

# OUTCOMES OF NATURAL VERSUS PROGRAMMED CYCLES AMONG WOMEN OVER 40



**2026 PCRS ANNUAL MEETING**

REPRODUCTIVE FRONTIERS:  
BRIDGING BIOLOGY, PRACTICE, AND POSSIBILITY  
MARCH 18-22 | RANCHO MIRAGE, CA

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# Disclosures

- Neither I nor members of my immediate family have any actual or potential financial interests to disclose relating to the content of this presentation.

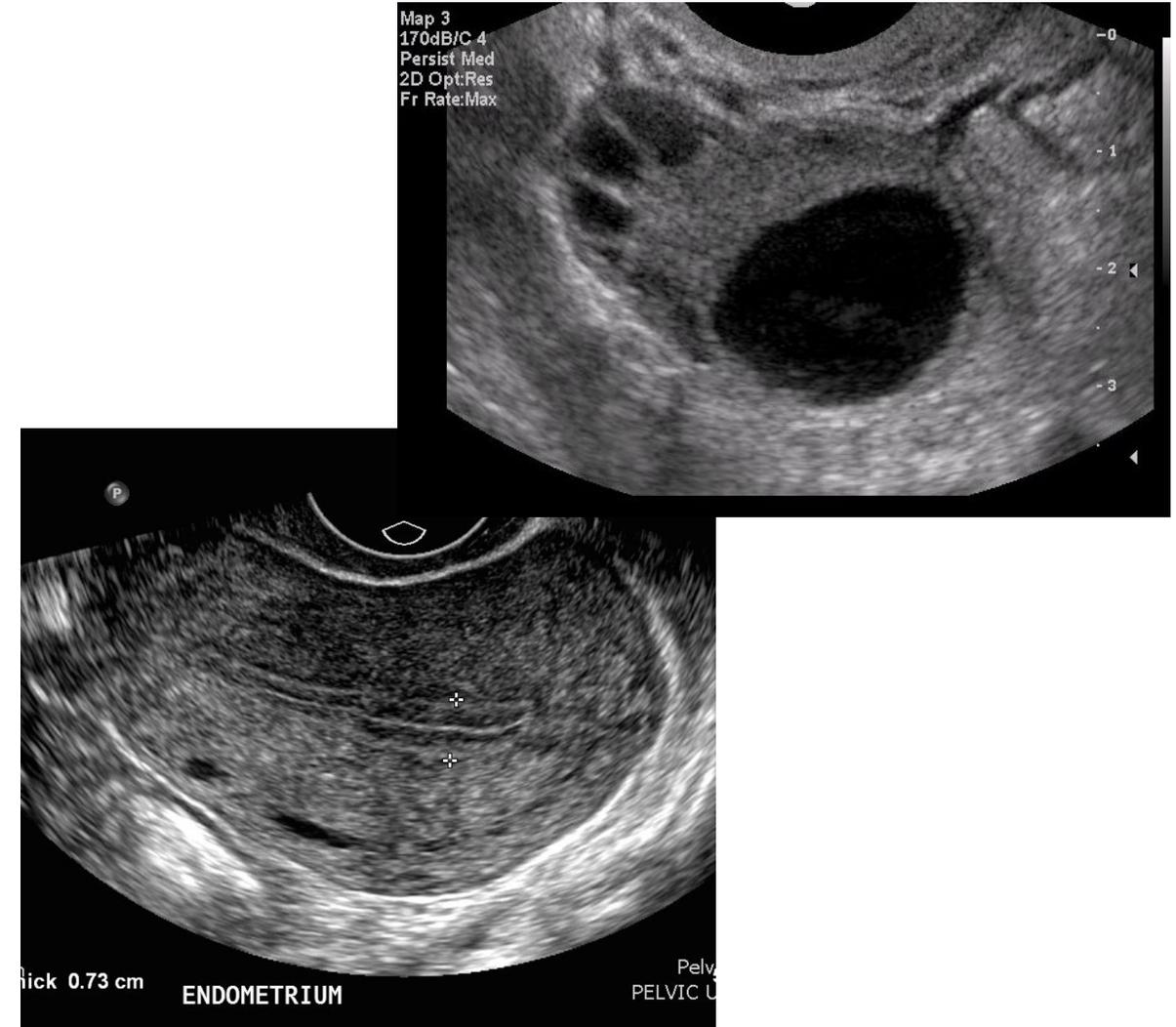
# Needs Assessment Statement and Expected Learning Outcomes

- Utilization of natural cycle embryo transfers has been increasing
- Outcomes in women over 40 are unknown
- To explore pregnancy outcomes in women over 40 undergoing natural frozen embryo transfer (FET)



# Background

- FET cycles require endometrial preparation via programmed or natural cycle protocols
- Most studies suggest similar pregnancy rates between protocol types<sup>1,2</sup>



Case courtesy of Alexandra Stanislavsky, Radiopaedia.org, rID: 30417  
Case courtesy of Matt A. Morgan, Radiopaedia.org, rID: 42531

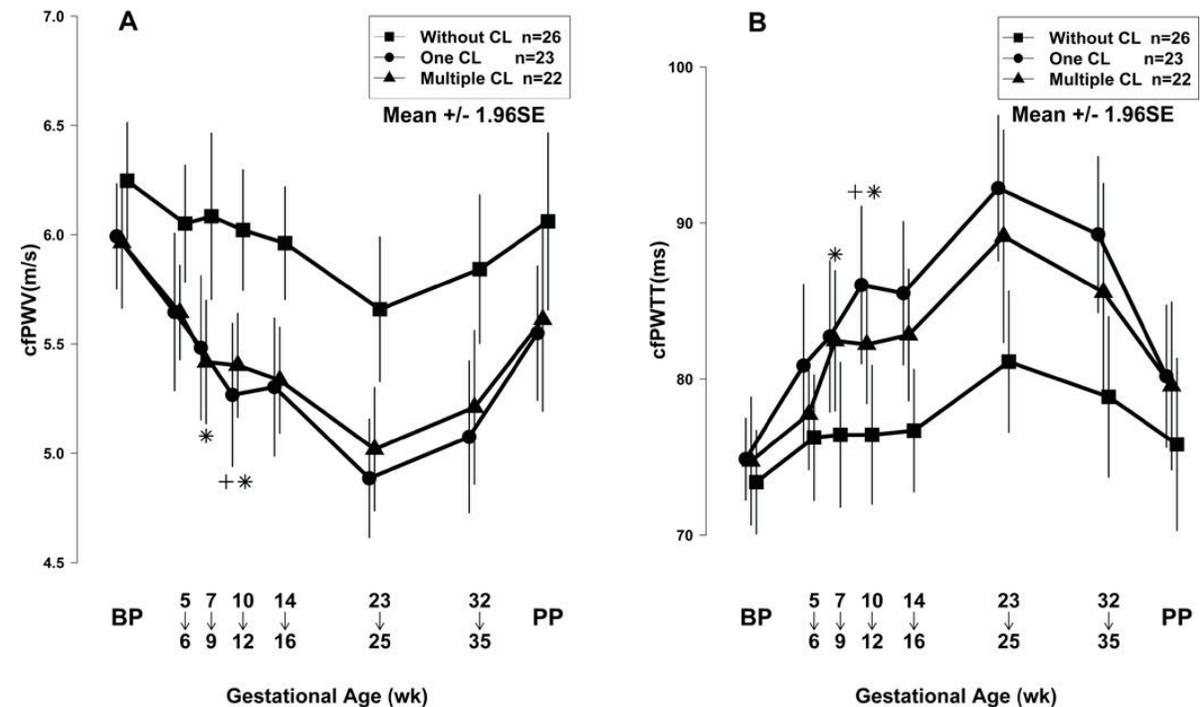
1. Wei et al., *BMJ*, 2026

2. Alur-Gupta et al., *Fertility and Sterility*, 2018



# Background

- Cycles without a corpus luteum (CL) seem to be associated with an increased risk of hypertensive disorders of pregnancy (HDP)<sup>3-5</sup>
  - Awaiting randomized trial data<sup>6</sup>
- Older patients have higher baseline risk of HDP but may be less likely to be offered this option



von Versen-Hoyneck et al., *Hypertension*, 2019

3. Makhjani et al., *RBMO*, 2020

5. Conrad et al., *AJOG*, 2022

4. Bortoletto et al., *Fertility and Sterility*, 2022

6. Baksh et al., *Trials*, 2021



# Objective

- To compare pregnancy outcomes in patients with advanced maternal age ( $\geq 40$  years) after single euploid FET based on type of endometrial preparation
- To understand patterns of cycle cancellation in women  $\geq 40$  who are offered a natural cycle



# Methods

- Retrospective cohort study of all autologous single euploid FETs in patients  $\geq 40$  years from January 2015 to September 2024 at a single fertility clinic
- Transfer cycles classified as natural versus programmed based on presence or absence of CL
  - True natural, modified natural (trigger), and stimulated natural (letrozole or rFSH + trigger)
  - All natural cycles received luteal progesterone supplementation
- Donor and surrogate cycles were excluded

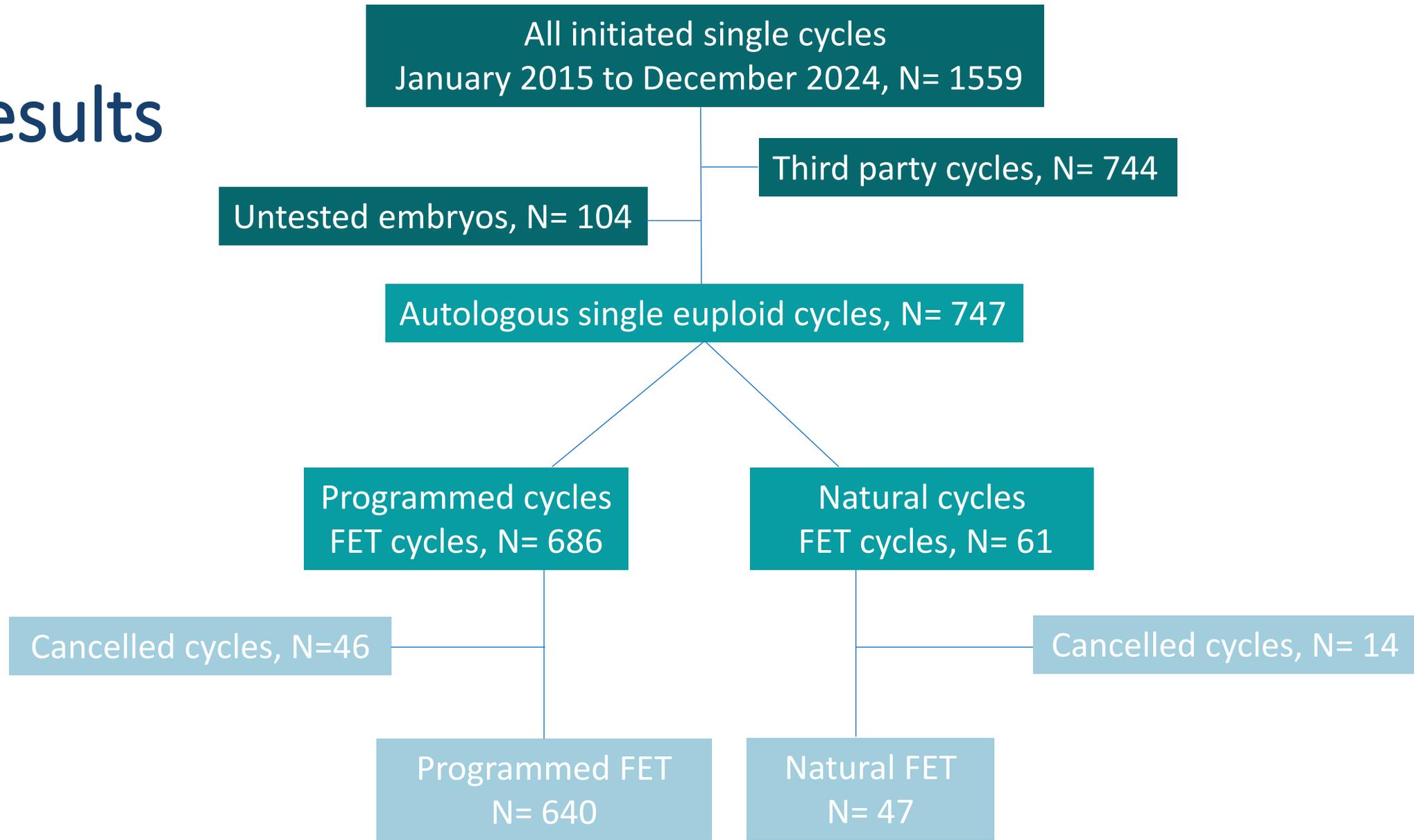


# Methods

- **Primary outcomes**
  - Clinical pregnancy rate, miscarriage rate, and live birth rate
- **Secondary outcomes**
  - Cancellation rate by cycle type and reason for cancellation



# Results



# Results

	Programmed Cycles (N= 640)	Natural Cycles (N= 47)	P- value
Age (mean, SD)	41.5 (2.2)	41.7 (2.0)	0.45
BMI (mean, SD)	25.0 (5.2)	23.8 (4.5)	0.01
Good morphologic embryo grade*, N(%)	386 (60.3)	28 (59.6)	0.92
Day 5 Embryos, N(%)	416 (65.0)	25 (53.2)	0.11

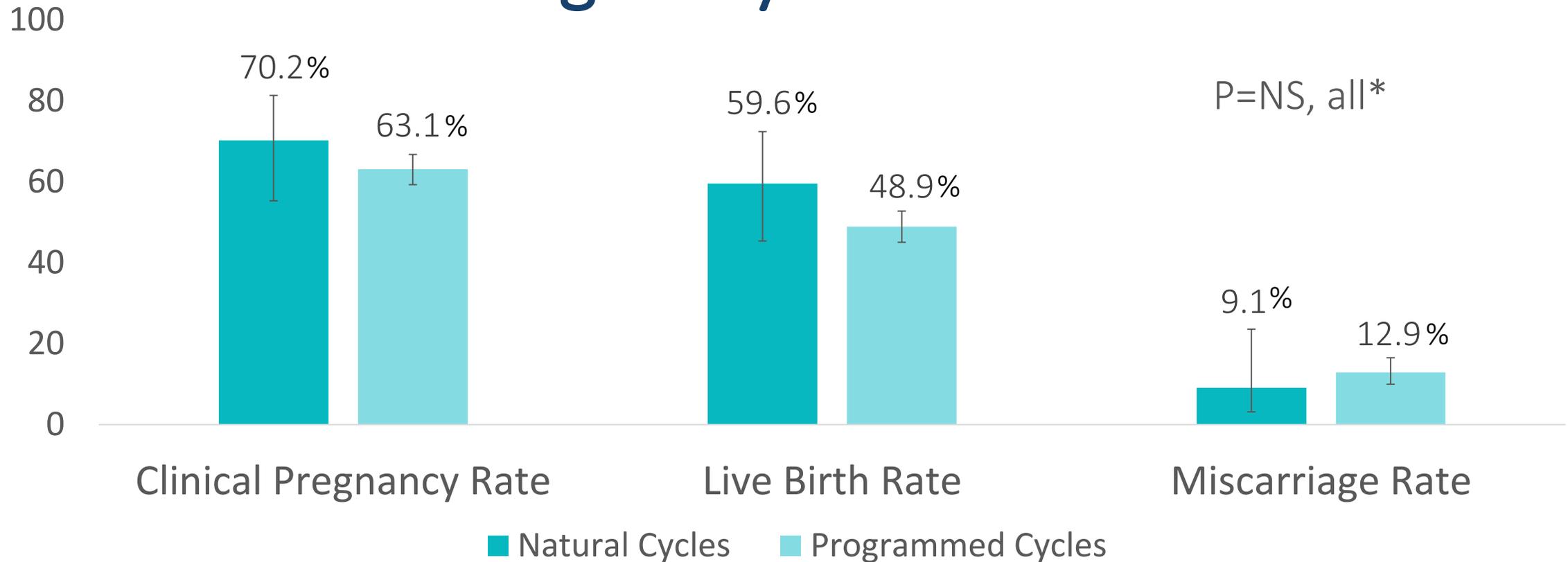
\*Gardner grade > BB

# Natural Cycle Characteristics

All Natural Cycles (N= 47)	
Natural cycle type, N(%)	
True natural	1 (2.1)
Modified natural	33 (70.2)
Stimulated natural	13 (37.7)
Endometrial thickness, mm (mean, SD)	10.2 (2.6)
Peak E2, pg/mL (mean, SD)	321.4 (353.2)



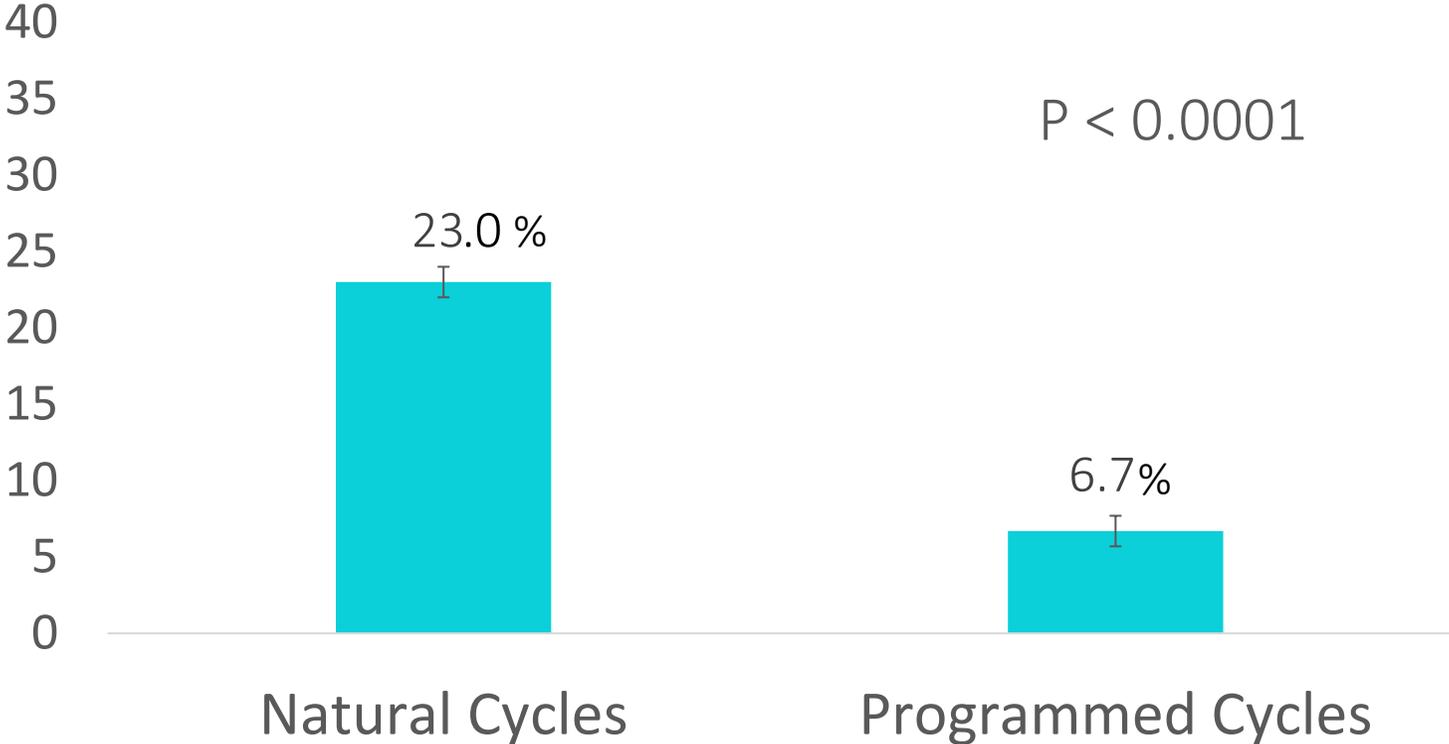
# Pregnancy Outcomes



\*Obtained in multivariable logistic regression model adjusting for age, embryo morphologic grade, day of embryo biopsy, and BMI



# Cycle Cancellation



# Reason for Cancellation

Reason for Cancellation	Cancelled Programmed Cycles (N= 46), N %	Cancelled Natural Cycles (N= 14), N %
Premature ovulation	40 (87.0)	8 (57.1)
No follicular response	NA	4 (28.6)
Inadequate EMT	6 (13.0)	2 (14.3)



# Reason for Cancellation

Reason for cancellation	Cancelled Programmed Cycles (N= 46), N %	Cancelled Natural Cycles (N= 14), N %
Premature ovulation	40 (87.0)	8 (57.1)
No follicular response	NA	4 (28.6)
Inadequate EMT	6 (13.0)	2 (14.3)

Of all initiated cycles, premature ovulation was the reason for cancellation in 13.1 % of natural cycles and 5.8% of programmed cycles.



# Key Findings

- Despite a trend toward improved outcomes in natural cycles, there was no statistical difference in pregnancy, live birth, and miscarriage rates between groups
- Higher cycle cancellation per initiated FET in natural cycles, most commonly due to premature ovulation





# Limitations

- Small sample size and retrospective nature
- Variation in FET protocols
- No adjustment for number of CL in natural cycles
- No assessment of obstetric or neonatal outcomes



# Conclusions

- Natural cycle FETs are a viable option for women over 40, though they carry a significantly higher risk of cycle cancellation
  - May be a pregnancy risk mitigation strategy for this population
- While natural cycles trended toward improved pregnancy outcomes compared to programmed cycles, no statistically significant differences were observed



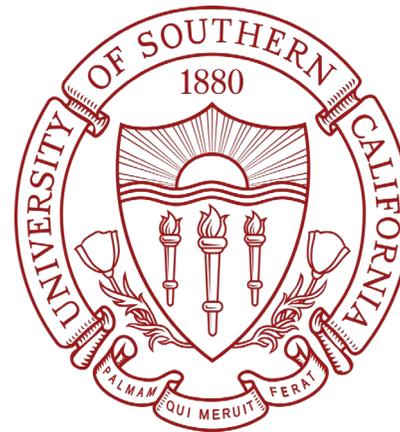
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# Thank you! Questions?

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Rachel Mandelbaum MD



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# Q&A



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