

# BIOLOGICAL ASPECTS OF INFERTILITY

**National Curriculum on Reproductive Psychiatry**

**Authors: Madhavi- Latha Nagalla, MD**



NATIONAL CURRICULUM IN  
REPRODUCTIVE  
PSYCHIATRY

# 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.



# RECOMMENDED READING

1] Katherine E. Williams, Wendy K. Marsh and Natalie L. Rasgon. *Mood disorders and fertility in women: a critical review of the literature and implications for future research. Human Reproduction Update* 2007;13(6):607–616.

2] Kimmel MC, Ferguson EH, Zerwas S, Bulk CM, Meltzer-Brody S. *Obstetric and gynecologic problems associated with eating disorders. Int J Eat Disord.* 2016 Mar;49(3):260-275.

3] Amritha Bhatt Nancy Byatt. *Infertility and Perinatal loss: when the bough breaks. Curr Psychiatry Rep* 2016; 18:31

4] Kirsten M Wilkins, Julia K Warnock, Elka Serrano. *Depressive symptoms related to infertility treatments. Psychiatr Clin N Am* 2010 Jun; 33(2):309-321

5] Rebecca S, Kathryn M. *On label and off label drug female infertility. Fertility and sterility* 2015 Mar;103



# INFERTILITY

Infertility is defined as the inability to conceive within 1 year of regular, unprotected intercourse in women less than 35 years of age and after six months of regular, unprotected intercourse in women 35 years and older.

Infertility can be primary or secondary.



# PREVALENCE

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 be 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

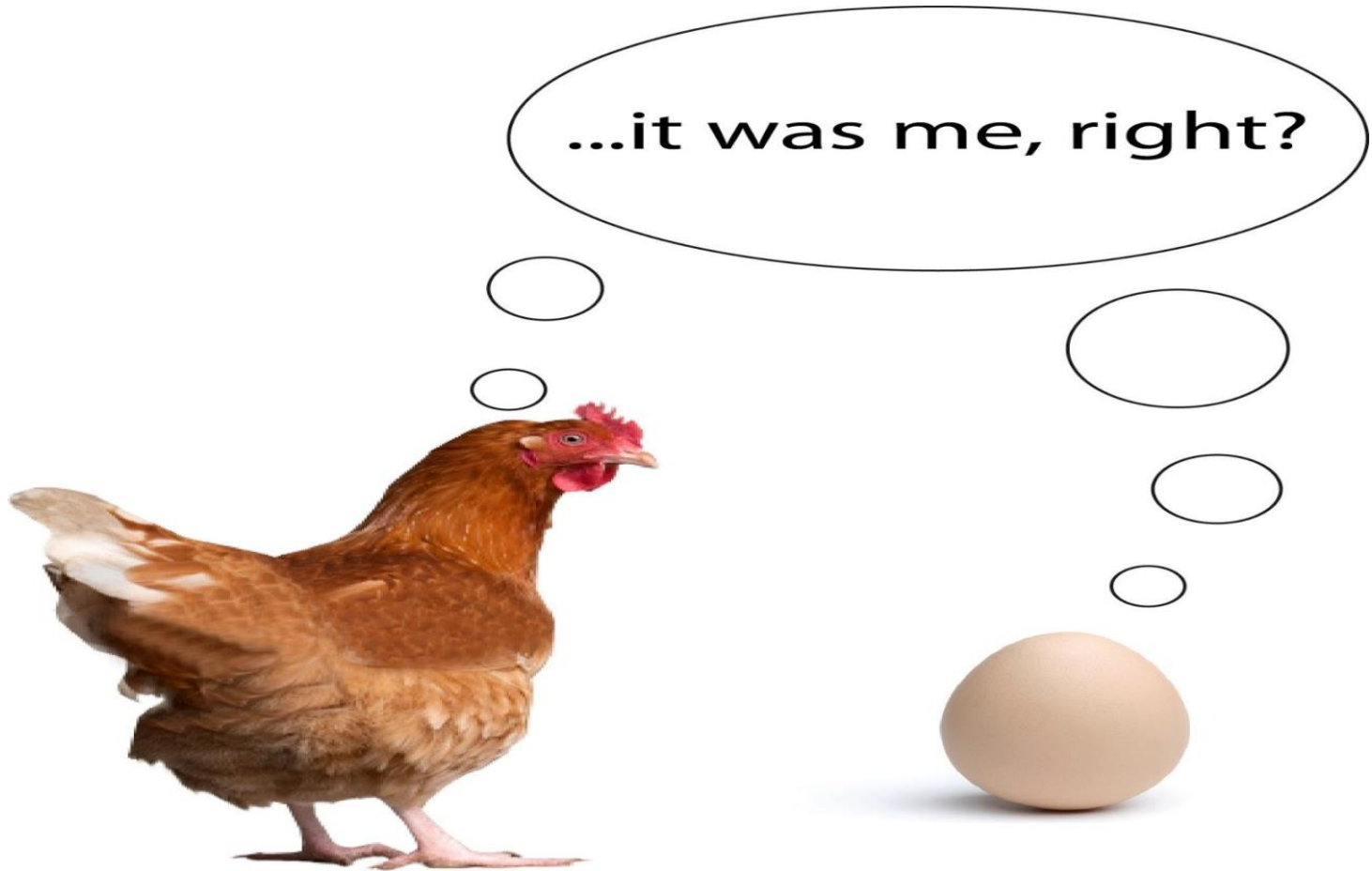
- **Semen Analysis**
- **Normal**

**Vol :** >1.5ml. **Conc:** 15million/ml. **Motility:**>40% \* **Total motile Count:** >20 million

- **Abnormal:** isolated abnormality in one parameter or TMC < 20 million
  - 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



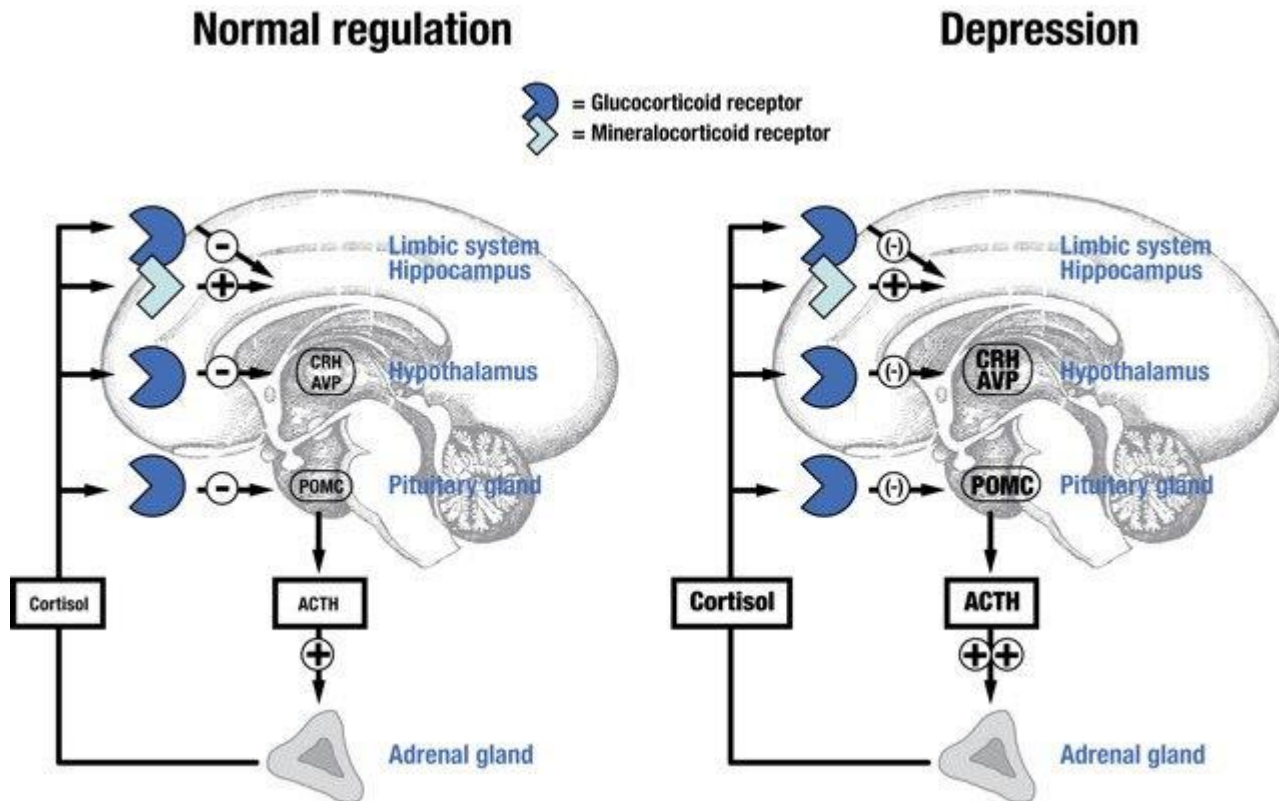
# DEPRESSION AND INFERTILITY

Proposed mechanisms:

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



# DISRUPTION OF THE HPA AXIS



Bosch, Oliver & Seifritz, Erich & Wetter, Thomas. (2012). Stress-related depression: Neuroendocrine, genetic, and therapeutical aspects. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 13. 10.3109/15622975.2012.665477.



NATIONAL CURRICULUM IN  
REPRODUCTIVE  
PSYCHIATRY

# INFERTILITY AND DEPRESSION

- Psychological distress
- Prevalence of Major Depressive Disorder (MDD) and persistent depressive disorder 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

*Amritha Bhatt, Nancy Byatt. Infertility and Perinatal loss: When the bough breaks. Curr Psychiatry Rep 2016;18:31*

*Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod. 2004;19(10):2313–2318*



# 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

*Kjaer TK, Jensen A, Dalton SO, et al. Suicide in Danish women evaluated for fertility problems. Hum Reprod. 2011; 26(9): 2401-7*





# 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
- Eating disorders can lead to anovulation, in which case fertility treatments to induce ovulation can improve pregnancy rates

*Kimmel MC, ferguson EH, Zerwas S, Bulk CM, Meltzer-Brody S. Obstetric and gynecologic problems associated with eating disorders. Int J Eat Disord. 2016 Mar;49(3):260-275*



# 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

*Boivin J, Griffiths E, Venetis CA. Emotional distress in infertile women and failure of assisted reproductive technologies:meta-analysis of prospective psychosocial studies. BMJ 2011 Feb 23;342:d223*

*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

*Friedman B, Rogers J, Shahine L, Westphal L, Lathi R. Effect of selective serotonin reuptake inhibitors on in vitro fertilization outcome. Fertil Steril 2009;92:1312–1314*



# 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

*Cesta CE, Viktorin A, Olsson H, Johansson V, Sjölander A, Bergh C, Skalkidou A, Nygren KG, Cnattingius S, Iliadou AN. Depression, anxiety and antidepressant treatment in women: association with in vitro fertilization outcome. Fertil Steril. 2016 Jun;105(6):1594-1602.e3.*



# PSYCHOTROPICS AND FERTILITY: MOOD STABILIZERS

## **Valproic acid:**

- Higher incidence of PCOS
- Case reports suggesting spermatic dysfunction with valproic acid

## **Lithium:**

- Hypothyroidism from lithium

*Hayashi T, Yoshida S, Yoshinaga A, Ohno R, Ishii N, Yamada T. Improvement of oligoasthenozoospermia in epileptic patients on switching anti-epilepsy medication from sodium valproate to phenytoin. Scand J Urol Nephrol. 2005;39(5):431-2.*



# PSYCHOTROPICS AND FERTILITY: ANTIPSYCHOTICS

- 2<sup>nd</sup> Generation antipsychotics and hyperprolactinemia
  - May ↑ prolactin levels even at low doses
    - Especially risperidone
  - Hyperprolactinemia may → ovulatory dysfunction (independent risk factor for infertility)
- 2<sup>nd</sup> Generation antipsychotics and spontaneous abortions
  - Olanzapine, risperidone, and quetiapine not associated with increased risk of spontaneous abortions in prospective comparative study

*McKenna K, Koren G, Tetelbaum M, Wilton L, Shakir S, Diav-Citrin O, Levinson A, Zipursky RB, Einarson A. Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. J Clin Psychiatry. 2005 Apr;66(4):444-9; quiz 546. doi: 10.4088/jcp.v66n0406. PMID: 15816786.*

*Bostwick JR, Guthrie SK, Ellingrod VL: Antipsychotic-induced hyperprolactinemia. Pharmacotherapy 29(1):64-73, 2009*



NATIONAL CURRICULUM IN  
REPRODUCTIVE  
PSYCHIATRY

# INFERTILITY TREATMENTS AND PSYCHIATRIC SYMPTOMS DUE TO INFERTILITY TREATMENTS

## FDA APPROVED MEDICATIONS:

MEDICATION	PSYCHIATRIC SYMPTOMS
Clomiphene	Anxiety, irritability, mood changes, transient psychosis
Gonadotropins	Mood swings, fatigue, irritability, depression, restlessness
GnRH antagonists	Mood swings, depression, insomnia
Progesterone	Mood swings

# INFERTILITY TREATMENTS AND PSYCHIATRIC SYMPTOMS DUE TO INFERTILITY TREATMENTS

- Clomiphene
  - Marked anxiety, sleep disturbance, headaches, visual disturbances, vertigo, hot flashes, mood swings, irritability, emotional lability, and symptoms similar to premenstrual syndrome
  - Mood changes in women with a history of premenstrual dysphoric disorder and postpartum depression
  - Psychosis may develop especially in women with bipolar disorder
    - Reversible but may require hospitalization
- Oral contraceptives
  - Depression
- GnRH analogs such as leuprolide
  - Case reports of acute psychosis, anxiety, and mood changes

*Grant ECG. Hormonal Contraception and Its Association With Depression. JAMA Psychiatry. 2017;74(3):301–302.*

*Burns LH. "Psychiatric Aspects of Infertility and Infertility Treatments," Psychiatric Clinics of North America (Dec. 2007): Vol. 30, No. 4, pp. 689–716.*



NATIONAL CURRICULUM IN  
REPRODUCTIVE  
PSYCHIATRY



# 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 fertilization (IVF)
- Intracytoplasmic sperm injection (ICSI)
- Pre-implantation genetic diagnosis (PGD)



# ASSISTED REPRODUCTIVE TECHNOLOGY: MENTAL HEALTH ISSUES

- IVF treatment per se does not increase the risk of postnatal depression
- However, women with a history of depression are twice as likely to develop a recurrence of depression during both infertility treatment as well as during a subsequent pregnancy and postpartum period

*Burns LH. "Psychiatric Aspects of Infertility and Infertility Treatments," Psychiatric Clinics of North America (Dec. 2007): Vol. 30, No. 4, pp. 689–716.*

*Stanhiser J, Steiner AZ: Psychosocial aspects of fertility and assisted reproductive technology. ObstetGynecolClin North Am 45(3):563-74, 2018*

*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*



NATIONAL CURRICULUM IN  
REPRODUCTIVE  
PSYCHIATRY

# SUMMARY

- Depressive or anxiety symptoms or disorders are common among women who experience infertility and in women going through 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

- Ajmal A, Joffe H, Nachtigall LB. Psychotropic induced hyperprolactinemia: a clinical review. *Psychosomatics* 2014 Jan-Feb;55(1):29-36
- Boivin J, Griffiths E, Venetis CA. Emotional distress in infertile women and failure of assisted reproductive technologies: meta-analysis of prospective psychosocial studies. *BMJ* 2011 Feb 23;342:d223
- Bosch, Oliver & Seifritz, Erich & Wetter, Thomas. (2012). Stress-related depression: Neuroendocrine, genetic, and therapeutical aspects. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. 13. 10.3109/15622975.2012.665477.
- Bostwick JR, Guthrie SK, Ellingrod VL: Antipsychotic-induced hyperprolactinemia. *Pharmacotherapy* 29(1):64-73, 2009
- Burns LH. "Psychiatric Aspects of Infertility and Infertility Treatments," *Psychiatric Clinics of North America* (Dec. 2007): Vol. 30, No. 4, pp. 689–716.
- Cesta CE, Viktorin A, Olsson H, Johansson V, Sjölander A, Bergh C, Skalkidou A, Nygren KG, Cnattingius S, Iliadou AN. Depression, anxiety and antidepressant treatment in women: association with in vitro fertilization outcome. *Fertil Steril*. 2016 Jun;105(6):1594-1602.e3.
- Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. *Hum Reprod*. 2004;19(10):2313–2318
- Friedman B, Rogers J, Shahine L, Westphal L, Lathi R. Effect of selective serotonin reuptake inhibitors on in vitro fertilization outcome. *Fertil Steril* 2009;92:1312–1314.



# REFERENCES AND FURTHER READING

- *Grant ECG. Hormonal Contraception and Its Association With Depression. JAMA Psychiatry. 2017;74(3):301–302.*
- *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*
- *Joham AE, Teede HJ, Ranasinha S, Zoungas S, Boyle J. Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: data from a large community-based cohort study. J Womens Health (Larchmt) 2015 Apr;24(4):299-307.*
- *Kjaer TK, Jensen A, Dalton SO, et al. Suicide in Danish women evaluated for fertility problems. Hum Reprod 2011; 26(9): 2401-2407*
- *McKenna, K & Koren, Gideon & Tetelbaum, M & Wilton, L & Shakir, Saad & Diav-Citrin, O & Levinson, A & Zipursky, Robert & Einarson, Adrienne. Pregnancy outcome of women using atypical antipsychotic drugs: A prospective comparative study. The Journal of Clinical Psychiatry 2005 66. 444-449.*
- *Seeman MV. Transient psychosis in women on clomiphene, bromocriptine, domperidone and related endocrine drugs. Gynecol Endocrinol 2015 Oct;31(10):751-754.*
- *StanhiserJ, Steiner AZ: Psychosocial aspects of fertility and assisted reproductive technology. ObstetGynecolClin North Am 45(3):563-74, 2018*
- *Vikström J; Sydsjö G; Hammar M; Bladh M; Josefsson A. Risk of postnatal depression or suicide after in vitro fertilisation treatment: a nationwide case- BJOG;2017;124(3):435-442*



THANK YOU



NATIONAL CURRICULUM IN  
REPRODUCTIVE  
PSYCHIATRY