MODULE 5, CHAPTER 2

00:00
The next section in Module 5 are GnRH analogues.

00:09
So just to review the natural process of GnRH which is produced by the hypothalamus, acts on the anterior pituitary to produce FSH and LH, and also we know with the FSH it encourages follicle development with a secretion of estrogen and inhibin. For LH on day 14 of the menstrual cycle the LH surge triggers ovulation and the formation of the corpus luteum where there is a secretion of progesterone and estrogen to support the endometrium to facilitate the implantation and growth of the developing embryo.

01:02
GnRH analogues. So stimulation with gonadotropins results in a premature LH surge in 20 to 25 percent of stimulated cycles in IVF. And of course this is not a desired outcome. Administration of GnRH analogues can prevent the endogenous release of FSH and LH thereby preventing premature LH surge. There are 2 molecules we use for this. A GnRH agonist which causes an initial flare effect but sustained administration of GnRH agonist results in a down regulation of FSH and LH secretion. By contrast, a GnRH antagonist immediately blocks the pituitary GnRH receptors and suppress FSH and LH release.

01:56
GnRH Agonists

00:02:01:12
GnRH agonists initially stimulate pituitary receptors and increase FSH and LH production, and this is known as the flare effect. Down regulation occurs within about 5 days with continued daily administration.

02:20
GnRH agonist is a class of GnRH receptor agonist mechanism of action is that it competitively binds to GnRH receptors on anterior pituitary gonadotrophs and causes a rapid and reversible suppression of a gonadotropin secretion. Contraindications include undiagnosed abnormal vaginal bleeding and pregnancy, side effects are hot flashes, mood swings and injection site reactions, typically symptoms or side effects that you would see in menopause.

03:02
So the types of agonists are short-acting injection which is given once a day subcutaneously injected. A long-acting depot injection which lasts for a month which is given IM or subcutaneous or nasal spray, which is taken 2 to 3 times a day. Most commonly used in IVF treatment are the short-acting injection and nasal spray,

So the dose may vary between short-acting at a dose of 0.1 milligram a day to the depot injection, which is 3.75 which is given in a single dose. The timing of administration varies according to the protocol used. In the long protocol which we'll look at in a little bit it starts in the early, mid or late luteal phase in the preceding cycle until human chorionic gonadotropin or hCG administration occurs. In the short or sometimes called flare protocol is started at the beginning of the cycle.

04:11
GnRH antagonist.

04:17
So a GnRH agonist antagonises the pituitary receptors without an initial release of endogenous gonadotropin. In other words, no flare effect.

04:32
It's mechanism of action is that it competitively binds to the GnRH receptor and immediately prevents the release of gonadotropins and sex steroids and competes with natural GnRH for a pituitary gland receptor sites in a dose dependent manner. Contraindications include pregnancy, moderate or severe hepatic or renal function. The side effects are few, including injection site reactions and occasionally nausea and headache.

05:08
For GnRH antagonist are typically started around 5 days of gonadotropin administration, or when the lead follicles reach around 14 millimeters in, this may be somewhat clinic specific. The GnRH antagonist dose will vary, but generally will be 0.25 milligrams given daily. The timing of administration, it's in the morning or evening and is administered once daily at a consistent time, for example, every morning or every evening. The GnRH antagonist treatment continues until the day of hCG administration.

05:53
So to summarize the GnRH analogues. GnRH agonists initially stimulate pituitary receptors and increase the FSH and LH production, causing the flare effect. Down regulation occurs with continued daily administration. They may be used to facilitate oocyte maturation otherwise known as the trigger in an antagonist cycle by causing an initial release of gonadotropins. GnRH antagonists are used for suppression of LH surge and prevention of premature ovulation. However, because antagonists antagonize pituitary receptors without an initial release of the endogenous gonadotropins they are sometimes also used for follicle synchronization or priming prior to COS or to prevent follicle growth in frozen-thaw cycles.

06:54
Progesterone luteal phase support.

06:59
Endogenous progesterone is a steroid that is secreted by the ovary, placenta and adrenal glands in the presence of adequate estrogen. Progesterone transforms a proliferative endometrium into a secretory endometrium, which is essential for the development of the decidual tissue. It's necessary to increase endometrial receptivity for the implantation of an embryo. And once an embryo is implanted, progesterone acts to maintain the pregnancy.

Luteal phase supplementation. A luteal phase defect occurs as a result of ovarian stimulation, in other words, in an IVF cycle we have artificially created luteal phase defect. And that is why exogenous progesterone is administered for luteal phase support.

07:56
Progesterone is a steroid sex hormone. It induces endometrial secretory transformation and promotes receptivity to implantation. The major contraindications are undiagnosed vaginal bleedings, breast cancer, cervical cancer, all other cancers and acute porphyria. The side effects include mood changes, breast tenderness, headache, muscle pain and muscle spasms. In other words, fairly minor side effects.

08:30
The dosage of progesterone can be given by IM injection, which is we don't see this too much in Canada, but you will see if you have patients from the United States they will be very familiar with IM injections if they've had IVF treatment there. It can be given by a vaginal gel, vaginal insert or vaginal capsule. The timing of administration is before or on the day of oocyte retrieval and continues until pregnancy is confirmed. In other words, until the placenta has taken over. The treatment continues until 10 to 12 weeks of gestation if the patient is pregnant.

09:16
So in summary, luteal phase support is that progesterone is required for a successful embryo implantation and maintenance of pregnancy. It increases endometrial receptivity and supports pregnancy. Luteal phase defects occur during stimulation cycles where exogenous progesterone is administered for luteal phase support.

The next section in module 5 is the general protocols COS.

09:49
We'll start with the agonist protocol otherwise known as the long protocol. In this protocol we start the GnRH agonist at day 21 of the cycle preceding the treatment cycle. FSH begins on day 2 to 3 of the treatment cycle starting, and that starts with the first day of menses, so would be on day 3 following menses. LH may be used and remember that if we have a hypo-hypo patient, for example, LH must be used. During the treatment cycle or the initial treatment cycle after the administration of FSH ultrasound may be done at baseline and then will be done periodically based on follicular response, as will the testing of estradiol.

hCG is given when there is a number of follicles that are 17 millimeters or more to trigger ovulation, which we don't want, but what we do want is the maturation effect of the hCG on the oocytes. At oocyte retrieval either the day before oocyte retrieval or the day of progesterone will be given for luteal support.

11:23
The agonist protocol or short protocol. The GnRH agonist begins at the beginning of the menstrual cycle, so after the first or second, generally on the first day of the bleed and will continue until the determination to move on to oocyte retrieval. FSH as in the long protocol will be given on day 2 to 3 of the cycle and will continue until the date of trigger and LH may be used.

And as with the long protocol the monitoring will be the same with periodic ultrasound and estradiol testing through to the point where the determination is made to trigger with hCG and to have oocyte retrieval 35 or 36 hours later. Progesterone will be given on the day before or the day of oocyte retrieval and continue through until the result is known. In other words, until there is a pregnancy test and if the pregnancy test is positive, it will continue to 8 to 12 weeks of pregnancy. And this would be the same for all protocols.

12:44
Antagonist protocol. With the antagonist protocol FSH is started on day 2 to 3 of the cycle as is with the other protocols we've discussed and with the GnRH antagonist not starting until 5 days of FSH administration due to its immediate effect to prevent ovulation. LH may be used as with other cycles, and all these medications will continue until the determination is made for hCG to be administered the same as with other cycles, as is the periodic testing with ultrasound to determine follicular growth and testing of serum estradiol.

At the day of retrieval or before progesterone will continue, as with the other protocols, and will continue until pregnancy test and a pregnancy test is positive until 8 to 12 weeks of pregnancy.

If there is concern of OHSS rather than hCG a GnRH agonist may be used which will can trigger ovulation. But if this is used, it is important to note that both estrogen and progesterone must be used for luteal support.

14:12
There is a type of treatment which is called natural cycle IVF which is gaining popularity, and there are some types of natural cycle IVF. There is one without modification. In other words, no exogenous hormones, which is not efficient because remember in a natural cycle, only 1 follicle will be will develop and be recruited and ovulate or have a possibility of an oocyte. And so this would be natural follicle recruitment and selection and an unsupported luteal phase. The advantage from a patient perspective is that there is avoidance of the gonadotropin injections. Some may use some modification with minimal stimulation, which includes some FSH, GnRH antagonist, hCG and luteal support.

The reason that patients may choose a natural or a natural modified cycle is to decrease medication costs and to decrease risks associated with COS, for example, ovarian hyperstimulation syndrome. And for those who do not wish to select and or cryopreserve embryos for cultural or personal reasons. However, it is associated with a much lower chance of pregnancy per cycle compared to IVF cycles with controlled ovarian stimulation.

15:46
At times, we may see in our patients that there is a poor response to ovarian stimulation that may not have been may or may not have been predicted. The Poseidon Classification defines diminished ovarian reserve as a basal AFC of less than 5 follicles or a serum AMH at less than 1.2 nanograms per millilitre.

For treatment strategies there is very little good quality data and there's been no single protocol to that has been proven to clearly be superior to other protocols. Although many options have been tried. High doses of gonadotropins have not been shown to be superior to a moderate dose, for example ovaries not responding to a moderate dose, they're not likely to respond to a high dose. Avenues for improvement may include better follicle synchronization, pre stimulation, testosterone priming or growth hormone, or in cases where there has been a very poor ovarian response to stimulation, egg donation or adoption may be considered rather than try a subsequent IVF cycle.

17:08
There are also times when if there is a poor outcome that poor or either an under response or an over response, that there will be different outcomes to what was expected. So criteria for cancelling a cycle

may be clinic specific, which generally include a poor response to stimulation within the low number of follicles, for example, less than 3 oocytes or if there's a high risk of OHSS.

An IVF cycle may be converted to an intrauterine insemination cycle with poor responders, and this is because intrauterine insemination is a relatively simple and less expensive than IVF and does provide a possibility of a positive outcome. It is a limitation for those with tubal defects or, for example, severe male factor where there would not be sufficient sperm in the ejaculate to warrant doing an intrauterine insemination.

And for patients with diminished ovarian response and for those older than 40 who have had a poor response to ovarian stimulation, they may wish to consider treatment with donor oocytes or other methods of family building, such as adoption. And just to point out that, of course, this is not generally an expected outcome for patients, and they do require a lot of support from the team.

18:48
In summary, ovarian stimulation protocols during the GnRH agonist long protocol, the agonist is typically started in the luteal phase of the preceding cycle. With this protocol, hCG must be used for the trigger.

Agonists may also be used for a short protocol to take advantage of the flare effect to stimulate follicle growth. In contrast, GnRH antagonists rapidly block GnRH receptors and gonadotropin release. They're safer than agonist protocols because in an antagonist protocol, a GnRH agonist may be used to trigger ovulation and substantially reduce the risk of OHSS. A natural cycle uses a reduced amount of hormonal treatment but has a lower success rate than agonist or antagonist protocols with COS.

19:45
Summary.

19:49
Both ovulation induction and controlled ovarian stimulation modify and supplement the endogenous pathways involved in the regulation of the ovarian cycle. OI is used to develop a single oocyte in anovulatory women. An aromatase inhibitor is the primary pharmacological agent used.

COS is used to develop multiple oocytes which are used for both intrauterine insemination and in vitro fertilization procedures. The main pharmacological agents used in COS include FSH with or without LH, GnRH agonist, GnRH antagonist, hCG and progesterone.

20:37
So there are several medications used in COS at various stages of treatment, each with a specific function, and these include priming, stimulation, suppression, trigger and luteal phase support.

20:56
The main protocols for COS are the GnRH agonist long protocol, the GnRH agonist short protocol and the GnRH antagonist protocol. And every clinic will have variations on these specific protocols. Protocols may be personalized based on previous response to cycles, patient age and factors such as ovarian reserve. Dosage adjustments of FSH are made based on patient response. OHSS is a serious complication of COS and occurs primarily when hCG is used in the ovulation trigger. An antagonist cycle with GnRH agonist

trigger is the gold standard to prevent OHSS in women at risk of OHSS. If pregnancy occurs following fresh embryo transfer, luteal phase support should continue until adequate endogenous estrogen/progesterone production occurs.

22:02
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