NATIONAL CURRICULUM IN REPRODUCTIVE PSYCHIATRY

NOTE: This script accompanies the self-study PowerPoint, it is to be used as supplement

SLIDE 2 :
At the conclusion of this self-directed study activity, learners will be able to
1. Define Infertility and describe the prevalence of infertility
2. Identify psychiatric symptoms related to Infertility and Fertility treatments
3. Identify how psychiatric symptoms and psychotropics affect fertility and fertility treatment outcomes.

SLIDE 3:
These are some recommended readings.

SLIDE 4:
What is Infertility?
Infertility is the inability to conceive within 1 year of regular unprotected intercourse. If the woman is more than 35 years of age, the time line comes down to 6 months. If the woman is 35 years or older and had regular unprotected intercourse for 6 months and was unable to conceive then she is described as going through infertility.
Infertility can be Primary or Secondary.
When a woman is unable to ever bear a child, either due to the inability to become pregnant or the inability to carry a pregnancy to a live birth, she would be classified as having primary infertility.
When a woman is unable to bear a child, either due to the inability to become pregnant or the inability to carry a pregnancy to a live birth following a previous ability to carry a pregnancy to a live birth, she would be classified as having secondary infertility.

SLIDE 5:
What is the prevalence of Infertility?
According to the Department of Health & Human Services and the CDC:

- Out of 100 **couples** in the United States, 12- 13 have trouble becoming pregnant
- About 10 in 100 (6.1 million) women in the United States ages 15–44 have difficulty becoming or staying pregnant

SLIDE 6:
What are the causes of Infertility?
About a third are due to female factors, about a third are due to male factors and the remaining third are a combination of male and female in addition to unexplained factors. In about 10% of the time, the etiology remains completely unexplained.

SLIDE 7:
Let's look at the various female factors.
Ovulatory dysfunction: Polycystic ovarian disease is one of the most common disorders affecting ovulation. According to a study by Joham et al. in 2015, infertility was 15-fold higher in women reporting PCOS, independent of BMI.
Maternal age: Egg count and quality deteriorate with age
Blockage of fallopian tubes
Endometriosis
Uterine fibroids
Endometrial polyps
Women with autoimmune diseases have elevated risk for primary ovarian insufficiency, likely resulting from the underlying inflammatory state, alterations of the hypothalamic-pituitary-gonadal (HPG) axis, and medication exposures.
Thyroid autoimmune disorders adversely affect conception and pregnancy outcomes

SLIDE 8:
Now let's look at male factors.

- Varicocele
- Some infections, such as gonorrhea or inflammation of the testicles, can affect sperm production or sperm health or can cause scarring that blocks the passage of sperm. Mumps orchitis can affect fertility.
- Ejaculation disorders like premature ejaculation, anejaculation (the failure to ejaculate), and retrograde ejaculation can have an effect on fertility.
- Despite its immune-privileged status, in pathological circumstances, the testicular immune response can lead to the development of Anti-Sperm Antibodies, and, in rare instances, to autoimmune epididymoorchitis.
- Cancers and nonmalignant tumors affecting the male reproductive organs and the surgery, radiation or chemotherapy to treat tumors can affect male fertility.
- Undescended testicles
  Diabetes Mellitus can cause ejaculatory and erectile dysfunction in men. Disorders such as Klinefelter's syndrome can affect fertility.
- Infections, trauma or abnormal development, such as with cystic fibrosis or similar inherited conditions which result in defective tubules that transport sperm can contribute to infertility.
- Problems with sexual intercourse like erectile dysfunction, premature ejaculation, painful intercourse, hypospadias or psychological or relationship problems that interfere with sex can cause infertility.
- Medications:
  - Sulfasalazine used in Inflammatory bowel disease may decrease sperm count and affect sperm motility.
  - Long term use of Anabolic steroids affects sperm count.
  - Surgeries such as vasectomy, inguinal hernia repairs, scrotal or testicular surgeries, prostate surgeries, and large abdominal surgeries performed for testicular and rectal cancers can prevent from having sperm in the ejaculate.

SLIDE 9-11
Basic infertility workup includes a proper history and physical exam, ovulation assessment, hysterosalpingogram and semen analysis. If the woman's age is greater than 35, consider FSH level.
Increased prolactin and thyroid dysfunction are common causes for ovulatory dysfunction. If these test results are abnormal, treat accordingly. If these tests are normal, consider ovulation inducing agents and refer to ART.
If hysterosalpingogram is abnormal, appropriate surgical treatment for tubal occlusion and uterine filling defects should be considered.
If FSH is elevated, repeat the lab again. If it is consistently elevated, consider discussing oocyte donation.
Regarding Semen analysis, instructions for collecting the sample should include abstinence from ejaculation for 48 to 72 hours. Because sperm generation time is just over two months, it is recommended to wait three months before repeat sampling.
If semen analysis is abnormal, test for FSH, LH, and testosterone in the male partner. If FSH and LH are elevated but testosterone is decreased, it indicates primary hypogonadism. Trauma to testicles, radiation or chemotherapy could be the causes. If all three are decreased, it indicates a problem at the higher level- Prolactinoma, pituitary deficiency. If all three are normal, then consider problems with ejaculation or obstruction of vas or epididymis or antisperm antibodies. All work up can be normal and infertility can be unexplained.

SLIDE 12:
So which comes first? Infertility or psychiatric symptoms?
Even when patients are assessed at the beginning of infertility evaluation and treatment, they may have struggled with difficulty conceiving for a very long time. So, it is difficult to assess the relationship between the onset of affective episode and fertility problems.

SLIDE 13:
Let's look at how Depression can affect fertility

- Depression causes elevated prolactin levels, which can result in infertility .
- Depression can cause disruption of the HPA axis.
  Thyroid dysfunction in depression can also result in ovulatory dysfunction.
- Changes in immune function associated with stress and depression may also adversely affect reproductive function.
- Further studies are needed to distinguish the direct effects of depression or anxiety from associated behaviors and conditions such as low libido, smoking, alcohol use and obesity that may interfere with reproductive success

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SLIDE 14:
Can Infertility cause depression and anxiety?

- Some studies show that the rates of major depressive disorder in women undergoing infertility treatment are as high as 17–19.5 % and up to 15.3 % in men.

- Rates of generalized anxiety disorder in women seeking infertility treatments are also high, at 23.2 %.
- Past history of MDD predicts MDD during infertility treatment among both men and women, even after controlling for other well-established risk factors like baseline levels of depression, anxiety, and lack of partner support.

SLIDE 15:
According to a study in Danish women by Kjaer et al., women who did not have a child after an initial fertility evaluation had a >2-fold greater risk of suicide than women who had at least one child after a fertility evaluation. Women with secondary infertility also had an increased risk for suicide compared with women who succeeded in having another child, although the risk estimate failed to reach significance.

SLIDE 16:
Can eating disorders affect fertility?
Despite speculation that women with histories of anorexia will have difficulty conceiving even when in remission, many studies have demonstrated no differences in rates of pregnancy. However, two studies have suggested lower prevalence of pregnancy in women with histories of AN. One of these two studies by Brinch et al. included only women who had a history of inpatient hospitalization for AN, which may represent a more medically compromised sample, and there is a possibility that the medical complications were affecting fertility.

SLIDE 17:
Can depression or anxiety affect the treatment outcome?
Studies show contradicting conclusions. In a Meta-analysis of prospective psychosocial studies Boivin et al showed that Pretreatment emotional distress is unlikely to affect chances of pregnancy after a single cycle of treatment with assisted reproductive technologies. But according to a study in 80 Turkish couples by Gurhan et al, depression has an effect on oocyte numbers. High state anxiety and higher depression scores on the oocyte pick up day resulted in lower pregnancy rates. Sperm motility was also inversely correlated with depression scores.

SLIDE 18:
Can psychotropics affect fertility?
The sexual side effects of SSRIs can have an effect on
outcomes.
A review of 950 patients was performed by Friedman et al. to investigate the impact of selective serotonin reuptake inhibitors (SSRIs) on in vitro fertilization outcome. The 41 patients (4.3%) taking an SSRI had a higher cycle cancellation rate but no statistically significant difference in pregnancy rate and live birth rate per cycle started. IVF cycle cancellation refers to cancellation of the egg retrieval because only a low number of follicles develop in the ovaries during the stimulation phase of treatment.

SLIDE 19:
A Nationwide register-based cohort study was conducted by Cesta et al., and this showed that women not on SSRI treatment for their depression or anxiety had reduced odds of pregnancy and live birth. Among the women who became pregnant, there were no statistically significant associations between exposure and miscarriage except for the women taking non-SSRI antidepressants

SLIDE 20:
Valproic acid is a well-documented teratogen, but the impact of this medication on fertility is currently unknown. Valproic acid in reproductive age group women is not usual practice. For any reason, if it is to be used, proper documentation with rationale and discussion of risks, benefits, side effects and alternatives should be considered and discussed with the patient and the spouse. Proper folic acid supplementation is to be considered.
Lithium has known effects on thyroid function, which can be a risk factor for infertility. Regular monitoring of thyroid function in addition to standard monitoring of lithium levels and kidney function are recommended for women on lithium undergoing fertility evaluation and/or treatment.

SLIDE 21:
Atypical antipsychotics, especially risperidone, may increase prolactin levels in women even at low doses. The associated hyperprolactinemia may lead to ovulatory dysfunction and thereby independently influence fertility.
According to a study by Mckenna et al., olanzapine, risperidone, and quetiapine are not associated with an increased risk of spontaneous abortions.

SLIDE 22:
Clomiphene is FDA approved for ovulation induction in unexplained and anovulatory infertility. Clomiphene has mixed estrogenic and antiestrogenic properties. It binds with estrogen receptors throughout the reproductive system. This reduces receptor concentrations by interfering with the normal process of estrogen receptor replacement. Depletion of estrogen receptors at the hypothalamus results in reduced perceived levels of circulating estrogen, which induces compensatory pulsatile gonadotropin releasing hormone secretion and increases ovarian follicular activity.
General side effects include bloating, abdominal discomfort, ovarian enlargement, vision changes, headaches, hot flashes, abnormal uterine bleeding.
Psychiatric symptoms include anxiety, irritability, mood changes, and even transient psychosis.
Synthetic gonadotropins are similar to endogenous gonadotropins in their mechanism of action. They are FDA approved for ovarian stimulation and ovulation induction in anovulatory women undergoing ART. General side effects include bloating, rash, abdominal or pelvic pain, ovarian enlargement, pain at the injection site. Psychiatric side effects include mood swings, fatigue, irritability, depression, and restlessness.
GnRH antagonists act by competitively blocking GnRH receptors on the pituitary gonadotroph. These are FDA approved for inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation. General side effects include hot flashes, head aches, nausea, vomiting,

abdominal discomfort, ovarian enlargement. Psychiatric side effects include mood swings, depression, and insomnia.
Progesterone prepares the uterine lining for embryo implantation. If it's discovered that the IVF treatment cycle resulted in a successful pregnancy, progesterone is often continued for the first 6-12 weeks post pregnancy. It is FDA approved for luteal phase support in early pregnancy.
General side effects include abdominal pain, bloating, headache, fatigue, GI disturbance, nausea. Mood swings are a common side effect of progesterone.

SLIDE 23:
Other medications that are used off label are Aromatase inhibitors, GnRH agonists, Dopamine agonists like Bromocriptine and Cabergoline, Metformin, Tamoxifen, Prednisone, and Dexamethasone.
Aromatase inhibitors prevent the conversion of androgens to estrogen and decrease amount of circulating estrogen.
GnRH agonists disrupt pulsatile stimulation of GnRH receptors and desensitize GnRH receptors and decrease secretion of LH and FSH. This prevents spontaneous LH surge and ovulation in ART.
Dopamine agonists like Bromocriptine and Cabergoline exert an inhibitory effect on the secretion of prolactin
Metformin is used to help with improving menstrual cycle regularity or hyperandrogenism in women with PCOS who cannot tolerate OCPs.
Tamoxifen is a Nonsteroidal anti-estrogen. It stimulates ovulation by blocking estrogen receptors in the hypothalamus.
Dexamethasone is used for ovulation induction in Clomid- resistant PCOS.
Prednisone can be used along with aspirin in management of antiphospholipid antibody syndrome.

SLIDE 24:
Let's have a word on the different assisted reproductive technologies
Ovulation induction by the ovulation inducers we discussed above is usually the first step.
Artificial insemination is the process of inserting the semen into the cervix/fallopian tubes/uterus. This is particularly helpful when there are mechanical difficulties with intercourse.
In vitro fertilization means fertilization of the egg by the sperm in an in vitro environment, i.e, the culture dish. This results in embryo or embryos and then they are transferred into the uterus.
ICSI follows the same process as IVF, except that in ICSI a single sperm is injected into each egg to achieve fertilization.
Pre-implantation genetic diagnosis is a process in which the embryos that are generated by IVF are screened for a genetic condition prior to the transfer of the embryo into a woman's uterus.

SLIDE 25
A Swedish study on 3532 women by Vikstrom and his colleagues in 2017 showed that IVF treatment does not increase the risk of postnatal depression. Women with a history of mental illness had increased risk for depression in the postpartum period.

SLIDE 26

In conclusion

- Depressive or anxiety symptoms or disorders are common among women who experience infertility and in women going through fertility treatments.
- Women with a prior history of MDD are at higher risk while going through infertility or fertility treatments.
- Treatment of psychiatric symptoms helps with better outcomes with fertility treatments.
- More evidence supporting SSRIs and second generation antipsychotics. Limited studies on other medications.