in pre-menopausal women with hormone-sensitive breast cancer. Aromatase inhibitors (e.g., exemestane) inhibit extra--varian production of estrogen and may further reduce circulating estrogens when combined with an LHRH agonist. These researchers examined the effects of estrogen suppression in pre-menopausal women following 8 weeks of treatment with exemestane and triptorelin versus triptorelin alone. Healthy pre-menopausal women were randomized to receive 3.75 mg triptorelin (T) on days 1 and 29 with 25 mg exemestane (EX) or matched placebo once-daily for 8 weeks, from day 1 to day 56. The primary objective was to evaluate the effect of T +/- EX on estradiol (E(2)) suppression by comparing the AUC (days 36 to 57) for the 2 treatments.**
- **Secondary objectives included evaluation of estrone (E(1)), LH, and FSH suppression; effects of EX on the T-induced gonadotrophin and estrogen flare; pharmacokinetics (PK); and safety. A total of 28 subjects (14 in each arm) were evaluable for efficacy and PK. Mean plasma estrogen levels (AUC (days 36 to 57)) were significantly lower for subjects who received T + EX than for subjects who received T alone (20.6 versus 54.0 pg d/ml [-62 %; $p < 0.05$], and 38.9 versus 198.0 pg d/ml [-80 %; $p < 0.01$] for E(2) and E(1), respectively). Co-administration of EX did not affect the initial flare or subsequent suppression of LH and FSH following the first dose of T, or the PK of T. Both treatments were well-tolerated.**
- **The authors concluded that co-administration of T and EX resulted in greater estrogen suppression than when T was given alone. They noted that these findings could translate into improved clinical outcomes for pre-menopausal breast cancer patients receiving LHRH agonists.**
- **Francis et al (2015) noted that suppression of ovarian estrogen production reduces the recurrence of hormone-receptor-positive early breast cancer in premenopausal women, but its value when added to tamoxifen is uncertain. These investigators randomly assigned 3,066 premenopausal women, stratified according to prior receipt or non-receipt of chemotherapy, to receive 5 years of tamoxifen, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression. The primary analysis tested the hypothesis that tamoxifen plus ovarian suppression (triptorelin was used in 80.7 % of the patients) would improve disease-free survival, as compared with tamoxifen alone. In the primary analysis, 46.7 % of the patients had not received chemotherapy previously, and 53.3 % had received chemotherapy and remained premenopausal.**
- **After a median follow-up of 67 months, the estimated disease-free survival rate at 5 years was 86.6 % in the tamoxifen-ovarian suppression group and 84.7 % in the tamoxifen group (hazard ratio for disease recurrence, second invasive cancer, or death, 0.83; 95 % confidence interval [CI]: 0.66 to 1.04; $p = 0.10$). Multi-variable allowance for prognostic factors suggested a greater treatment effect with tamoxifen plus ovarian suppression than with tamoxifen alone (hazard ratio, 0.78; 95 % CI: 0.62 to 0.98). Most recurrences occurred in patients who had received prior chemotherapy, among whom the rate of freedom from breast cancer at 5 years was 82.5 % in the tamoxifen-ovarian suppression group and 78.0 % in the tamoxifen group (hazard ratio for recurrence, 0.78; 95 % CI: 0.60 to 1.02).**
- **At 5 years, the rate of freedom from breast cancer was 85.7 % in the exemestane-ovarian suppression group (hazard ratio for recurrence versus tamoxifen, 0.65; 95 % CI: 0.49 to 0.87). the authors concluded that adding ovarian suppression to tamoxifen did not provide a significant benefit in the overall study population. However, for women who were at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal, the addition of ovarian suppression improved disease outcomes. Further improvement was seen with the use of exemestane plus ovarian suppression.**

- **The authors also noted that "Any benefit from ovarian suppression must be weighed against the adverse effects. Adding ovarian suppression to tamoxifen resulted in increased adverse events -- most notably, menopausal symptoms, depression, and adverse events with possible long-term health implications such as hypertension, diabetes, and osteoporosis. When exemestane is combined with ovarian suppression, adverse sexual, musculoskeletal, and bone-density effects are more frequent than with tamoxifen plus ovarian suppression. Longer follow-up is required, because SOFT is currently underpowered, and the overall survival analysis is premature after 5% of patients have died".**
- **In a systematic review and meta-analysis, Bedaiwy and assocaites (2011) examined if GnRHa co-treatment with chemotherapy provides better reproductive outcomes for women at risk of POF as a side-effect of gonadotoxic chemotherapy. Electronic and manual searches (e.g., MEDLINE, EMBASE, CENTRAL) up to January 2010 were performed to identify RCTs comparing GnRH co-treatment with chemotherapy alone in pre-menopausal women. Main outcome measures included incidence of POF after treatment, incidence of women with resumption of ovulation, POF after an initial normal cycle, normal cycles but abnormal markers of ovarian reserve, spontaneous occurrence of pregnancy after treatment, and time to re-establishment of menstruation; data were also extracted to allow for an intention-to-treat analysis. A total fo 28 RCTs were identified, but only 6 met the inclusion criteria.**
- **Data were only available for the incidence of women with new onset of POF, resumption of ovulation, and occurrence of pregnancy. The incidence of POF or resumption of ovulation both demonstrated a statistically significant difference in favor of the GnRH co-treatment. The occurrence of spontaneous pregnancy showed no statistically significant difference between GnRH co-treatment and the control groups. The authors concluded that evidence from RCTs suggests a potential benefit of GnRH co-treatment with chemotherapy in pre-menopausal women, with higher rates of spontaneous resumption of menses and ovulation but not improvement in pregnancy rates. Data relating to study quality and possible bias for the majority of the outcomes in this review were not available, denoting possible selective reporting of trial data.**
- **Del Mastro et al (2011) examined the effect of the temporary ovarian suppression obtained by administering triptorelin during chemotherapy on the incidence of early menopause in young patients with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. The PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients-Gruppo Italiano Mammella 6) study, a parallel, randomized, open-label, phase III superiority trial, was conducted at 16 sites in Italy and enrolled 281 patients between October 2003 and January 2008. Patients were pre-menopausal women with stage I through III breast cancer who were candidates for adjuvant or neoadjuvant chemotherapy. Assuming a 60 % rate of early menopause in the group treated with chemotherapy alone, it was estimated that 280 patients had to be enrolled to detect a 20 % absolute reduction in early menopause in the group treated with chemotherapy plus triptorelin.**
- **The intention-to-treat analysis was performed by including all randomized patients and using imputed values for missing data. Before beginning chemotherapy, patients were randomly allocated to receive chemotherapy alone or combined with triptorelin. Triptorelin was administered intramuscularly at a dose of 3.75 mg at least 1 week before the start of chemotherapy and then every 4 weeks for the duration of chemotherapy. Main outcome measure was incidence of early menopause (defined as no resumption of menstrual activity and post-menopausal levels of FSH and estradiol 1 year after the last cycle of chemotherapy). The clinical and tumor characteristics of the 133 patients randomized to chemotherapy alone and the 148 patients randomized to chemotherapy plus triptorelin were similar.**

- **Twelve months after the last cycle of chemotherapy (last follow-up, August 18, 2009), the rate of early menopause was 25.9 % in the chemotherapy-alone group and 8.9 % in the chemotherapy plus triptorelin group, an absolute difference of -17 % (95 % CI: -26 % to -7.9 %; p < 0.001). The odds ratio for treatment-related early menopause was 0.28 (95 % CI: 0.14 to 0.59; p < 0.001). The authors concluded that the use of triptorelin-induced temporary ovarian suppression during chemotherapy in pre-menopausal patients with early-stage breast cancer reduced the occurrence of chemotherapy-induced early menopause.**
- **In an editorial that accompanied the afore-mentioned study, Rugo and Rosen (2011) noted that GnRH agonist therapy to suppress ovarian function during chemotherapy is an additional treatment that can potentially expand fertility possibilities in patients with hormone-insensitive disease. On the other hand, they stated that the use of GnRH agonists concomitant with chemotherapy can not be recommended as a standard treatment and should be approached with caution in women with hormone-sensitive disease.**
- **In a prospective randomized trial, Munster et al (2012) evaluated the effectiveness of triptorelin to preserve ovarian function in women treated with chemotherapy for early-stage breast cancer. Pre-menopausal women age 44 years or younger were randomly assigned to receive either triptorelin or no triptorelin during (neo)adjuvant chemotherapy and were further stratified by age (less than 35, 35 to 39, greater than 39 years), estrogen receptor status, and chemotherapy regimen. Objectives included the resumption of menses and serial monitoring of FSH and inhibin A and B levels. Targeted for 124 patients with a planned 5-year follow-up, the trial was stopped for futility after 49 patients were enrolled (median age of 39 years; range of 21 to 43 years); 47 patients were treated according to assigned groups with 4 cycles of adriamycin plus cyclophosphamide alone or followed by 4 cycles of paclitaxel or 6 cycles of fluorouracil, epirubicin, and cyclophosphamide.**
- **Menstruation resumed in 19 (90 %) of 21 patients in the control group and in 23 (88 %) of 26 in the triptorelin group (p = 0.36). Menses returned after a median of 5.8 months (range of 1 to 19 months) after completion of chemotherapy in the triptorelin versus 5.0 months (range of 0 to 28 months) in the control arm (p = 0.58). Two patients (aged 26 and 35 years at random assignment) in the control group had spontaneous pregnancies with term deliveries. Follicle-stimulating hormone and inhibin B levels correlated with menstrual status. The authors concluded that when stratified for age, estrogen receptor status, and treatment regimen, amenorrhea rates on triptorelin were comparable to those seen in the control group. Thus, these findings indicated that the use of GnRH agonists in pre-menopausal patients treated with contemporary neoadjuvant chemotherapy does not offer a benefit in preserving ovarian function compared with patients not treated with GnRH, and it should not be recommended.**
- **Commenting on the study by Munster et al, Partridge (2012) stated that "the role of ovarian suppression through chemotherapy remains uncertain for prevention of premature menopause. The value of this strategy is especially unclear for fertility preservation because of the lack of rigorous data from any study to show that actual fertility outcomes are improved with GnRH treatment throughout chemotherapy. Given the current level of evidence, women who are interested in future fertility and the providers who are assisting them in these often difficult decisions should not rely on GnRH agonist treatment during chemotherapy for preservation of menstrual and ovarian function or fertility".**
- **Endocrine Society Guidelines on endocrine therapy of transsexual persons (Hembree, et al., 2009) recommend the use of gonadotropin analogues. For female-to-male transsexual persons, the guidelines state that gonadotropin-releasing hormone analogues or depot medroxyprogesterone may also be used to stop menses prior to testosterone treatment and to reduce estrogens to levels found in biological males. For male to female**

transsexual persons, the guidelines states that estrogens may be used with or without antiandrogens or a GnRH agonist. The guidelines discuss a study by Dittrich, et al., which reported a series of 60 male to female transsexual persons who used monthly the GnRH agonist goserelin acetate in combination with estrogen, and found this regimen to be effective in reducing testosterone levels with low incidence of adverse reactions.

- **Lupaneta Pack: Endometriosis is defined as the presence of normal endometrial mucosa (glands and stroma) abnormally grows in locations other than the uterine cavity. About one third of women with endometriosis remain asymptomatic while some women with endometriosis have some degree of pelvic pain. Treatment options for symptomatic endometriosis include oral contraceptives, nonsteroidal anti-inflammatory drugs, high-dose progestins, androgenic agents and GnRH agonists. Several GnRH agonists including leuprolide acetate have been shown to be effective in reducing the pelvic pain associated with endometriosis, often when other medical therapies are failed.**
- **However, treatment with GnRH agonist is associated with hypoestrogenic side effects, including progressive bone loss and vasomotor symptoms, such as hot flashes and headache and vaginal dryness. The use of hormonal add back therapy can alleviate the hypoestrogenic symptoms associated with a GnRH agonist, while preserving therapeutic efficacy.**
- **Lupaneta Pack is a kit consisting of the co-packaging of two previously FDA approved drugs including leuprolide acetate for depot suspension for intramuscular use and norethindrone acetate tablets for oral use. It is indicated for the management of initial and recurrent painful symptoms of endometriosis. Leuprolide acetate, a gonadotropin-releasing hormone (GnRH), inhibits the production of estrogen through negative feedback of pituitary gonadotropins resulting in decreasing endometrial implants and symptoms of endometriosis such as pelvic pain.**
- **Norethindrone acetate, a progestin, is used to decrease the hypoestrogenic effects associated with leuprolide acetate and possibly mitigate bone mineral density loss. Norethindrone acetate is a progestin that has both estrogenic and androgenic properties and is effective as an add-back regimen without estrogen supplementation. Norethindrone add-back therapy has been shown beneficial effects on bone mineral density and vasomotor symptoms associated with GnRH agonist therapy. There have been postmarketing reports of convulsions in patients on leuprolide acetate (e.g. Lupron Depot) therapy. These included patients with and without concurrent medications and comorbid conditions.**
- **Lupaneta Pack (leuprolide acetate and norethindrone acetate) should not be utilized in persons with known hypersensitivity to Lupron (leuprolide acetate), gonadotropin releasing hormone (GnRH), GnRH analogs, or any of the excipients in the formulations. Lupaneta Pack should be discontinued if there is a sudden partial or complete loss of vision or sudden onset of proptosis, diplopia, or migraine.Observe patients with history of depression and Lupaneta Pack should be discontinued if the depression recurs to a serious degree.Two different package configurations of Lupaneta Pack(1-month) and Lupaneta Pack (3-month) kits are available: 1 month package of Lupron Depot (leuprolide acetate) 3.75 mg for IM injection with 30 tablets of 5 mg norethindrone acetate tablets. 3 month package of Lupron Depot (leuprolide acetate) 11.25 mg for IM injection with 90 tablets of 5 mg norethindrone acetate tablets.**
- **The recommended dosage for endometriosis is: Lupron Depot (leuprolide acetate) 3.75 mg IM once per month in combination with norethindrone acetate 5 mg orally once daily for 6 months; or Lupron Depot (leuprolide acetate) 11.25 mg IM once every three months in combination with norethindrone acetate 5 mg orally once daily for 6 months. If endometriosis symptoms recur after the initial course of therapy, a single retreatment**

course of not more than 6 months may be considered. Maximum total duration of therapy is 12 months.

- **Ovarian Preservation During Chemotherapy: The American College of Rheumatology's guidelines on "Screening, treatment, and management of lupus" (2012) failed to achieve consensus on the use of leuprolide for fertility preservation. Park et al (2014)examined the effects of a GnRH agonist (GnRHa) depot (leuprolide) in women with gynecologic cancer receiving chemotherapy while taking a continuous add-back on the prevention of premature ovarian failure. A total of 14 pre-menopausal patients with gynecological malignancies who had undergone conservation of ovaries surgery received a GnRH-a depot plus add-back until chemotherapy was completed; 4 weeks thereafter, a hormonal profile (FSH) was measured. The mean FSH level was 15.8 IU/L. All patients exhibited a restoration of ovarian failure during follow-up; 1 patient became pregnant during the follow-up period.**
- **The authors concluded that in the short-term, GnRHa appeared to protect ovarian function and ability to achieve pregnancy following chemotherapy. They stated that the result of this study needs further elucidation in a large randomized controlled trial (RCT).**
- **Kim et al (2014) determined the impact of concurrent use of GnRHa on relapse-free and overall survival, and established the oncologic safety of ovarian protection with GnRHa. Pre-menopausal women aged between 20 and 40 years who received adjuvant chemotherapy for breast cancer from January 2002 to April 2012 were classified into 2 groups: (i) treatment with GnRHa for ovarian protection during chemotherapy, (ii) without ovarian protection. A propensity score matching strategy was used to create matched sets of 2 groups with age, pathologic stage, hormone receptor, and Her2 status. A total of 101 patients treated with concurrent GnRHa during chemotherapy were compared with 335 propensity score-matched patients.**
- **Among them, 81.2 % were younger than 35 years and 58.4 % were hormone responsive. Survival analysis using stratified Cox regression showed that women treated with concurrent GnRHa had better recurrence-free survival (adjusted hazard ratio [HR] 0.21, p = 0.009; unadjusted HR 0.33, p = 0.034). The authors concluded that ovarian protection using GnRHa can be safely considered for young women with breast cancer in terms of oncologic outcomes. Moreover, they stated that further studies are needed to evaluate the long-term outcomes of concurrent GnRHa use with chemotherapy.**
- **In a systematic review and meta-analysis, Vitek and associates (2014) examined if concurrent use of GnRHa with chemotherapy preserves ovarian function in women with breast cancer who did not use tamoxifen. Pre-menopausal women with breast cancer treated with chemotherapy who did not receive tamoxifen were included in this analysis. Main outcome measures were OR of resumption of menses 1 year or more after chemotherapy. Searches were conducted in PubMed, Scopus, Cochrane Trials Register, and the National Research Register through March 2014, and all randomized trials that reported resumption of menses 1 year or more after GnRHa with chemotherapy or chemotherapy alone among women with breast cancer who did not receive tamoxifen were included.**
- **A total of 4 studies were analyzed in the meta-analysis and included 252 patients (GnRHa with chemotherapy, n = 131; chemotherapy alone, n = 121). There was no significant difference in the rate of return of menses between the 2 groups (OR, 1.47; 95 % CI: 0.60 to3.62). Heterogeneity among the trials was not significant (I2 = 16.6 %). The authors concluded that concurrent GnRHa with chemotherapy may not preserve ovarian function in women with breast cancer; furthermore, randomized data were limited regarding fertility after concurrent use of GnRHa with chemotherapy.**
- **Bildik et al (2015) stated that RCTs of the co-administration of GnRHa with adjuvant chemotherapy to preserve ovarian function have shown contradictory results. This fact,**

together with the lack of a proven molecular mechanism of action for ovarian protection with GnRHa places this approach as a fertility preservation strategy under scrutiny. These researchers provided in-vitro evidence for or against the role of GnRHa in the prevention of chemotherapy-induced damage in human ovary. This translational research study of ex-vivo and in-vitro models of human ovary and granulosa cells was conducted in a university hospital between 2013 and 2015. Ovarian cortical pieces (n = 15, age of 14 to 37 years) and mitotic non-luteinized (COV434 and HGrC1) and non-mitotic luteinized human granulosa cells (HLGC) expressing GnRH receptor were used for the experiments.

- **The samples were treated with cyclophosphamide, cisplatin, paclitaxel, 5-FU, or TAC combination regimen (docetaxel, adriamycin and cyclophosphamide) with and without GnRHa leuprolide acetate for 24 hours. DNA damage, apoptosis, follicle reserve, hormone markers of ovarian function and reserve (estradiol (E2), progesterone (P) and anti-mullerian hormone (AMH)) and the expression of anti-apoptotic genes (bcl-2, bcl-xL, bcl-2L2, Mcl-1, BIRC-2 and XIAP) were compared among control, chemotherapy and chemotherapy +-GnRHa groups. The greatest magnitude of cytotoxicity was observed in the samples treated with cyclophosphamide, cisplatin and TAC regimen. Exposure to these drugs resulted in DNA damage, apoptosis and massive follicle loss along with a concurrent decline in the steroidogenic activity of the samples. Co-administration of GnRHa and chemotherapy agents stimulated its receptors and raised intracellular cAMP levels.**
- **But it neither activated anti-apoptotic pathways nor prevented follicle loss, DNA damage and apoptosis induced by these drugs. The authors concluded that GnRHa treatment with chemotherapy did not prevent or ameliorate ovarian damage and follicle loss in-vitro. They stated that these data can be useful when consulting a young patient who may wish to receive GnRH treatment with chemotherapy to protect her ovaries from chemotherapy-induced damage.**
- **Elgindy and colleagues (2015) examined if GnRH analog administration during chemotherapy can protect against development of ovarian toxicity. MEDLINE (1966 to present), EMBASE (1980 to present), Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov were searched through March 2015 using the phrases: "gonadotropin-releasing hormone", "chemotherapy" and "premature ovarian failure". Hand-search on conference abstracts, SCOPUS, and ISI Web of Science were also searched. Published English-language RCTs comparing resumption of ovarian function between GnRH analogs plus chemotherapy with chemotherapy without GnRH analogs were included. Studies including women with pelvic metastases or recent history of receiving chemotherapy were excluded.**
- **Accordingly, 10 eligible trials (907 women) were analyzed. The primary outcome was the proportion of women with resumed ovarian function (defined as resumption of menstruation, prevention of chemotherapy-induced ovarian failure, or both) at the longest follow-up after the end of chemotherapy. Secondary outcomes were evaluating ovarian reserve parameters and pregnancy. Risk ratio was used to integrate qualitative results and MD was used for quantitative data. Gonadotropin-releasing hormone analog co-treatment did not significantly increase ovarian function resumption (320/468 [68.4 %] in GnRH analog arm and 263/439 [59.9 %] in the chemotherapy alone arm; risk ratio 1.12, 95 % CI: 0.99 to 1.27).**
- **No protective effect existed after subgroup analyses (type of malignancy [p = 0.31], age [p = 0.14], and GnRH analog type [p = 0.44]). These researchers noted that GnRH analogs did not protect any of ovarian reserve parameters, whether FSH (MD -2.63, 95 % CI: -7.33 to 2.07), antral follicle count (MD 1.66, 95 % CI: -0.69 to 4.01), or AMH (MD 0.31, 95 % CI: -0.41 to 1.03). Spontaneous pregnancy was also comparable (RR 1.63, 95 % CI: 0.94 to 2.82). The authors concluded that GnRHa administration during chemotherapy did not appear to**

protect the ovaries from gonadal toxicity. It is not a reliable method for fertility preservation.

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- Reviewed by a Board Certified Internist
- Reviewed by David Evans, MD, Medical Director, Active Health Management- August 2016

Footnotes

[A] If norethindrone acetate is contraindicated, then retreatment is not recommended. Bone density is recommended before retreatment begins to ensure that values are within normal limits.

[B] Lupron-Ped is administered as a single intramuscular injection. The starting dose 7.5 mg, 11.25 mg, or 15 mg for 1 month administration is based on the child's weight: < 25 kg body weight - 7.5 mg dose; > 25-37.5 kg body weight - 11.25 mg dose; > 37.5 kg body weight - 15 mg dose.If total down regulation is not achieved then the dose should be titrated up by 3.75 mg every four weeks. This dose is considered the maintenance dose. Lupron Depot-Ped is administered as a single intramuscular injection. The doses are either 11.25 mg or 30 mg for 3-month administration. Discontinuation of leuprolide for central precocious puberty should be considered at age 11 for girls and age 12 for boys.

[C] Note: Treatment of infertility may be subject to specific limitations under some benefit plans. Most HMO plans exclude injectable infertility drugs from coverage.

[D] The Adolescent has demonstrated a long lasting and intense pattern of gender non conformity or gender dysphoria (whether suppressed or expressed) and gender dysphoria emerged or worsened with the onset of puberty and any coexisting psychological, medical or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such as the adolescent's situation and functioning are stable enough to start treatment, and the adolescent has given informed consent and particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process

[E] Up to 6 months per treatment -- because of lack of safety data with long-term use, and concerns in available peer-reviewed medical literature regarding effects on bone density.

[F] Lupron-Ped is administered as a single intramuscular injection. The starting dose 7.5 mg, 11.25 mg, or 15 mg for 1 month administration is based on the child's weight: < 25 kg body weight - 7.5 mg dose; > 25-37.5 kg body weight - 11.25 mg dose; > 37.5 kg body weight - 15 mg dose.If total down regulation is not achieved then the dose should be titrated up by 3.75 mg every four weeks. This dose is considered the maintenance dose. Lupron Depot-Ped is administered as a single intramuscular injection. The doses are either 11.25 mg or 30 mg for 3-month administration. Discontinuation of leuprolide for central precocious puberty should be considered at age 11 for girls and age 12 for boys.

[G] 1 implant every 12 months. The implant is inserted subcutaneously and provides continuous release of histrelin (50 to 60 mcg/day for Vantas) for 12 months of hormonal therapy.

[H] 1 implant every 12 months. The implant is inserted subcutaneously and provides continuous release of histrelin (65 mcg/day for Supprelin LA) for 12 months of hormonal therapy.

[I] 1 mg given subcutaneously daily. If receiving leuprolide acetate suspension (Lupron Depot), dosing is: Lupron Depot 7.5 mg for 1-month administration, given as a single intramuscular injection every 4 weeks.Lupron Depot 22.5 mg for 3-month administration, given as a single intramuscular injection every 12 weeks.Lupron Depot 30 mg for 4-month administration, given as a single intramuscular injection every 16 weeks.Lupron Depot 45 mg for 6-month administration, given as a single intramuscular injection every 24 weeks.

[J] Lupron-Ped is administered as a single intramuscular injection. The starting dose 7.5 mg, 11.25 mg, or 15 mg for 1-month administration is based on the child's weight:< 25 kg body weight - 7.5 mg dose; > 25-37.5 kg body weight - 11.25 mg dose; > 37.5 kg body weight - 15 mg dose. If total down regulation is not achieved then the dose should be titrated up by 3.75 mg every four weeks. This dose is considered the maintenance dose. Lupron Depot-Ped is administered as a single intramuscular injection. The doses are either 11.25 mg or 30 mg for 3-month administration. Discontinuation of leuprolide for central precocious puberty should be considered at age 11 for girls and age 12 for boys.

[K] Up to 6 months per treatment -- because of lack of safety data with long-term use, and concerns in available peer-reviewed medical literature regarding effects on bone density.

[L] Degarelix is contraindicated and considered not medically necessary for persons with hypersensitivity to Degarelix.

Codes

CPT® : 11980

HCPCS: J1950, J3315, J3355, J9155, J9202, J9217, J9218, J9219, J9225, J9226, S0122, S0187