MODULE 5, CHAPTER 1

00:00
Module 5. Molecules and protocols used in ovarian stimulation.

00:06
So note to you as a viewer during this module, you will learn about the molecules used in assisted reproductive technologies or ART. All references within will only include the molecule name and therapeutic class. In other words, I will not be discussing brand names.

00:25
The objectives of this module are to identify similarities and differences between ovulation induction or OI and controlled ovarian stimulation or COS, to review the molecules used in assisted reproductive technologies and how they are used, to understand the risk ovarian hyperstimulation syndrome and hCG administration, and to detail the general protocols for COS, to understand the mechanism of action of the molecules used in COS and the role of treatment in the cycle and to describe the timing of administration.

01:07
We'll start with introduction to ovarian stimulation.

01:13
So just a quick review of the female reproductive cycle with the gonadotropins that is, the hormones you see in the middle screen and the influence on follicular development and the endometrium. Assisted reproductive technologies may include the use of medications to stimulate the ovaries and induce ovulation in patients with anovulatory oligo-ovulatory infertility, or to hyperstimulate the ovaries in a controlled fashion in ovulatory patients.

01:48
There are two classes of ovarian stimulation. One is ovulation induction, where the intention is a single follicle to develop. Is used in women who otherwise do not ovulate regularly and it may be used with or without intrauterine insemination. The second class is controlled ovarian stimulation, or COS, which is intended to induce the development of more than one follicle and is often used in women who already ovulate regularly in order to increase the number of eggs or oocytes that have a chance to be fertilized in a single cycle. It may be used with intrauterine insemination or invitro fertilization.

02:35
We just look at this table to look at the difference between OI and COS for the number of eggs stimulated and released. In OI it's ideally only one and in COS more than one. Fertilization in OI is in vivo or COS can be in vivo or in vitro. The determinants of risk of multiple pregnancy in OI would be the number of follicles that develop in that cycle. In COS it would be the number of follicles that develop or the number of embryos transferred.

03:12
Ovulation induction.

03:15
So for looking at the potential causes of anovulation or oligo-ovulation and the indications for ovulation induction, a number of conditions resulting in anovulation/oligo-ovulation may be treated with OI such as hypothalamic, or what we've learned is called hypo-hypo, pituitary disorders such as hyperprolactinemia, metabolic disorders, polycystic ovary syndrome, for example, and other endocrine disorders.

03:52
To restore ovulation, sometimes lifestyle interventions may be all that's necessary to including optimizing wellness and nutrition to target a healthy BMI, women who are greatly overweight or underweight may not ovulate regularly, and also general lifestyle interventions, such as avoiding excess alcohol and recreational use of illicit substances and avoiding potentially hazardous environmental toxins.

04:27
So for OI, there are 2 main drug regimens. They are both oral and one is called aromatase inhibitor, which is aromatase inhibitor that temporarily blocks the conversion of androgens to estrogens. It's considered a first line treatment for ovulatory infertility, but remains off label, which means the medication was generally intended for other use other than ovulation induction.

CFAS supports the use of an aromatase inhibitor for the treatment of ovulatory dysfunction and unexplained infertility. The other oral agent is the selective estrogen receptor modulator, or SERM, as it's sometimes called. It temporarily blocks estrogen receptors in the brain. It was discontinued by its Canadian distributor but, is still compounded in some areas.

The other drug regimen are injectable which are gonadotropins follicle stimulating hormone with or without LH.

05:42
So we look at aromatase inhibitor and look at its class, its mechanism of action, which is it lowers systemic estrogen concentrations and prevents negative feedback on FSH. It increases and prolongs age and secretion and stimulates follicular growth. It's not to be taken during pregnancy. Side effects include mood changes, hot flashes, headaches, vaginal dryness and others.

06:16
The dosing and administration of aromatase inhibitor are starting with a low dose, lower dose of 2.5 and then increasing as needed. For example, if someone in the initial cycle using a 2.5milligram dose or did not have a successful outcome, it can be titrated up in subsequent cycles, noting that there is a limit to the number of cycles that a woman should have.

The timing, it starts at 2 to 5 days of the menstrual cycle. If a woman is not ovulating or if there's no menstruation, it can be started at any time. The treatment duration is typically 5 days but may be extended. This would be patient and physician dependent to induce ovulation.

07:13
So looking at selective estrogen receptor modulator, we see its class and the mechanism of action is that it blocks estrogen negative feedback at the hypothalamus, which results in an increased FSH and luteinizing hormone release. It should not be administered during pregnancy or if there's hormone dependent tumors, any ovarian cyst, except if there it is a case of polycystic ovary or if there's liver disease. The side effects

are similar to the aromatase inhibitor, but it also include the possibility of visual symptoms. And if these occur, the medication should be stopped immediately.

07:59
The dosage similar to the aromatase inhibitor started a lower dose and is titrate it up in subsequent cycles if there's not a successful outcome. The timing starts at 2, sorry day 2 to day 5 of the cycle or at any time if there's no ovulation, menstruation. The treatment is duration is 5 days.

08:23
In summary, for ovulation induction anovulation and oligo-ovulation may be due to a number of factors, including hypothalamic pituitary or PCOC and other endocrine disorders. It may be amenable to lifestyle modification and or pharmacotherapy. An aromatase inhibitor nonsteroidal acting by lowering estrogen concentrations and inhibiting negative feedback on FSH. Side effects of aromatase inhibitors are a result of decreased estrogen levels, such as mood changes, hot flashes, headaches and fatigue. It's typically administered during the early proliferative phase of the menstrual cycle for 5 days. Ovulation occurs about 5 to 10 days after the last tablet is administered, and aromatase inhibitor and selective estrogen receptor modulator are not effective for OI in patients with hypogonadotropic hypogonadism who are menopausal.

09:26
The next section in Module 5 is controlled ovarian stimulation.

09:33
So when we look at the indications for controlled ovarian stimulation, we know that they may be used with IUI, that's intrauterine insemination to induce the development of several 2 to 4 mature follicles. There needs to be an awareness of the risk of multiple pregnancy.

They may be used with IVF to induce the development of numerous mature follicles for egg collection. Here, the risk of multiple risk multiple birth sorry, can be controlled by how many embryos are transferred back to the uterus. Surplus good quality embryos may be cryopreserved.

10:17
In looking at patient considerations for COS we need to determine the ovarian reserve, which refers to the follicle and oocyte quantity. Tests used to assess ovarian reserve, as we've learned before, include day 3 FSH with its companion tested yesterday, day 3 antral follicle count and anti-müllerian hormone.

10:49
We also need to or, we would like to identify high responders. High ovarian response are individuals with a high AMH, a high AFC antral follicle count, or who have had a high number of eggs or oocytes retrieved in a previous cycle. Ovarian hyperstimulation syndrome is a complication of COS as a result of the exogenous administration of gonadotropins. Patients at increased risk for OHSS are identified and preventative strategies are taken to control complications. Predictors of ovarian response include, again, the ovarian reserve testing of AMH antral follicle count and to a lesser extent, the basal FSH. And also, patient age is a determining factor.

11:47
So considerations for controlled ovarian stimulation. We need to understand that there is a balance between the number of oocytes retrieved, efficacy and safety. If we look at this graph and we look at the x axis for risk of OHSS and the Y axis looking at live birth rate per cycle, it does not follow that the more oocytes retrieved result in a higher live birth. In fact, you can see that after 20 eggs retrieved, the live birth rate levels off.

12:31
So controlled ovarian stimulation treatments involve a number of stages. Priming is a process that helps to synchronize or may improve ovarian response to hormone therapy. The molecules used for this are oral contraceptives, estrogen or androgens. Stimulation is where follicles are stimulated to grow and have an effect on oocyte maturation, and for these gonadotropins that are used with FSH or FSH and LH. Suppression is to prevent premature ovulation prior to egg collection. And for GnRH agonist or GnRH antagonist is used.

Trigger induces oocyte maturation and ovulation for egg retrieval and for this human chorionic gonadotropin, or commonly known as hCG, and or GnRH agonists and finally luteal support to increase endometrial receptivity for implantation. And for this, we use progesterone with or without estrogen.

13:52
Let's look at priming. For priming medication may be given before the first step of IVF hormone therapy cycles, which suppress one's own hormone production. And the goal of these treatments are to synchronize follicle development and to prevent cyst formation. Also to assist with scheduling oocyte retrieval, improves ovarian response to hormone therapy and to prevent spontaneous LH surge. It also can shorten the length of the GnRH antagonist treatment and reduce the amount of this medication required. The types of priming used or oral contraceptives, oral estrogens or androgens, if we know someone may be a poor responder.

14:45
Well, first start looking at follicle stimulating hormone.

14:52
So follicle stimulating hormone is a large heterodimeric glycoprotein. Its action is the growth of follicles to reach pre-ovulatory stages and induction of an aromatase enzyme that converts androgens to estrogens.

15:14
So FSH, its class is gonadotropin, its mechanism is to stimulate the growth of immature oocytes into mature follicles prior to ovulation and stimulation of follicular development and steroid production. The contraindications would be existing high circulating FSH indicating primary gonadal behavior or an ovarian cyst or an enlargement not due to PCOS. The side effects are numerous and one thing that we need to know, most importantly, is the increase or the possibility of increase of multiple ovulation or multiple birth and OHSS.

16:03
So FSH dosage and administration. The doses of FSH depend on the goal of treatment and other factors for ovulation induction and that is where we don't want too many follicles because we're not doing IVF. It may use doses between 25 to 150 international units a day. For IVF the doses are 100 to 300 international units a day. And the choice of initial dose is based on clinical experience, judgment and patient factors. Patient weight for example, and age. Doses of greater than 450 international units a day are not recommended since there's no evidence of clinical benefit. So, for example, if someone is not responding to a dose of 300 they're unlikely to respond more favorably to a dose of greater than 450 international units. It's administered by subcutaneous injection with repeated doses every 24 hours until there is adequate follicular development.

For ovulation induction typically starts at 25 to 100 international units a day, and with incremental adjustments. The lowest dose consistent with the expectation of good results should be used. For ART or if we're doing IVF, it starts in the early follicular phase, typically at doses between 100 to 300 international units a day, the dose adjustment generally begins after the first 4 to 5 days of treatment based on response.

17:49
Before treatment with FSH is instituted, a gynecologic endocrinologic evaluation must be performed, including assessment of pelvic anatomy and primary ovarian failure, that diagnostic group should be excluded by the determination of their gonadotropin levels. For anovulatory women the goal is to have 1 follicle measuring 15 to 18 millimeters in size before ovulation. If 3 or more follicles greater than 15 millimeters are found, the cycle may be canceled, and this is due to the risk of multiple pregnancy. Or, converted to IVF to reduce the risk of multiple pregnancy where we have control over the number of embryos transferred. For ART, that is IVF, higher doses are given to stimulate a greater number of follicles for fertilization in vitro because we do have the control of the number of embryos transferred.

If there's a suspicion of a risk of OHSS the optimal dose of FSH to retrieve no more than 15 to 20 eggs is the goal and to balance the risk for OHSS.

19:08
Luteinizing hormone.

19:11
So the functions of endogenous, that is in vivo LH is to stimulate the endogenous synthesis as a substrate for estrogen. Along with FSH, LH stimulates the growth of follicles to reach pre-ovulatory stages and the LH surge triggers ovulation. Luteinization of the ruptured follicle and maintenance of the corpus luteum, in other words, progesterone production to maintain the endometrium to facilitate implantation and continued development of the embryo.

For patients who are hypogonadotropic hypogonadal, that is hypo-hypo, the treatment of hypo-hypo with FSH alone leads to early follicular development but not pregnancy. And this is why it is absolutely necessary to use exogenous LH combined with FSH as it is required for the estrogen production and endometrial development.

20:17
So LH is a gonadotropin. Its mechanism of action is to stimulate androgens synthesis as a substrate for estrogen and stimulates the growth of follicles in the later stages of follicular development. It is administered in combination with FSH. The contraindications of LH administration are primary ovarian insufficiency and uncontrolled thyroid or adrenal failure, untreated tumors of the hypothalamus and pituitary gland, ovarian cyst, ovarian, uterine or mammary carcinoma. The side effects include headache, pelvic abdominal pain with the more serious side effect being OHSS. Exogenous LH is used concomitantly with FSH for stimulation of follicular development in those with hypogonadotropic hypogonadal infertility with profound LH deficiency.

21:17
So the dosage of LH starts at once daily dose of 75 international units, in fact, doses greater than 225 international units per day are not routinely recommended, and it is also administered by subcutaneous injection. Its treatment can begin at any time but should not normally exceed 14 days unless there are signs of follicular development. The treatment is tailored to the patient's response by measuring follicle size by ultrasound and estrogen response.

21:55
Human chorionic gonadotropin.

21:59
So endogenous hCG is biologically similar to LH but has a much longer half life and is produced after implantation by trophoblast. It stimulates progesterone secretion by the corpus luteum and prolongs its function. But exogenous hCG which we use as an ovulation trigger, mimics a physiologic pattern of the mid cycle LH surge and is given once adequate ovarian response is reached as determined by follicular size and estradiol level.

00:22:37:18
hCG is also a gonadotropin and as mentioned, it mimics the endogenous LH surge and triggers ovulation, as well as promoting development and maintenance of the corpus luteum and production of progesterone. The contraindications of hCG are primary ovarian insufficiency, thyroid disease, adrenal insufficiency, hypothalamic pituitary tumors, ovarian enlargement or a cyst ovarian uterine or mammary cancer, pregnancy or fibroids. Side effects are range from application site disorders with the most serious risk of OHSS and multiple pregnancies.

23:25
hCG is available in recombinant or urinary derived forms. The dose for recombinant hCG is 250 micrograms administered by subcutaneous injection or urine derived administered by intramuscular or subcutaneous injection. The timing of administration is when an adequate follicular development is indicated by ultrasound, when at least one follicle reaches maturity. If, for example, greater than 15 millimeters.

24:00
For hCG we need to consider that early OHSS symptoms appear within the first 7 days after hCG administration. Late OHSS is associated with the hCG from a pregnancy that is produced by the trophectoderm. The hCG is withheld in cases of excessive ovarian response, such as multiple follicular development and clinically significant ovarian enlargement or excessive estradiol production.

The methods used to reduce the risk of OHHS are to cancel the treatment cycle and by withholding the hCG to cancel the first fresh embryo transfer and cryopreserve the embryos and avoid administration of hCG for luteal phase support. Also, the use of a dopamine agonist on the day of trigger may reduce the risk of OHHS.

25:05
Section completed. Please access the online classroom portal Digital Chalk to review and complete the exercises related to this content section.