

Diagnosing Infertility - Helping Your Patients Through The Process

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Disclosures

- Ferring
- Natera

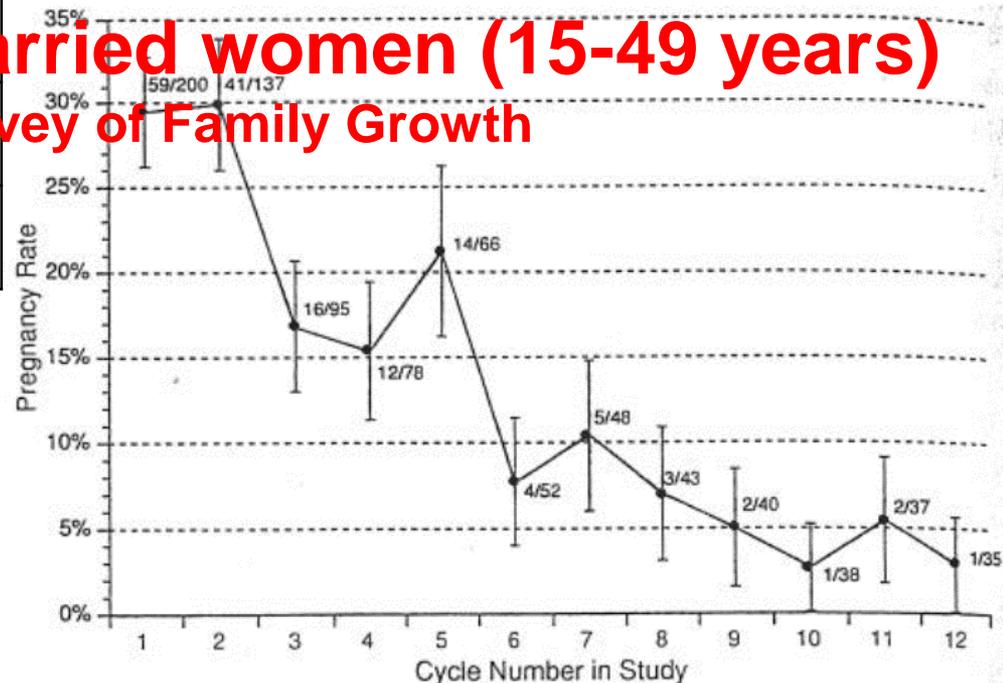
Objectives

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

Time Required for Conception

Time of Exposure	% pregnant
3 months	57%
6 months	72%
1 year	85%
2 years	93%

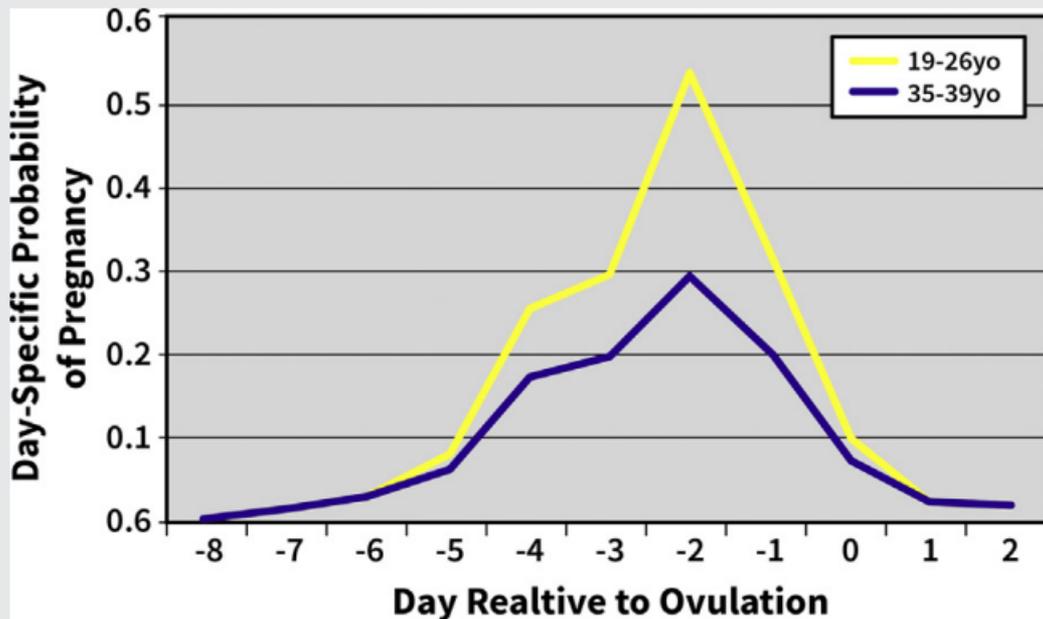
Impacts 1 in 5 (19%) married women (15-49 years)
National Survey of Family Growth



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.

The Fertile Window



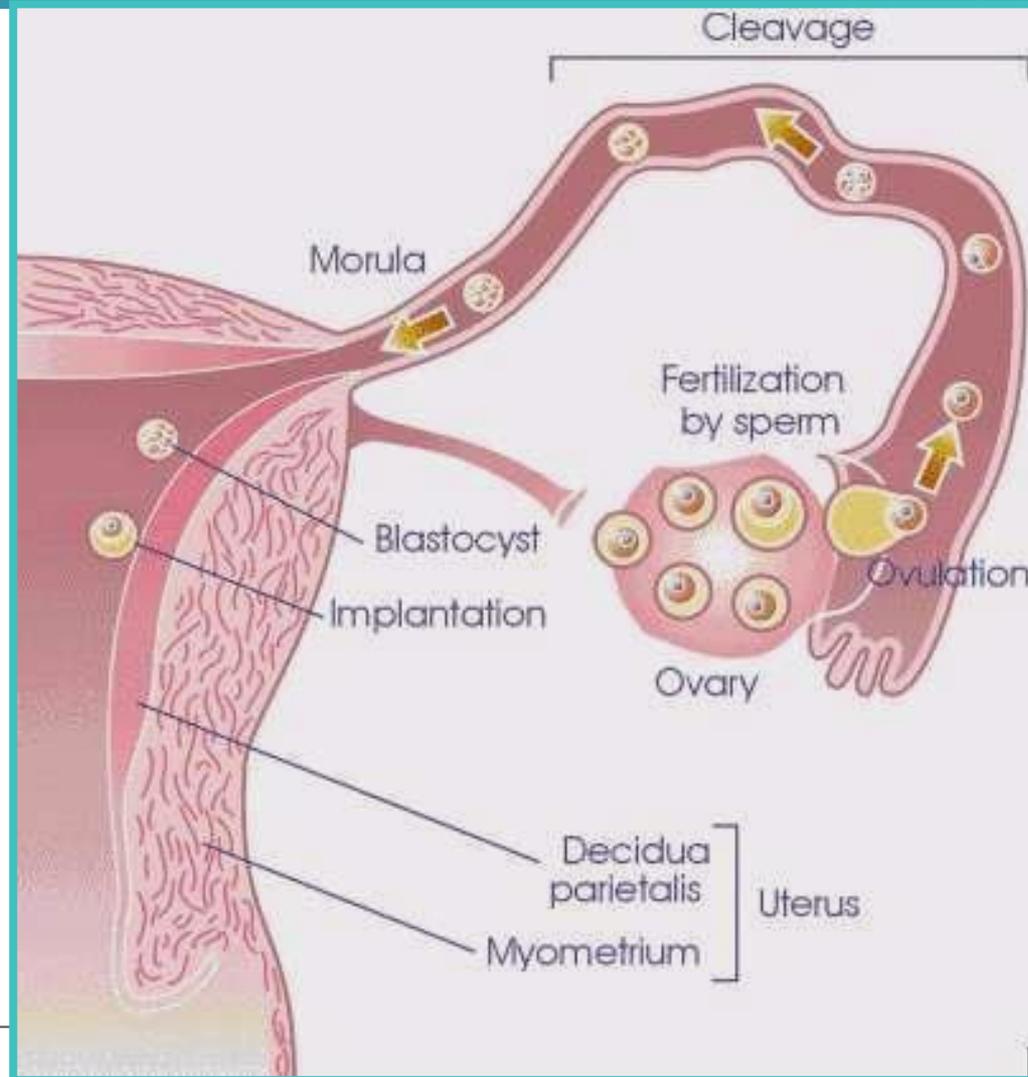
Probability of pregnancy resulting from recurrent intercourse by woman's age and cycle day. Data from Stanford and Dunson (17).

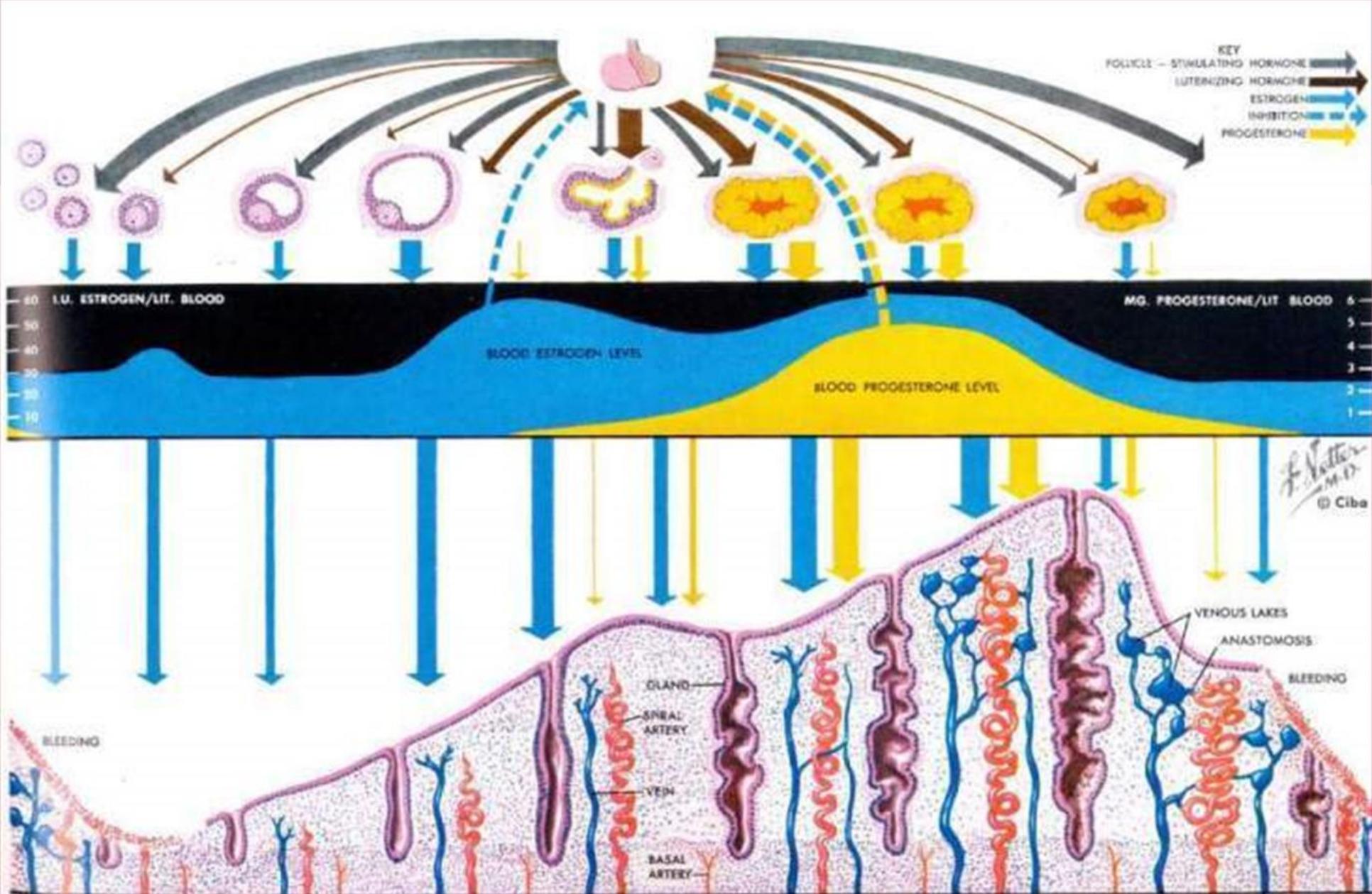
Practice Committee of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility. *Fertil Steril* 2021.

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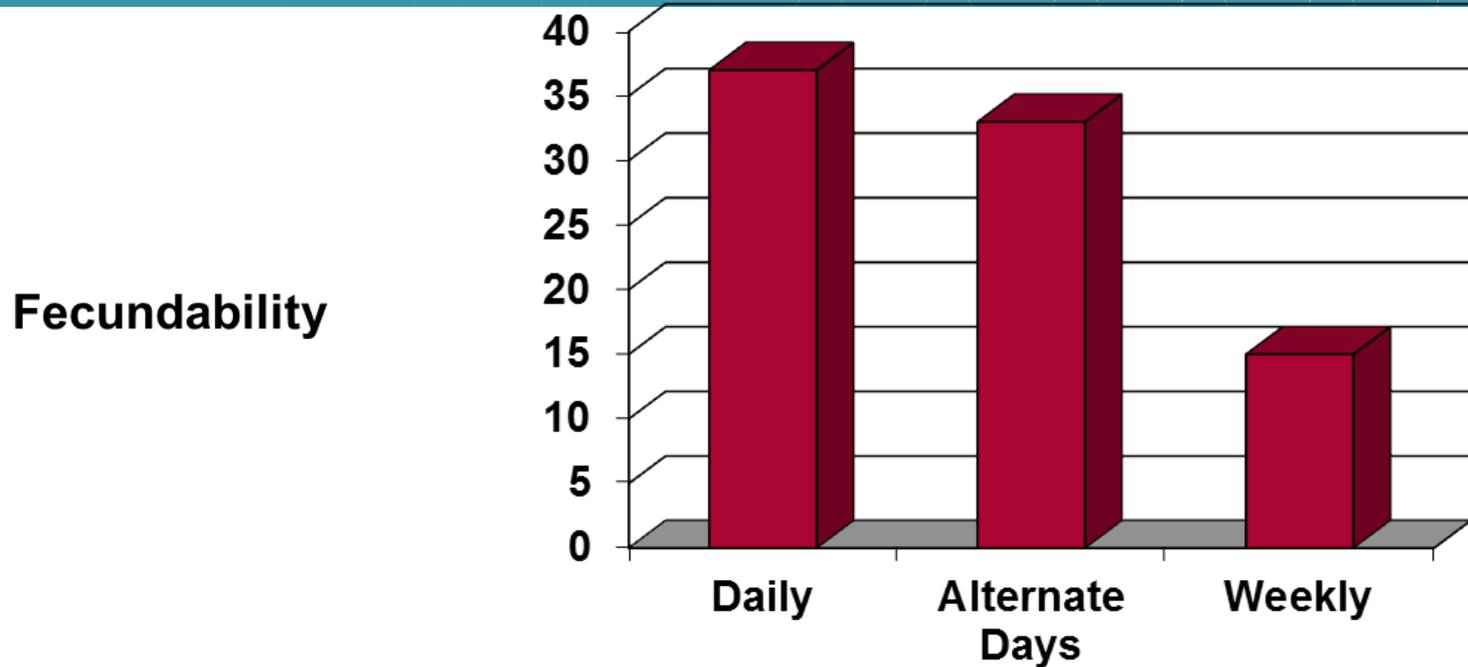
- The fertile window spans the 6 day interval ending on the day of ovulation
- Peak fecundability occurs within 2 days before ovulation
- The likelihood of success decreases with increasing age

Requirements for Conception





Natural Fertility Frequency of Intercourse



- Reproductive efficiency increases with the frequency of intercourse and is highest when intercourse occurs every 1 to 2 days
- The stress associated with infertility can reduce sexual esteem, satisfaction, and the frequency of intercourse

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

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

	Diets	Supplements
	N = 50	N = 50
Views by Uploader Credentials, (%)		
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 ←
Likes by Uploader Credentials, (%)		
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 ←
Quality and Reliability Scores		
DISCERN score†	3.0 ± 0.86 (0.57)	2.4 ± 0.96 (0.42)
GQS 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

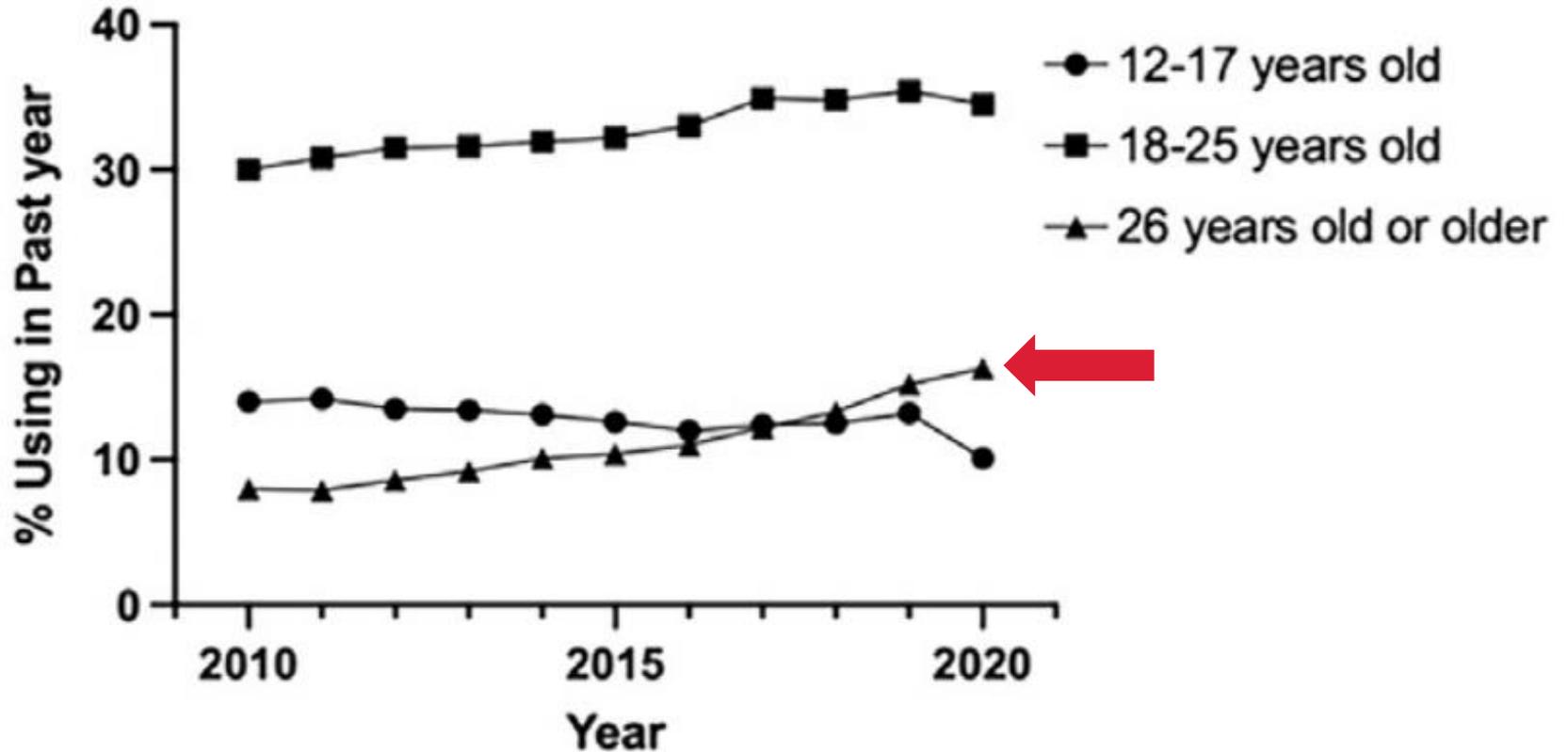
**Nutritional professionals include nutritionists and registered dieticians

†Reported values include mean ± standard deviation (Cohen Kappa statistic)

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

Cannabis Use



Cannabis Use

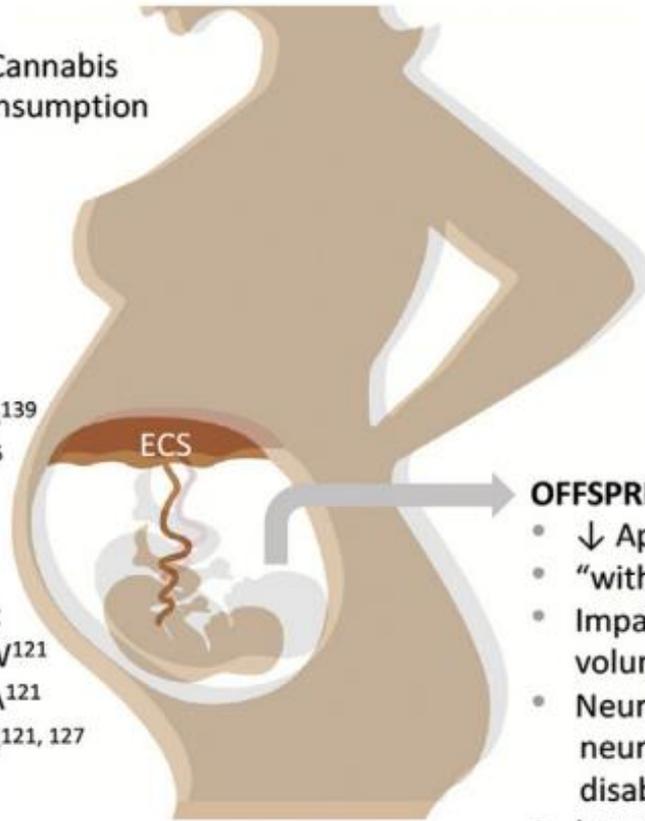


PLACENTA:

- Impaired steroidogenesis¹³⁹
- Impaired development¹³⁵
- Impaired transport¹³⁵

FETUS:

- LBW¹²¹
- SGA¹²¹
- PTB^{121, 127}



OFFSPRING:

- ↓ Apgar score, ↑ NICU admission^{22, 121,123,125,126}
- “withdrawal”-like syndrome¹⁴⁷
- Impaired brain development (↓ gray matter volume)^{5,145,146}
- Neurobehavioral, neurocognitive and neuropsychiatric disorders (ASD, intellectual disability, learning disorders, ↑ PLE)¹⁴⁷⁻¹⁵⁶
- Impaired long term reproductive health¹⁴⁴

ASD, autism spectrum disorder; IUGR, intrauterine growth restriction; PLE, psychotic-like experience; PTB, preterm birth; SGA, small for gestational age.

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

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

Preconception Counseling

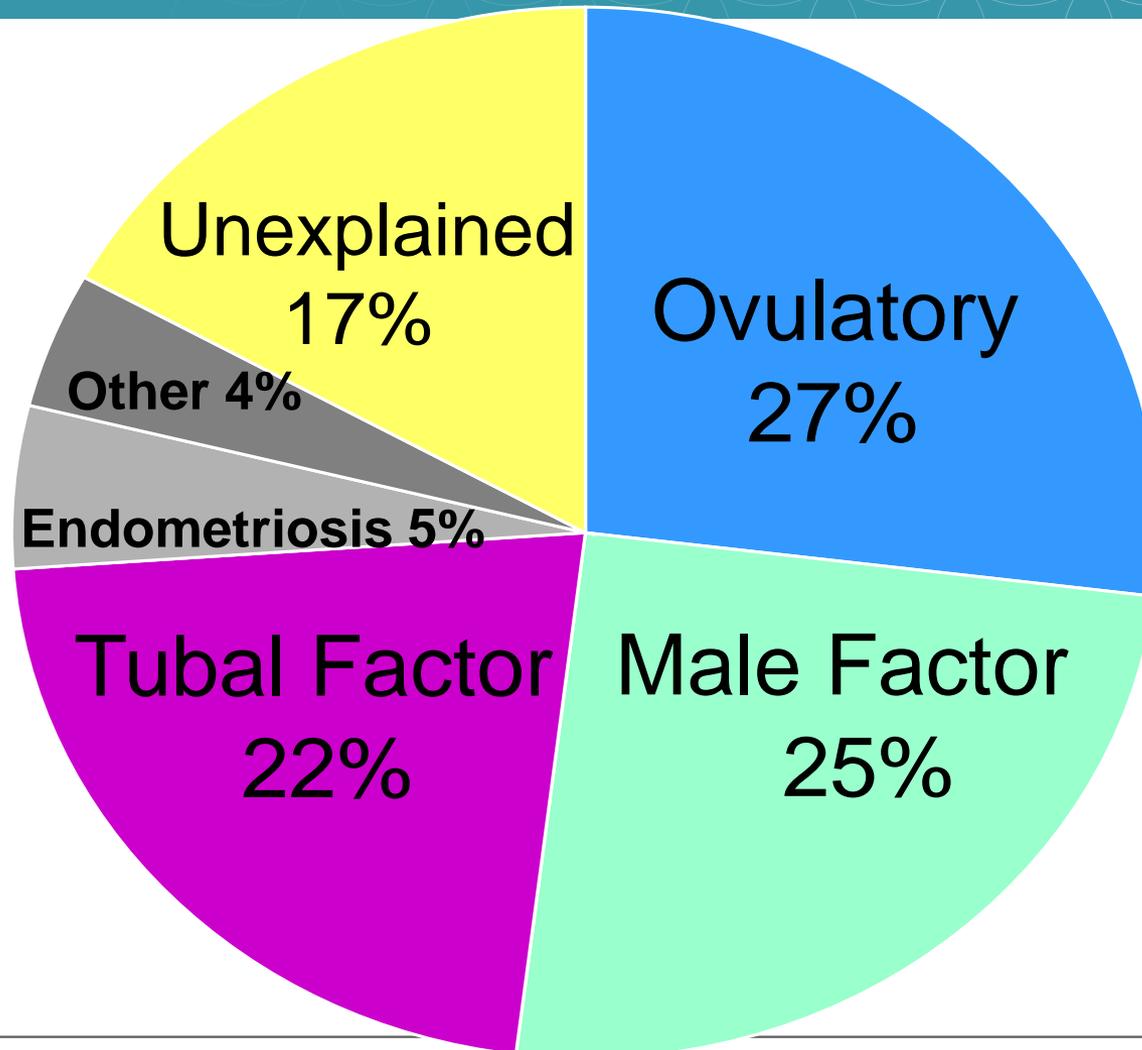
- Family Planning and Pregnancy Spacing
- Genetic Risk Factors
- Optimize Medical Conditions and review current medications
 - diabetes, hypertension, psychiatric illness, and thyroid disease
- Vaccinations
 - COVID-19
 - Influenza
 - Rubella
 - Varicella
 - Measles
- Prenatal Vitamins/ Folic Acid



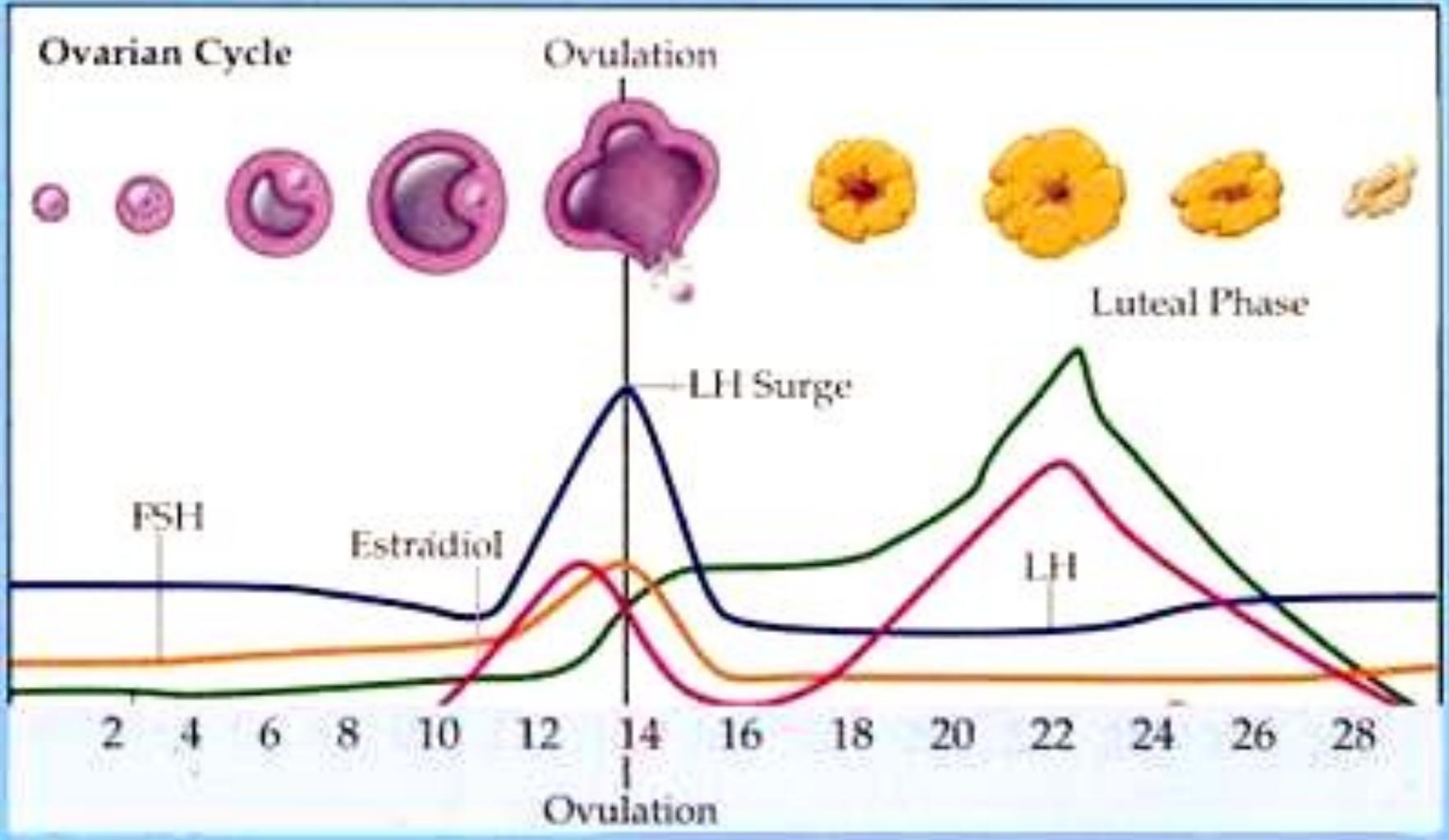
Preconception Genetic Screening

- 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, mucopolysaccharidosis type IV, Niemann-Pick disease type A, Dihydrocholesterol Dehydrogenase Deficiency, Familial Hyperinsulinism, Glycogen Storage Disease Type 1a, Maple Syrup Urine Disease, Nemaline Myopathy, Usher Syndrome Type I, 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

Diagnosis in Infertile Couples



Ovulation



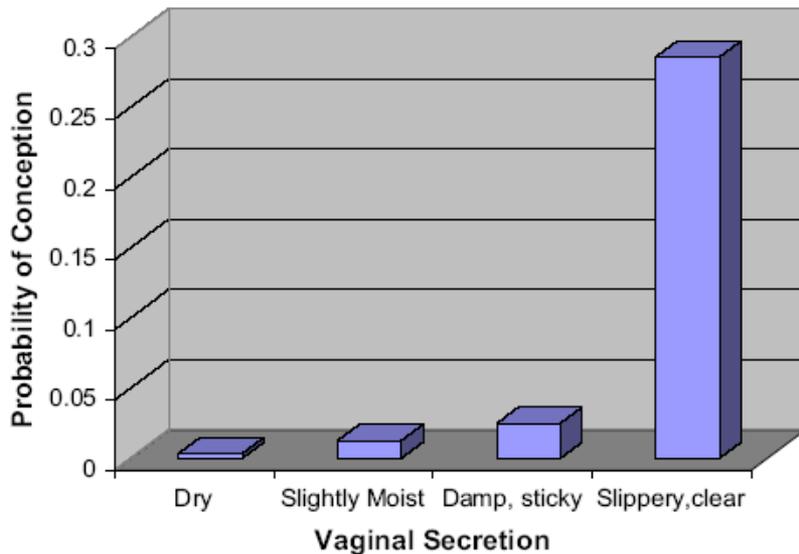
Natural Fertility: Menstrual History

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

Natural Fertility: Monitoring Ovulation

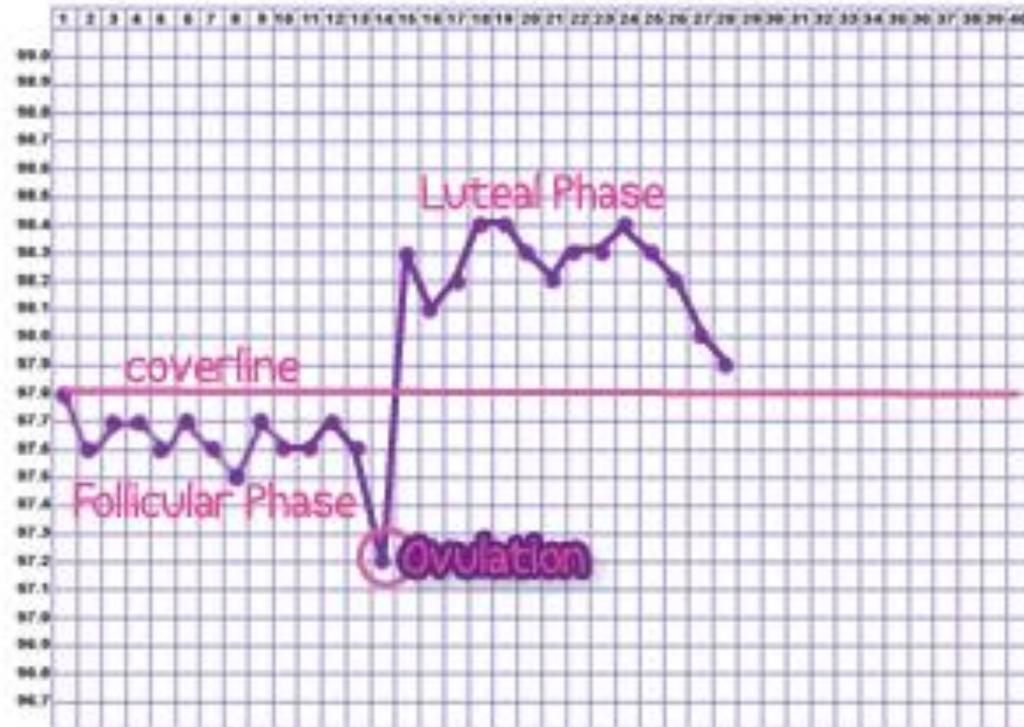
- Cervical mucus

- 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

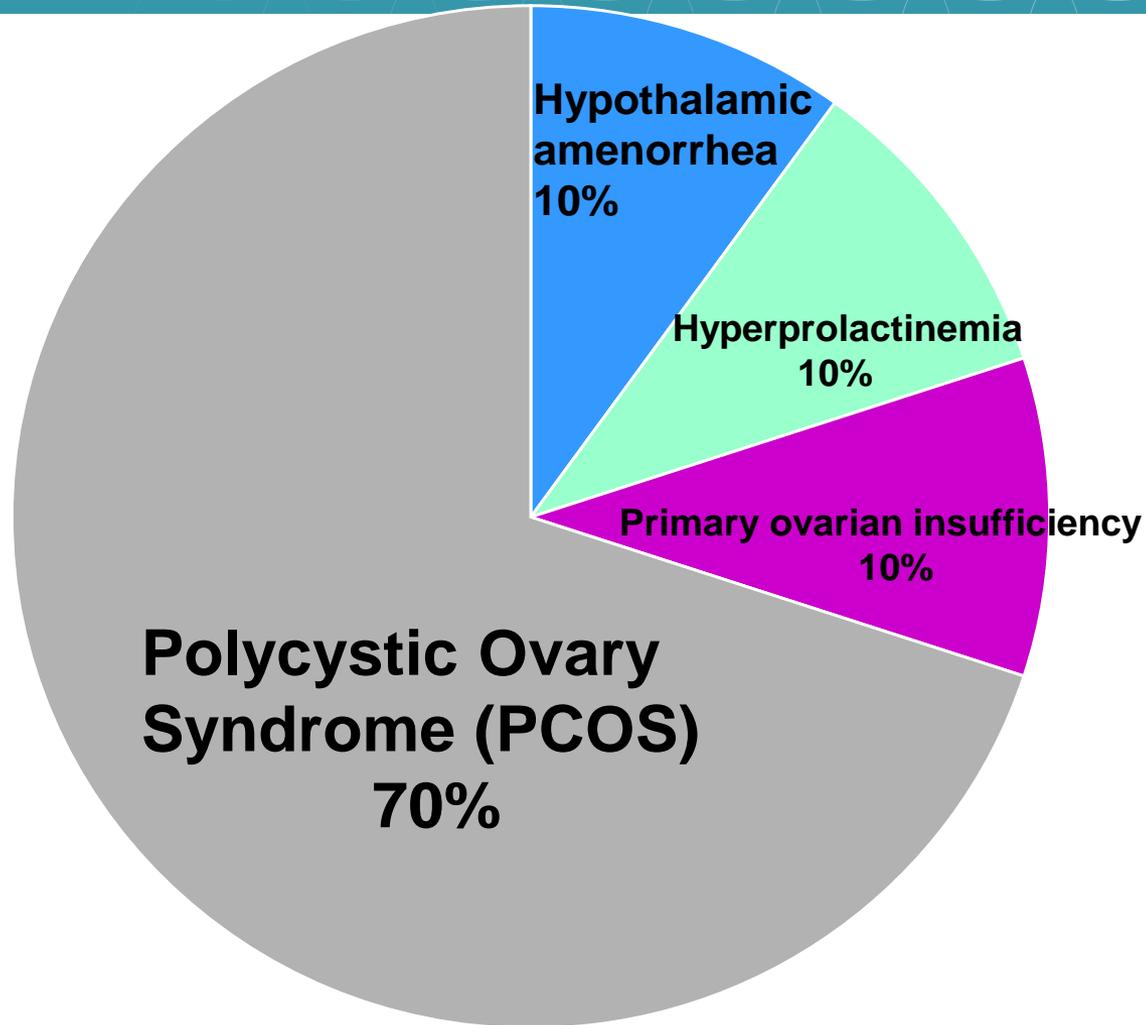


Natural Fertility: Monitoring Ovulation

- 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 $> 3\text{ng/ml}$



Ovulatory Dysfunction

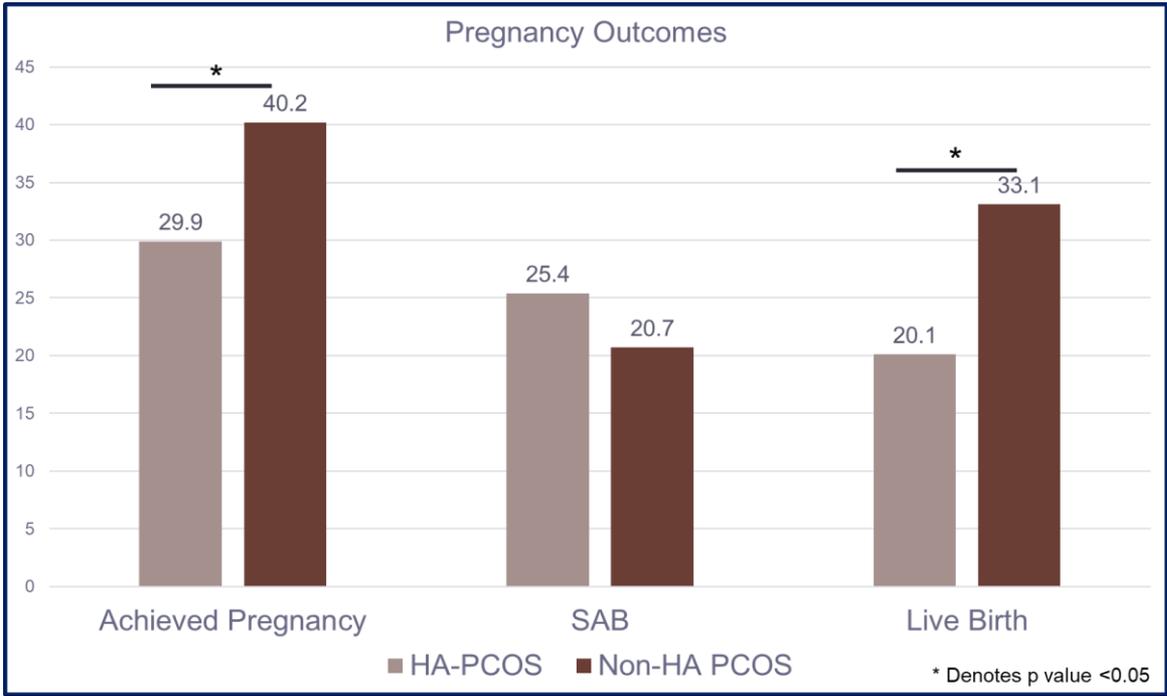


COMPARING THE PHENOTYPES OF PCOS BY NIH 1990, ROTTERDAM 2003, AND AES 2006

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

International Evidence Based Guideline for PCOS 2018

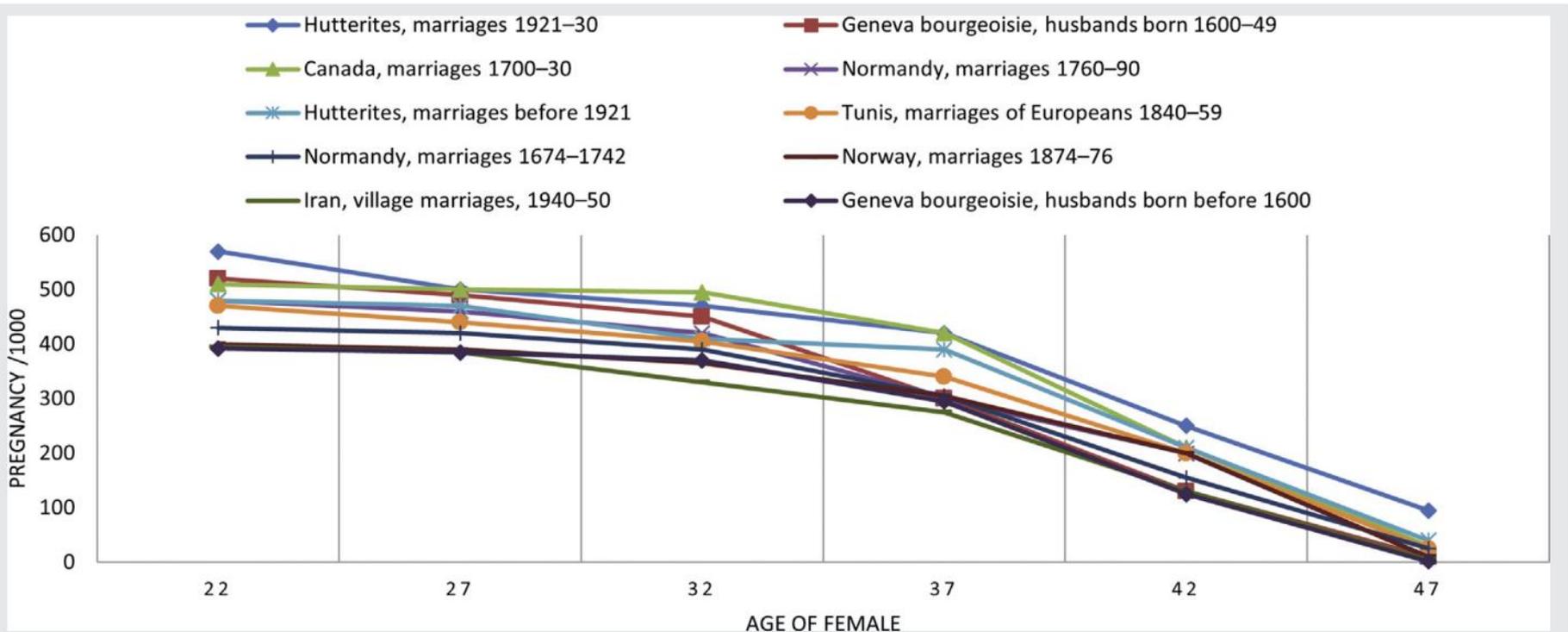
PCOS Phenotype Impacts Outcomes



The PCOS group had a lower odds of live birth (OR 0.51, CI 0.31-0.76), CI 0.44-0.92)
 Hyperandrogenism/Hyperandrogenemia in PCOSs predictive of pregnancy outcomes.
 Adjusting for BMI (adjusted OR 0.50, CI 0.32-1.0)

Hyperandrogenemia in normally menstruating women is not predictive of pregnancy outcomes.
 Adjusting for BMI (adjusted OR 0.74, CI 0.50-1.1)

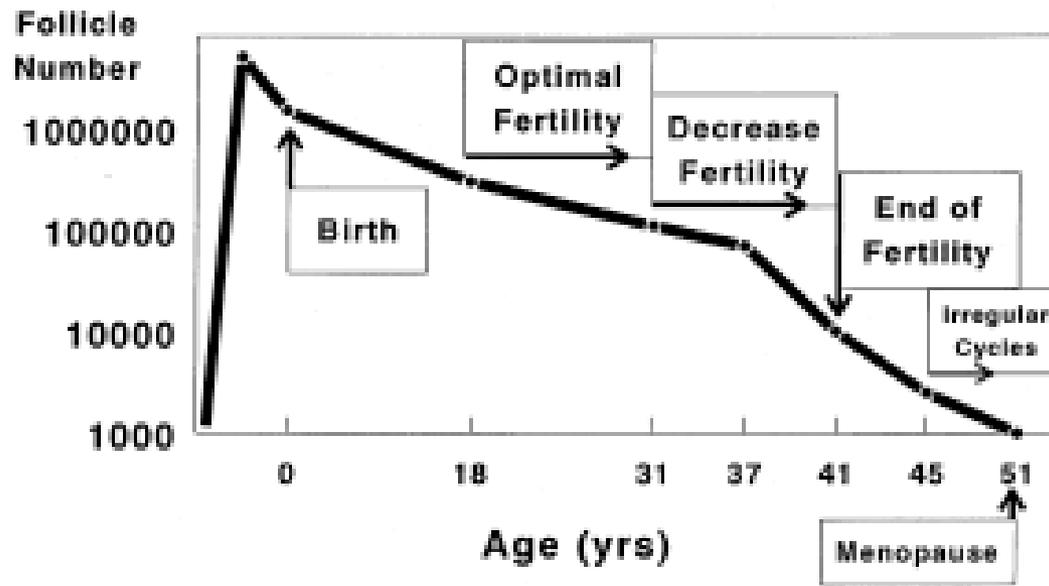
Age and Fertility



Pregnancy rate (per 1,000 women) in various populations at different times in history. Modified from Larsen et al. (7).

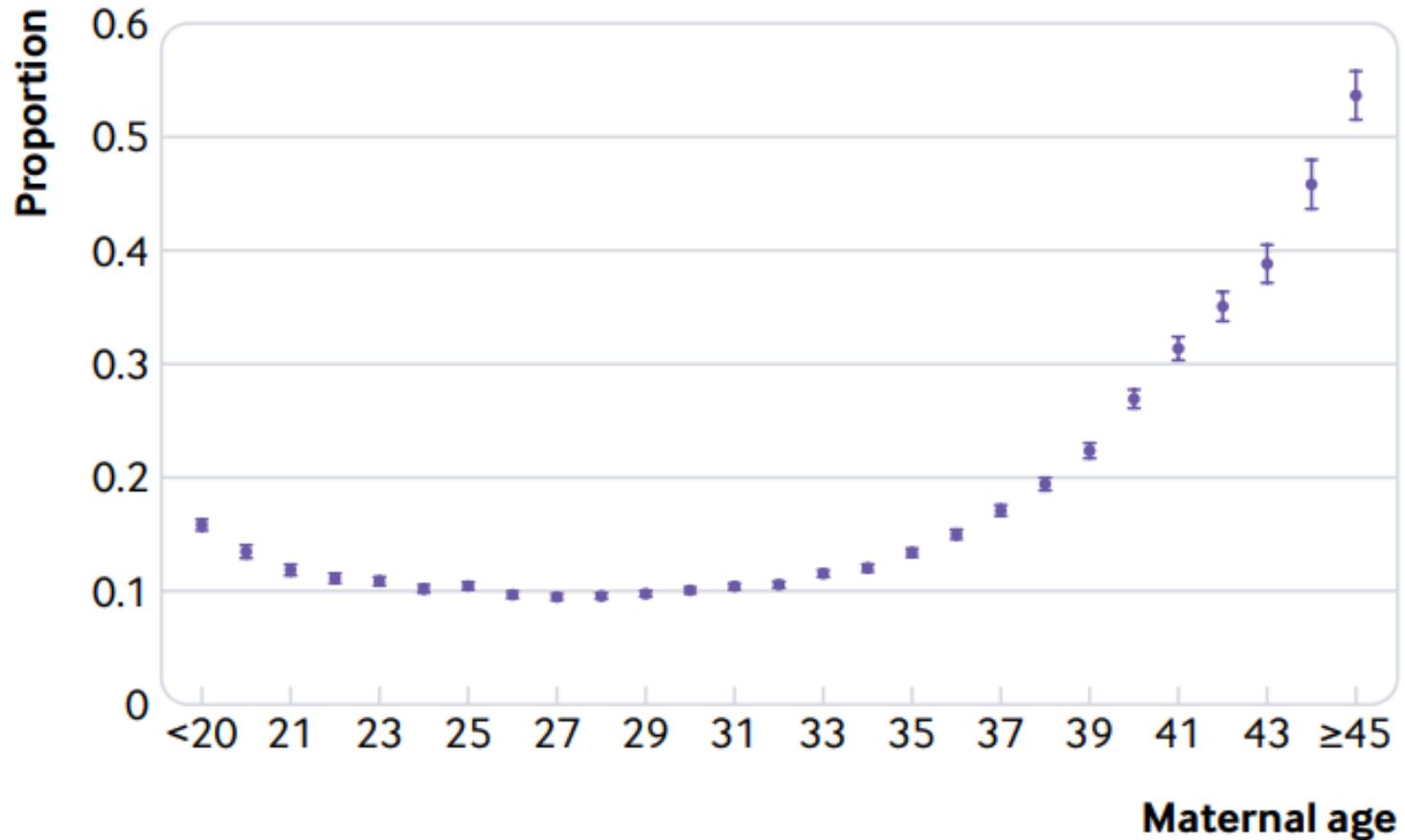
Practice Committee of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility. *Fertil Steril* 2021.

The Declining Follicle Pool



- The human ovary has a finite number of oocytes.
- The pool of primordial follicles is formed during fetal life.
- A small number of this resting pool of primordial follicles is activated into growth daily.
- The depletion of oocytes leads to menopause.

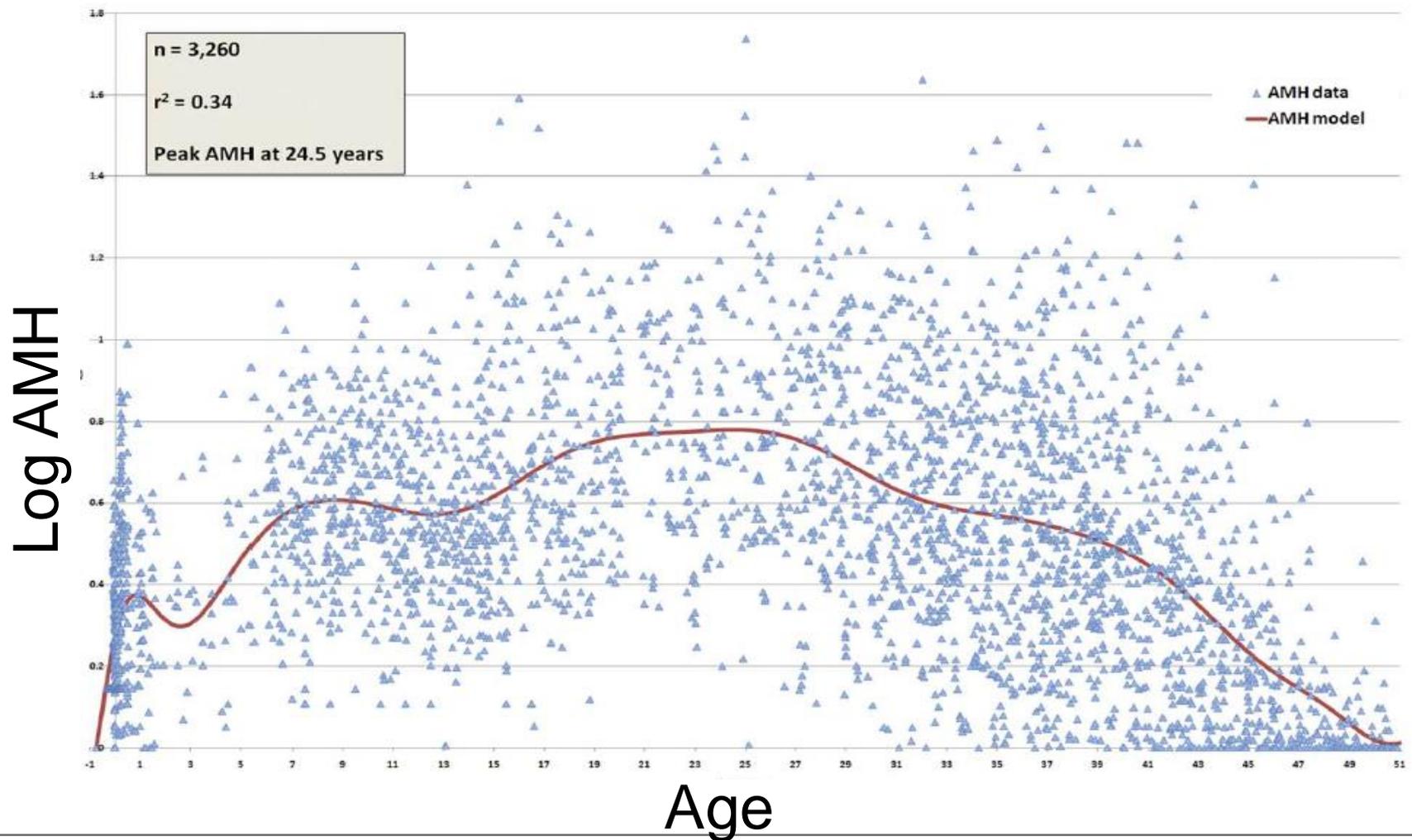
Age Related Decline of Oocyte Quality – Miscarriage Rates



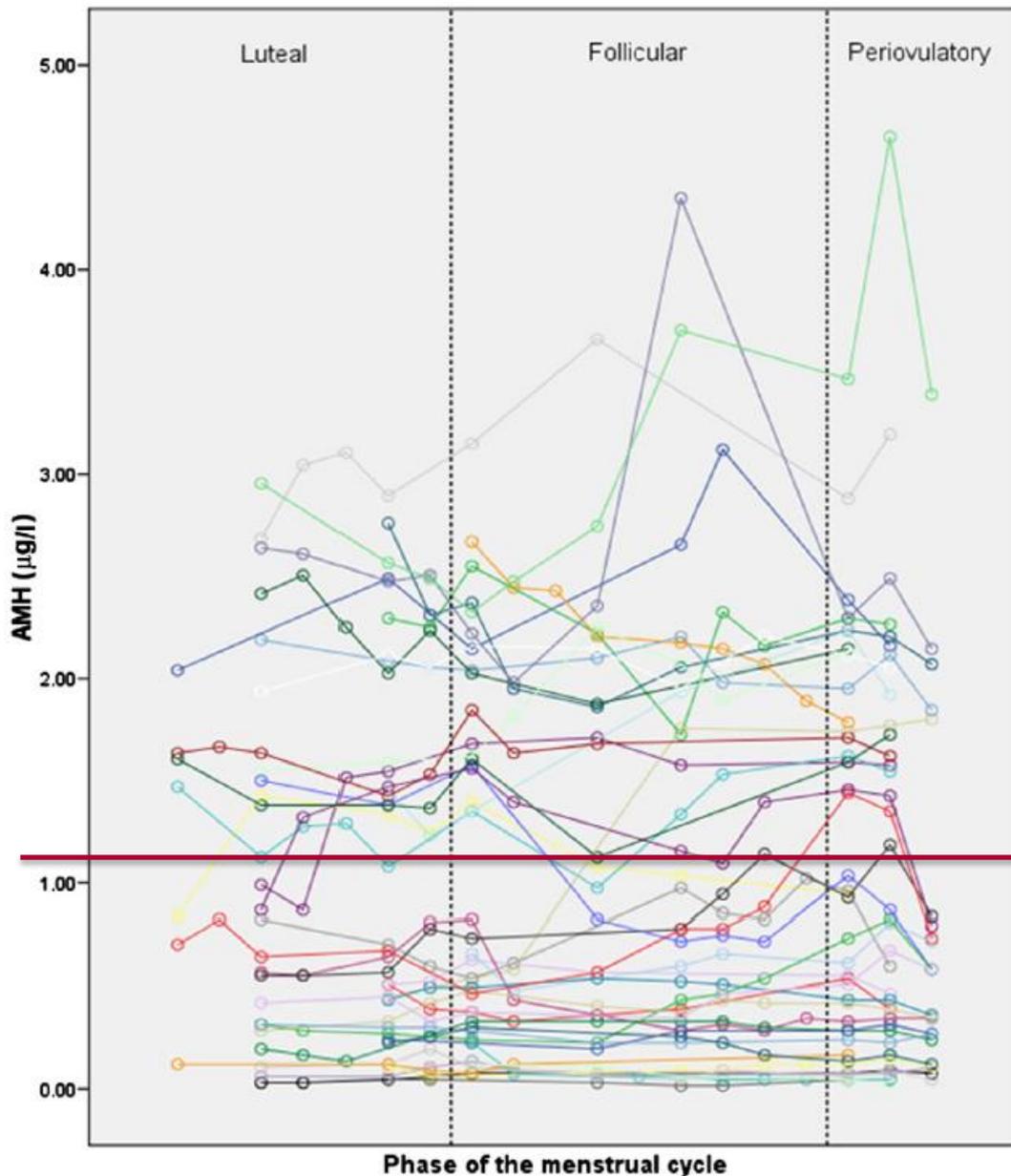
Evaluation of Ovarian Age

- Basal FSH and Estradiol levels
- Antral Follicle Count/ Ovarian Volume
- Antimullerian hormone (Mullerian Inhibiting Substance)

AMH values from conception to menopause



Is AMH cycle-dependent?



- 44 healthy women with regular cycles
- Serum AMH measured CD2-4 until 4 days post LH surge
- Individual patient plots show:
 - Low AMH stays stable
 - High AMH shows fluctuation
- **If AMH <1.0 ng/dL, there is little fluctuation across the menstrual cycle**

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 ^a	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.

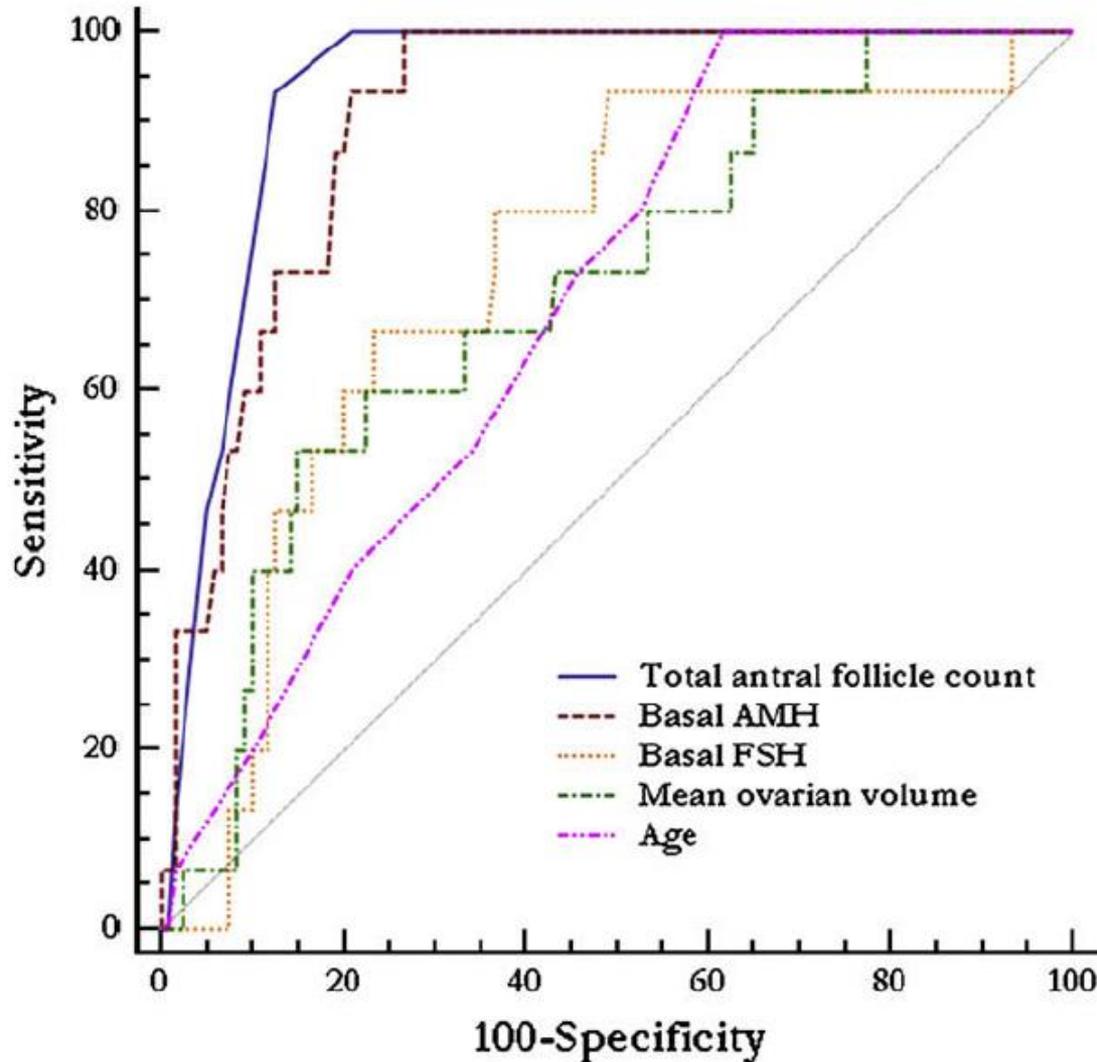
PPV = positive predictive value; NPV = negative predictive value; +LR = positive likelihood ratio.

^a Optimum cutoff level.

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

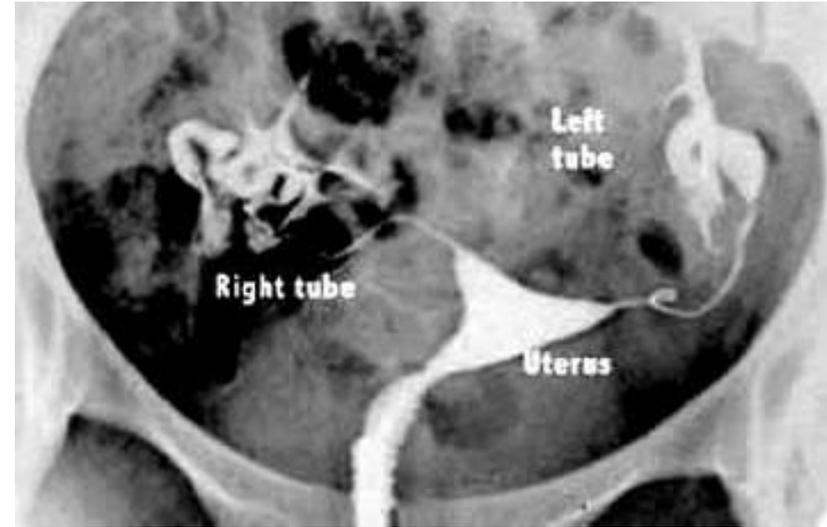
Optimal value to predict good ovarian response is 10

Basal Markers of Ovarian Reserve

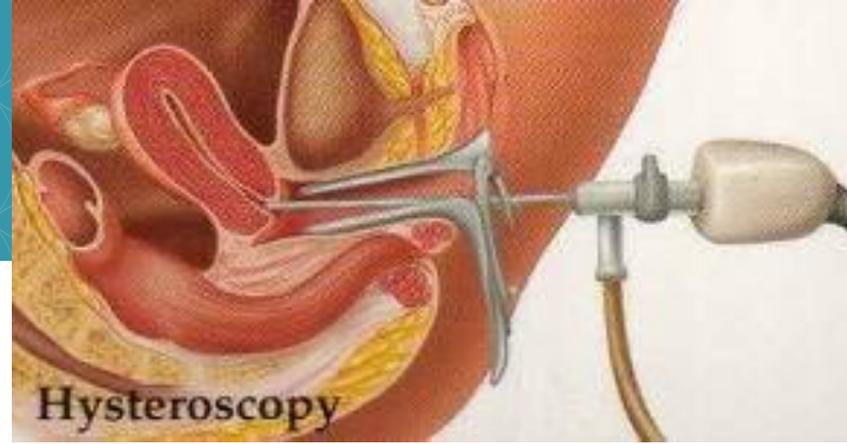


Hysterosalpingogram (HSG) and Sonohysterography

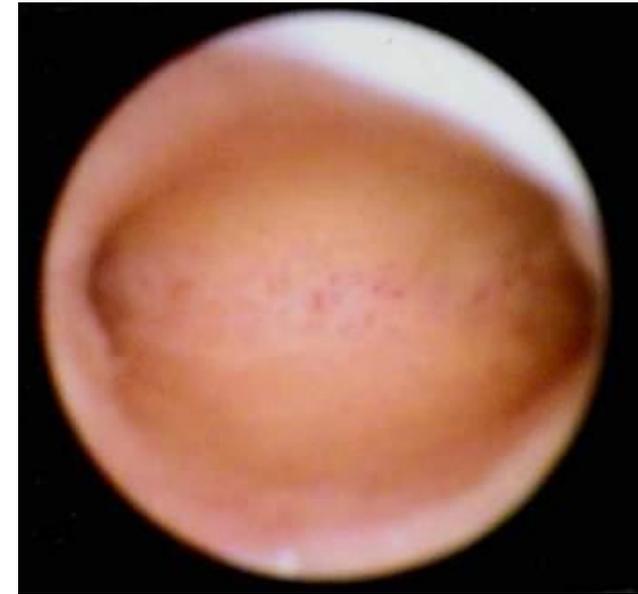
- **Hysterosalpingogram (HSG)**
- Tubal Patency
- Uterine Cavity
 - low sensitivity (50%) and positive predictive value (PPV) (30%) for intrauterine pathology.
- **Sonohysterography (SHG)**
- defines the size and shape of the uterine cavity
- high (>90%) PPV and negative predictive value for the detection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



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



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. Eisman¹ · Margareta D. Pisarska¹ · Sahar Wertheimer¹ · Jessica L. Chan¹ · Alin Lina Akopians² · Mark W. Surrey² · Hal C. Danzer² · Shahin Ghadir² · Wendy Y. Chang² · Carolyn J. Alexander² · Erica T. Wang¹

^a Mean, standard deviation

^b Median (interquartile range)

^c ≥ 1 prior failed ET compared to controls

^d ≥ 3 prior failed ET compared to controls

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 ^a	P value ^b
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

^a ≥ 1 prior failed ET compared to controls

^b ≥ 3 prior failed ETs compared to controls

Endometrial Biopsy

JAMA | Original Investigation

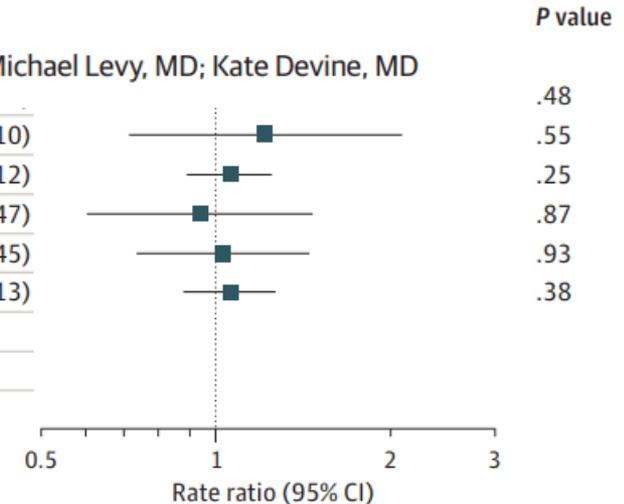
Effect of Timing by Endometrial Receptivity Testing vs Standard Timing of Frozen Embryo Transfer on Live Birth in Patients Undergoing In Vitro Fertilization A Randomized Clinical Trial

Figure 2.

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

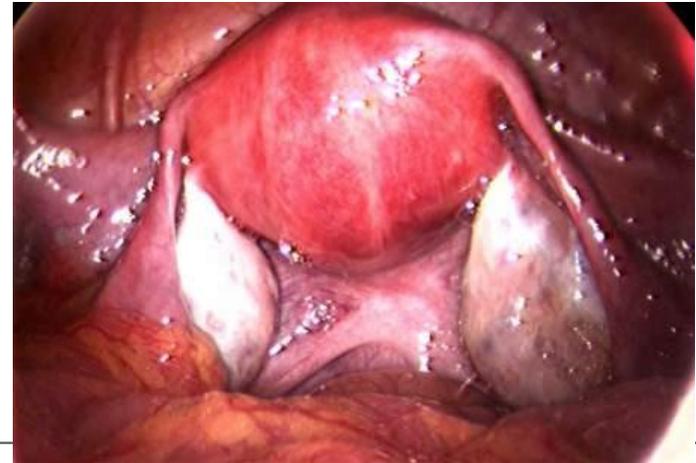
Total pati
Biochemi

Biochemical pregnancy loss ^{b,c}	29 (9.9)	25 (8.1)	-1.8 (-2.8 to 6.4)	1.21 (0.71-2.10)
Clinical pregnancy ^d	262 (68.8)	281 (72.8)	-4.0 (-10.4 to 2.4)	0.94 (0.80-1.12)
Clinical pregnancy loss ^{c,e}	36 (13.7)	41 (14.6)	0.9 (-6.8 to 5.0)	0.94 (0.60-1.47)
Total pregnancy loss ^f	65 (22.1)	66 (21.5)	-0.6 (-6.0 to 7.2)	1.03 (0.73-1.45)
Live birth ^g	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		
Stillbirth	2	1		



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.



Endometriosis and Infertility

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

Endometriosis

nature genetics

Article

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

Single-cell transcriptomic analysis of endometriosis

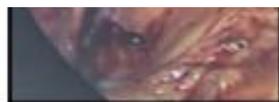
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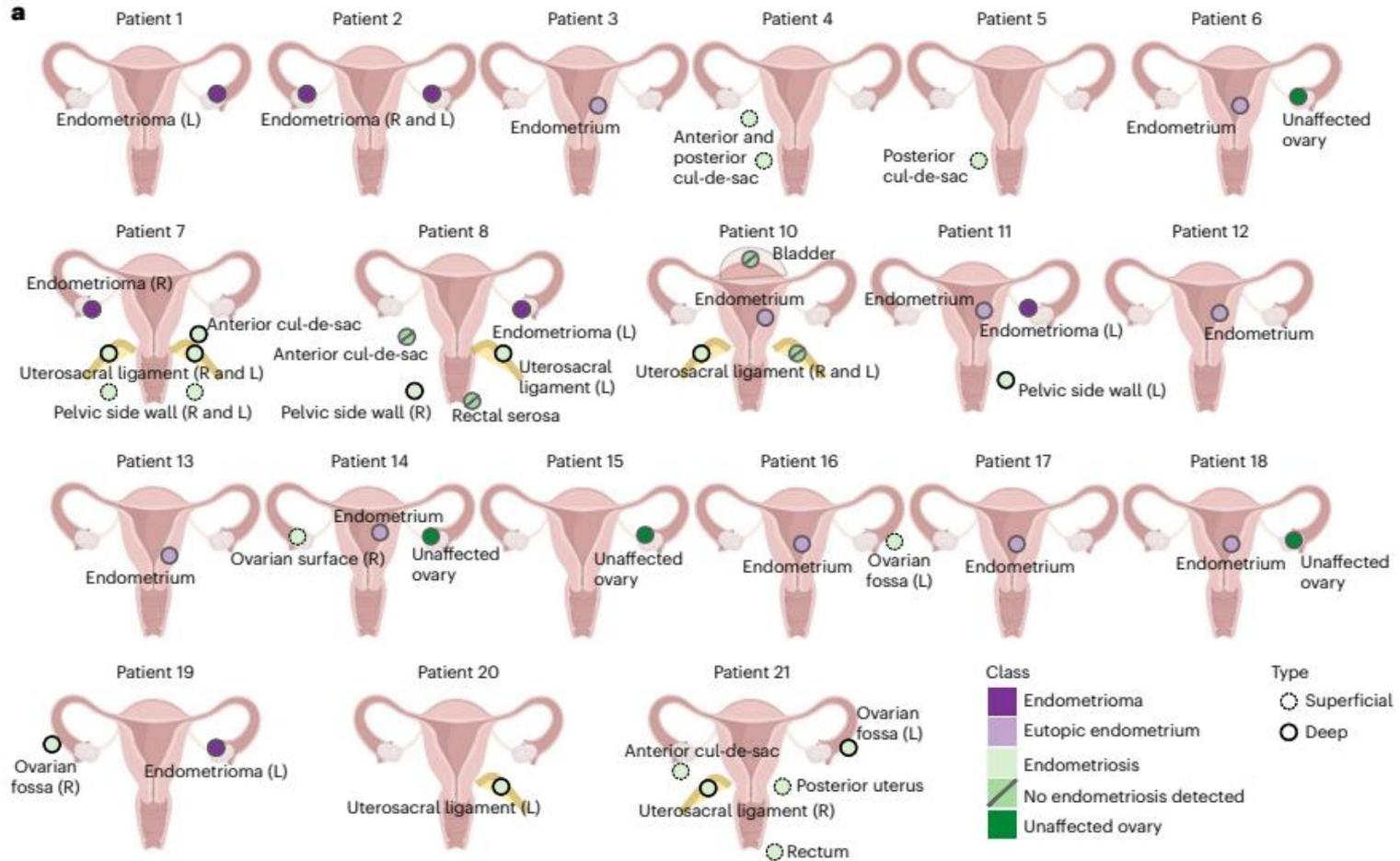
Published online: 9 January 2023

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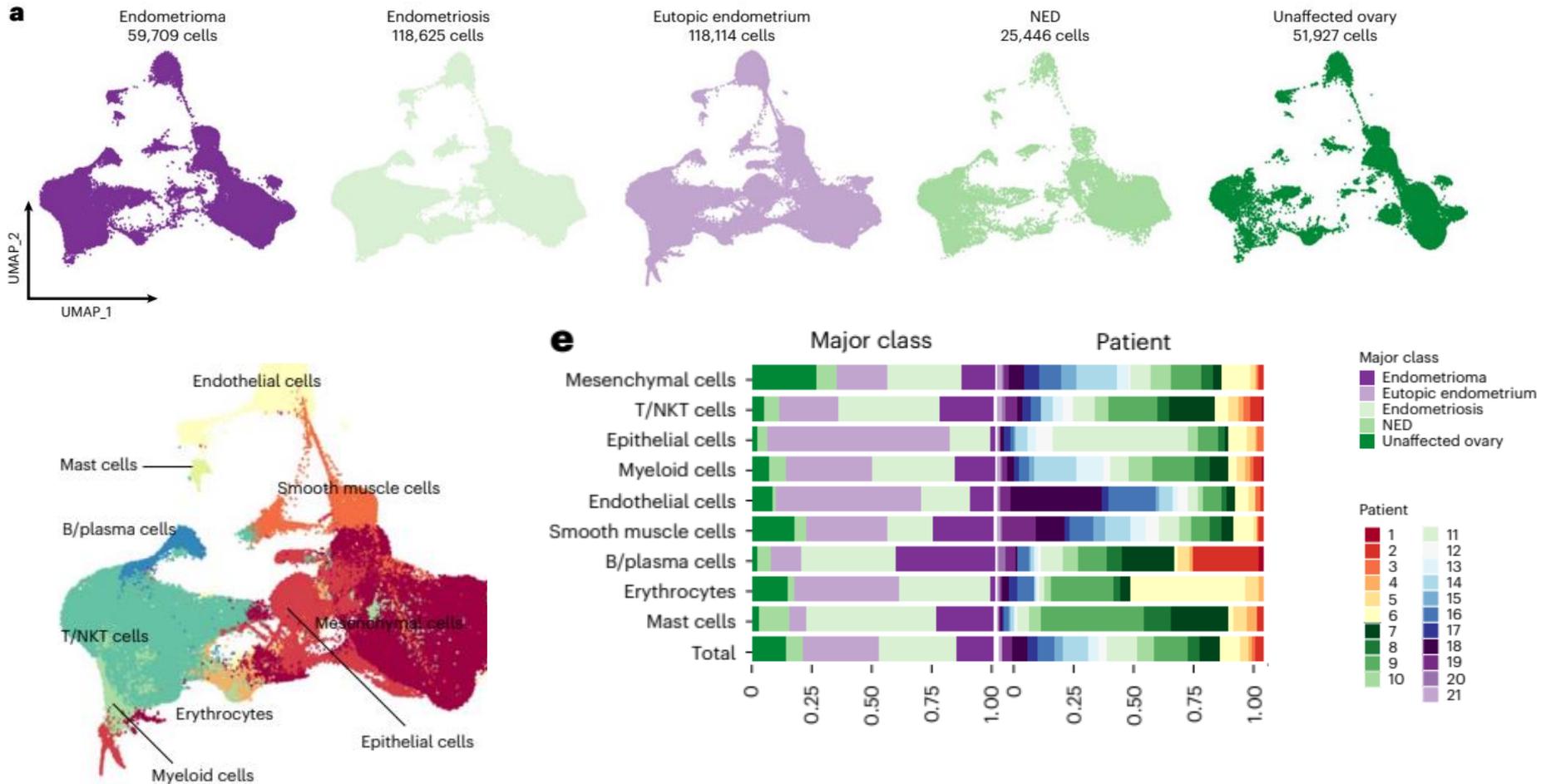
Marcos A. S. Fonseca^{1,2,18}, Marcela Haro^{1,2,18}, Kelly N. Wright^{3,18}, Xianzhi Lin^{1,2,18}, Forough Abbasi^{1,2}, Jennifer Sun^{1,2}, Lourdes Hernandez^{1,2}, Natasha L. Orr⁴, Jooyoon Hong⁴, Yunhee Choi-Kuaea⁵, Horacio M. Maluf⁶, Bonnie L. Balzer⁶, Aaron Fishburn⁶, Ryan Hickey⁶, Ilana Cass^{1,2,17}, Helen S. Goodridge^{7,8}, Mireille Truong³, Yemin Wang^{1,2,4,9}, Margareta D. Pisarska^{10,11}, Huy Q. Dinh^{12,13}, Amal EL-Naggar^{7,14}, David G. Huntsman^{4,9}, Michael S. Anglesio^{1,4,15}, Marc T. Goodman⁵, Fabiola Medeiros^{6,19}, Matthew Siedhoff^{3,19} & Kate Lawrenson^{1,2,5,16,19}✉



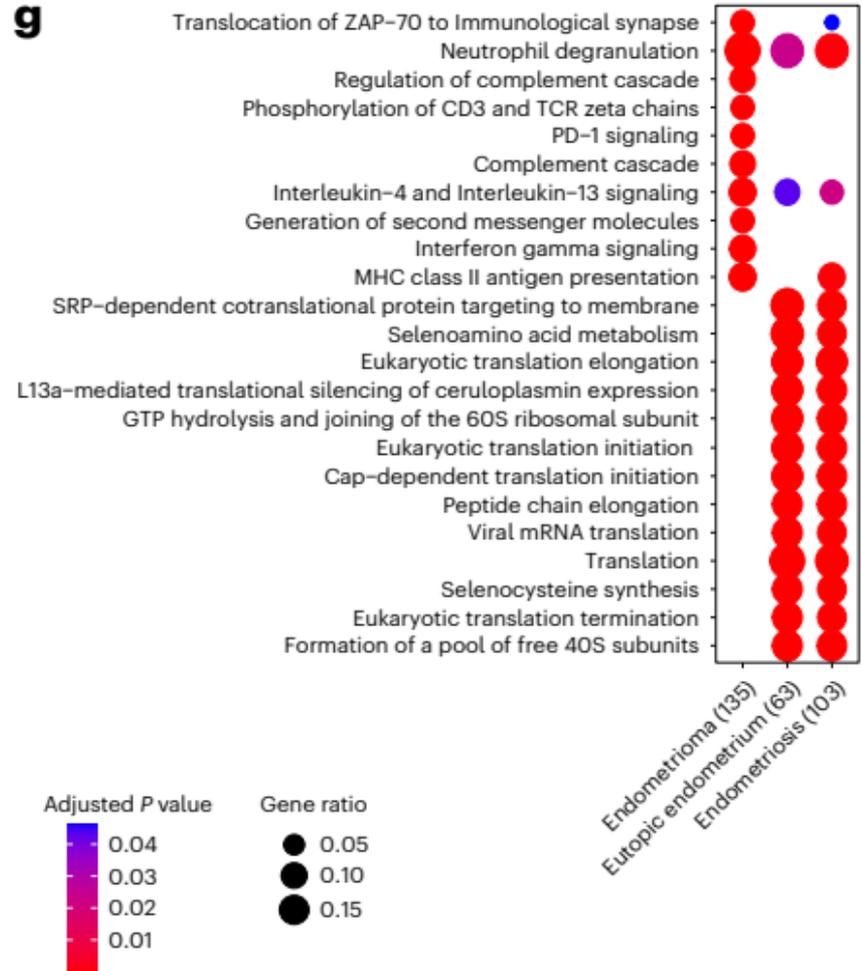
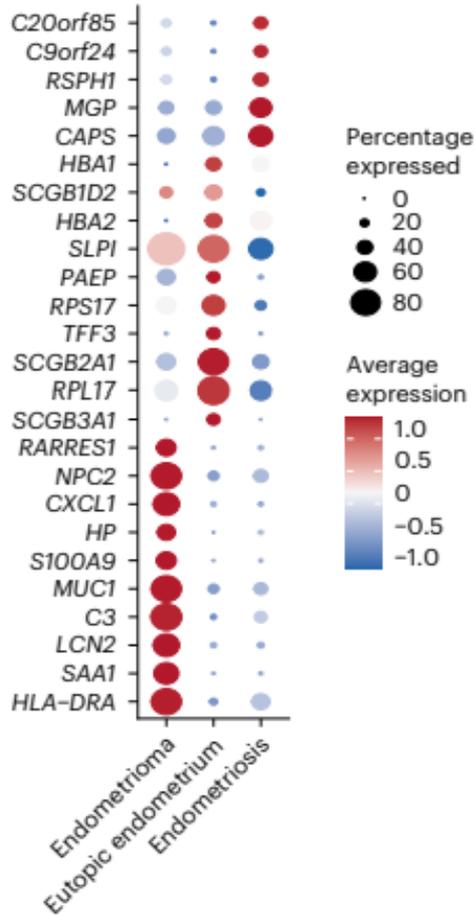
Endometriosis



Endometriosis

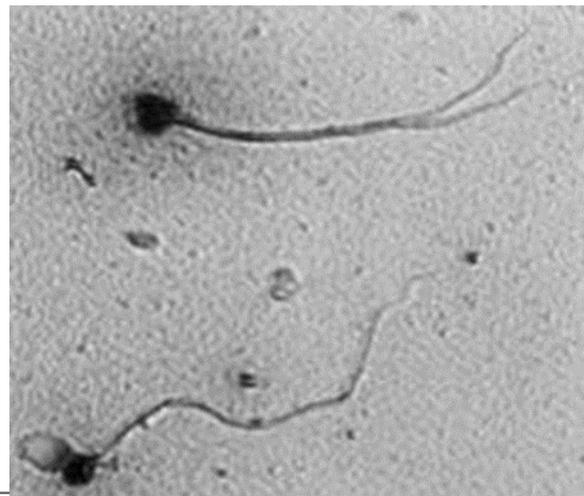


Endometriosis



Male Evaluation Semen Analysis

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



Male Evaluation – Fertile Male

VARIABLE	SEMEN MEASUREMENT		
	CONCENTRATION	MOTILITY	MORPHOLOGY
	× 10 ⁶ /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.

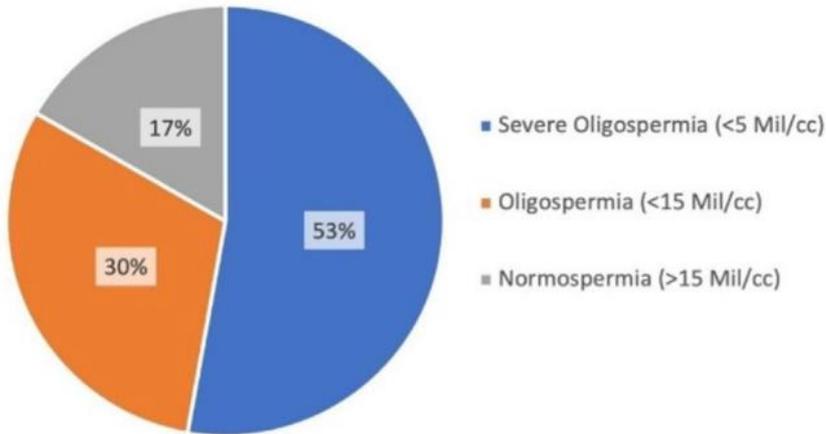
N=696 fertile

N=765 infertile

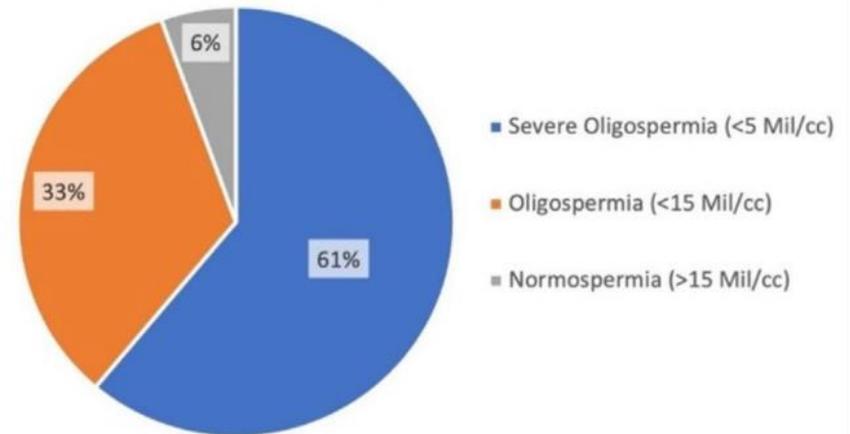
- Extensive overlap between fertile and subfertile
- Strongest single predictor is morphology

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.

Ledesma. 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

Male Infertility and Medications

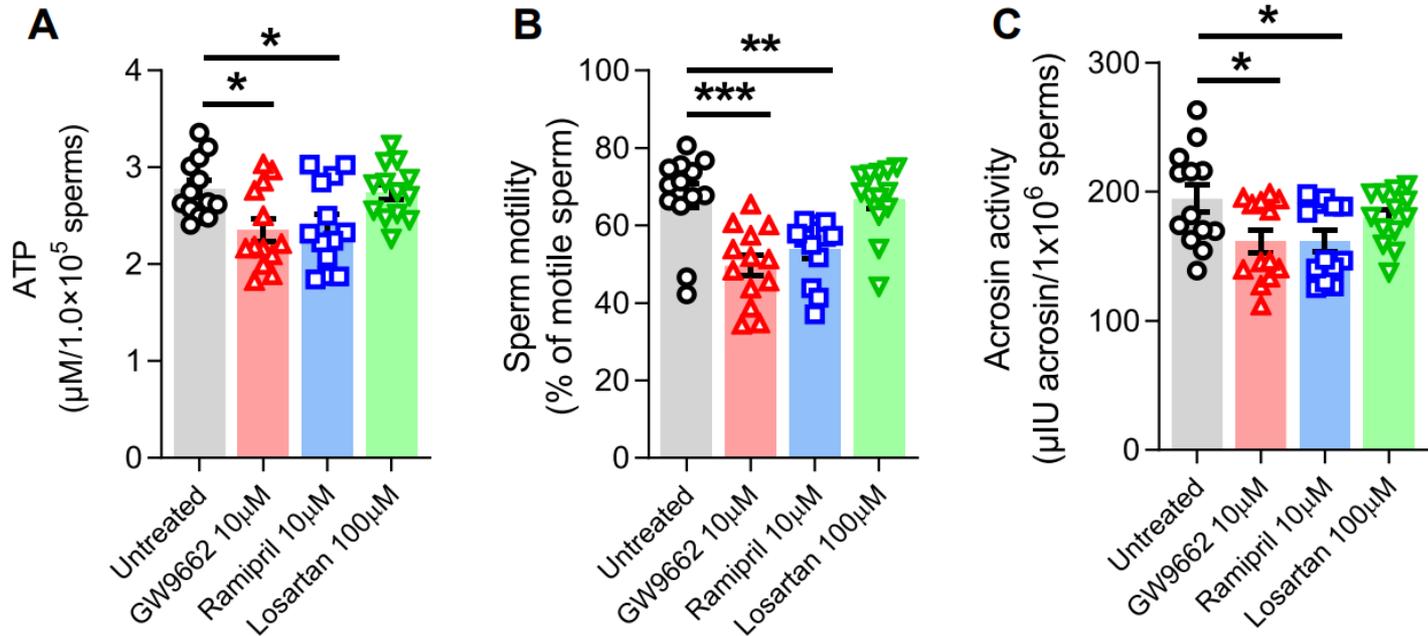


Figure 7. The metabolic and physiologic effect tACE in human sperm. Human sperm were treated for 12 h with either 10 μM GW9662 or 10 μM ramipril or 100 μM losartan and then (A) production of ATP, (B) motility, and (C) acrosin activity were determined as described in the [Experimental procedures](#). Untreated samples were used as a control. Sperm representative motility video is shown in [Video S2](#). Data are presented as means \pm SEM ($n = 13/\text{group}$). An one-way ANOVA with Bonferroni's correction for multiple comparisons was used to analyze group comparisons. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. tACE, testis angiotensin-converting enzyme.

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.

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.

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outcomes!***



