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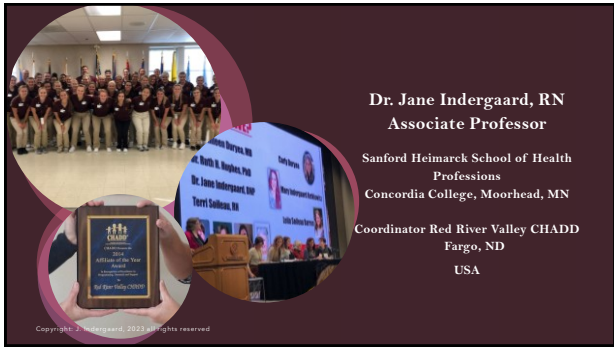
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### Disclaimer

- The primary purpose of this presentation is to educate and inform based on a review of recent available research and best evidence
- It is not intended to replace current scope or standards of practice for individual professionals in their discipline.
- It does not constitute medical, or treatment advice.

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### Sex Disparity ADHD Diagnosis, Presentation, Treatment

- Differences in incidence and expression of ADHD
- Research historically on males
- More prone to underdiagnosis, misdiagnosis or diagnosed later
- Males are referred & treated more often than females

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### Why do girls get missed?



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#### Girls are different than boys

- Have a distinct symptom presentation (Quinn) - predominantly inattentive
- Are better able to mask or mitigate the impact of their symptoms
- Often present with symptoms of depression and anxiety - which often get diagnosed first (Quinn)

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These noted differences beg the question...

Do women have divergent patterns when it comes to ADHD?

Why does ADHD present differently?

What mechanisms are involved?

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Most obvious explanation is the major biological distinction between genders:

**Presence of the menstrual cycle associated with variation in sex steroid hormone levels**  
(Haimov-Kochman & Berger, 2014)

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Hormonal Fluctuations:  
Influence on the Experience of Women with ADHD

Not well understood

Very little collective research

Evidence available driven by anecdotal, clinical, personal observation AND...

...Need to understand and safely support women with ADHD as experienced across the lifespan



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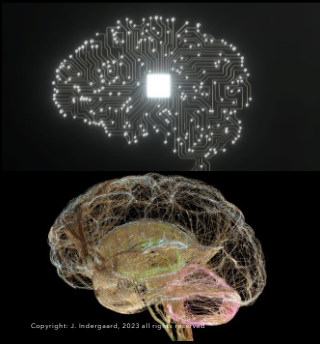
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Key Points: Gonadal  
Hormone Effects on Brain

- A. Have impact on major neurotransmitter (NT) systems
- B. Impact synaptic plasticity
- C. Modulate neuronal activity
- D. Regulate intracellular signaling systems

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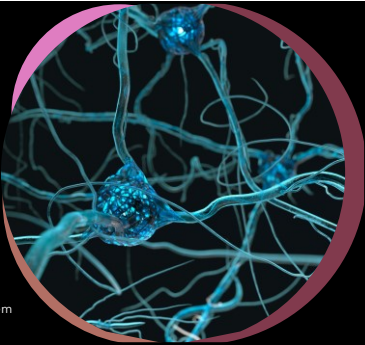
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Brain is a Target  
Organ for  
Estrogen

- Hormone related increases found in concentrations of NT
- Modulates cognitive function
- Promotes release of monoamines
- Interacts with dopaminergic system

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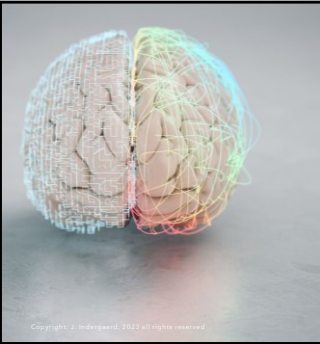
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Hormonal  
Fluctuations:  
Neurotypical Women

- Impact brain's architecture, metabolism, hemostasis
- Impact neurotransmitter levels (Serotonin, Dopamine, NE)
- Modulate functioning of Dopamine (EF), ACTH (Memory), Serotonin (Mood)
- Higher Levels of E associated with increased EF and attention
- Low or fluctuating levels of E associated with various cognitive disruptions

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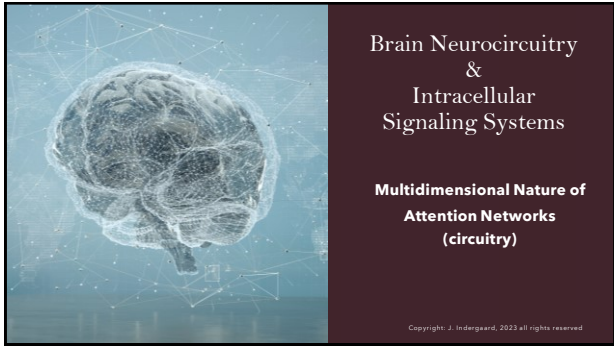
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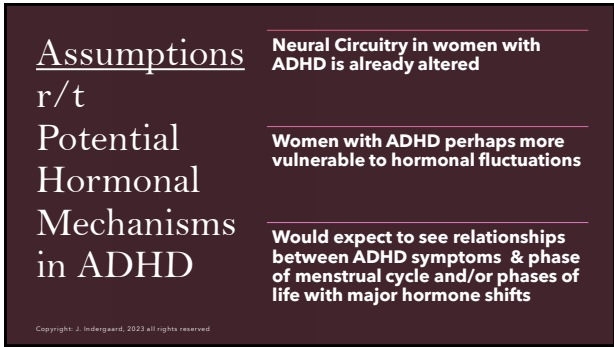
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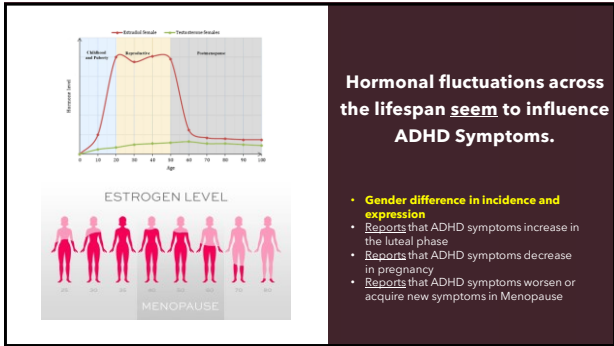
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## Hormone Fluctuations and ADHD

- ☐ Puberty
- ☐ Menstrual Cycle
- ☐ Pregnancy/Peripartum
- ☐ Climacteric/Menopause

✓ All linked with large changes in hormone levels  
✓ Potential activational effects on neural circuitry and behavior

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## Prepuberty

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EARLY MENSES IS ASSOCIATED WITH MORE SEVERE SYMPTOMS OF INATTENTION AND RISK TAKING (OSTOJIC & MILLER, 2016)

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## Puberty, Adolescence Young Adulthood

- SEX HORMONES PRODUCED
- PHYSICAL SEXUAL DEVELOPMENT
- MENARCHE
- ESTROGEN PRODUCTION HIGH/STEADY

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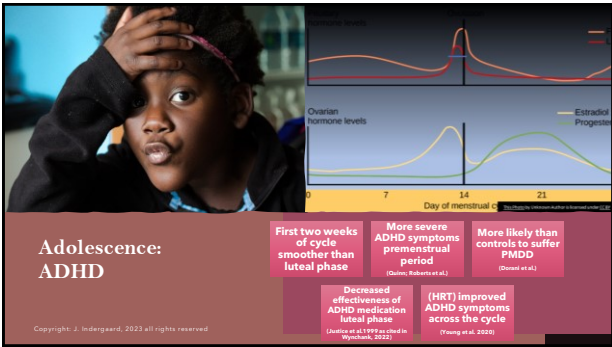
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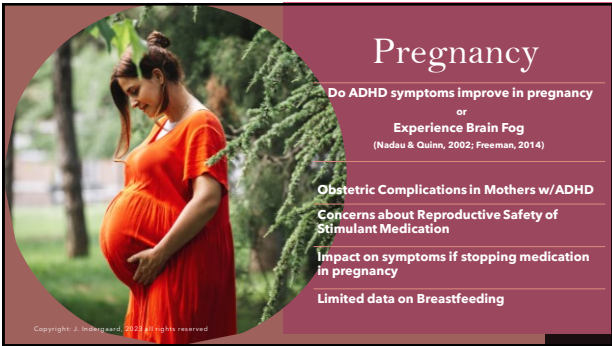
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### Obstetric Complications and ADHD

- ✓ Mothers w/ ADHD had *higher rates* of every outcome except HPV than controls
- ✓ Patients on stimulant medication statistically *lower rates* of every outcome (except HPV) than ADHD moms w/o any recorded medication
- ✓ Non-stim medication still showed lower rates but *not as robustly* as stimulant medication

Walsh, Rosenberg, Hale (2022)

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### CDC Alerts

- First trimester stimulant medication risks
- End of Pregnancy medication negative effect on fetus
- 20-30% increase in C-section and need for NICU
- Breastfed babies possible impact appetite, sleep, development

National Birth Defects Prevention Study 1998-2011  
As cited by Anderson et al. 2018

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### Did the CDC "Over-reach"?!

Kolding et al., 2021  
Koren et al., 2020  
Huybrechts et al., 2018

Questioned:  
confidence intervals/?significance  
Variables/confounding factors

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Kolding et al., 2021

Koren et al., 2020

Huybrechts, et al., 2018

Exposure to Methylphenidate not associated with increased risk of malformations overall (inclusive of prenatal and postnatal diagnoses)

Increased risk of cardiac malformations

Methylphenidate exposure in early pregnancy associated with small but significant increased risk for major malformations, attributed largely to increased risk of cardiac formations (echo!)

Small increase in risk of cardiac malformations associated with intrauterine exposure to methylphenidate, but not to amphetamines

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Baker et al.,  
2022

Prospective  
Observational  
Study

But what about stopping medication:  
*Functional Impairment?*

Medication Status	AISRS	EPDS	WFIRS
Discontinued n = 5	No increase	Significant increase	Increased Family Function Impairment
Maintained n = 12	No increase	No depressive symptoms	No reported change
Adjusted n = 8	No increase	No depressive symptoms	No reported change

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APA Summary  
and suggestions:

Benefit must be robust enough to justify potential exposure!

While stimulants do not appear to be associated with major congenital malformations must consider individually the risk/benefit ratio for every woman/baby

If functional impairment risk strong - may have to take medications and monitor carefully (echo)

If fetal risk tolerance unacceptable - recommend attention to driving, work function with increased external supports, accommodations, adjustments

Try drug abstinence trial before conception (with supports in place) may be useful

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Postnatal



More prone to PPD (post-partum depression) Dorani et al., 2021

Hormonal Fluctuations, functional demands and transitions lead to depressive symptoms - Maternity increases demands on EF!

Consider exacerbation of ADHD when seeing depressive and anxiety symptoms (Tax EF)

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Climacteric (Menopause)

Exacerbation of symptoms

Onset of new symptoms

Increased inattention

More vulnerable to mood disorders

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Menopause  
Interesting Finding...

➤ Neurotypical women develop symptoms similar to ADHD  
(Camera et al., 2022; Pines, 2016))

➤ Role of HRT, Atomoxetine, Lisdexamfetamine  
(Shanmugan et al. 2016)

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Would Seem  
Estrogen is the  
Culprit but...



Empirical support  
for hormonal  
influence on ADHD  
is limited

Recent research  
suggests  
mechanisms are  
much more  
complex than  
simply estrogen

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Evidence that  
Estrogen is  
part of a  
Larger System

Author	Finding	Implication
Roberts et al. 2018 n=32	Studied covariants of E2, P4, T Conducted Cycle Phase Analysis of ADHD sx across cycle	Effects across cycle are a state-like variable of endogenous steroid changes
Zhuang et al. 2020	Studied E2 and P4 combinations in late follicular and early luteal phase	E mediates ADHD sx by interacting with other sex hormones
Sahin et al. 2018	ADHD group = lower levels GPER Low GPER significant r/t ADHD sx	GPER variations may affect ADHD symptoms

Estrogen *itself* does not impact ADHD presentation

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Sahin, Altun, Kurutas, Findikli, 2018



Basis of Study	Findings
<ul style="list-style-type: none"><li>Estrogen exerts its effect through 2 classes of receptors</li><li>Role of GPER 1 (membrane receptor) implicated in psychiatric diseases</li><li>Evaluated serum Estrogen and GPER levels in children with ADHD and matched healthy controls</li></ul>	<ul style="list-style-type: none"><li>Estrogen levels similar in both groups</li><li>GPER levels significantly lower in ADHD group</li><li>LRA showed significant association between GPER levels and ADHD (p&lt;0.05)</li><li>No association between estrogen levels and ADHD</li><li>No significant differences in GPER and estrogen levels between ADHD subtypes</li></ul>

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Pharmacotherapy  
and Gender

Koh, Groen, Fuernmair, Tschu (2020)

- Prescription rates
- Effect on inattention, hyperactivity, impulsivity (MPH)
- Onset/peak/duration (MPH)
- Effect of non-stimulants (ATX)
- Effect on hyperactivity, impulsivity, emotional dysregulation (ATX)
- Role of Hormone influences (dexAMP)

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Conclusions:  
Role of Sex  
Hormones in  
ADHD  
Symptoms

Hormonal fluctuations across lifespan *seem* to influence exacerbation of ADHD symptoms

Literature is limited/ but point to some intriguing associations

Evidence accumulating on role of estrogen as part of a larger system (Covariance of levels, genotypic risk, GPER receptor density, balance of other reproductive hormones)

Cyclical effects across menstrual cycle are a more state-like variable = suggest possibility that EF and Psychostimulant response might vary across the cycle

BOTTOM LINE

Neuroendocrinology, Anecdotal and limited evidence suggest there is an impact of hormonal fluctuation on sx of women with ADHD - but it remains unclear why/how?

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Implications  
for Research

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Do it!

Evaluate activational hormone effects and mechanisms on ADHD symptoms over the female lifespan  
(Attention to transitional benchmarks)

Evaluate activational hormone effects and mechanisms on ADHD symptoms across the menstrual cycle  
(Study Estrogen in the context of a much bigger system)

Measure and evaluate subtle hormonal fluctuations and combinations' influence on neuronal circuits implicated in expression of ADHD symptoms  
(GPER differences in affected vs non-affected individuals)

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### Clinical Applications- Further study and investigations on:

- Stimulant effects and safety in pregnancy
- Effect of hormonal fluctuations on medication efficacy
- Specific medication class effect differences for females
- Effect of adjunctive therapies (i.e. HRT) on mitigation of ADHD symptom exacerbation

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### Implications for Practice: Gynecology/Psychiatry/General Practitioners

- Be aware of extra vulnerability of women with ADHD to hormonal fluct at every stage	- Optimize comprehensive Multimodal treatment for ADHD across every life stage	- Treat ADHD sx before or along with tx for comorbidities (maybe just increase in ADHD). esp PP	- Consider earlier onset and earlier cessation of stim medication (dosing)
- Consider lesser effect of stimulant med during luteal phase/ as well as increased risk PMDD	- Consider risk/benefit ratio in stimulant use during pregnancy/ accommodations and supports	- HRT may be indicated both for menstrual cycle and menopause symptom exacerbation	- Non-stimulants may be more effective than stim for women, esp. menopause (low-dose E may augment stim effects)

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## Questions?

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This presentation was developed and provided by the author for:

Scientific Session 7: Women and ADHD  
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*3rd Southern African Multidisciplinary  
ADHD Virtual Congress*  
on 09/03/2022

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