MODULE 2, CHAPTER 1

00:01
Module 2, overview of infertility.

00:06
In this module, we will review the epidemiology of infertility in Canada, outline the many causes of infertility to better understand this complex medical condition and discuss the most common infertility disorders.

00:23
Epidemiology of infertility.

00:27
The World Health Organization, or WHO, definition of infertility states that infertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.

00:46
Infertility. The definition has been adopted by major organizations, including Health Canada, which adopts the WHO definition, but adds that for women who are over 35 years, infertility can be determined at six months.

01:08
Let's just talk about the LGBTQ2 population. Well, most people in this population who are seeking assisted human reproduction services do not have fertility issues themselves, but they are dealing with situational fertility in that the person cannot have a child biologically due to their circumstance. These individuals may require fertility treatments, including insemination with a sperm donor or treatment using donor gametes, eggs, sperm or embryo or a surrogate.

In fact, some clinics in large urban areas of Canada report that up to 15 to 25 percent of their clients are from the LGBTQ to communities. This is the Human Reproduction Act. Regulations pose obstacles for this community in that all donation of gametes are to be altruistic and cannot be paid for. And this provides or creates an obstacle in addition to the cost of pursuing infertility treatments.

The AHRA Act has been amended and he has produced a comprehensive guideline that was released in May of 2020 which specifically outlines compensation for donors or surrogates.

02:42
CFAS has third party reproduction testing requirement for donors. This, however, has not been enacted into law except for sperm donors as of February 2020 under Health Canada, which has outlined specifically donor testing requirements in addition to organizational requirements of storage of donor sperm and quality control practices.

03:14
So, is the monthly chance of conception constant? You will see here no, it is not. If we take 200 healthy couples attempting conception for the first time in women age 23 to 37, we'll see that after 1 to 2 cycles, the monthly conception rate is 30 percent. However, the longer that someone attempts conception without success, their monthly conception rate decreases.

03:45
And age definitely does impact the probability of conception as a woman ages, her chances of conception decreased dramatically, as you can see in this graph.

03:58
And by extension, we can see that the probability of infertility increases with age. So, you can see on this graph how the chance of conception decreases or probability of infertility increases dramatically as a woman ages.

04:16
So when to investigate for infertility? When we look at the previous graphs, we can see that it is recommended to proceed with fertility investigation and or treatment after only 6 months of failed, unprotected, unprotected relations in women aged 35 or older. Or, if there are any other concerns that may cause infertility, then investigations can be or should be started sooner than the one year in the WHO definition.

04:51
In Canada, the prevalence of infertility among heterosexual couples is 16 percent or roughly 1 in 6. It also coincides with an increased incidence of infertility, which is in a decline in the overall Canadian fertility rate. For example, in 2016 it was 1.54 children per woman and the average age of mothers at childbirth was over 30.

05:19
So we see that there are factors contributing to increased use of ART technologies, and some of these are societal, such as delaying marriage and parenthood, pursuing a career, for example, increased public awareness of the availability of ART technologies. We have the increasing population of LGBTQ2 couples seeking to build a family and also single parents seeking to build a family. In addition, there have been scientific advances which allow for cryopreservation ova. For example, for women who are experiencing cancer.

06:01
So we see in this graph just out of interest that people are delaying childbirth and as a result, the percentage of mothers over 35 of age is increasing. And even though there is increasing awareness, there still are a large number of individuals who are often unaware of the risk to fertility and childbearing associated with age. And they do rely on ART as they know what's available to bear children. This graph shows that women who are 35 to 44 are 8 times more likely to seek medical assistance with women the same age who already have children.

06:45
So causes of infertility. This is a review of a diagram we've seen earlier, but anything just simply put, anything that interferes with the transport of sperm and egg or anything that interferes with the cyclic nature of the menstrual cycle will be a cause for infertility.

07:13
So when we look at maternal age and fertility, egg quality diminishes with age, meaning that the chance of chromosomal abnormalities increases and can lead to miscarriage. So as a woman ages her chance of a pregnancy decrease, but her risk of miscarriage increases.

07:39
By contrast, if we look at donor oocytes, if donor oocytes are used in treatment, the outcome will be the same as the is in relation to the age of the donor and not the recipient.

07:58
In summary, the epidemiology of infertility is a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular unprotected sexual intercourse. Fertility interventions may be initiated in less than a year based on medical, sexual and reproductive history, age, physical findings and diagnostic testing.

08:22
Causes of infertility include both male and female factors. And as maternal age increases, the percentage of pregnancies per month declines, however, the risk of chromosomal abnormalities increases, as does the percentage of miscarriages. Although IVF success rates decline after age 35in women using their own eggs, success rates with donor egg are independent of the age of the recipient.

08:51
The next section in module 2 is female infertility disorders.

08:59
For the causes of infertility in females, there are 4 main groups of infertility disorders: ovulatory, pelvic and tubal disorders, uterine disorders and unexplained or idiopathic.

09:16
Female causes of female infertility ovulatory disorders.

09:24
We are going to look at 2 pituitary disorders here, hyperprolactinemia and hypogonadotropic hypogonadism, also referred to as hypo-hypo. And both of these can result in an anovulation.

09:43
We will first, look at hyperprolactinemia.

09:47
Hyperprolactinemia, increased levels of prolactin in the blood. Prolactin is a hormone secreted by the anterior pituitary gland and has a role in reproduction and lactation. High levels of serum prolactin, suppress GnRH release from the hypothalamus and result in depressed levels of pituitary FSH and LH secretion, which in turn lead to a minimal follicle growth and minimal ovarian production of estrogen and progesterone. As a result, women with hyperprolactinemia often have irregular menstrual cycles or amenorrhea which is the absence of menstrual cycles.

10:33
Causes of hyperprolactinemia may be natural physiological state such as pregnancy, lactation, stress or nipple stimulation. Or if there's a disorder, it may be caused by prolactinomas, which are benign prolactin-secreting tumors in the pituitary, hypothyroidism and some medications, primarily ones used for psychiatric or psychological treatment.

11:02
To diagnose hyperprolactinemia is a serum test where we see persistently high prolactin levels. In fact, it's recommended to do more than 1 test for when doing serum testing. Treatment can include stopping a medication if it's known to produce hyperprolactinemia, to deal with the microadenomas, which are the little tumors in the pituitary with medications or primarily a dopamine agonist. And for amenorrhea, dopamine agonist or oral contraceptives can be of value.

If medication doesn't work for treatment, surgical removal of tumors may be used to treat, although is not as common, and if hypothyroidism is identified, then simply a replacement with a medication called thyroxine can remedy the situation.

12:04
Now we'll look at hypogonadotropic hypogonadism, hypo-hypo.

12:11
Hypo-hypo is a clinical syndrome that results from gonadal insufficiency due to abnormal pituitary gonadotropin levels, and this is due to a dysfunction in gonadotropin releasing hormone or GnRH release.

And it results in low levels of FSH and LH as also low levels of progesterone and estrogen. The typical symptoms are amenorrhea, no menstrual cycles, oligomenorrhea, which is irregular cycles, and it's frequently the reason why women seek medical attention. Also, failure to progress through puberty. In other words, no secondary sexual characteristics, including menstruation.

13:02
There are acquired causes of hypo-hypo, which you can see here, including infiltrated of diseases such as hemochromatosis, trauma, some medications, tumors, et cetera.

13:15
To diagnose hypo-hypo in serum testing, we see low levels of FSH and LH, lack of menstrual cycles, a lack of secondary sexual development, and a peculiar sign is anosmia, which is loss of sense of smell. And this would be more related to a genetic cause of hypo-hypo.

To treat cyclic estrogen and progesterone can be used or gonadotropin therapy, particularly if the plan is to seek conception, combination of FSH and LH and just to note that LH must always be used in the hypo-hypo population and human chorionic gonadotropin, hCG to trigger ovulation.

14:08
In summary, pituitary disorders include hyperprolactinemia, which is an increase serum prolactin that causes suppression of GnRH from the hypothalamus and results in depressed levels of pituitary FSH and LH secretion. There are many causes, including pituitary tumors, some medications and hypothyroidism, and it may be treated with dopamine agonists or by addressing the underlying cause, for example, stopping medications that are causing hyperprolactinemia.

Hypo-hypo is a dysfunction in GnRH leading to decreased FSH and LH secretion. When fertility is desired. It may be treated by gonadotropin therapy using both FSH and LH.

The next section in Module 2, is female ovulatory disorders.

15:05
The ovary. The ovulatory disorders we will discuss here are polycystic ovarian syndrome which is PCOS, premature ovarian insufficiency POI sometimes called premature ovarian failure or premature menopause.

15:25
Polycystic ovary syndrome PCOS is estimated to affect 7 to 10 percent of reproductively aged women. There is criteria called Rotterdam criteria that requires at least 2 of the following 3 elements for diagnosis of PCOS where there is oligo/anovulation, hyperandrogenism, or polycystic ovary seen on ultrasound. However, it should be noted that the Rotterdam criteria also emphasizes that PCOS is a diagnosis of exclusion. In other words, there's no androgen secreting tumor or other disorders that may be causing PCOS or PCOS like symptoms.

16:15
For the treatment of PCOS, the treatment will vary depending on if pregnancy or ovulation is desired. If it is, then the focus is on facilitating ovulation, which may be remedied by lifestyle modifications such as weight loss and adding in medications. First line therapy would be aromatase inhibitor to have ovulation occur. A second line is biguanide and also second line gonadotropins to have ovulation occur.

If insulin resistance is identified, then biguanide is a medication that would be used to treat that. If there is no pregnancy or ovulation desire the focus is on regulating menses and reducing the acne/hirsutism and other symptoms and signs of PCOS. And first line would be hormonal contraception and lifestyle modification again, such as weight loss or weight control or and using antiandrogens.

17:31
Although ultrasound is not required in the diagnosis of PCOS, you will see it commonly used as a diagnostic tool. The polycystic ovary will contain 12 or more follicles and these would be antral follicles or 25 or more using ultrasound technology. You can see on the right the diagram shows the classical image of a polycystic ovary and the multiple follicles that you see in the antral region of the ovary is often

referred to as string of pearls and is used as a diagnostic description. Just to note that ultrasound here would be a transvaginal ultrasound is the usual mode of ultrasound.

18:22
So androgen excess is a central defect in PCOS patients. It's triggered by other factors such as obesity and insulin resistance. These androgens have an antagonistic effect on ovulation and estrogen priming of the endometrium.

So for diagnosis, if there are abnormal testosterone or DHEA levels, that would be a sign that PCOS would be the diagnosis. For treatment, oral contraceptive pills, antiandrogens and lifestyle modification and the effects on fertility are anovulation or oligoovulation. And also, just to note that the symptoms that are experienced by these women are often have an impact on their psychological state and self-esteem with obesity, hirsutism, acne and other things that are not acceptable to them.

19:26
We will look at premature ovarian insufficiency, it's also known as hypergonadotropic hypogonadism, as there is more FSH required to stimulate the ovaries for the to produce the menstrual cycle and decreased estrogen. It can be referred to as premature menopause. POI is defined as menopause occurring prior to age 40 and present as amenorrhea, either primary or secondary, meaning primary if a woman has never had a pregnancy or conception or secondary. Menopausal symptoms, including hot flashes and vaginal dryness, and if there's a genetic reason, absence of breast development and menstrual cycles.

The endocrine hallmarks are elevated FSH and LH production by the anterior pituitary and low estrogen production from the ovary.

20:32
So causes of POI can be spontaneous, idiopathic means it happens and there's no identified reason, however many times it will be genetic, such as with Turner Syndrome or a fragile X permutation, an autoimmune disorder or infection. It can be induced, which happens if there is a bilateral oophorectomy or bilateral ovarian cystectomies that greatly reduce ovarian tissue or as a result of chemotherapy or radiation, and also can produce environmental toxins and pelvic vessel embolization, such as after pelvic trauma.

21:24
Diagnosis of POI can be identifying hypergonadotropic hypogonadism in the setting of amenorrhea, abnormal bleeding patterns, as we mentioned, anovulation or cycles or irregular cycles, high FSH, which are identified through 2 separate tests at least one month apart, low estradiol or low anti-müllerian hormone, which is also called AMH and also by karyotyping which would only be done if there was a suspected genetic reason.

POI can be treated with hormonal contraception or replacement to resume menstrual cycles, or if there is not a response to, for example, gonadotropin treatment, IVF using donor eggs. The effects of infertility or cessation of menses at less than age 40, and the absence of follicular development.

22:28
Karyotyping which would be done if there was suspected genetic cause for POI can account for 20 to 25 percent of POI cases and are most commonly related to X chromosome aberrations, such as Turner Syndrome.

22:46
In summary, for ovarian disorders, PCOS is a biochemical and clinical hyperandrogenism where there are regular cycles or anovulation and is diagnosed by the Rotterdam criteria, it can be treated actually quite successfully with pharmaceuticals and lifestyle modifications.

POI leads to cessation of menses at less than age 40 and depletion of ovarian reserve is diagnosed by amenorrhea, elevated FSH and LH and low estrogen. Evaluation of causes may include genetic testing and can be treated with hormone therapy and IVF using donor eggs.

23:34
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