Module 2

Infertility: Therapeutics and Medication Profiles

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Disclosure: Ann Scalia, Mary Vietzke and Kajaal Patel are employees of Walgreens. There will be discussion of off-label use of medications in fertility treatment during this activity.

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Objectives

- Review an IVF cycle timeline
- Describe the mechanism of action of various infertility medications in the body
- Discuss how fertility medications are supplied, administration, storage requirements as well as common side effects

Phases of the Menstrual Cycle

First day of menses is cycle-day 1 and is onset of follicular phase

<table>
<thead>
<tr>
<th>Follicular</th>
<th>Ovulatory</th>
<th>Luteal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment of multiple follicles</td>
<td>Midcycle surge of Luteinizing hormone (LH) required for final maturing of the oocyte</td>
<td>Starts after LH surge.</td>
</tr>
<tr>
<td>Emergence and growth of dominant follicle</td>
<td>LH levels increase tenfold due to rising estradiol. Initiation of follicle rupture, which generally occurs 36 hours after the surge</td>
<td>Formation of the corpus luteum = P4 production</td>
</tr>
<tr>
<td>Follicular development occurs with secretion of estradiol</td>
<td></td>
<td>Coordinated in endometrium as it prepares for possible implantation</td>
</tr>
<tr>
<td>Rising levels estradiol associated with endometrial proliferation</td>
<td></td>
<td>Absence of pregnancy the corpus luteum declines</td>
</tr>
</tbody>
</table>

Sources:
Reproductive Axis

• Regular ovulatory cycles achieved through integration of stimulatory and inhibitory signals from the hypothalamus, pituitary and ovary
• Initiated by pulsatile secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus into the pituitary portal
• GnRH regulates the pituitary synthesis and release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) into the circulation

Stauss, Berkeri, Yen & Jaffé’s Reproductive Endocrinology: physiology, pathophysiology, and clinical management. 2014: 141-142.

Hypothalamic-Pituitary-Gonadal Axis

LH
and
FSH

ovary or testes

Estrogen

or

Testosterone

### Follicle Stimulating Hormone (FSH)
- Gonadotropin hormone secreted by the anterior pituitary
- Essential for follicular growth
- Critical for recruitment of follicles and selection
- Responsible for initiation/maintenance of spermatogenesis in the male together with testosterone

### Luteinizing Hormone (LH)
- Gonadotropin hormone secreted by the anterior pituitary
- Needed for growth of the preovulatory follicle
- LH surge initiates the luteinization and ovulation of the dominate follicle
- Ruptured follicle becomes corpus luteum which contributes to the production of continued progesterone and estrogen

### Estrogen
- Steroid hormone produced by the ovary and needed for the maturing follicle and oocyte
- Estradiol is the most potent form of estrogen
- Estradiol levels begins to rise significantly by cycle day 7 once the dominant follicle is established

### Testosterone
- Primary male hormone produced by the testes
- Responsible for the development of sperm, (spermatogenesis), male physical characteristics, and sex drive
- Produced in small quantities by the ovaries in women

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**Fertility Medications**

- Medications associated with Ovulation Induction (OI) and Controlled Ovarian Stimulation (COS)
- Mechanism of action
- Storage information
- Medication administration
- Considerations
Ovulation Induction Medications: Two Fold

Correct Ovulatory Dysfunction
- Oligo-ovulation
- Anovulation

Controlled Ovarian Stimulation (COS)
- Intrauterine Insemination (IUI)
- In Vitro Fertilization (IVF)
- Donor/Third party Reproduction

Oral Contraceptive Pills (OCP)
- Oral contraceptive pills, may be prescribed to regulate a patient’s menstrual cycle
- In an ART cycle:
  - Used to “suppress or downregulate” activity in the ovaries in the prestimulation phase
  - Allows manipulation of the patient's cycle to fit into a set schedule (Batching)
- Combination hormonal OCP
  - Progestin component of a combination pill prevents ovulation by inhibiting gonadotropin secretion of LH; also alters endometrium
  - Estrogenic component suppresses FSH

Oral Medications: Ovulation Induction

Oral Medications
- Clomiphene Citrate
- Letrozole

Timing
- Timed Intercourse
- Intrauterine Insemination


Anti-Estrogens

- Initial treatment of choice for most anovulatory or oligo-ovulatory infertile women desiring pregnancy
- Clomiphene Citrate is the most widely used anti-estrogen for treating anovulatory women
- In ovulatory women, CC treatment increases GnRH pulse frequency
- Has estrogenic and anti-estrogenic actions so give lowest dose possible due to anti-estrogenic effects on cervical mucus and endometrium which are counterproductive to initiation of pregnancy

### Clomiphene Citrate (CC)

#### Clomiphene Citrate

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism of Action</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Indicated for the treatment of ovulatory dysfunction in anovulatory women desiring pregnancy with unexplained fertility</td>
<td>• Ovulatory stimulant that may compete with estrogen for estrogen-receptor-binding sites (i.e. hypothalamus, pituitary, ovary, endometrium, vagina, and cervix)</td>
<td>• Patients should be advised that blurring or other visual symptoms may occasionally occur during therapy which may render activities as driving a car/operating machinery more hazardous than usual, and to notify their MD immediately</td>
</tr>
<tr>
<td>• FDA approved for ovulation induction in women with unexplained and anovulatory infertility</td>
<td>• Initiates preovulatory gonadotropin surge and subsequent rupture of follicles by release of pituitary gonadotropins initiating steroidogenesis and folliculogenesis, resulting in growth of ovarian follicle and increase in the circulating estradiol levels</td>
<td>• Patients are advised to discontinue CC and have a complete ophthalmological evaluation carried out promptly</td>
</tr>
<tr>
<td>• Off-label reproductive use - Induce multiple follicle response with intrauterine Insemination (IUI) and in treatment of select male infertility issues</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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### Clomiphene Citrate

#### Trade/Drug name or available as

<table>
<thead>
<tr>
<th>Trade/Drug name or available as</th>
<th>Route of administration</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomiphene Citrate</td>
<td>Oral</td>
<td>Ovarian enlargement; hot flashes; pelvic discomfort, distension, bloating; nausea and vomiting; breast tenderness; visual symptoms (blurred vision, floaters, photophobia, diplopia, scotomata) headache</td>
</tr>
</tbody>
</table>

#### Manufacturer

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>How supplied</th>
<th>Dose per container</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple manufacturers</td>
<td>Clomiphene Citrate USP, 50mg tablet Color: White</td>
<td>Box of 30 unit dose tablets</td>
</tr>
</tbody>
</table>

#### Dosage and Administration

<table>
<thead>
<tr>
<th>Therapy should begin after careful diagnostic evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial course of therapy: 1 tablet (50 mg) daily for 5 days on days 3-7 or 5-9 of menstrual cycle as determined by physician</td>
</tr>
<tr>
<td>Second course of therapy: 2 tablets (100mg) daily, as a single dose, for 5 days on day 3-7 or 5-9 of menstrual cycle if ovulation does not occur after first course of therapy. Second course can begin as early as 30 days in the absence of confirmed pregnancy</td>
</tr>
<tr>
<td>Increasing the dosage or duration of therapy beyond 100 mg/day for 5 days is not recommended by the US FDA</td>
</tr>
<tr>
<td>If ovulation does not occur after 3 courses of therapy, further treatment is not recommended and the patient should be re-evaluated. If 3 ovulatory responses occur, but pregnancy has not been achieved, further treatment is not recommended. Long-term cyclic therapy is not recommended beyond a total of about 6 cycles</td>
</tr>
</tbody>
</table>

#### Storage

| Store tablets at controlled room temperature 59°F-86°F (15°C-30°C). Protect from heat, light, and excessive humidity, and store in closed containers |

CLOMIPHENE CITRATE (prescribing information). Sellersville, PA: Teva Pharmaceuticals USA, Revised August 2012.
Aromatase Inhibitors

- Used off-label for reproductive use
  - Ovarian stimulation and ovulation induction in women who are anovulatory as well as unexplained fertility, PCOS
  - Letrozole is most widely used (often in combination with gonadotropins)
- Must have intact H-P-O axis
- Prevents conversion of androgens to estrogen thereby decreases estrogen
- Increases pituitary FSH secretion
- No antiestrogenic effects on endometrium

Letrozole

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism of Action</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer</td>
<td>Selective aromatase inhibitor that inhibits the conversion of androgens to estrogens</td>
<td>Off-label reproductive use: Ovulation induction/ovarian stimulation protocols similar to clomiphene citrate started on Cycle day 3, 4 or 5 daily for 5 days</td>
</tr>
<tr>
<td>Extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy</td>
<td>Inhibits aromatase enzyme by competitively binding to the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues</td>
<td>Controversial risk of birth defects with Letrozole use; Half-life 2d so theory excreted before pregnancy occurs</td>
</tr>
<tr>
<td>First &amp; second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer</td>
<td>Off-label reproductive use: Ovarian stimulation/ovulation induction for women who are anovulatory, unexplained fertility, Polycystic Ovary Syndrome (PCOS) or women undergoing a fertility preservation cycle with estrogen-receptor cancers</td>
<td></td>
</tr>
</tbody>
</table>

## Letrozole

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<thead>
<tr>
<th>Trade/Drug name or available as</th>
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<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femara Letrozole</td>
<td>Oral</td>
<td>Hot flashes, night sweats, muscle pain, fatigue, nausea, vomiting, vaginal bleeding and/or irritation, breast pain, and hair loss</td>
</tr>
</tbody>
</table>

### Manufacturer

- **Multiple Manufacturers:**
  - Generic: Breckenridge, Mylan
  - Brand: Novartis

### How supplied

- 2.5 mg film-coated tablet of Letrozole Tablets, USP
- Bottles of 30 tablets
- Bottles of 1000 tablets

### Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

### Dosage and Administration

- Off Label reproductive use for ovulation induction and ovarian stimulation: 2.5mg to 5mg daily, as a single dose, for 5 days starting on cycle day three to five individualized per prescriber preference

### The Role of Gonadotropins

- Indicated for women that do not respond to clomiphene citrate
- Indicated for use with ART-IVF to stimulate multiple follicles
- Act directly on the ovary
- Ovarian function must be documented
- Must be given by injection
- Careful monitoring and evaluation
Infertility Advanced Treatment Stages

Gonadotropins Currently on the Market

- Both hMG and FSH products are called gonadotropins. They are used alone or in conjunction with one another in all ovulation induction and IVF fertility cycles

<table>
<thead>
<tr>
<th>Urinary (hMG)</th>
<th>Menotropins for injection (Menopur®) (FSH/LH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant (FSH only)</td>
<td>Follitropin beta injection (Follistim® AQ)</td>
</tr>
<tr>
<td></td>
<td>Follitropin alpha injection (Gonal-f® Multi-Dose)</td>
</tr>
<tr>
<td></td>
<td>Follitropin alpha (Gonal-f® RFF SDV/Redi-Ject Pen)</td>
</tr>
</tbody>
</table>
# Urinary Human Menopausal Gonadotropin (hMG)

## Menotropins for Injection

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism of Action</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of multiple follicles and pregnancy in ovulatory women as part of an Assisted Reproductive Technology (ART) Cycle</td>
<td>Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are active components in Menotropins for Injection</td>
<td>Available only as Menopur® containing 75IU FSH and 75IU LH activity per vial</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are active components in Menotropins for Injection</td>
<td>Produces ovarian follicular growth and maturation in women who do not have primary ovarian failure</td>
<td>Often prescribed with another FSH only formulation to add back LH</td>
</tr>
<tr>
<td>Produces ovarian follicular growth and maturation in women who do not have primary ovarian failure</td>
<td>Available only as Menopur® containing 75IU FSH and 75IU LH activity per vial</td>
<td>Administration supplies not included with medication - need to prescribed by specific center</td>
</tr>
<tr>
<td>Available only as Menopur® containing 75IU FSH and 75IU LH activity per vial</td>
<td>Recommended injection sites are either side of lower abdomen alternating sides</td>
<td></td>
</tr>
</tbody>
</table>

## Gonadotropins Currently on the Market

<table>
<thead>
<tr>
<th>Trade/Drug name or available as</th>
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<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopur®</td>
<td>Subcutaneous</td>
<td>Abdominal cramps or pain, enlarged abdomen, headache, injection site reactions (pain and inflammation), ovarian hyperstimulation syndrome (OHSS)</td>
</tr>
</tbody>
</table>

### Manufacturer

- **Ferring**

#### How supplied

- 5 single dose vials of lyophilized powder or pellet with 75 IU FSH and 75 IU LH activity
- 5 single dose 2 mL vials of diluent – 0.9% Sodium Chloride for Injection, USP
- 5 O-Cap vial adapter
- 1 vial sterile diluent can be used to reconstitute up to 5 additional vials

#### Dose per container

- Single dose

### Dosage and Administration

- Treatment usually begins on cycle day 2 or 3 and is administered daily
- Continue treatment until adequate follicular development is evident, and then administer HCG
- Therapy should not exceed 20 days

### Storage

- Lyophilized powder may be stored refrigerated or at room temperature (3° to 25° C/37° to 77°F) until dispensed
- Use immediately after reconstitution. Discard unused material
- Protect from light
**Recombinant Follicle Stimulating Hormone (r-FSH)**

### Indication

**In Women**
- Induction of ovulation and pregnancy in anovulatory infertile women in whom the cause of infertility is functional and not due to Primary Ovarian Failure (POF)
- Pregnancy in normal ovulatory women undergoing Controlled Ovarian Stimulation (COS) as part of an IVF or Intracytoplasmic Sperm Injection (ICSI) Cycle

**In Men**
- Induction of spermatogenesis in men with primary and secondary hypogonadotrophic hypogonadism (HH) in whom the cause of infertility is not due to primary testicular failure

### Mechanism of Action

**In Women**
- Follicle-stimulating hormone (FSH), the active component in Follicitropin beta, is required for normal follicular growth, maturation, and gonadal steroid production
- FSH level is critical for onset/duration of follicular development, and for the timing and number of follicles reaching maturity in women who do not have POF

**In Men**
- Administered with hCG stimulates spermatogenesis

### Considerations

- Available as Follistim® AQ Cartridge
- Patient MUST have a Follistim® Pen (for use only with Follistim® AQ Cartridge) to administer medication which is free of charge
- Use is contraindicated in patients with a neomycin or streptomycin hypersensitivity
- Check with patient and MD before dispensing
Recombinant Follicle Stimulating Hormone (r-FSH)

**Follitropin Alpha Injection**

<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th><strong>Mechanism of Action</strong></th>
<th><strong>Considerations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In Women</strong></td>
<td><em>Follicle-stimulating hormone (FSH) is the primary hormone responsible for follicular recruitment and development</em></td>
<td><em>Available only as Follitropin alfa for injection:</em></td>
</tr>
<tr>
<td>• Indicated for the induction of ovulation and pregnancy in the anovulatory infertile patient in whom the cause of infertility is functional and not due to primary ovarian failure</td>
<td>• FSH level is critical for onset /duration of follicular development, and consequently for the timing and number of follicles reaching maturity in women who do not have POF</td>
<td>• Gonad-1® RFF SDV</td>
</tr>
<tr>
<td>• Development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) program</td>
<td>• In Men</td>
<td>• Gonad-1® RFF Redi-ject Pen</td>
</tr>
<tr>
<td><strong>In Men</strong></td>
<td>• FSH is the primary hormone responsible for spermatogenesis</td>
<td>• Color-coded according to strength</td>
</tr>
<tr>
<td>• Induction of spermatogenesis in men in conjunction with hCG with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure</td>
<td>• In MV, package contains administration syringes calibrated in FSH unit markings (FSH IU)</td>
<td>• Gonal-1® MDV</td>
</tr>
</tbody>
</table>


**Dosage and Administration**

The recommended dosing follows a stepwise approach and is individualized for each person:

1. **Ovulation Induction for anovulatory women**
   - Starting daily dose of 50 IU daily for at least the first 7 days. Subsequent dosage adjustments are made at weekly intervals based upon ovarian response. If an increase in dose is indicated, the increase should be made by 25 or 50 IU of Follistim AQ at weekly intervals until indication of an adequate ovarian response. The maximum, individualized, daily dose of Follistim AQ is 250 IU.

2. **Assisted Reproductive Technologies - Controlled ovarian stimulation as part of an In Vitro Fertilization (IVF) Cycle for women with normal ovulatory function**
   - Starting daily dose of 200 IU for at least the first 7 days of treatment. After the first 7 days of treatment, the dose can be adjusted up or down based upon ovarian response. Maximum, individualized, daily dose of Follistim AQ is 500 IU. Follistim is administered for 7-12 days until a sufficient number of follicles of adequate size are present. Dosing is then stopped and final maturation of the oocytes is induced by administering hCG.

3. **Induction of spermatogenesis in men**
   - Pretreatment with hCG to normalize testosterone levels is required prior to concomitant therapy with Follistim AQ and hCG. Follistim is given subcutaneously at a dosage of 450 IU per week, as either 225 IU twice weekly or 150 IU three times per week, in combination with the same hCG dose.
### Recombinant Follicle Stimulating Hormone (r-FSH)

<table>
<thead>
<tr>
<th>Trade/Drug name or available as</th>
<th>Manufacturer</th>
<th>How supplied</th>
<th>Dose per container</th>
</tr>
</thead>
</table>
| Gonal-f® RFF (folitropin alpha) | EMD Serono | • Gonal-f® RFF Redi-ject is a disposable, prefilled multiple-dose delivery pen containing a sterile, ready-to-use liquid formulation of folliculin alpha. Each Redi-ject is supplied in a carton containing 29G x 1/2 inch disposable needles to be used for administration  
• Formulations:  
  • One Gonal-f® RFF Redi-ject pen containing 300 IU per 0.5 mL and 5 single-use disposable 29G x ½ needles  
  • One Gonal-f® RFF Redi-ject pen containing 450 IU per 0.75 mL and 7 single-use disposable 29G x ½ needles  
  • One Gonal-f® RFF Redi-ject containing 900 IU per 1.5 mL and 14 single-use disposable 29G x ½ needles | Disposable Multiple dose pen |

### Storage
- Store refrigerated 2°C to 8°C (36°F to 46°F) until dispensed
- Upon dispensing, store Redi-ject refrigerated 2°C to 8°C (36°F to 46°F) until the expiration date, or at room temperature 20° to 25°C (68° to 77°F) for up to three months or until the expiration date, whichever occurs first
- After the first injection, store refrigerated 2°C to 8°C (36°F to 46°F) or at room temperature 20°C to 25°C (68°F to 77°F) for up to 28 days
- Protect from light. Do not freeze
- Discard unused material after 28 days

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### Recombinant Follicle Stimulating Hormone (r-FSH)

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<thead>
<tr>
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<th>Dose per container</th>
</tr>
</thead>
</table>
| Gonal-f® Multidose Vial | EMD Serono | • 1 vial Gonal-f® Multi-Dose 450 IU, in a sterile, lyophilized powder form  
  • 1 1 mL pre-filled syringe of Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol)  
  • 6 syringes calibrated in FSH Units (IU FSH) for injection with affixed 27 gauge ½ inch needle  
  • 1 vial Gonal-f® Multi-Dose 1050 IU, in a sterile, lyophilized powder form  
  • 2 1 mL pre-filled syringe of Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol)  
  • 10 syringes calibrated in FSH Units (IU FSH) for injection affixed 27 gauge ½ inch needle | Multi dose vial |

### Storage
- Multi-Dose powder vials may be stored refrigerated or at room temperature (2°-25°C/36°-77°F)
- Following reconstitution, the Multi-Dose vial may be stored refrigerated or at room temperature (2°-25°C/36°-77°F)
- Protect from light
- Discard unused reconstituted solution after 28 days

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Recombinant Follicle Stimulating Hormone (r-FSH)

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<th>Dose per container</th>
</tr>
</thead>
</table>
| Gonal-f™ RFF (follitropin alpha) | EMD Serono  | • Gonal-f™ RFF 75 IU Vials  
10 vials of Gonal-f™ RFF 75 IU sterile, lyophilized powder in single-dose vials  
• 10 mL prefilled syringes of Sterile Water for Injection, USP  
• 10 18-gauge needles for reconstitution  
• 10 29-gauge needles for administration | Single dose vial |

**Storage**
- Lyophilized vials may be stored refrigerated or at room temperature (2°- 25°C/36°- 77°F)
- Protect from light
- Use immediately after reconstitution
- Discard unused material


Recombinant Follicle Stimulating Hormone (r-FSH)

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<tr>
<th>Trade/Drug name or available as</th>
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<th>Common side effects</th>
</tr>
</thead>
</table>
| Gonal-f™ Multidose Vial  
Gonal-f™ RFF SDV  
Gonal-f™ RFF Redi-ject Pen (follitropin alpha) | Subcutaneous | Abdominal pain, nausea, enlarged abdomen, headache, injection site reactions (bruising, pain, inflammation), ovarian hyperstimulation, flatulence, diarrhea, ovarian cysts |

**Dosage and Administration**
Recommended dosing for Gonal-f or Gonal-f RFF to stimulate development of the follicle is stepwise and must be individualized for each patient:
1. Infertile patients with oligo-anovulation
   - Initial dose of the first cycle should be 75 IU per day. Incremental adjustment in dose of up to 37.5 IU may be considered after 14 days. Further dose increases could be made, if necessary, every seven days. Over the course of treatment, doses may range up to 300 IU per day depending on the individual patient response. Treatment duration should not exceed 35 days
2. Assisted Reproductive Technologies
   - Initial dose initiated in early follicular phase of 150 IU - 225 IU per day and continued until adequate follicular development is achieved. Therapy in most cases should not exceed 10 days. Dose adjustments may be considered after five days based on response and adjusted no more than 75-150 IU each time. Doses greater than 450 IU per day are not recommended
3. Male patients with Hypogonadotropic Hypogonadism - Induction of spermatogenesis
   - Pretreatment with HCG to normalize testosterone levels is required prior to concomitant therapy with Gonal-f™ and HCG. Gonal-f™ 150 IU is administered subcutaneously three times a week in conjunction with the appropriate dose of HCG. Dose may be increased to a maximum dose of 300 IU three times per week. Gonal-f™ may need to be administered for up to 18 months to achieve adequate spermatogenesis

Ovarian Hyperstimulation Syndrome (OHSS)

- OHSS is a medical event separate from uncomplicated ovarian enlargement during a controlled ovarian stimulation cycle.
- Symptoms of OHSS:
  - Mild symptoms include short-term abdominal discomfort, ovarian enlargement, mild nausea/vomiting, diarrhea and abdominal distension.
  - Severe symptoms include rapid weight gain, tense ascites, dyspnea, oliguria, abnormal labs (hemodynamic instability).
  - Life-threatening complications include serious lung (ARDS), hemorrhage, thromboembolism, renal failure.

GnRH

GnRH Analogs

GnRH Agonist
- Binds to a receptor and exhibits a desired response
  - Leuprolide Acetate

GnRH Antagonist
- Binds to a receptor and inhibits another molecule from binding to the receptor, thus inhibiting the desired response
  - Cetrorelix Acetate
  - Ganirelix Acetate


GnRH Agonist

Leuprolide Acetate Injection

**Indication**
- Leuprolide acetate injection is indicated in the palliative treatment of advanced prostatic cancer, endometriosis, uterine fibroids, precocious puberty
- Infertility off-label use
  - Suppresses gonadotropin secretion by the pituitary
  - Can be used as downregulation when given during luteal phase of cycle (~day 21)
  - Prevents premature LH surge during COS

**Mechanism of Action**
- Acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses
- Following an initial stimulation of gonadotropins, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis
- Effect is reversible upon discontinuation of drug therapy

**Considerations**
- Available only as generic
- Prescriber may request a compound version called Leuprolide Micro-Dose

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**Trade/Drug name or available as** | **Manufacturer** | **How supplied** | **Dose per container**
---|---|---|---
Leuprolide Acetate 1mg/0.2ml 14 Day Kit | Sandoz | Multi-dose vial | Multi-dose vial

**Route of administration**
- Subcutaneous

**Common side effects**
- Injection site reactions (bruising, soreness), vaginal bleeding, pelvic pain, breast tenderness, hot flashes, vaginal dryness, constipation, headache, weakness, dizziness

**Dosage and Administration**
- The dosing follows a stepwise approach and is individualized for each person dependent upon ART procedure
- Usual dose is 1 mg (0.2 mL or 20 unit mark) administered as a single daily subcutaneous injection

**Storage**
- Store below 77°F (25°C)
- Do not freeze
- Protect from light; store vial in carton until use

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**Fertility medication information: Leuprolide acetate. DailyMed Web site.**
### GnRH Antagonist

**Ganirelix Acetate Injection**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism of Action</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| • Indicated for the inhibition of premature LH surges in women undergoing controlled ovarian stimulation (COH) | • Acts by blocking the GnRH receptors on the pituitary gonadotroph and subsequent transduction pathway. It induces a rapid, reversible suppression of gonadotropin secretion  
• If discontinued, pituitary LH and FSH levels are fully recovered within 48 hours | • Available as generic version only in PFS  
• Barrel of the syringe is not marked  
• Started once daily during the mid to late portion of follicular phase until day of hCG trigger  
• Needle shield contains latex—confirm severity with patient and MD before dispensing  
• Do not refrigerate |

---

### GnRH Antagonist

<table>
<thead>
<tr>
<th>Trade/Drug name or available as</th>
<th>Route of administration</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganirelix 250mcg/0.5ml</td>
<td>Subcutaneous</td>
<td>Injection site reactions (bruising, and soreness), abdominal pain, headache, vaginal bleeding, nausea, symptoms of ovarian hyperstimulation may occur</td>
</tr>
</tbody>
</table>

**Manufacturer**

<table>
<thead>
<tr>
<th>How supplied</th>
<th>Dose per container</th>
</tr>
</thead>
</table>
| • Prefilled 1 mL syringe containing 250 mcg/0.5 mL aqueous solution of Ganirelix Acetate  
• Prefilled syringe is affixed with a 27 gauge ½-inch needle  
• Prefilled disposable syringe with affixed 27 gauge ½ inch needle containing 0.5 mL an aqueous solution of Ganirelix Acetate 250mcg | Single dose Prefilled syringe |

**Dosage and Administration**

- Ganirelix 250mcg may be administered once daily during the mid to late portion of the follicular phase. It is usually started on stimulation day 5 or 6 and should be continued daily until the day of hCG administration. Needle shield contains natural rubber latex

**Storage**

- Store at 25°C (77°F)  
- Excursions permitted to 15–30°C (59–86°F)  
- Protect from light

---

*GANIRELIX ACETATE (prescribing information). Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC.; Merck & Co., Inc.; March 2016.*
### GnRH Antagonist

#### Cetrorelix Acetate for Injection

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism of Action</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Indicated for the inhibition of premature LH surges in women undergoing controlled ovarian stimulation</td>
<td>• Competes with natural GnRH for binding to receptors on pituitary cells and thus controls the release of LH and FSH in a dose-dependent manner</td>
<td>• Available only as Cetrotide®</td>
</tr>
<tr>
<td></td>
<td>• Onset of suppression within 2 hours and maintained by continuous dosing</td>
<td>• Administered after starting gonadotropin stimulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Day 5 or day 6 and continued daily until the day of hCG trigger</td>
</tr>
</tbody>
</table>

#### Trade/Drug name or available as

- Cetrotide 0.25mg

#### Route of administration

- Subcutaneous

#### Common side effects

- Local injection site reactions (redness, bruising, swelling, itching and soreness), headache, nausea, symptoms of ovarian hyperstimulation syndrome may occur

#### Manufacturer

- EMD Serono

#### How supplied

- 1 vial with lyophilized powder for reconstitution
- 1 pre-filled syringe with diluent – sterile water for injection
- One 20 gauge needle
- One 27 gauge needle
- 2 alcohol swabs

#### Dose per container

- Single dose

#### Dosage and Administration

- Ovarian stimulation therapy with gonadotropins (FSH, hMG) is started on cycle Day 2 or 3
- Cetrorelix 0.25 mg is administered on either stimulation day 5 (morning or evening) or day 6 (morning) and continued daily until the day of hCG administration

#### Storage

- Store refrigerated 2-8 °C (36-46 °F)
- Store the packaged tray in the outer carton in order to protect from light
Human Chorionic Gonadotropin (hCG)

Chorionic Gonadotropin for Injection, USP

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism of Action</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure, and who has been appropriately pretreated with gonadotropins&lt;br&gt;<strong>In Men:</strong>&lt;br&gt;• Prepubertal cryptorchidism not due to anatomic obstruction&lt;br&gt;• Treatment of hypogonadotropic hypogonadism (hypogonadism secondary to a pituitary deficiency) in males</td>
<td>• Action of hCG is virtually identical to pituitary LH, although hCG appears to have a small degree of FSH activity&lt;br&gt;• LH participates with FSH in the development/maturation of ovarian follicle, mid-cycle LH surge triggers ovulation. hCG can substitute for LH in this function&lt;br&gt;• Stimulates production of gonadal steroid hormones by stimulating corpus luteum of the ovary to produce progesterone and Leydig cells of testes to produce androgens&lt;br&gt;• During pregnancy, hCG secreted by the placenta maintains the corpus luteum after LH secretion decreases, supporting continued secretion of estrogen and progesterone</td>
<td>• Available as Chorionic Gonadotropin, Novarel®, Pregnyl®&lt;br&gt;10,000 USP Units per 10mL MDV with 10 mL diluent&lt;br&gt;• Infertility patient usually takes 10,000 units medication powder as single dose but it is usually mixed with 1mL, NOT the full 10 mL volume of diluent&lt;br&gt;• Pregnyl and Novarel are Latex-Free&lt;br&gt;• Time-sensitive medication&lt;br&gt;➢ Given following the last dose of gonadotropins&lt;br➢ Egg retrieval scheduled 36 hours after injection&lt;br➢ Taken too soon or too late can impact and possibly ruin a cycle&lt;br➢ Referred to as “trigger shot”</td>
</tr>
</tbody>
</table>

Human Chorionic Gonadotropin

<table>
<thead>
<tr>
<th>Trade/Drug name or available as</th>
<th>Route of administration</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Chorionic Gonadotropin (hCG)&lt;br&gt;10,000 USP Units/Vial&lt;br&gt;(Urinary hCG)</td>
<td>Intramuscular or may be administered subcutaneously (off-label) as per prescriber preference</td>
<td>Headache, irritability, restlessness, fatigue, edema, gynecomastia pain, redness, swelling at the site of injection, hypersensitivity reactions, both localized and systemic in nature, have been reported.</td>
</tr>
</tbody>
</table>

Dosage and Administration

- Dosage regimen will depend upon the indication for use, the age and weight of the patient and the physician’s preference
- Usually administered as 5,000 to 10,000 USP units one day following the last dose of gonadotropin

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>How supplied</th>
<th>Dose per container</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresenius Kabi USA</td>
<td>• Chorionic Gonadotropin for Injection, USP, is supplied in two-vial package&lt;br&gt;• One 10 mL multiple dose vial of lyophilized powder or pellet of Chorionic Gonadotropin for injection, USP, 10,000 USP&lt;br&gt;• One 10 mL vial of diluent – Bacteriostatic Water for Injection, USP</td>
<td>Usually single dose for fertility patients&lt;br&gt;Available as multiple dose vial</td>
</tr>
</tbody>
</table>

Storage

- Store at 20° to 25°C (68° to 77°F)

Human Chorionic Gonadotropin

<table>
<thead>
<tr>
<th>Trade/Drug name or available as</th>
<th>Route of administration</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novarel 10,000 USP units/vial (Urinary hCG)</td>
<td>Intramuscular or may be administered subcutaneously (off-label) as per prescriber preference</td>
<td>Headache, irritability, restlessness, fatigue, edema, gynecomastia, pain, redness, swelling at the site of injection. Hypersensitivity reactions, both localized and systemic in nature, have been reported.</td>
</tr>
</tbody>
</table>

**Dosage and Administration**

- **Dosage regimen will depend upon the indication for use, the age and weight of the patient and the physician’s preference**
- **Usually administered as 5,000 to 10,000 USP units one day following the last dose of gonadotropin**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>How supplied</th>
<th>Dose per container</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferring</td>
<td>• Chorionic Gonadotropin for Injection, USP, is supplied in two vial package • One 10 mL multiple dose vial of lyophilized powder or pellet of Chorionic Gonadotropin for Injection, USP, 10,000 USP • One 10 mL vial of diluent – Bacteriostatic Water for Injection, USP • 1 vial of Chorionic Gonadotropin for Injection, USP • 1 vial of Bacteriostatic Water for Injection, USP, 10 mL</td>
<td>Usually single dose for fertility patients Available as multiple dose vial</td>
</tr>
</tbody>
</table>

**Storage**

- Store dry product at 20° to 25°C (68° to 77°F), excursions permitted between 15° and 30°C (59° and 86°F) [See USP Controlled Room Temperature]
- **REFRIGERATE RECONSTITUTED PRODUCT AT 2° to 8°C (36° to 46°F) AND USE WITHIN 30 DAYS**
# Chorionic Gonadotropin (r-hCG)

## Cetrorelix Acetate for Injection

### Indication
- Indicated for the induction of final follicular maturation /early luteinization in infertile women who have undergone pituitary desensitization and been appropriately pretreated with follicle stimulating hormones as part of an ART program.
- Indicated for the induction of ovulation (O) and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.

### Mechanism of Action
- Physicochemical, immunological, and biological activities of recombinant hCG compare to placental/human pregnancy urine-derived hCG.
  - Stimulates late follicular maturation and initiates rupture of the pre-ovulatory ovarian follicle.
  - Analogue of LH that binds to the LH/hCG receptors of the ovary to effect these changes in the absence of endogenous LH surge.
  - In pregnancy, hCG, secreted by the placenta, maintains the corpus luteum to provide the continued secretion of estrogen/progesterone necessary to support the first trimester of pregnancy.

### Considerations
- Available as Ovidrel® PreFilled Syringe 250 µg/0.5mL.
- Time-sensitive medication.
  - Given following the last dose of gonadotropins.
  - Egg retrieval scheduled 36 hours after injection.
  - Taken too soon or too late can impact and possibly ruin a cycle.
- Referred to as “trigger shot.”
- Very common for prescriber to order 2 syringes (500 µg total) for IVF cycle.

---

### Trade/Drug name or available as

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovidrel 250 µg/0.5mL (Recombinant hCG)</td>
<td>Subcutaneous use only</td>
</tr>
</tbody>
</table>

### Manufacturer

<table>
<thead>
<tr>
<th>How supplied</th>
<th>Dose per container</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMD Serono</td>
<td>One prefilled liquid single dose syringe containing 0.515 mL (257.5 µg) of choriogonadotropin alfa able to deliver 250 µg of choriogonadotropin alfa in 0.5 mL. Single dose</td>
</tr>
</tbody>
</table>

### Dosage and Administration

Infertile women undergoing Assisted Reproductive Technologies (ART) or Ovulation Induction (OI):
- Usually administered 1 or 2 Ovidrel® PreFilled 250 µg Syringes per prescriber preference.
- Ovidrel should be administered one day following the last dose of the follicle stimulating agent.
- Ovidrel should not be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography.
- Administration should be withheld in situations where there is an excessive ovarian response, as evidenced by clinically significant ovarian enlargement or excessive estradiol production.

### Storage
- Store refrigerated between 2-8°C (36-46°F) before being dispensed to the patient to allow the product to be used until the expiry date shown on the syringe or carton.
- Ovidrel may be stored by the patient for no more than 30 days at room temperature (up to 25°C (77°F)) but must be used within those 30 days otherwise discarded.
- Protect from light.
Role of GnRH Agonist as a Trigger

• Alternative type of trigger using leuprolide acetate that may be ordered by a fertility office if the patient is responding too well to medications
• May also be referred to as “Lupron” trigger
• Cannot be used as a trigger if a patient has already used Leuprolide for downregulation in their cycle
• Most common dosages in a vial or PFS:
  – 1 mg (20 units)
  – 2 mg (40 units)
  – 4 mg (80 units)
  – 5mg (100 units)

Role of Progesterone

• Progesterone for luteal phase support of the endometrium is needed in stimulation cycles
• Used to build up lining of endometrium for successful implantation
• Many formulations are available: vaginal gel, vaginal insert, vaginal suppositories, capsules, compounded micronized progesterone that can be used vaginally or orally, troches, and oil-based intramuscular (IM) injections in various strengths
• Administration begins the day of egg retrieval and continues until pregnancy test

Stauss, Barbieri, Yen & Jaffe’s Reproductive Endocrinology: physiology, pathophysiology, and clinical management, 2014: 704-706
### Progesterone

#### Progesterone Gel 8%

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism of Action</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicated for progesterone supplementation or replacement as part of an Assisted Reproduction Technology (ART) cycle for infertile women with progesterone deficiency</td>
<td>Progesterone is a naturally occurring steroid secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.</td>
<td>• Available as Crinone® 8% (90mg) vaginal gel • Special patient instructions available in package insert FOR USE AT ALTITUDES ABOVE 2500 FEET.</td>
</tr>
</tbody>
</table>

#### Trade/Drug name or available as

| Crinone 8% (gel formulation) | Vaginal | Headache, constipation, diarrhea, nausea, vomiting, depression, libido decreased, nervousness, somnolence, breast enlargement, nocturia |

#### Dosage and Administration

- Dosage regimen will depend upon the indication for use, the age and weight of the patient and the physician’s preference
- Recommended Dosage for ART Luteal Support: 90 mg (one applicator) vaginally once or twice daily

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>How supplied</th>
<th>Dose per container</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergan (Formerly Actavis)</td>
<td>• 8% gel single dose vaginal applicator containing 1.3 gm of gel delivering 1.125gm gel containing 90mg of progesterone • A box contains 15 single dose prefilled 1.3gm applicators • 8% gel (containing 90 mg progesterone) in a single use, one piece, disposable, vaginal applicator with a twist-off top • 4% gel (45 mg) in a single use, one piece, disposable, white polyethylene vaginal applicator with a twist-off top. Each applicator contains 1.3 g of gel and delivers 1.125 g of gel</td>
<td>Single dose</td>
</tr>
</tbody>
</table>

#### Storage

- Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F)

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**Progesterone**

**Progesterone 100mg, USP Insert**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism of Action</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Indicated to support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women</td>
<td>• Progesterone is a naturally occurring steroid secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium</td>
<td>• Available as Endometrin® (progesterone) Vaginal Insert</td>
</tr>
<tr>
<td></td>
<td>• Progesterone is necessary to increase endometrial receptivity for implantation of an embryo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Once implantation occurs, progesterone acts to maintain a pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Upon insertion the effervescent tablet dissolves and deliver progesterone to the vaginal tissue</td>
<td></td>
</tr>
</tbody>
</table>

**Trade/Drug name or available as**

Endometrin® (effervescent tablet formulation)

**Route of administration**

Vaginal

**Common side effects**

Abdominal pain, nausea, abdominal distension, constipation, vomiting, fatigue, urinary tract infection, headache, symptoms of ovarian hyperstimulation syndrome may occur, vaginal bleeding

**Dosage and Administration**

• Administered vaginally two or three times daily starting the day after oocyte retrieval and continuing for up to 10 weeks total duration

**Manufacturer**

Ferring

**How supplied**

• 21 disposable vaginal applicators
• 21 individually foil pouch packed 100 mg progesterone vaginal inserts - white to off-white oblong-shaped tablet

**Dose per container**

Single dose

**Storage**

• Store at 20 - 25°C (68 - 77°F); excursions permitted between 15 - 30°C (59 - 86°F)
### Progesterone

#### Progesterone Injection

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism of Action</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Indicated in amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer</td>
<td>• Transforms proliferative endometrium into secretory endometrium</td>
<td>• Available as Progesterone Injection USP 50mg/mL in a sesame oil base</td>
</tr>
<tr>
<td>• Off-Label Reproductive Use: Used to support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an ART cycle</td>
<td>• Inhibits the secretion of pituitary gonadotropins, which prevents follicular maturation and ovulation</td>
<td>• Mixing/administration supplies not included with medication - need to prescribed by specific center</td>
</tr>
<tr>
<td></td>
<td>• Progestosterone is one of the hormones essential for regular menstrual periods</td>
<td>➢ Treat each 10mL vial as 10 doses unless prescriber indicates volume being injected</td>
</tr>
<tr>
<td></td>
<td>• Progestosterone is intended for administration by injection into a muscle mass. Following injection, the medication is absorbed into the bloodstream</td>
<td>➢ Physicians may order 18 gauge needle to withdraw / 22 gauge needle for IM injection due to viscosity of medication</td>
</tr>
</tbody>
</table>

#### Indication

- Progestosterone In Oil (injectable formulation)

#### Route of administration

- Intramuscular

#### Common side effects

- Breakthrough bleeding, spotting, change in weight (increase or decrease), changes in cervical secretions, breast tenderness, secretion of breast milk, pain, irritation, and/or redness at the injection area, acne, alopecia and hirsutism, depression, fever, insomnia, nausea, somnolence, mood swings, irritability

#### Dosage and Administration

- Dosage regimen will depend upon the indication for use, the age and weight of the patient and the physician’s preference
- Dosage in ART Luteal Phase Support: 25mg to 50 mg intramuscularly once daily

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>How supplied</th>
<th>Dose per container</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple - Westward, Actavis</td>
<td>Progestosterone Injection USP, 50 mg/mL is available in 10 mL multiple dose vials, individually boxed</td>
<td></td>
</tr>
<tr>
<td>Multi-dose vial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Storage

- Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]
## Indication
- Indicated for use in the prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving conjugated estrogens tablets. They are also indicated for use in secondary amenorrhea.
- Off-label reproductive use: Used to support embryo implantation and early pregnancy by corpus luteal supplementation as part of an ART cycle.

## Mechanism of Action
- Oral dosage form of micronized progesterone which is chemically identical to progesterone of ovarian origin.
- Off-label reproductive use:
  - Insertion into the vagina to allow for better absorption of progesterone through vaginal wall.

## Considerations
- Available as Prometrium® capsules.
- Off-label reproductive use:
  - Vaginal route of administration.
  - Prometrium® contains peanut oil and should never be used by patients allergic to peanuts.

---

### Trade/Drug name or available as
- Prometrium (Micronized progesterone in soft gelatin capsule formulation)

### Route of administration
- Vaginal (off-label use) or Oral as per prescriber preference

### Common side effects
- Headache, breast tenderness, joint pain, depression, dizziness, abdominal bloating, hot flashes, urinary problems, abdominal pain, vaginal discharge, nausea / vomiting, chest pain, diarrhea, night sweats, breast pain, swelling of hands and feet, vaginal dryness, constipation

### Dosage and Administration

#### Recommended Dosage for ART Luteal Support:
- 200mg orally 3-4 times daily

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>How supplied</th>
<th>Dose per container</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbbVie</td>
<td>Available as:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PROMETRIUM (progesterone, USP) 100 mg capsules – round, peach-colored</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PROMETRIUM (progesterone, USP) 200 mg capsules – oval, pale yellow-colored capsules</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single dose</td>
<td></td>
</tr>
</tbody>
</table>

### Storage
- Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)
- Protect from excessive moisture
- Dispense in tight, light-resistant container
Endometrial support: Estrogen

- May be prescribed for additional support for the uterine lining, embryo implantation and resulting pregnancy
- Used in IVF cycles, before and after a frozen embryo transfer and in pregnancy
- Available formulations:
  - Estradiol valerate injection (intramuscular injection)
  - Estradiol tablets (oral and occasional inserted vaginally)
  - Estradiol patch (Estradiol transdermal system)
  - Vivelle dot (Estradiol transdermal system)
  - Minivelle (Estradiol transdermal system)

Ancillary Medications Used in Infertility

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Off-label Use</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>Synthetic adrenal corticosteroid with various metabolic effects</td>
<td>Ovulation induction in clomiphene-resistant PCOS; before embryo transfer in ART</td>
<td>Acne, Weight gain, Immunosuppression, Hypertension, Nausea, vomiting, Confusion</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Inhibits D2 receptors and exerts a direct inhibitory effect on the secretion of prolactin</td>
<td>Treatment of infertility of pituitary origin; treatment of OHSS</td>
<td>Headache, Nausea, vomiting</td>
</tr>
<tr>
<td>Bromocriptine,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabergoline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil (Viagra)</td>
<td>Increases uterine artery blood flow, endometrial thickness by augmenting the vasodilatory effects of nitric oxide</td>
<td>Female infertility with uterine/endometrial factor; increase endometrial thickness in ART</td>
<td>Headache, Flushing, Nausea, Back pain, Myalgia, Dizziness, Rash</td>
</tr>
</tbody>
</table>

*For full information, please refer to prescribing information (PI)
### Ancillary Medications Used in Infertility

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Off-Label Use</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Decreases gluconeogenesis, intestinal absorption of glucose, and improves insulin sensitivity</td>
<td>Improve menstrual cycle regularity or hyperandrogenism in women with PCOS who cannot tolerate OCPs</td>
<td>GI disturbance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abdominal discomfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td>Low-Dose</td>
<td>Inhibition of the synthesis of prostaglandin which reduces inflammation and decreases platelet aggregation</td>
<td>Possible improved implantation; treatment of antiphospholipid antibody syndrome</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Aspirin 81mg</td>
<td></td>
<td></td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>DHEA</td>
<td>Precursor to testosterone and E2 and may increase follicular production by insulin-like growth factor 1 (IGF-1)</td>
<td>Prior to IVF in women with decreased ovarian reserve</td>
<td>Acne</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dermatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild hirsutism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Manic reactions:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(combined with antidepressant or alcohol)</td>
</tr>
</tbody>
</table>

*For full information, please refer to prescribing information (PI)*


### Common Compounded Medications

- **Sterile:**
  - Leuprolide acetate Micro-dose
  - Leuprolide acetate trigger
  - Low-Dose human chorionic gonadotropin
  - ½ or ⅓ dose Ganirelix acetate
  - Micro-Dose HCG alfa (Ovidrel)

- **Non-Sterile:**
  - Progesterone suppositories
  - Progesterone/estradiol suppositories
  - Estradiol suppositories
  - Progesterone troches
  - Micronized progesterone capsules
  - Sildenafil suppositories
IVF Cycle Timeline

*Only one of these protocols is used to prevent premature ovulation per prescriber preference.

Review the Objectives

• Review an IVF cycle timeline
  ➢ Understanding reproductive hormones in the menstrual cycle will allow a greater appreciation for how infertility medications are utilized and prescribed

• Describe the mechanism of action of various infertility medications in the body
  ➢ Please review all the tables created on medications used in fertility

• Discuss how fertility medications are supplied, administration, storage requirements as well as common side effects
  ➢ Please review all the medication tables
  ➢ For full information regarding the medications reviewed in this module, it is the pharmacist responsibility to be knowledgeable of the prescribing information contained in the package insert
    • Including but not limited to contraindications, precautions and adverse reactions
Thank You

References

• CHORIONIC GONADOTROPIN [prescribing insert]. Fresenius, Kabi, Lake Zurich, IL February 2016.
• CRINONE®8% (progesterone gel) [prescribing information]. Parsippany, NJ: Actavis Pharma, Inc., August 2014.
• FEMARA® (letrozole tablets) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation., January 2014
• FOLLISTIM® AQ Cartridge [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC., Merck & Co., INC; December 2014.
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