BIOLOGICAL ASPECTS OF INFERTILITY

National Curriculum on Reproductive Psychiatry

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LEARNING OBJECTIVES

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.


INFERTILITY

Infertility is defined as the inability to conceive within 1 year of unprotected intercourse, in women less than 35 years of age; and after six months of regular intercourse without use of contraception in women 35 years and older.

Infertility can be primary or secondary.
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
CAUSES OF INFERTILITY

What are the causes of Infertility?

- Male factors
- Female factors
- Unexplained
CAUSES OF INFERTILITY - FEMALE FACTORS

- Ovulation disorders
- Maternal age
- Blockage of fallopian tube
- Endometriosis
- Uterine fibroids
- Endometrial polyps
- Autoimmune diseases
CAUSES OF INFERTILITY - MALE FACTORS

• Problems with sperm production - varicocele, infections, medications, undescended testicles, Klinefelter’s syndrome, tumors
• Problems with sperm transportation - infections, cystic fibrosis
• Erection, ejaculation and other coital issues
1. Menstrual Cycle History
   - Interval
   - Dysmenorrhea
   - Spotting?

2. Ovarian Reserve testing
   - Day 3 FSH, Estradiol
   - Antimullerian hormone level (any day in the cycle)
   - Antral Follicle Count (transvaginal ultrasound)

3. TSH, Prolactin level (most add routinely, some add if irregular menses noted)

4. HSG

5. Semen Analysis

* If all the above tests return with normal results the couple has unexplained infertility.
1. Ovarian Factor:

- **Menstrual Cycle History**
  - Regular q24-35d → patient is **Ovulatory**
  - Irregular or absent → patient is **Anovulatory**
    - add TSH, PRL level

**DDx:** PCOS, Hypothalamic amenorrhea, perimenopause/menopause, ovarian insufficiency/failure, primary amenorrhea, other endocrine disorders: hypo/hyper-thyroidism, hyperprolactinemia, other medical conditions, eating disorder

- **Ovarian reserve testing:**
  - Day 3 FSH/Estradiol
  - Anti-Mullerian hormone (AMH)
  - Antral follicle Count (AFC)

- **Normal:**
  - FSH <10
  - E2 <70
  - AMH >1.0 (AMH >1.5 for women under 35 is more ideal)

- **Abnormal:**
  - FSH >10
  - E2 >70
  - AMH <1.0
  - AFC will vary based on age. < 6 is very low. In women <35yo >15 is optimal.

**DDx:**
1. Diminished ovarian reserve
2. Premature Ovarian Insufficiency
3. Ovarian failure
2. Tubal Factor
- **HSG**
  - **Patent**
  - **Blocked:** Unilateral, Bilateral, partial, hydrosalpinx
    - Unilateral: can still do IUIs
    - Bilateral: needs IVF
    - Hydrosalpinx: tube with fluid needs to removed surgically prior to embryo transfer

3. Uterine factor
- **HSG**
  - **Normal**
  - **Abnormal:** Filling defects or appearance of uterine anomaly
    - Filling defect: **DDx:** uterine polyp, uterine fibroids, adhesions
      * saline infusion sonohysterogram can also evaluate the uterine cavity. May be needed to confirm diagnosis.
    - Uterine anomaly: **DDx:** arcuate, septum, bicornuate, unicornuate, didelphys, T-shaped
      * MRI needed to distinguish

4. Sperm Factor
- **Semen Analysis**
  - **Normal**
    - **Vol:** >1.5ml.  **Conc:** 15million/ml.  **Motility:** >40%  * **Total motile Count:** >20million
  - **Abnormal:** isolated abnormality in one parameter or TMC <20million
    - repeat SA to confirm abnormality
    - **Male hormone panel:** FSH, LH, Testosterone, Estradiol
    - Refer to male fertility specialist: physical exam: ? Varicocele, testicular mass, Small testicular volume

  **DDx:** idiopathic, obstructive, ejaculatory dysfunction, hypogonadism- primary vs. secondary, cancer, varicocele
DEPRESSION AND INFERTILITY

...it was me, right?
DEPRESSION AND INFERTILITY

Proposed mechanisms:

1. Disruption of the HPA axis
2. Thyroid dysfunction
3. Elevated prolactin levels
4. Behaviors associated with depression /anxiety
INFERTILITY AND DEPRESSION

- Psychological distress
- Prevalence of Major Depressive Disorder (MDD) and dysthymia was 17% and 9.8% respectively
- Rates of Generalized Anxiety Disorder in women seeking infertility treatments is 23.2%.
- Past history of MDD predicts MDD during infertility


INFERTILITY AND SUICIDE

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.

EATING DISORDERS AND INFERTILITY

• Many studies have demonstrated no differences in rates of pregnancy.
• Studies that suggested a possible association included only women who had a history of inpatient hospitalization for anorexia nervosa.

PSYCHIATRIC SYMPTOMS AND TREATMENT OUTCOMES

• Studies show inconclusive conclusions
• One study showed pretreatment emotional distress is unlikely to affect chances of pregnancy
• A different study showed that low oocyte numbers were associated with higher depression scores
• Higher state anxiety and depression scores correlated with lower pregnancy rates

Gurhan et al Association of Depression and Anxiety with Oocyte and Sperm Numbers and Pregnancy Outcomes during in vitro Fertilization Treatment. Psychol rep 2009, 104(3): 796-806
PSYCHOTROPICS AND FERTILITY- SSRIs

- Sexual side effects of psychotropics
- Higher cycle cancellation rate but no statistically significant difference in pregnancy rate and live birth rate per cycle started

PSYCHOTROPICS AND FERTILITY- SSRIs

• Reduced odds of pregnancy and live birth in women with a depression/anxiety diagnosis with no antidepressants.
• No statistically significant associations between exposure and miscarriage except for the women taking non-SSRI antidepressants.

PSYCHOTROPICS AND FERTILITY-MOOD STABILIZERS

Valproic acid:
• Higher incidence of PCOS
• Case reports suggesting spermatic dysfunction with valproic acid

Lithium:
• Hypothyroidism from lithium

PSYCHOTROPICS AND FERTILITY-
ANTIPSYCHOTICS

• Atypical antipsychotics and hyperprolactinemia
• Atypical antipsychotics and spontaneous abortions?
INFERTILITY TREATMENTS AND PSYCHIATRIC SYMPTOMS DUE TO INFERTILITY TREATMENTS

FDA APPROVED MEDICATIONS:

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>PSYCHIATRIC SYMPTOMS</th>
</tr>
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<tbody>
<tr>
<td>Clomiphene</td>
<td>Anxiety, irritability, mood changes, transient psychosis</td>
</tr>
<tr>
<td>Gonadotropins</td>
<td>Mood swings, fatigue, irritability, depression, restlessness</td>
</tr>
<tr>
<td>GnRH antagonists</td>
<td>Mood swings, depression, insomnia</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Mood swings</td>
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INFERTILITY TREATMENTS AND PSYCHIATRIC SYMPTOMS DUE TO INFERTILITY TREATMENTS

OFF LABEL USE:

• Aromatase inhibitors
• GnRH agonists
• Dopamine agonists
• Metformin
• Tamoxifen
• Prednisone
• Dexamethasone
ASSISTED REPRODUCTIVE TECHNOLOGY [ART]

- Ovulation induction
- Artificial insemination/Intrauterine insemination
- In-vitro fertilisation (IVF)
- Intracytoplasmic sperm injection (ICSI)
- Pre-implantation genetic diagnosis (PGD)
ASSISTED REPRODUCTIVE TECHNOLOGY-MENTAL HEALTH ISSUES

• 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.

Vikström J; Sydsjö G; Hammar M; Bladh M; Josefsson A. Risk of postnatal depression or suicide after in vitro fertilisation treatment: a nationwide case-control study. BJOG;2017;124(3):435-442
SUMMARY

• 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.
REFERENCES AND FURTHER READING

• Gurhan et al Association of Depression and Anxiety with Oocyte and Sperm Numbers and Pregnancy Outcomes during in vitro Fertilization Treatment. Psychol rep 2009, 104(3): 796-806
REFERENCES AND FURTHER READING

• Kjaer TK, Jensen A, Dalton SO, et al. Suicide in Danish women evaluated for fertility problems. Hum Reprod 2011; 26(9): 2401-2407
• Vikström J; Sydsjö G; Hammar M; Bladh M; Josefsson A. Risk of postnatal depression or suicide after in vitro fertilisation treatment: a nationwide case-control study. BJOG;2017;124(3):435-442
THANK YOU