


**Diagnosing Infertility -  
Helping Your Patients Through The  
Process**

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Professor, Cedars-Sinai Medical Center

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**Disclosures**

- Ferring
- Natera

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**Objectives**

- Define Infertility
- Understand the options to improve natural fertility
- Understand the evaluation for infertility
- Some new developments in the fertility evaluation

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### Time Required for Conception

Time of Exposure	% pregnant
3 months	57%
6 months	79%
1 year	85%
2 years	93%

**Impacts 1 in 5 (19%) married women (15-49 years)**  
**National Survey of Family Growth**

Cedars Sinai | Fertil and Steril 1996;65: 503-9  
 JAMA 1966; 161: 855  
<https://www.cdc.gov/reproductivehealth/infertility/index.html> - text=infertility%20common%20conception%20rate%20survey%20of%20family%20growth

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### New Definition of Infertility

- **“Infertility” is a disease, condition, or status characterized by any of the following:**
  - The inability to achieve a successful pregnancy based on a patient's medical, sexual, and reproductive history, age, physical findings, diagnostic testing, or any combination of those factors.
  - The need for medical intervention, including, but not limited to, the use of donor gametes or donor embryos in order to achieve a successful pregnancy either as an individual or with a partner.
  - In patients having regular, unprotected intercourse and without any known etiology for either partner suggestive of impaired reproductive ability, evaluation should be initiated at 12 months when the female partner is under 35 years of age and at 6 months when the female partner is 35 years of age or older.

Cedars Sinai | Practice Committee of the American Society for Reproductive Medicine Fertility and Sterility 2023 5

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### The Fertile Window

- The fertile window spans the 6 day interval ending on the day of ovulation
- Peak fecundability occurs within 2 days before ovulation
- The likelihood of success decreases with increasing age

Probability of pregnancy resulting from recurrent intercourse by woman's age and cycle day. Data from Stanford and Dunson (17).  
 Practice Committee of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility. Fertil Steril 2021.  
 Practice Committee of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility. Fertil Steril 2021.  
 Wilcox NEJM 1995  
 Dunson DB. Hum Reprod 1999  
 Stanford JB. Am J Epidemiol 2007  
 ASRM Practice Committee, 2021

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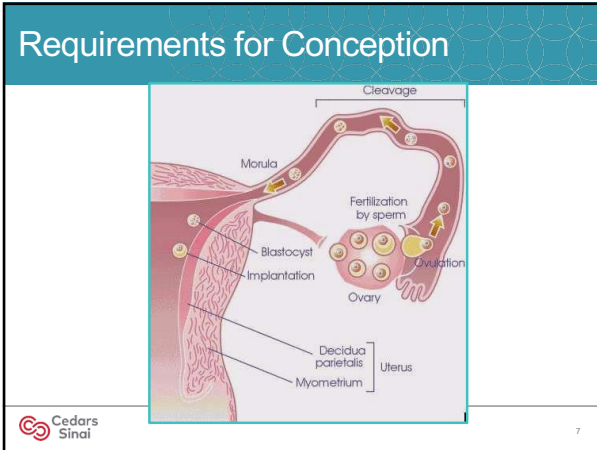
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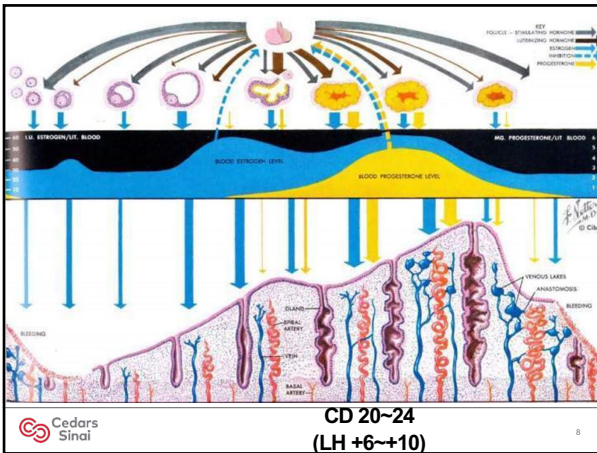
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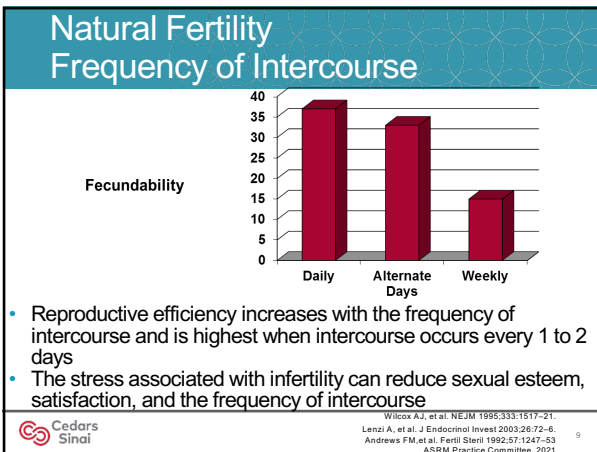
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### Lifestyle Factors That May Impact Fertility - Females

- Weight - Fertility rates decrease in very thin or obese women
- Diet - Robust Data on dietary variations is lacking
  - Healthy Food Consumption may improve ovulatory dysfunction infertility
- Smoking - significantly more likely to be infertile (OR, 1.60; 95% CI, 1.34–1.91)
- Caffeine Consumption –
  - High (500 mg; >5 cups of coffee per day) decreased fertility (OR, 1.45; 95% CI, 1.03–2.04)
  - Medium (over 200 to 300 mg per day 2–3 cups per day) increase the risk of miscarriage
  - Moderate (1–2 cups per day) no apparent adverse effects on fertility or pregnancy outcomes

 ASRM Practice Committee, 2021 10

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### Social Media - New Source of Information on Diets and Supplements for PCOS?

	Diets N = 50	Supplements N = 50
<b>Views by Uploader Credentials, (%)</b>		
Blogger	33.5	1.8
Fitness instructor/Health coach	0.4	4.2
Healthcare professional*	33.1	1.3
Nutrition professional**	23.7	34.2
Patient	9.3	58.5
<b>Likes by Uploader Credentials, (%)</b>		
Blogger	44.1	2.3
Fitness instructor/Health coach	0.7	3.9
Healthcare professional*	24.2	1.7
Nutrition professional**	15.6	51.9
Patient	15.4	40.2
<b>Quality and Reliability Scores</b>		
DISCERN score†	3.0 ± 0.86 (0.57)	2.4 ± 0.96 (0.42)
GOS score†	3.0 ± 0.9 (0.52)	3.0 ± 0.9 (0.60)
JAMA score†	2.5 ± 0.8 (0.44)	2.8 ± 0.6 (0.56)

**Poor Scores** \*Healthcare professionals include physicians, nurses, advanced practitioners, and chiropractors  
\*\*Nutritional professionals include nutritionists and registered dietitians  
†Reported values include mean ± standard deviation (Cohen Kappa statistic)

 Moran et al. Fertil Steril in press 11

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### Lifestyle Factors That May Impact Fertility - Males

- Smoking –
  - Decreased sperm density, motility and abnormalities in sperm morphology
  - Data do not demonstrate conclusively that smoking decreases male fertility
- Alcohol – Chronic Consumption
  - Lower sperm counts, motility, morphology, seminal fluid volume
  - Lower testosterone
  - Increased risk of sexual dysfunction
  - Increased risk of ejaculatory dysfunction
  - Premature ejaculation

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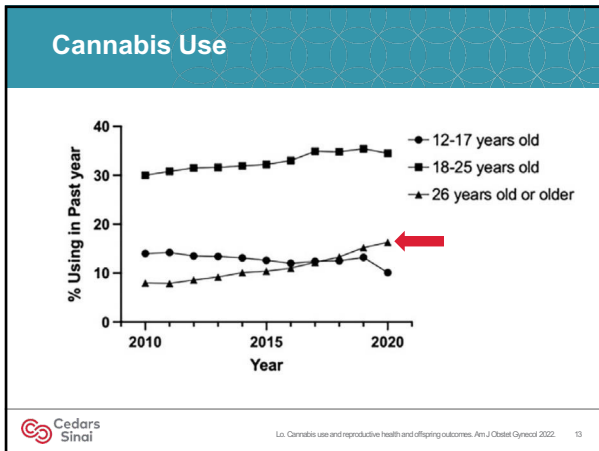
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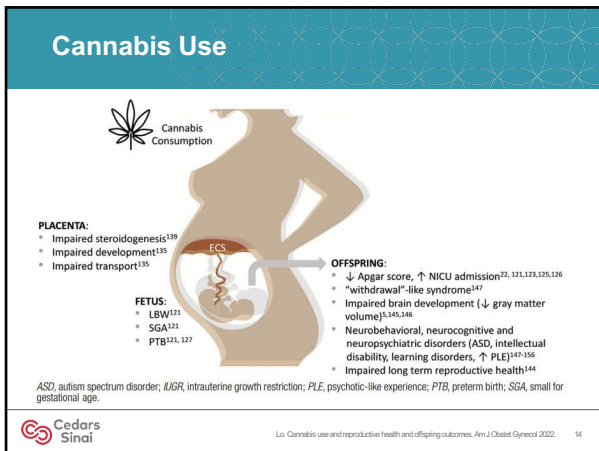
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- ### Cannabis Use - Female Reproductive Function
- Prevalence of infertility increased in users (RR, 1.7; CI 95%, 1.0–3.0)
  - No association with time to pregnancy
  - Alters reproductive hormones (FSH and LH)
  - Ovulation
    - Delays ovulation
    - More anovulatory cycles than non-users (43% vs 15%)
    - Twice as likely to experience infertility secondary to ovulatory dysfunction
  - IVF
    - 25% fewer oocytes retrieved
    - 28% fewer oocytes fertilized
  - Pregnancy loss more than double
  - Animal Studies – alters reproductive hormones, menstrual cycle length, ovulatory dysfunction
- Cedars Sinai | Lo. Cannabis use and reproductive health and offspring outcomes. Am J Obstet Gynecol 2022. ASRM Practice Committee Opinion 2022. 15

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### Cannabis Use - Male Reproductive Function

- Alters reproductive hormones (FSH and LH)
- 29% lower sperm counts
- Mixed reports on erectile dysfunction, orgasmic dysfunction, premature or delayed ejaculation
- Animal studies - THC can adversely affect spermatogenesis via inhibition of Leydig cell function, reduction in gonadotropins, testicular atrophy, and abnormal sperm morphology
- Alters methylation in sperm – affected genes identified are involved in early development, including neurodevelopment and cancers
- Significantly associated with sudden infant death syndrome, after adjusting for tobacco and alcohol co-use
- National Survey of Family Growth and North American Preconception Cohort Study no association to time to pregnancy



Lo. Cannabis use and reproductive health and offspring outcomes. Am J Obstet Gynecol 2022; ASRM Practice Committee, 2021

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### Preconception Counseling

- Family Planning and Pregnancy Spacing
- Genetic Risk Factors
- Optimize Medical Conditions and review current medications
  - diabetes, hypertension, psychiatric illness, and thyroid disease
- Vaccinations
  - COVID-19
  - Influenza
  - Rubella
  - Varicella
  - Measles
- Prenatal Vitamins/ Folic Acid



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### Preconception Genetic Screening

- All Ethnic Backgrounds
  - Cystic Fibrosis
  - Spinal Muscular Atrophy
- African-American/Mediterranean/South East Asian
  - Hemoglobin electrophoresis (sickle cell or thalassemia)
- French Canadian/Creole - Tay Sachs disease
- Ashkenazi Jewish
  - Cystic Fibrosis, Tay Sachs disease, Canavan disease, Familial Dysautonomia, Bloom Syndrome, Fanconi anemia group C, Gaucher disease, Glycogen storage disease type 1a, mucopolidosis type IV, Niemann-Pick disease type A, Dihydrofolate reductase Deficiency, Familial Hyperinsulinism, Glycogen Storage Disease Type 1a, Maple Syrup Urine Disease, NemaLine Myopathy, Usher Syndrome Type IF, Usher Syndrome Type III
- Persian Jewish
  - Pseudocholinesterase deficiency, Congenital hypoaldosteronism, Polyglandular deficiency, Hereditary inclusion body myopathy
- Family History of Developmental Delay/ Ataxia/ Fragile X Syndrome/POF/Elevated FSH
  - Fragile X premutation
- Universal Screening



ACOG, ACMG, ASRM

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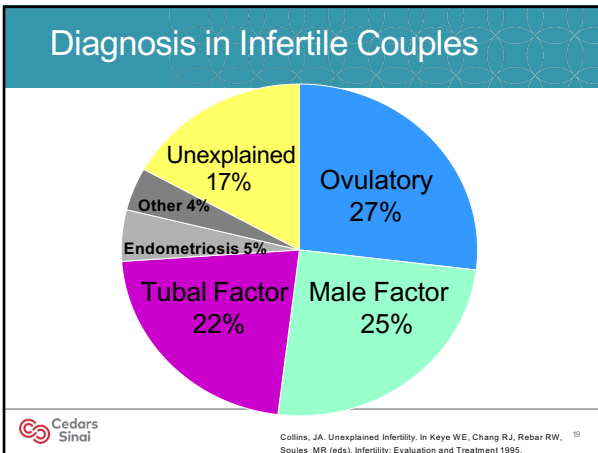
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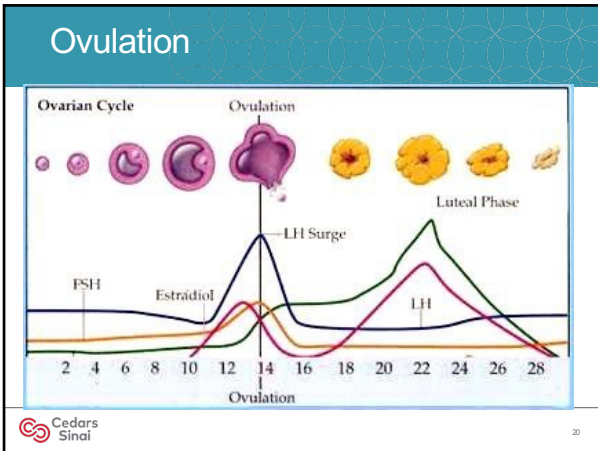
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### Natural Fertility: Menstrual History

- Nonhirsute women -
  - Prevalence of ovulatory cycles with normal menstrual history is 99.5%
- Eumenorrheic women with hirsutism
  - Prevalence of regular ovulation decreases to 60%

Cedars Sinai | Optimizing Natural Fertility Practice Committee of the American Society for Reproductive Medicine 2021 | 21

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### Natural Fertility: Monitoring Ovulation

- Cervical mucus**
  - Pregnancy rates at peak mucous (38%) vs. (15% to 20%)
  - More accurate than a menstrual calendar
- BBT**
  - Temperature taken upon awakening
  - A biphasic pattern signifies ovulation
  - Predicts the LH surge only within 2-3 days

**Vaginal Secretion**

Vaginal Secretion	Probability of Conception
Dry	~0.02
Slightly Moist	~0.05
Damp, sticky	~0.15
Slippery, clear	~0.38

**BBT Graph**

The graph shows a biphasic temperature pattern. The y-axis represents temperature in degrees Fahrenheit (97.0 to 99.0). The x-axis represents days of the cycle. Key features include:
 

- coverline**: A horizontal line indicating the average temperature.
- Follicular Phase**: The period of lower temperature before ovulation.
- Ovulation**: The point where temperature begins to rise.
- Luteal Phase**: The period of higher temperature after ovulation.

**Cedars Sinai**  
 Optimizing Natural Fertility Practice Committee of the American Society for Reproductive Medicine 2021

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### Natural Fertility: Monitoring Ovulation

- Ovulation Detection Devices**
  - may decrease the time to conception
  - ovulation may occur anytime within the 2 days thereafter
  - false-positive test results occur in approximately 7% of cycles
- App based technologies are not predictive of ovulation and may not add to traditional methods of ovulation detection
- Day 22-24 Progesterone
  - Midluteal phase > 3ng/ml

**Cedars Sinai**  
 Optimizing Natural Fertility Practice Committee of the American Society for Reproductive Medicine 2021

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### Ovulatory Dysfunction

Condition	Percentage
Polycystic Ovary Syndrome (PCOS)	70%
Hypothalamic amenorrhea	10%
Hyperprolactinemia	10%
Primary ovarian insufficiency	10%

**Cedars Sinai**  
 Reindollar RH, et al. Am J Obstet Gynecol 1986; 155: 531-43.

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### COMPARING THE PHENOTYPES OF PCOS BY NIH 1990, ROTTERDAM 2003, AND AES 2006

Characteristics	Phenotypes			
	A	B	C	D
Hirsutism/HA	√	√	√	
Ovulatory dysfunction	√	√		√
Polycystic ovaries	√		√	√
NIH1990	√	√		
Rotterdam 2003	√	√	√	√
AES 2006	√	√	√	

International Evidence Based Guideline for PCOS 2018

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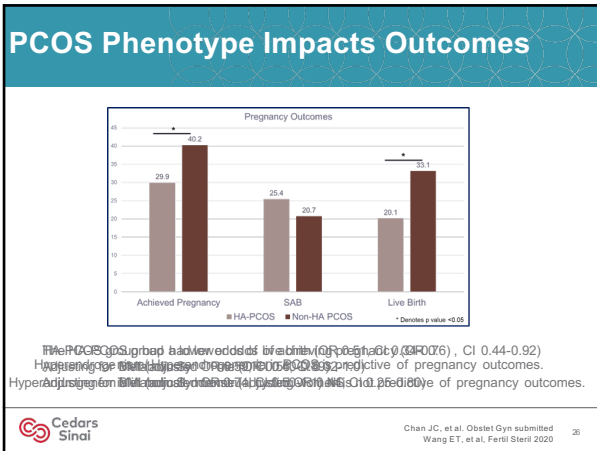
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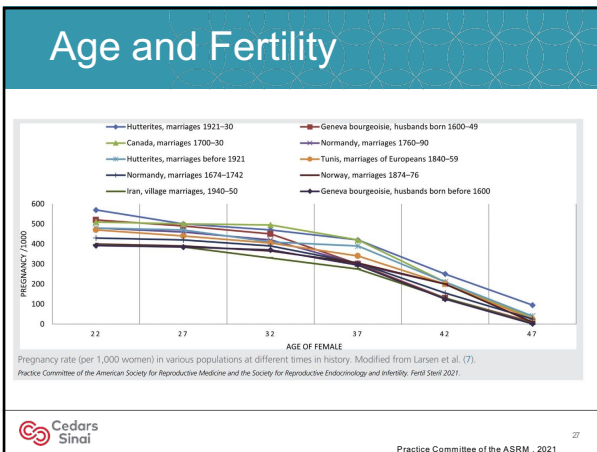
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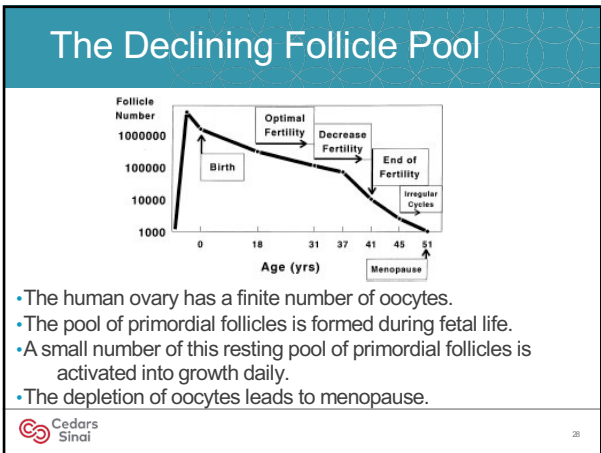
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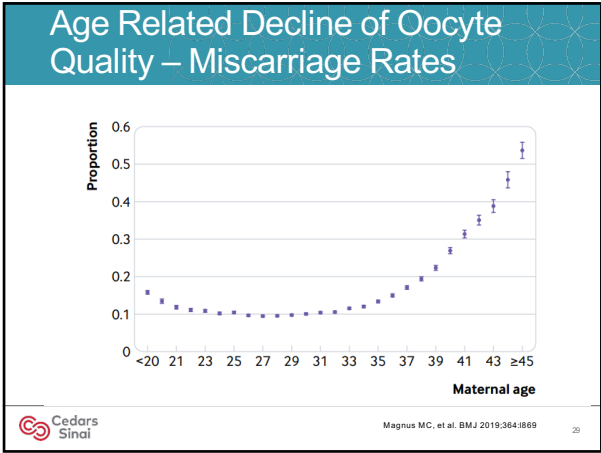
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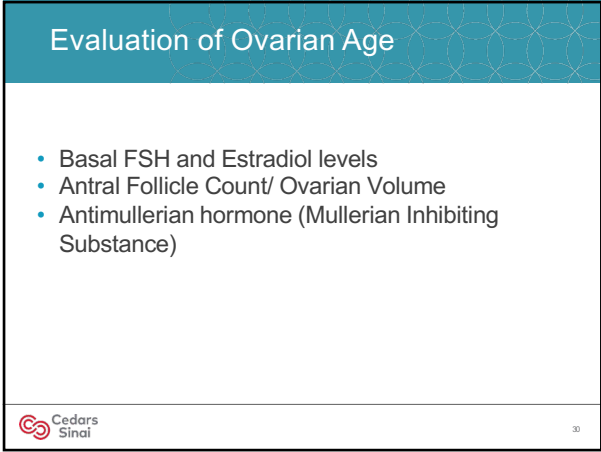
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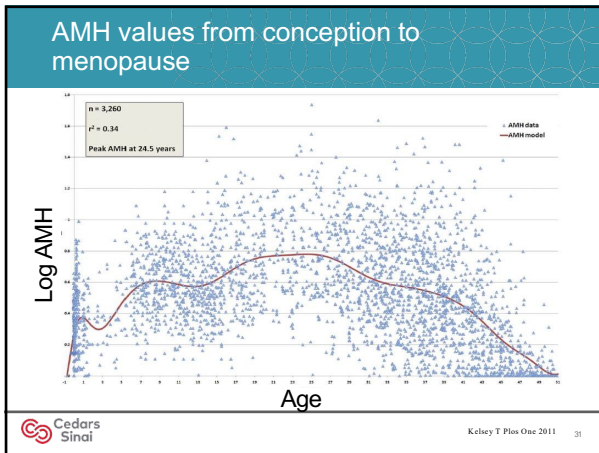
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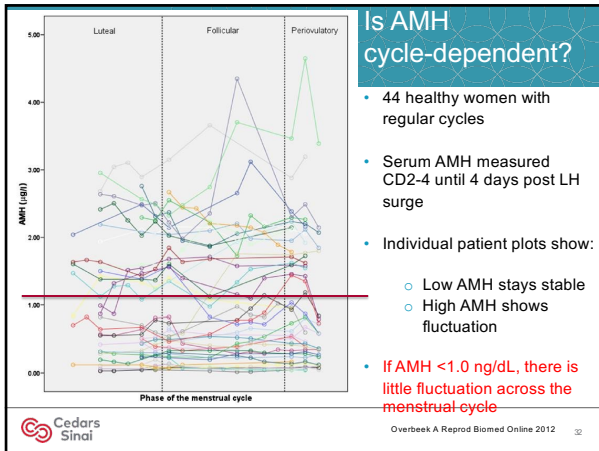
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### Antral Follicle Count

Antral follicle count cutoff levels (total count)	Subjects this applied to (n)	Sensitivity	Specificity	PPV	NPV	+LR	Post-test probability
≤ 7	4	0.13	0.98	0.45	0.90	9.00	52.9%
≤ 8	13	0.47	0.95	0.54	0.93	9.33	53.8%
≤ 9	15	0.53	0.93	0.49	0.94	8.00	50.0%
≤ 10 <sup>a</sup>	29	0.93	0.88	0.49	0.99	7.47	48.3%
≤ 11	40	1.00	0.79	0.37	1.00	4.80	37.5%

Note: The shift from the pretest probability (11.1%) to the post-test probability of poor response according to the antral follicle count is shown.  
PPV = positive predictive value; NPV = negative predictive value; +LR = positive likelihood ratio.  
<sup>a</sup> Optimum cutoff level.

Jayaprakasan. AMH and 3D-US markers of ovarian reserve. Fertil Steril 2008.

Optimal value to predict good ovarian response is 10

Cedars Sinai  
Jayaprakasan, et al. Fertil and Steril 2010 33

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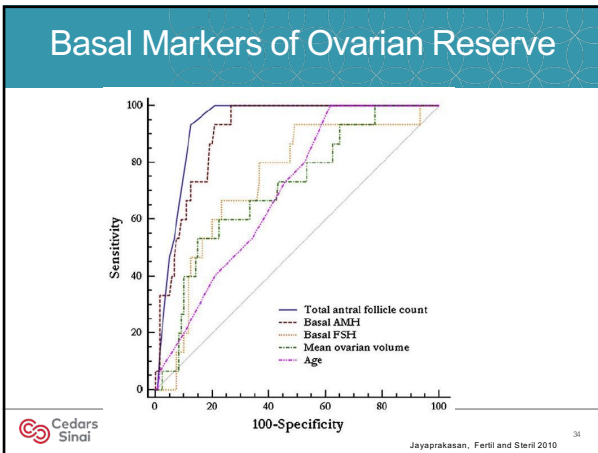
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### Hysterosalpingogram (HSG) and Sonohysterography

- Hysterosalpingogram (HSG)**
  - Tubal Patency
  - Uterine Cavity
  - low sensitivity (50%) and positive predictive value (PPV) (30%) for intrauterine pathology.
- Sonohysterography (SHG)**
  - defines the size and shape of the uterine cavity
  - high (>90%) PPV and negative predictive value for the detection of intrauterine pathologies (endometrial polyps, submucous myomas, synechiae)
  - hysterosalpingo-contrast sonography 76%–96% sensitivity for tubal patency

Cedars Sinai | ASRM Practice Committee Opinion 2011

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### Hysteroscopy

- Definitive method for the diagnosis and treatment of intrauterine pathologies
- Sensitivity of 88% and specificity of 85% to predict tubal patency through direct visualization of fluid or air bubble flow into the tubal ostia

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## Endometrial Biopsy

Journal of Assisted Reproduction and Genetics (2021) 38:645–650  
<https://doi.org/10.1007/s10815-020-02041-9>

ASSISTED REPRODUCTION TECHNOLOGIES

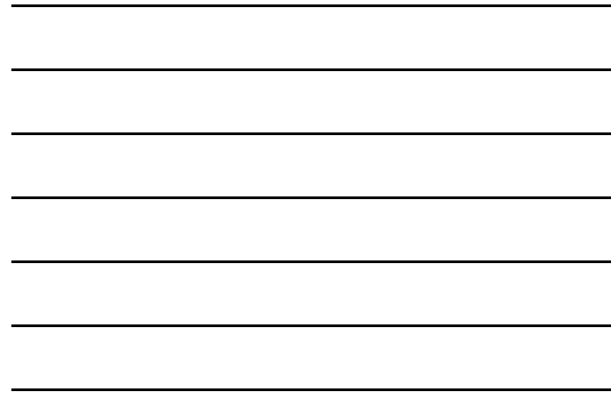
**Clinical utility of the endometrial receptivity analysis in women with prior failed transfers**

Laura E. Eisman<sup>1</sup> · Margareta D. Pisarska<sup>1</sup> · Sahar Wertheimer<sup>1</sup> · Jessica L. Chan<sup>1</sup> · Alin Lina Akopians<sup>2</sup> · Mark W. Surrey<sup>2</sup> · Hal C. Danzer<sup>2</sup> · Shahin Ghadir<sup>2</sup> · Wendy Y. Chang<sup>2</sup> · Carolyn J. Alexander<sup>2</sup> · Erica T. Wang<sup>1</sup>

<sup>a</sup>Mean (standard deviation)  
<sup>b</sup>Median (interquartile range)  
<sup>c</sup>≥ 1 prior failed ET compared to controls  
<sup>d</sup>≥ 3 prior failed ET compared to controls

Cedars Sinai | Eisman, L.E. et al. JARG 2021 37

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## Endometrial Biopsy

**Table 2** Pregnancy outcomes in the subsequent FET cycle after ERA test: cases vs. controls

	≥ 1 prior failed ET N = 131	≥ 3 prior failed ETs N = 20	Controls N = 91	P value <sup>a</sup>	P value <sup>b</sup>
Conception (n/N (%))	92/131 (70)	12/20 (60)	70/90 (78)	0.213	0.099
Clinical pregnancy (n/N (%))	78/130 (60)	10/20 (50)	60/90 (67)	0.315	0.161
Ongoing pregnancy/live birth (n/N (%))	57/121 (47)	5/18 (28)	43/80 (54)	0.357	0.046

<sup>a</sup> ≥ 1 prior failed ET compared to controls  
<sup>b</sup> ≥ 3 prior failed ETs compared to controls

Cedars Sinai | Eisman, L.E. et al. JARG 2021 38

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## Endometrial Biopsy

JAMA | Original Investigation

**Effect of Timing by Endometrial Receptivity Testing vs Standard Timing of Frozen Embryo Transfer on Live Birth in Patients Undergoing In Vitro Fertilization: A Randomized Clinical Trial**

Figure 2.

Nicole Doyle, MD, PhD; Samad Jahandideh, PhD; Micah J. Hill, DO; Eric A. Widra, MD; Michael Levy, MD; Kate Devine, MD

Outcome	Endometrial Receptivity Testing	Standard Timing	Rate Ratio (95% CI)	P value
Biochemical pregnancy loss <sup>a,b</sup>	29 (8.9)	25 (8.1)	-1.8 (-2.8 to 6.4)	1.21 (0.71-2.10)
Clinical pregnancy <sup>a</sup>	262 (68.8)	281 (72.8)	-4.0 (-10.4 to 2.4)	0.94 (0.80-1.12)
Clinical pregnancy loss <sup>a,c</sup>	36 (13.7)	41 (14.6)	0.9 (-6.8 to 5.0)	0.94 (0.60-1.47)
Total pregnancy loss <sup>a</sup>	65 (22.1)	66 (21.5)	-0.6 (-6.0 to 7.2)	1.03 (0.73-1.45)
Live birth <sup>a</sup>	223 (58.5)	239 (61.9)	-3.4 (-10.3 to 3.5)	0.95 (0.79-1.13)
Ectopic pregnancy	3	1		
Therapeutic abortion	1	0		
Stillbirths	2	1		


Cedars Sinai | Doyle, et al. JAMA. 2022;328(21):2117-2125. doi:10.1001/jama.2022.20438 39

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## Laparoscopy

- Laparoscopy is indicated when there is evidence or strong suspicion of endometriosis, pelvic/adnexal adhesions, or significant tubal disease.
- Laparoscopy is no longer part of the initial work up for infertility.



**Cedars Sinai** Optimal evaluation of the infertile female  
The Practice Committee of the American Society for Reproductive Medicine 2021 40

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## Endometriosis and Infertility

- Fecundity:
  - Control population: 0.15 — 0.20
  - Endometriosis population: 0.02 — 0.10
- 6 – 8x more likely to have Endometriosis

**Cedars Sinai** The Practice Committee of the American Society for Reproductive Medicine. Endometriosis. Fertil Steril 2012 41

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## Endometriosis

nature genetics


Article <https://doi.org/10.1038/s41588-022-01254-1>

### Single-cell transcriptomic analysis of endometriosis

Received: 23 June 2021  
Accepted: 28 October 2022  
Published online: 9 January 2023

Check for updates

Marcos A. S. Fonseca<sup>1,2</sup>, Marcella Haro<sup>1,2,3</sup>, Kally N. Wright<sup>1,2</sup>, Xianzhi Lin<sup>1,2</sup>, Forough Abbasi<sup>1,2</sup>, Jennifer Sun<sup>1,2</sup>, Lourdes Hernandez<sup>1,2</sup>, Natasha L. Orr<sup>1,2</sup>, Jooyoon Hong<sup>1</sup>, Yunhee Choi-Kuase<sup>1</sup>, Horacio M. Maluf<sup>1</sup>, Bonnie L. Balzer<sup>1</sup>, Aaron Fishburn<sup>1</sup>, Ryan Hickey<sup>1</sup>, Ilana Casa<sup>1,2</sup>, Helen S. Goodridge<sup>1,2</sup>, Minellee Truong<sup>1</sup>, Yemin Wang<sup>1,2</sup>, Margareta D. Pisarska<sup>1,2</sup>, Huy G. Dinh<sup>1,2</sup>, Amal EL-Naggar<sup>1,2</sup>, David G. Huntsman<sup>1,2</sup>, Michael S. Anglesio<sup>1,2</sup>, Marc T. Goodman<sup>1,2</sup>, Fabiola Medeiros<sup>1,2</sup>, Matthew Siehoff<sup>1,2</sup> & Kate Lawrenson<sup>1,2</sup>✉



**Cedars Sinai** Fonseca, et al. Nat Genetics 2023 42

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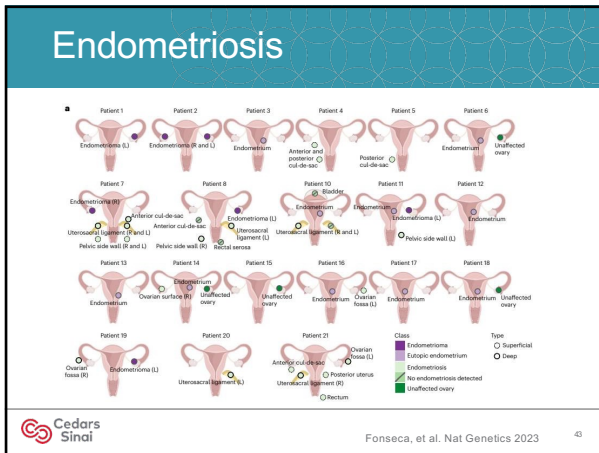
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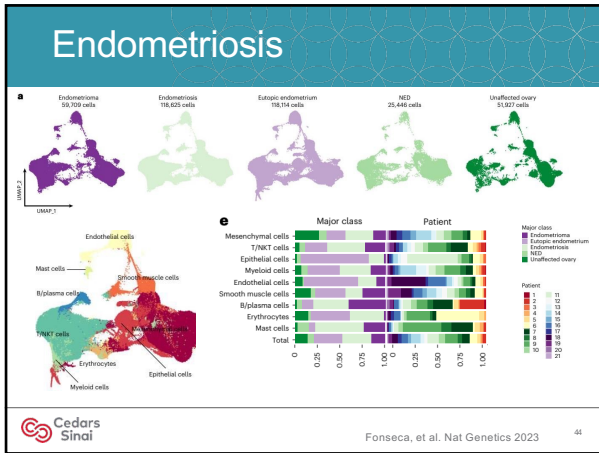
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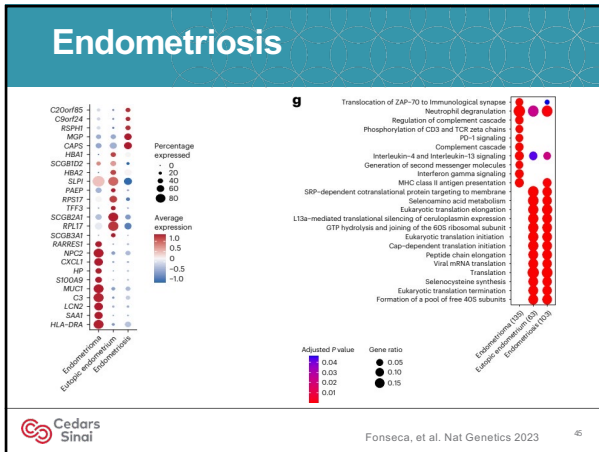
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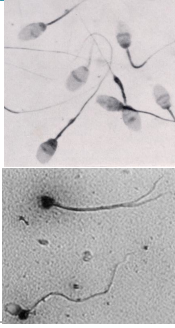
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## Male Evaluation Semen Analysis

- Volume ≥ 1.5 cc
- Conc. ≥ 15M/ml
- Progressive Motility > 32%
- Total Motility > 40%
- Morphology >3%




WHO Criteria 46

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## Male Evaluation – Fertile Male


VARIABLE	SEMEN MEASUREMENT		
	CONCENTRATION	MOTILITY	MORPHOLOGY
	× 10 <sup>6</sup> /ml	%	% normal
Fertile range	>48.0	>63	>12
Indeterminate range	13.5–48.0	32–63	9–12
Univariate odds ratio for infertility (95% CI)	1.5 (1.2–1.8)	1.7 (1.5–2.2)	1.8 (1.4–2.4)
Subfertile range	<13.5	<32	<9
Univariate odds ratio for infertility (95% CI)	5.3 (3.3–8.3)	5.6 (3.5–8.3)	3.8 (3.0–5.0)

\*CI denotes confidence interval.

N=696 fertile

N=765 infertile

- Extensive overlap between fertile and subfertile
- Strongest single predictor is morphology


Guzick, D.S., et al. New England J Med 2001; 345:1388 47

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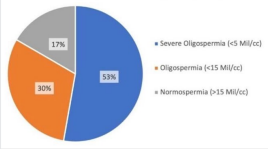
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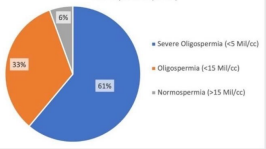
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## Male Infertility and Anabolic Steroid Use

Sperm Concentration at 6-Month Follow-up, Initially with Severe Oligospermia or Azoospermia (n=36)




Sperm Concentration at 6-Month Follow-up, Initially with Azoospermia (n=18)



Sperm concentration at 6-month follow-up for patients initially with severe oligospermia or azoospermia. Lederman, Fertility after AS Use, Fertil Steril 2023.

- Subsequent fertility
- 37.5% achieved a successful subsequent pregnancy
- 33.3% used assisted reproductive technology
- 66.7% conceived naturally


Lederman, Fertility after AS Use, Fertil Steril 2023. 48

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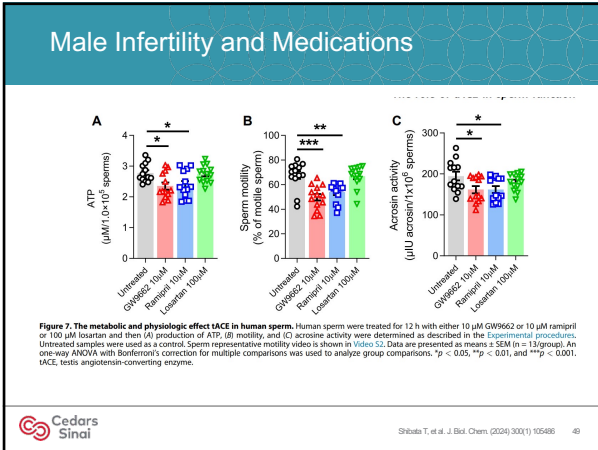
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### Conclusion

- Initial Evaluation- conducted based on reproductive needs of the individual or couple
- Consider referral to Reproductive Endocrinology and Infertility Subspecialist
- Cannabis use does alter reproductive function, additional studies are needed.
- Social Media for healthcare information is largely created by non-healthcare professionals and overall video popularity is not correlated with video quality.
- Anabolic steroids and other medications impact sperm, even following discontinuation.

Cedars Sinai 50

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### Moving towards precision medicine

- PCOS phenotyping is important - it determines pregnancy outcomes
- Endometrial biopsy for endometrial receptivity is not recommended
- Endometriosis is heterogenous and new treatments will need to be tailored to the type of disease.

Cedars Sinai 51

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# Acknowledgements

- **Pisarska Lab**
  - Tania Gonzalez, PhD
  - Laura Eisman, MD
  - Amy Flowers, PhD
  - Bryn Wilson, MD
  - Katharine VanHise, MD
  - Katherine Moran, MD
- **Prenatal Biorepository**
  - Allyson Novoa
  - Akhila Swarna
- **Faculty**
  - Erica Wang, MD MAS
  - Jessica Chan, MD MSCE
- **Fellows**
  - Bryn Wilson, MD
  - Katharine VanHise, MD
  - Ally Kosturakis, MD
- **CFRM Staff**
- **Maternal Fetal Medicine Division**
  - John Williams III MD
- **Division of Functional Genomics**
  - Kate Lawrenson, PhD
  - Simon Gayther, PhD
- **Pediatrics**
  - Charles Simmons, MD
- **University of Virginia**
  - Charles Farber, PhD
  - Steve Rich, PhD
  - Stephen Turner PhD
- **Division of Endocrinology**
  - Alex Koepffel PhD
- **Mark Goodarzi, MD PhD**
- **Lundquist Institute**
  - Jerome Rotter, MD
  - Ida Chen, PhD
  - Kent Taylor, PhD
- **UCLA**
  - Hsian-Rong Tseng, PhD



**Our patients for participating  
in our studies to improve  
outcomes!**




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