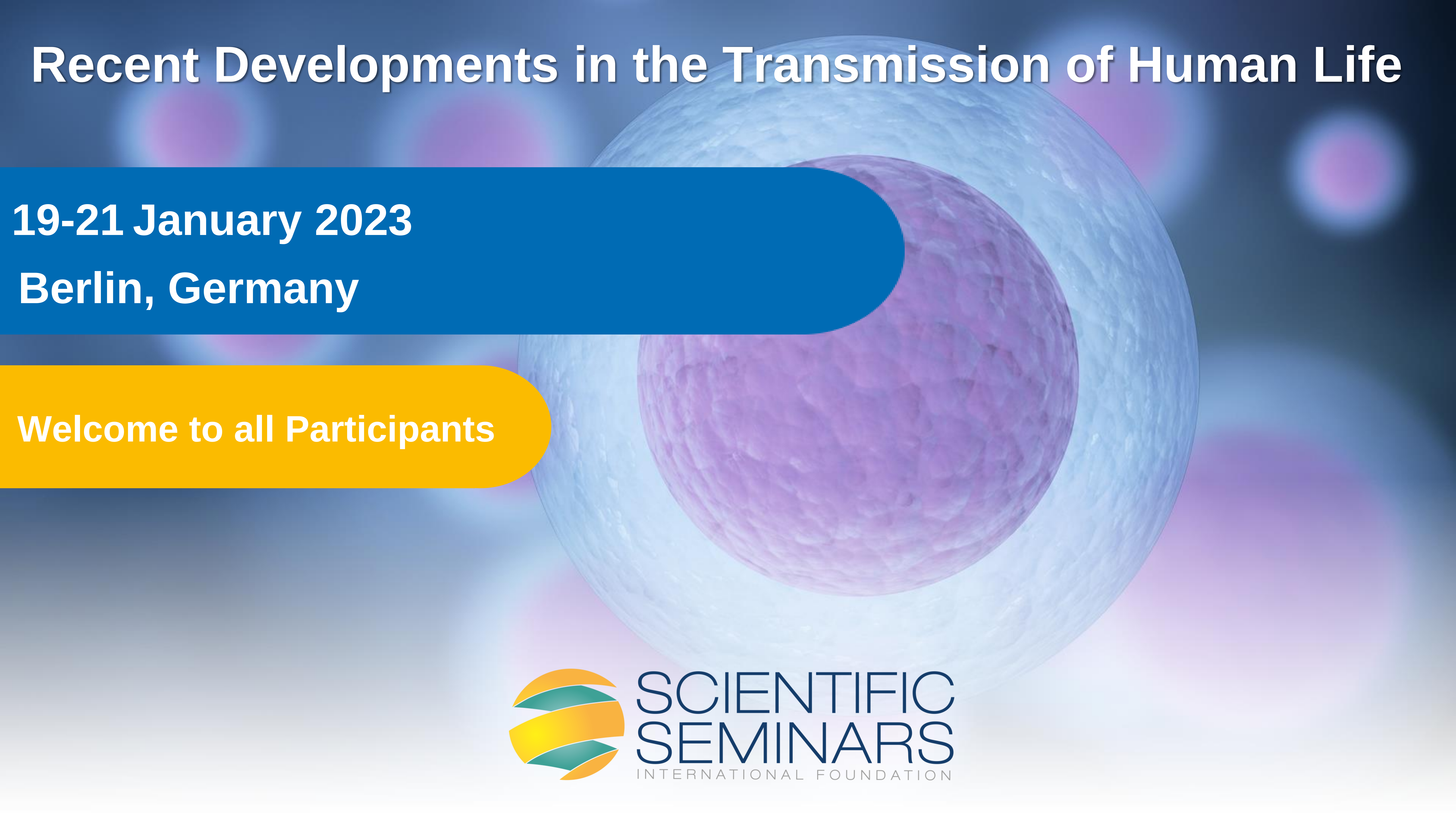

Recent Developments in the Transmission of Human Life

19-21 January 2023

Berlin, Germany

Welcome to all Participants

SCIENTIFIC SEMINARS
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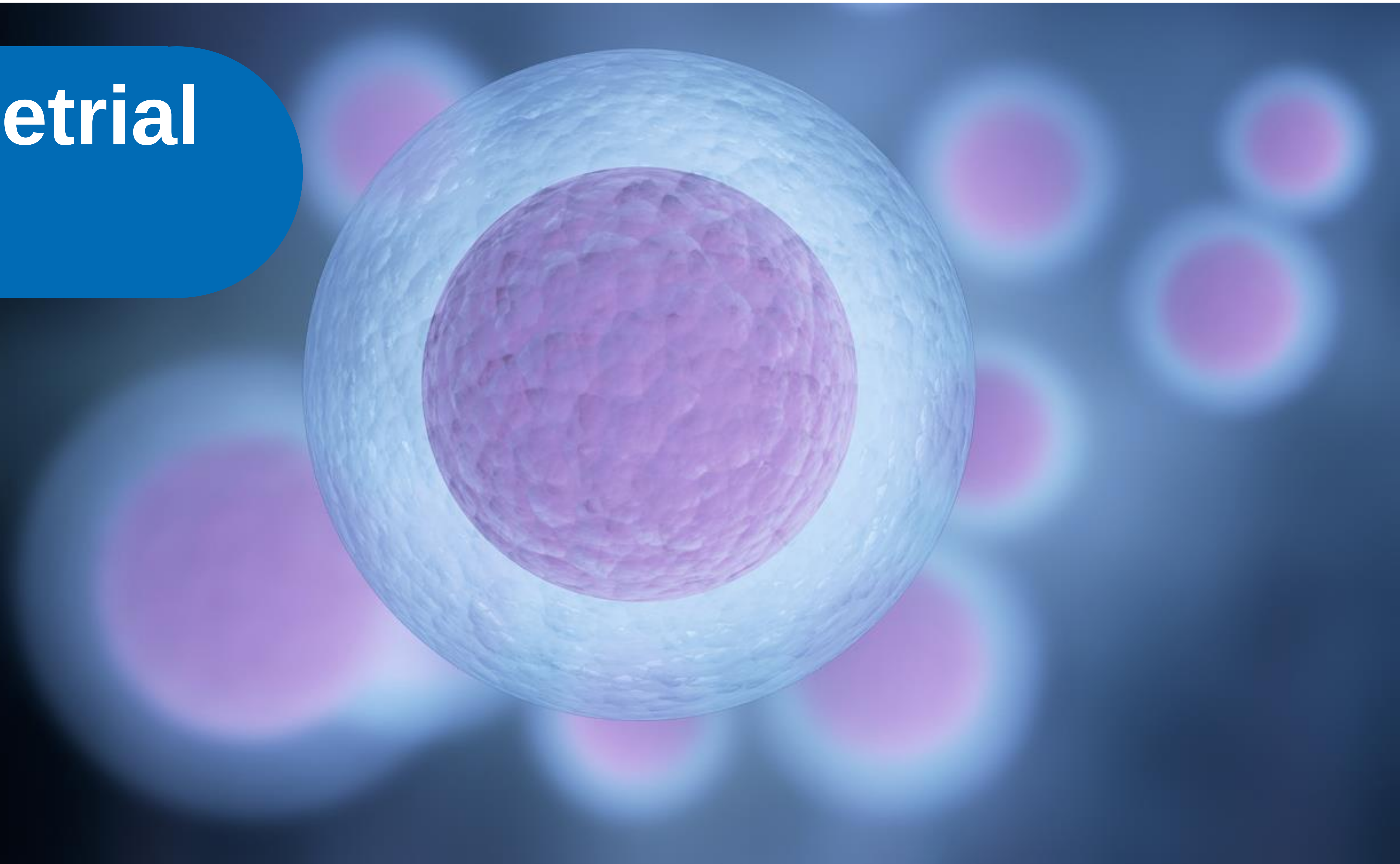
Recent Developments in the Transmission of Human Life



Ima[gyn]ing Endometrial Receptivity

Prof Roger Pierson MS PhD
FEAS FCAHS

Indigenous Land Acknowledgement

Alberta

We acknowledge that what we call Alberta is the traditional and ancestral territory of many peoples, presently subject to Treaties 6, 7, and 8. Namely: the Blackfoot Confederacy – Kainai, Piikani, and Siksika – the Cree, Dene, Saulteaux, Nakota Sioux, Stoney Nakoda, and the Tsuu T'ina Nation and the Métis People of Alberta. This includes the Métis Settlements and the Six Regions of the Métis Nation of Alberta within the historical Northwest Metis Homeland. We acknowledge the many First Nations, Métis and Inuit who have lived in and cared for these lands for generations. We are grateful for the traditional Knowledge Keepers and Elders who are still with us today and those who have gone before us. We make this acknowledgement as an act of reconciliation and gratitude to those whose territory we reside on or are visiting.

Saskatchewan

We acknowledge we are on Treaty 6 Territory and the Homeland of the Métis. We pay our respect to the First Nations and Métis ancestors of this place and reaffirm our relationship with one another.

Faculty Disclosure

RAP is the President and CSO of the Synergyne Group of companies

Synergyne Imaging Technologies and Synergyne Consulting hold the IP to computer software used for ultrasonographic image analyses

Consults on design and central analysis of global clinical trials

RAP has had recent consulting and/or research relationships with:

Ferring Pharmaceuticals
EMD Serono
GlaxoSmithKline
Temple Therapeutics
Besins Healthcare

Learning Objectives

1) Assist in understanding that ultrasound imaging can tell you more than you think!

2) Introduce a new non-invasive tool to assess endometrial receptivity.

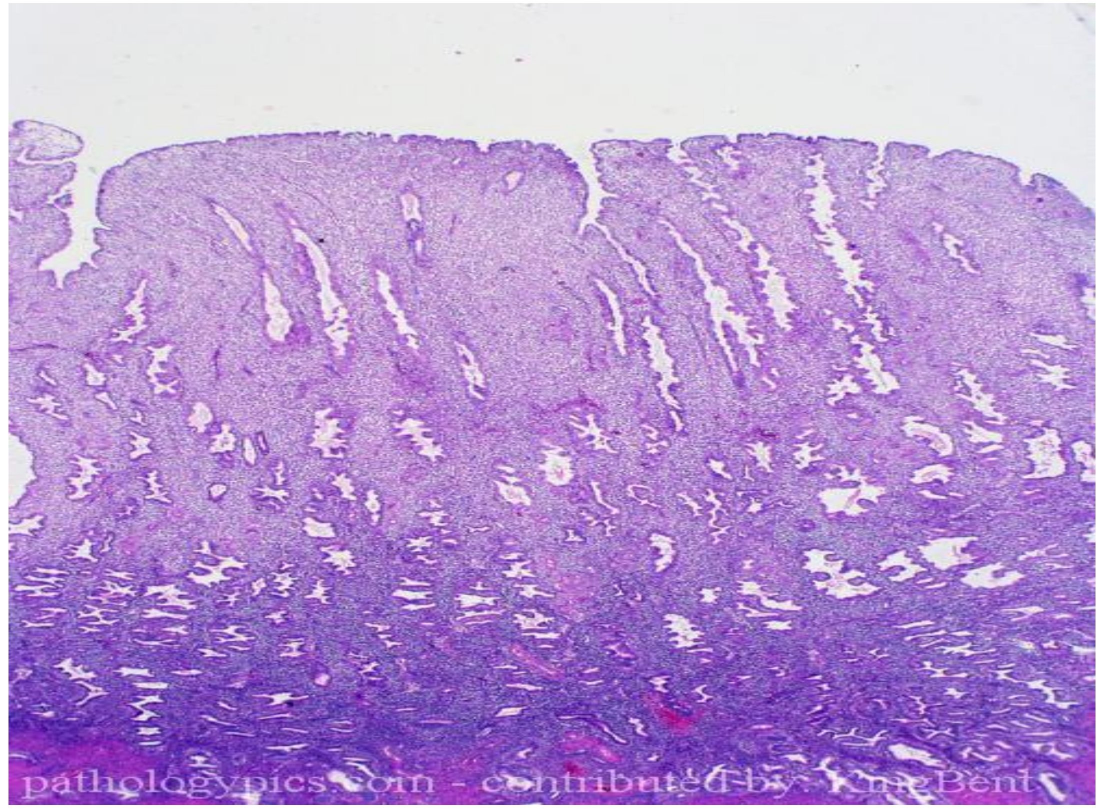
3) Discuss a new data driven approach supporting the routine use of ultrasound based endometrial receptivity (usER) diagnostic testing.

The Endometrium

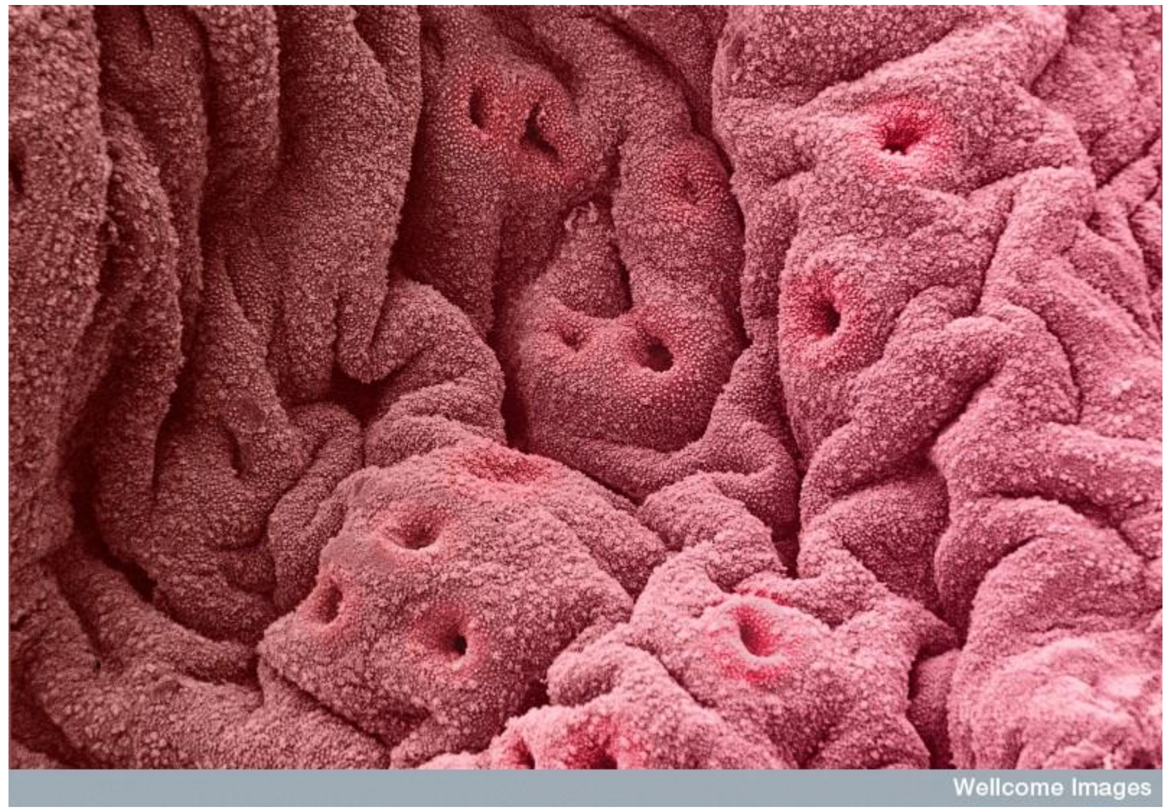
Is an exquisitely sensitive bio-assay of ovarian function

Is the site of embryo implantation and early development

Despite, or because of, pharmaceutical interventions during IVF treatment, endometrial development conducive to successful implantation of an embryo/blastocyst varies from patient-to-patient, drug-to-drug and cycle-to-cycle



pathologypics.com - contributed by: Kim Bent



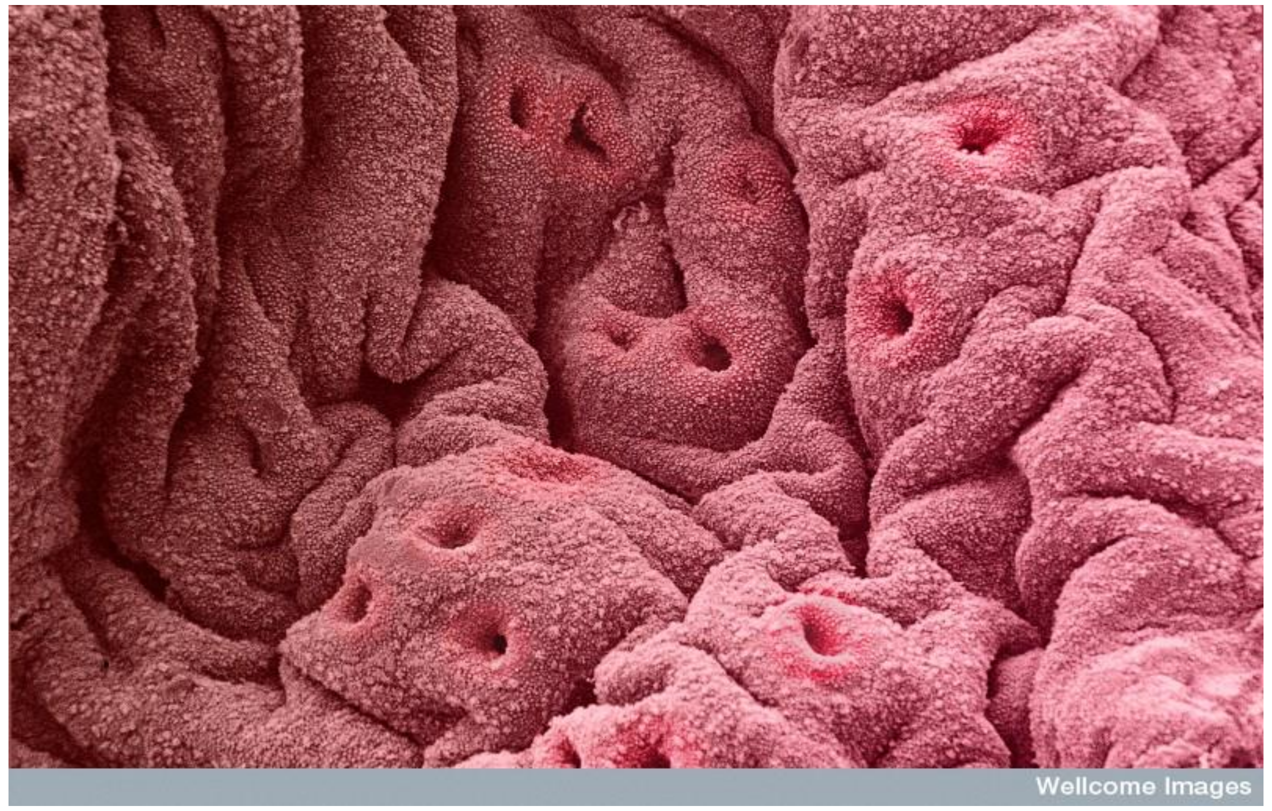
Wellcome Images

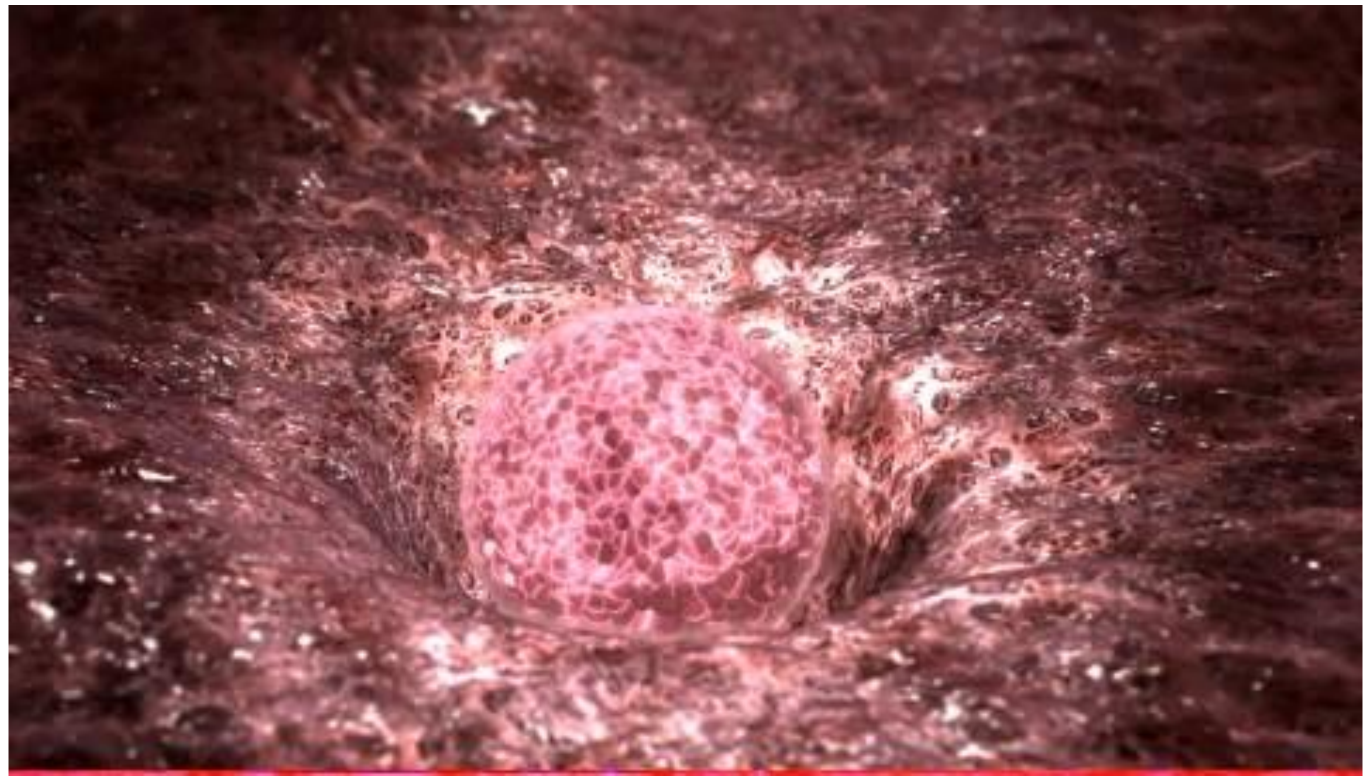
Endometrial Receptivity

Endometrial morphology and junctional zone contractile activity are intimately interconnected

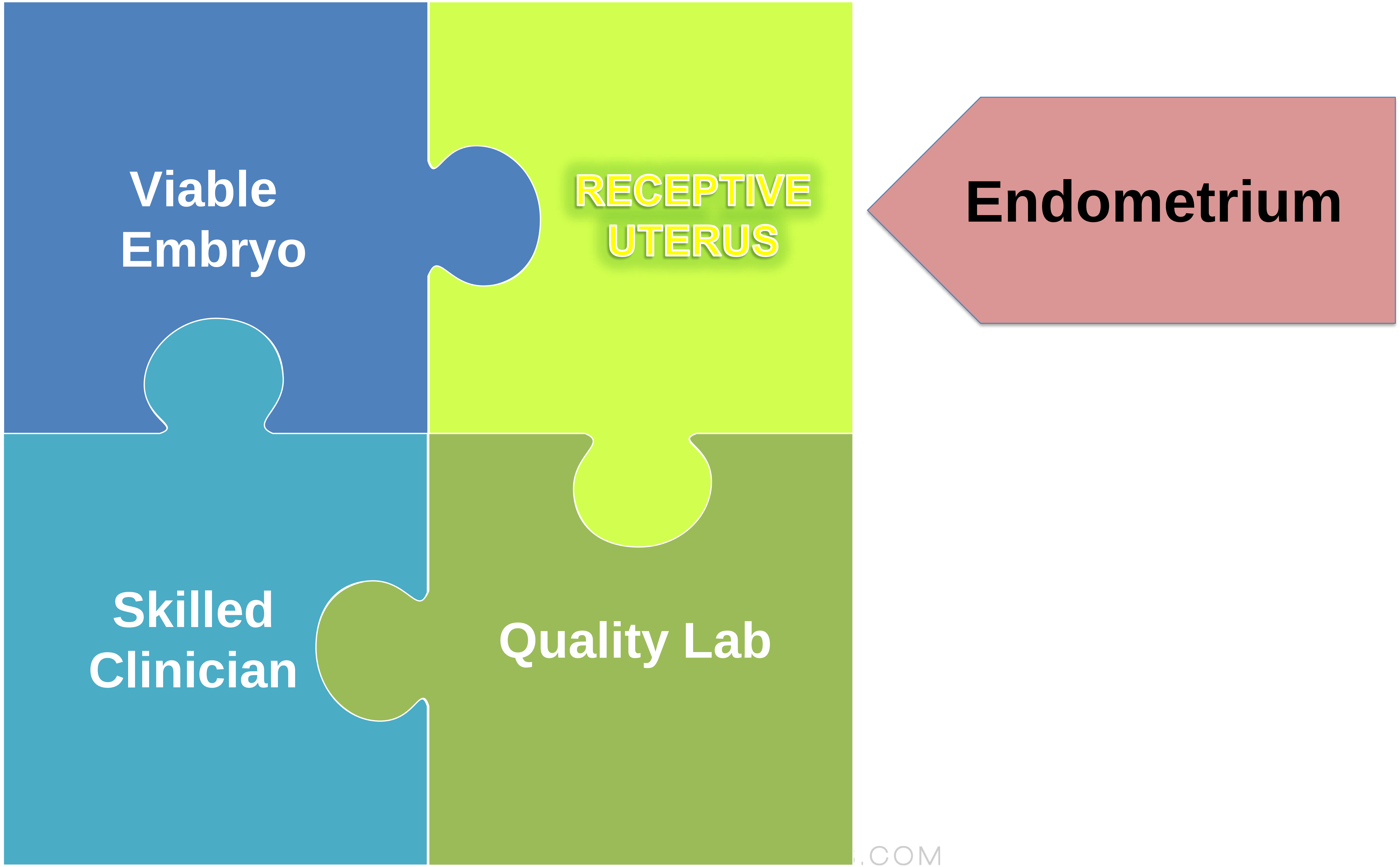
Each must be “just right” for optimal fertility

What if…. We could see it?


Wellcome Images



Critical Elements for IVF Success


Viable Embryo

RECEPTIVE UTERUS

Skilled Clinician

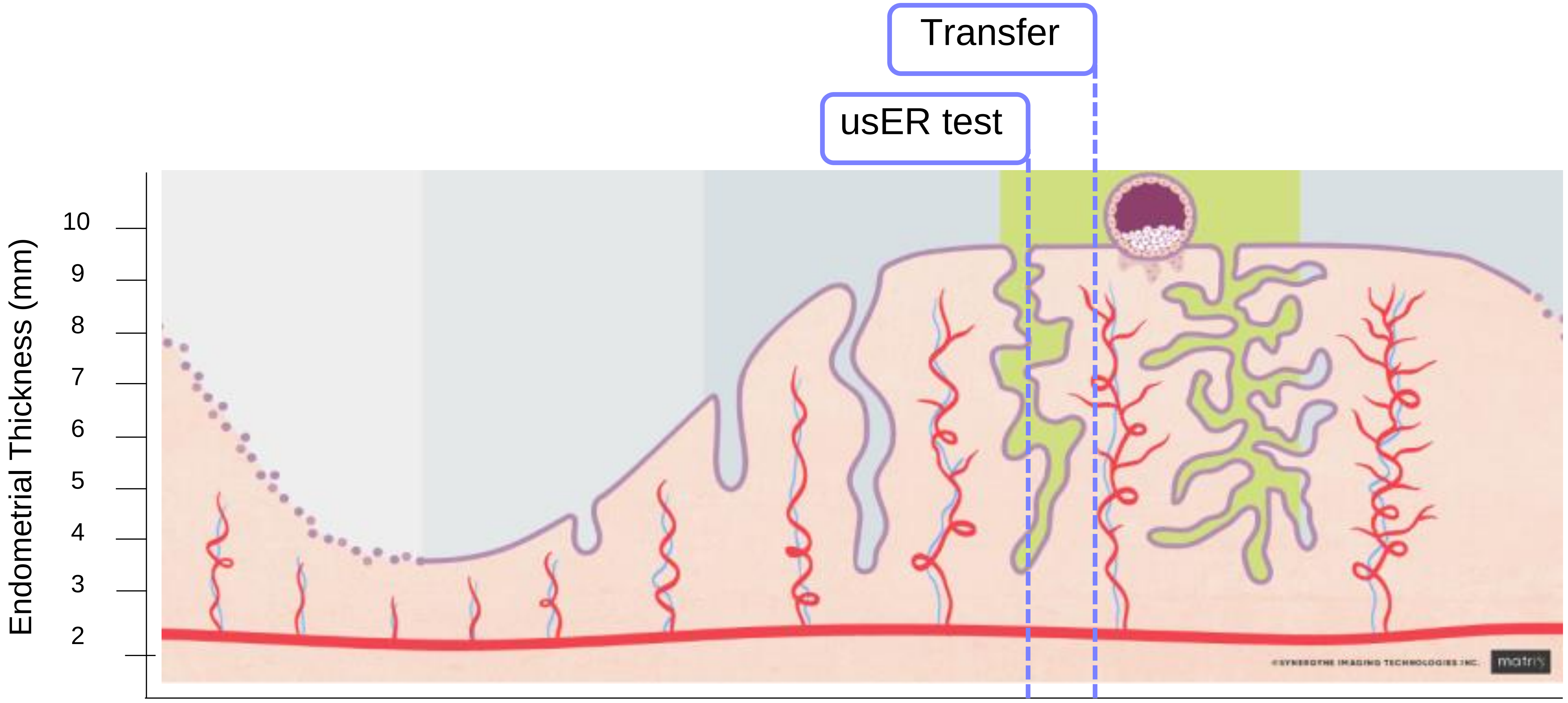
Quality Lab

Endometrium

.COM

What is usER (Matris™)?

- Non-invasive ultrasound based diagnostic tool for assessment of endometrial receptivity.
- Designed for use on a 'per-cycle' basis.
- Can be conducted prior to each considered embryo transfer.
- Ultrasound taken 2 days prior to each considered embryo transfer (fresh or frozen).
- Detailed assessment of endometrial preparation.


Transfer
usER test
Endometrial Thickness (mm)
10
9
8
7
6
5
4
3
2
©SYNERGYNE IMAGING TECHNOLOGIES INC.
matris

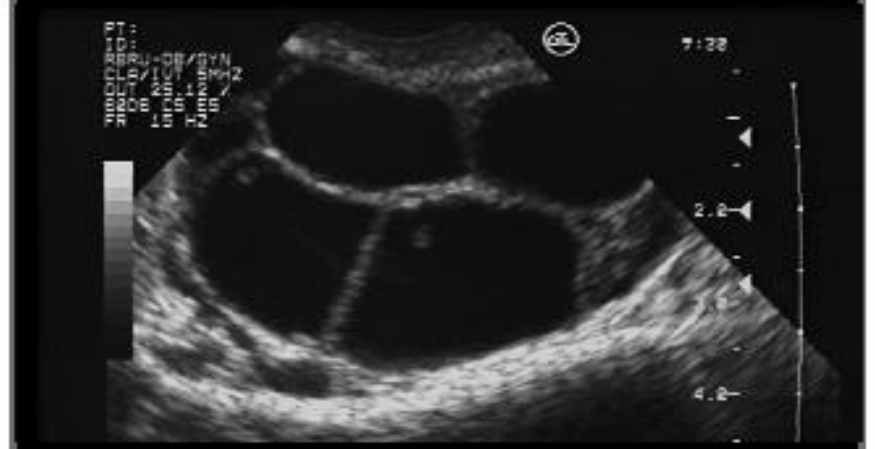
After Baerwald and Pierson, J US ObGyn 2004; 24,453

Ultrasound imaging can tell you more than you think…

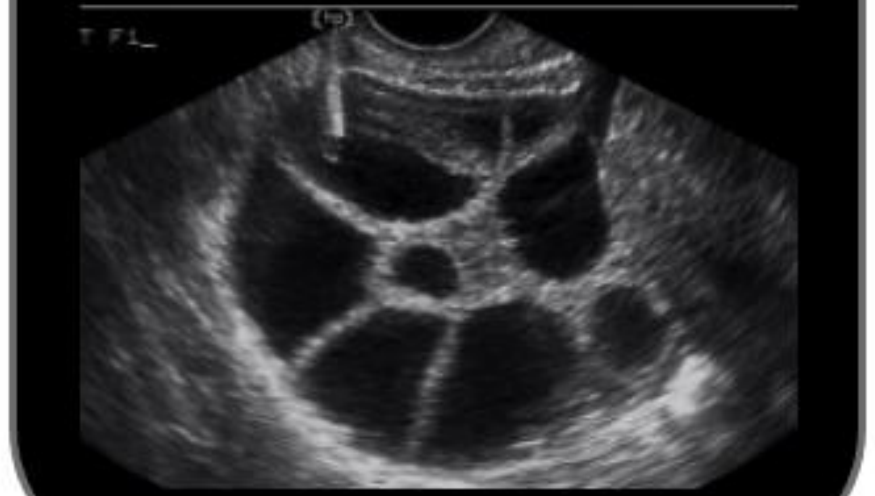
Routine utilization of ultrasound in IVF

OVARY

Follicle Monitoring

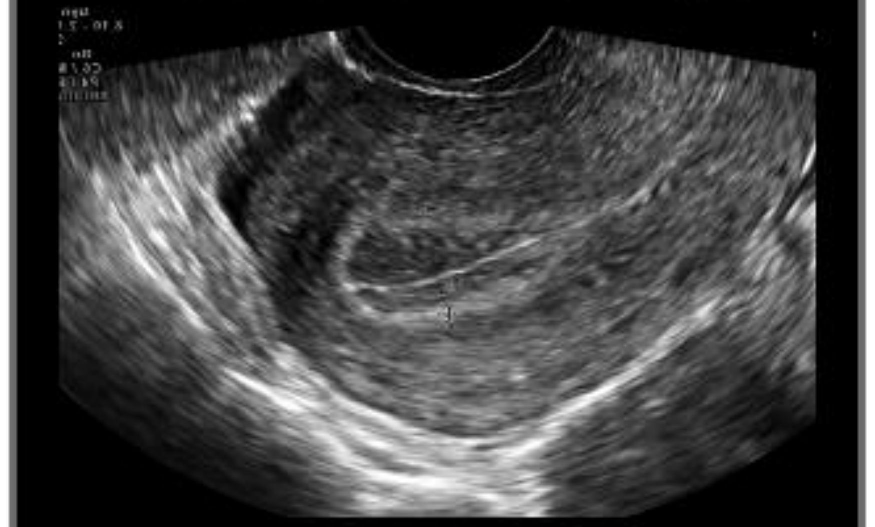


Guided Oocyte Retrieval

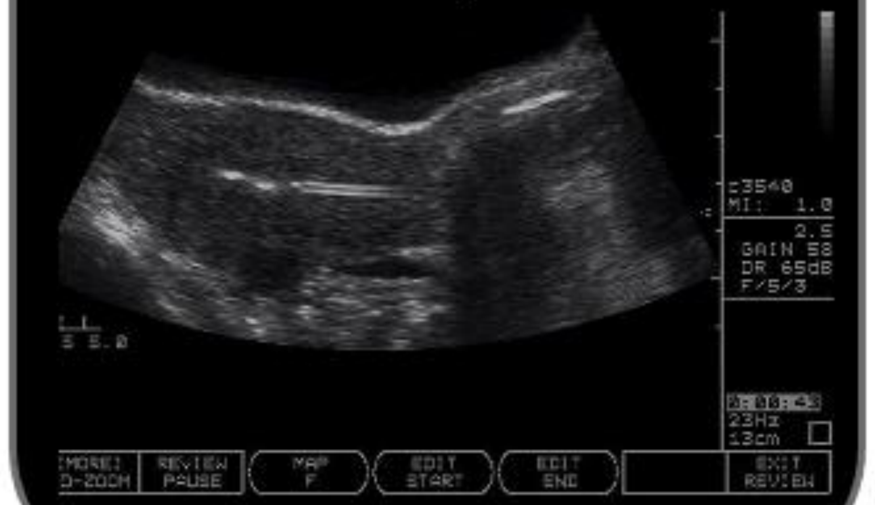


UTERUS

Endometrial Thickness

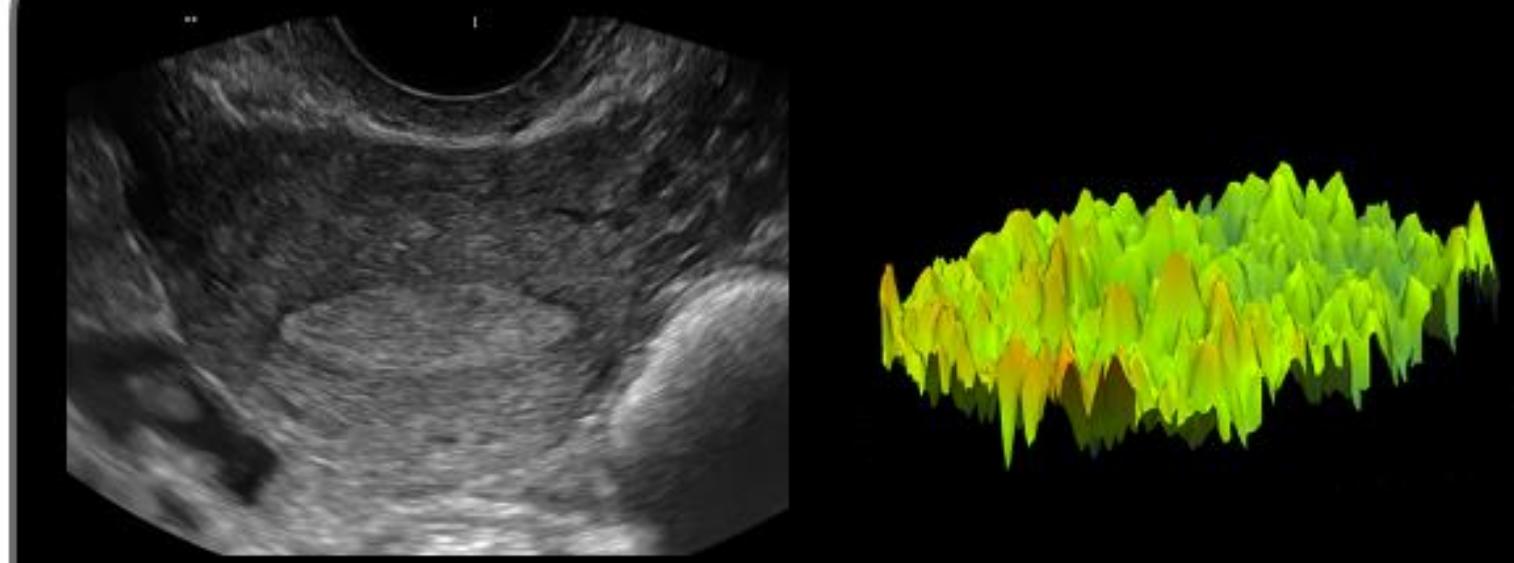


Guided Embryo Transfer



usER: Reference Lab for Endometrial Ultrasound

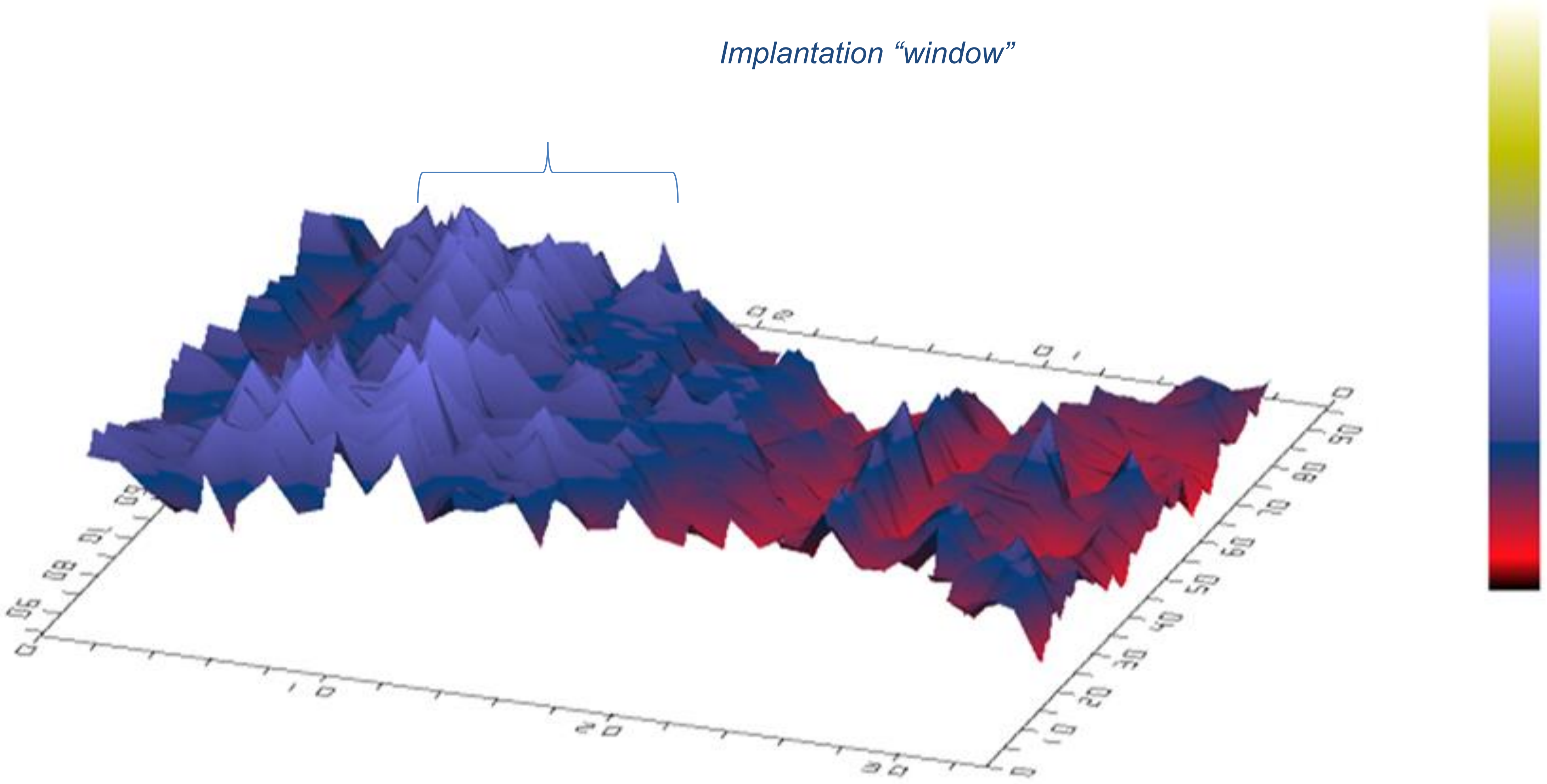
usER



- Image acquisition
- Image uploaded to Synergyne computer lab
- 5 stage multi-tiered computer-based image analytic process
- Scores assigned based on 40+ metrics of endometrial receptivity assessed utilizing precision purpose-built software.

Image-based Endometrial Receptivity Analyses

- Analysis of a standard ultrasound image using proprietary image analysis technology
- This technology can create an endometrial receptivity “map” across the menstrual cycle.

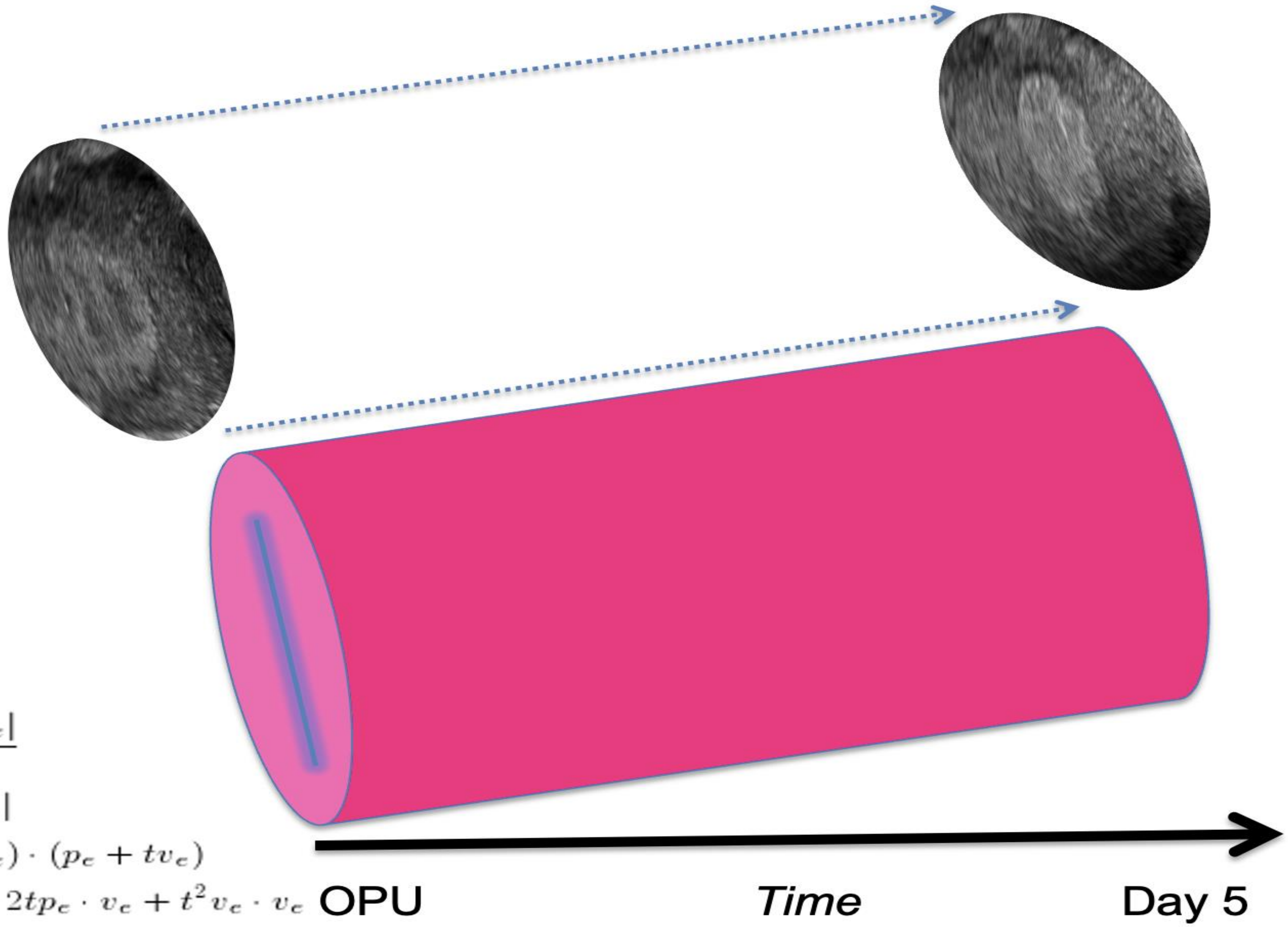


Implantation “window”

$$
\begin{aligned}
t &= \frac{|p_e + tv_e|}{s_b} \\
s_b t &= |p_e + tv_e| \\
s_b^2 t^2 &= (p_e + tv_e) \cdot (p_e + tv_e) \\
&= p_e \cdot p_e + 2tp_e \cdot v_e + t^2 v_e \cdot v_e \\
0 &= (v_e \cdot v_e - s_b^2)t_e^2 + (2p_e \cdot v_e)t + p_e \cdot p_e
\end{aligned}
$$

© Synergyne Imaging Technology Inc.

Endometrial Calculus


OPU
Time
Day 5

$$\begin{aligned} t &= \frac{|p_e + tv_e|}{s_b} \\ s_b t &= |p_e + tv_e| \\ s_b^2 t^2 &= (p_e + tv_e) \cdot (p_e + tv_e) \\ &= p_e \cdot p_e + 2tp_e \cdot v_e + t^2 v_e \cdot v_e \\ 0 &= (v_e \cdot v_e - s_b^2) t_e^2 + (2p_e \cdot v_e) t + p_e \cdot p_e \end{aligned}$$

RECEPTIVE
UTERUS

Clinical recommendations from usER scores:

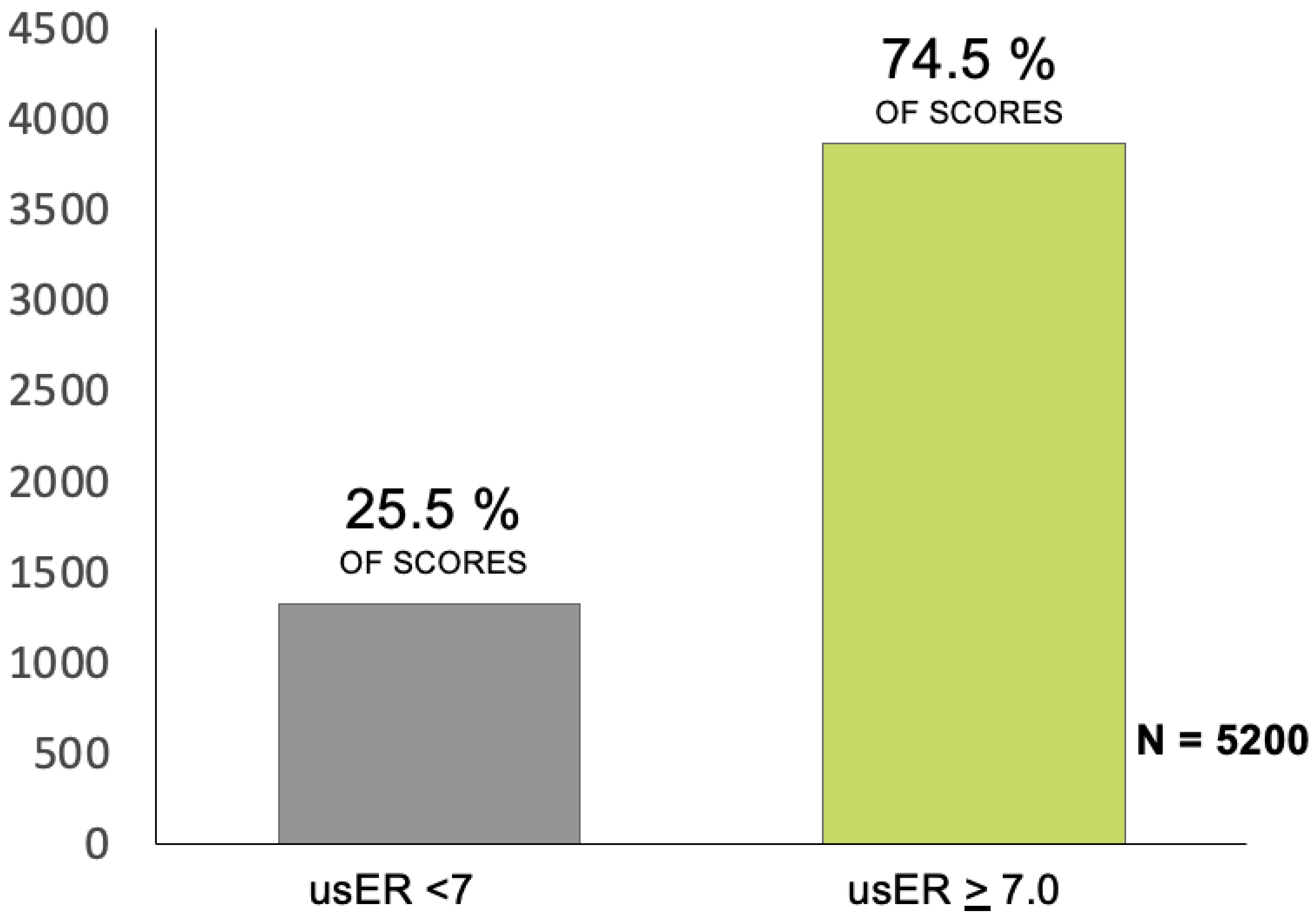
- Each usER test result is communicated on a report sheet through a private secure HIPAA/PIPEDA compliant clinic portal account.
- A numerical endometrial receptivity score (0 – 10)
- Clinical recommendations are provided for each score range based on quantitative pregnancy outcome data from over 5000 cycles.

usER Score	Classification	Endometrium	Clinical RX (as per physician)
≥ 7	Optimal	• High state of receptivity • Excellent glandular development • Endometrial response to circulating hormones is appropriate • Exhibits characteristics associated with high probability of pregnancy	Proceed to Embryo Transfer
6 – 6.5	Sub-Optimal	• Receptivity is weaker than expected in optimal cycle • Glandular development is suboptimal • Not well prepared for implantation • Exhibits characteristics associated with lower probability of pregnancy	Embryo Transfer Not Recommended
≤ 5.5	Deficient	• Poor state of endometrial receptivity • Glandular development is not appropriate for stage of cycle • Exhibits characteristics associated with low/ extremely low probability of pregnancy	Embryo Transfer Not Recommended

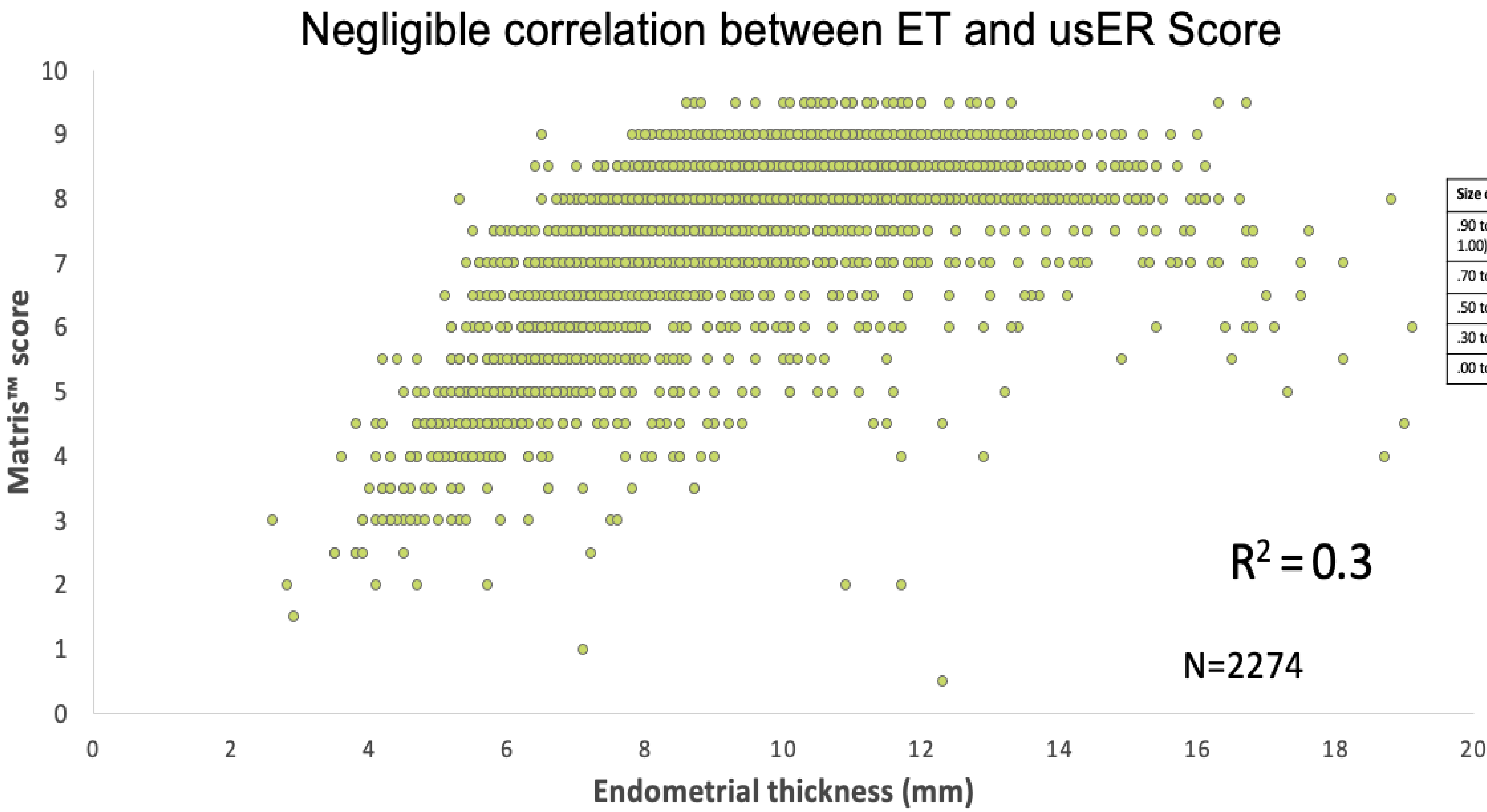
What percentage of cycles are likely to be recommended for deferral of embryo transfer?

usER Score Distribution

Approximately 25.5% of Cycles are Sub-optimal for Embryo Transfer



How does usER differ from standard endometrial thickness measurement?



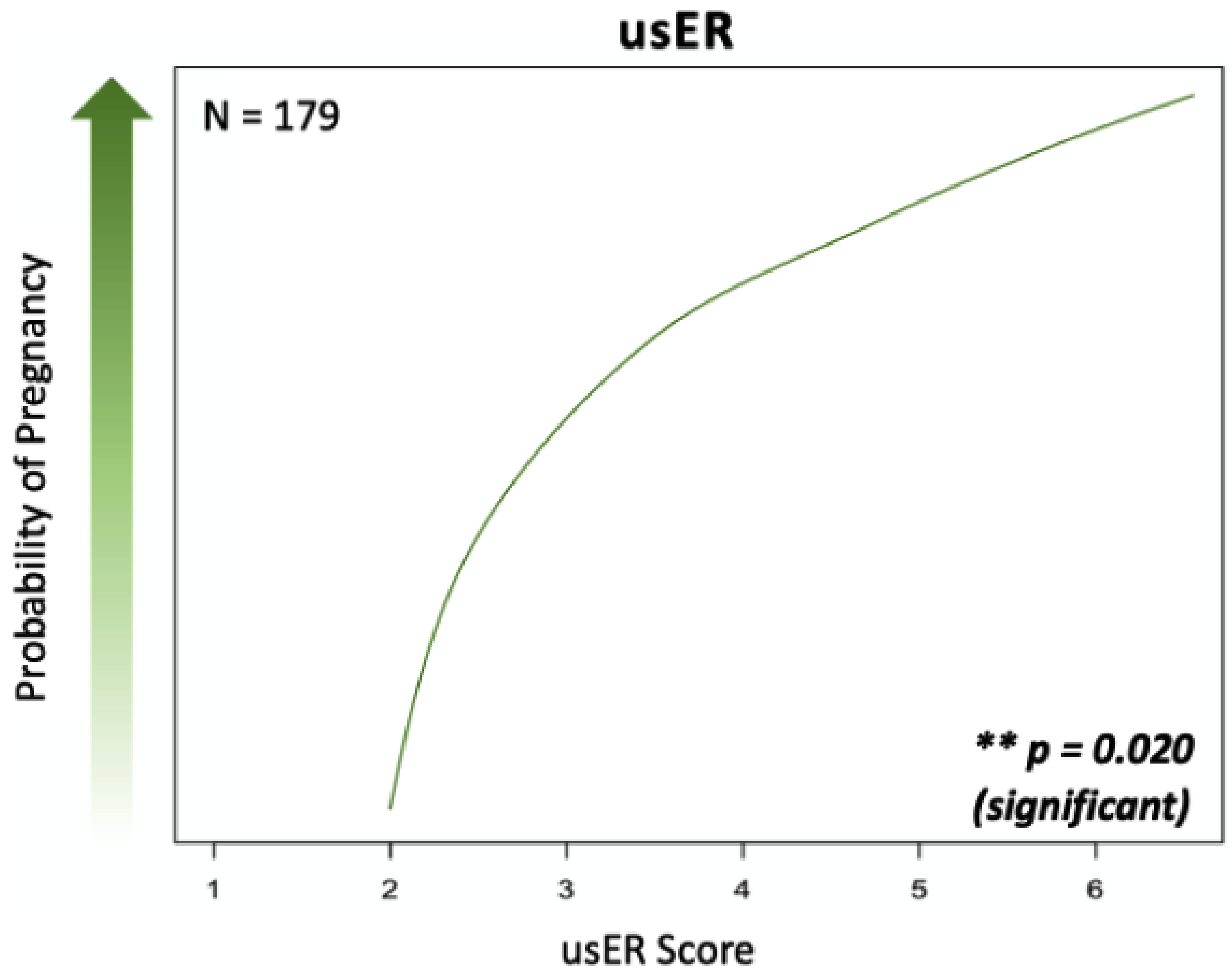
Size of correlation	Interpretation
.90 to 1.00 (-.90 to -1.00)	Very high positive (negative) correlation
.70 to .90 (-.70 to -.90)	High positive (negative) correlation
.50 to .70 (-.50 to -.70)	Moderate positive (negative) correlation
.30 to .50 (-.30 to -.50)	Low positive (negative) correlation
.00 to .30 (.00 to -.30)	Negligible correlation

Pierson HE et al. (2021) Fertility and Sterility 116(3): e312

Does usER accurately identify ‘low probability’ endometria?

Patient Demographics	usER score 7 or above (n, %, or mean)	usER score below 7 (n, %, or mean)	p-value
Number of frozen cycles (n)	1383	389	--
Number of fresh cycles (n)	314	190	--
Number of cycles total (n)	1697	579	--
Percent total cycles fresh vs frozen embryo			.00401 (chi-square)
Number of cycles received embryo transfer (n)	1611	179	<0.0001 (chi-square)
Average patient age (years)	36.663	36.578	.9875 (MannWhitney)
Patient age range (years)	24-50	24-52	--
Primary Infertility Diagnosis:			.704 (chi-square)
Male Factor Infertility (%)	349	110	
Female Factor Infertility (%)	763	276	
Male and Female Factor Infertility (%)	189	61	
Unknown / Idiopathic Infertility (%)	395	132	

A significantly higher percentage of cycles with low usER scores did not receive embryo transfer. This is attributed to the clinical guidance to defer embryo transfer when the scores are below 7.



Pierson HE et al. (2021) Fertility and Sterility 116(3): e312

Embryo conservation through deferral of low probability cycles

- usER accurately identifies low-probability cycles.
- Statistical analysis of all usER cycles conducted at a single clinic with outcomes recorded (n = 2274)
- 835 pregnant (47% per SET)
- 954 not pregnant (53% per SET)
- 485 no embryo transfer

- 579 cycles - deferral recommended
- 179 proceeded to SET against recommendation.

400 Embryos deferred from transfer.

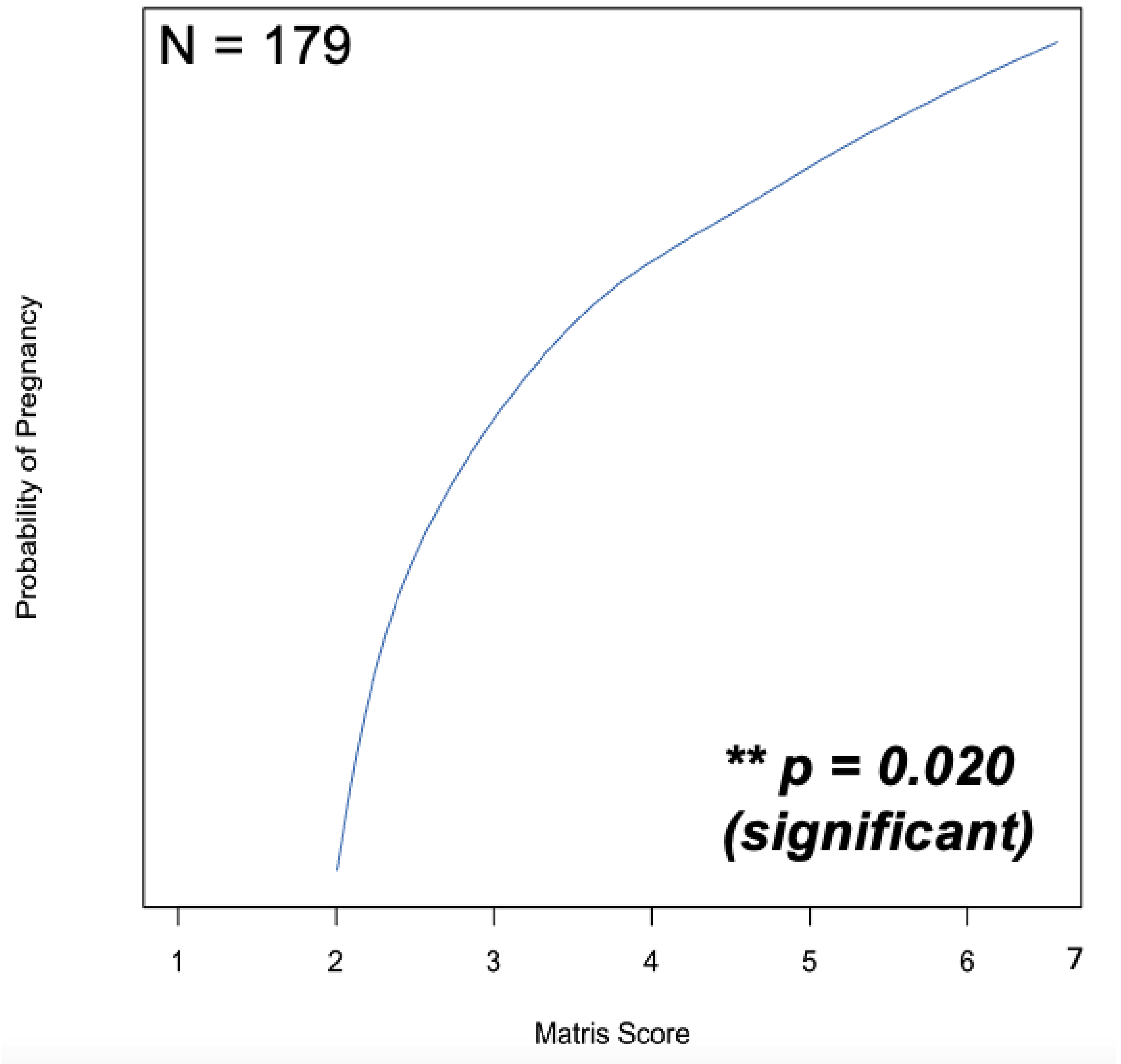
Subtract no ET due to ‘dead thaw’ / no embryo

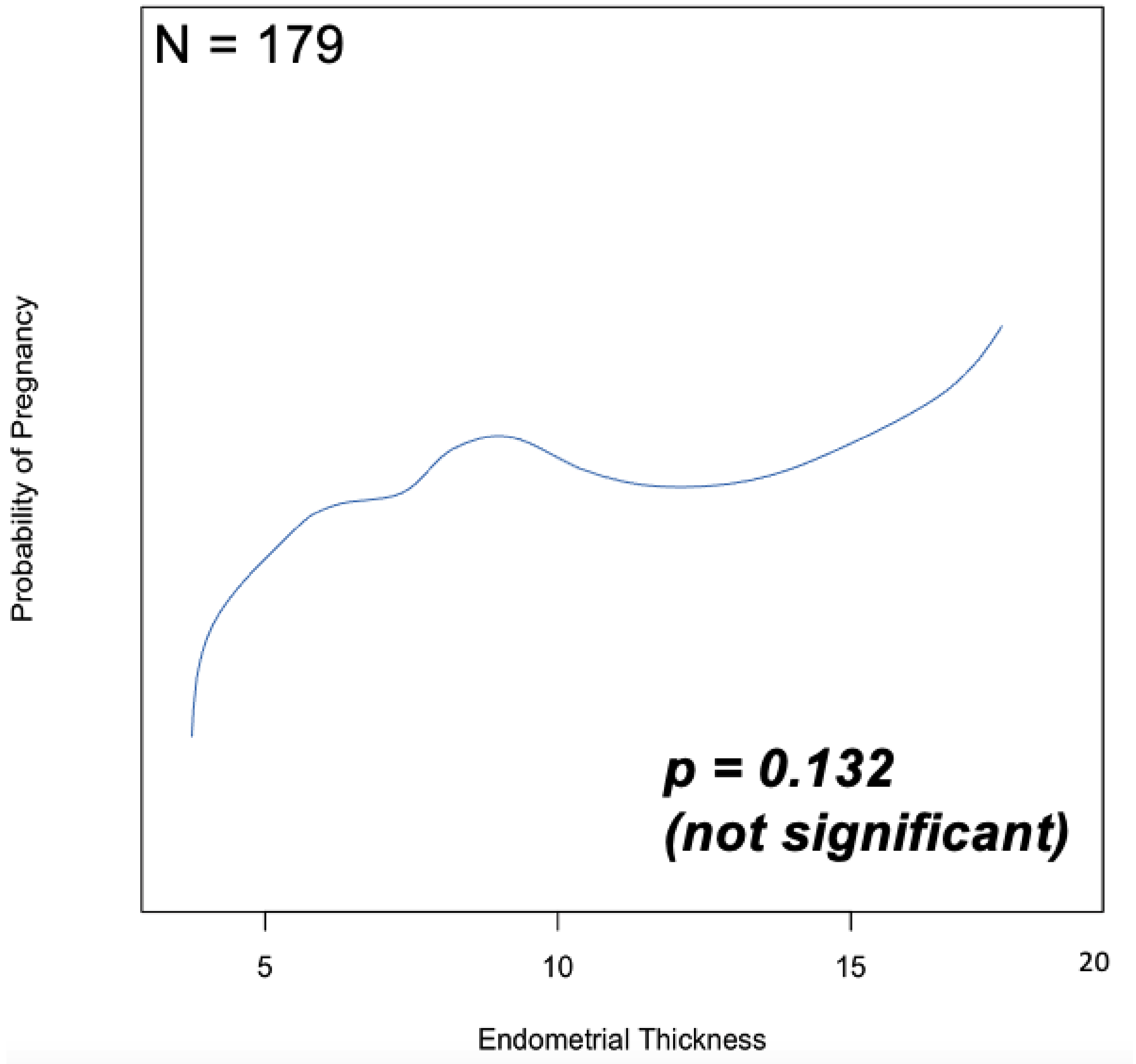
314 Embryos conserved

- Regression analysis of the 179 low usER scores ($\leq$ 6.5) reliably predicted the outcome of ‘not pregnant’(*p*=0.020).
- ET was not a significant predictor of pregnancy outcome (*p*=0.132).

Pierson HE et al. (2021) Fertility and Sterility 116(3): e312

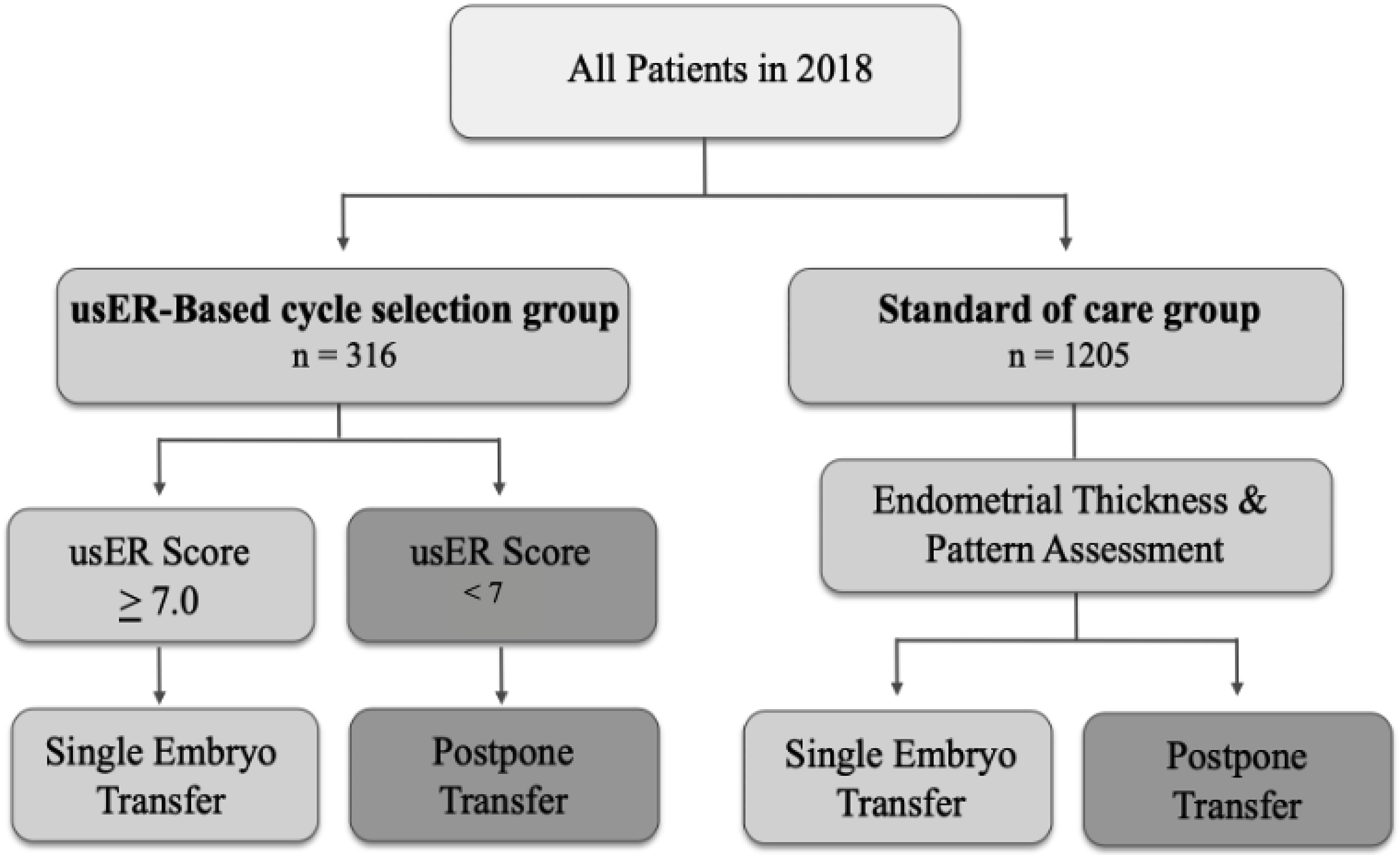
If usER score is correlated with pregnancy outcome… Is it providing information that thickness measures do not?





Pierson HE et al. (2021) Fertility and Sterility 116(3): e312

Retrospective analysis of outcomes justifies decision to defer low probability cycles identified by usER testing



All Patients in 2018

usER-Based cycle selection group
n = 316

usER Score
≥ 7.0

Single Embryo Transfer

usER Score
< 7

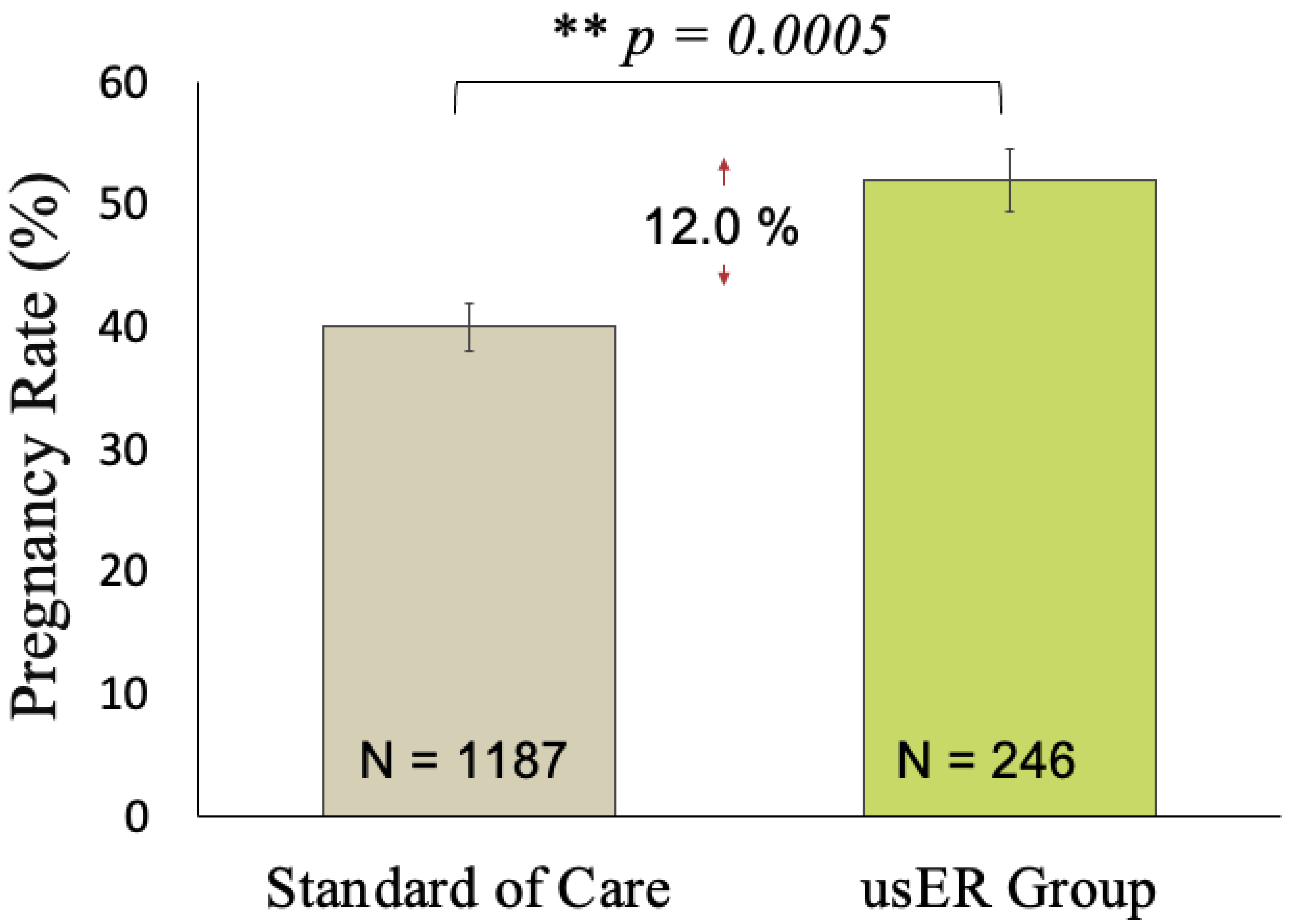
Postpone Transfer

Standard of care group
n = 1205

Endometrial Thickness & Pattern Assessment

Single Embryo Transfer

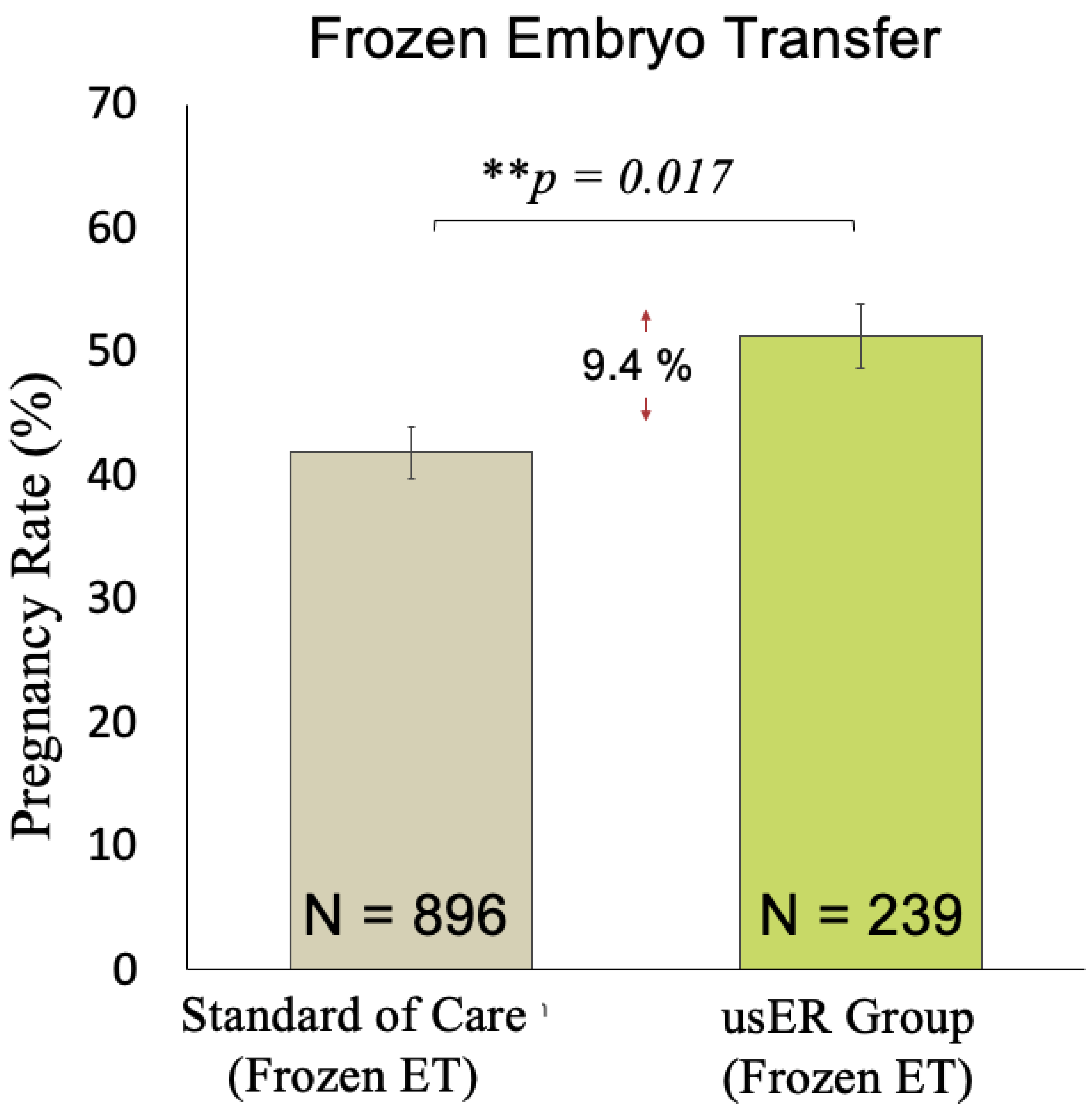
Postpone Transfer

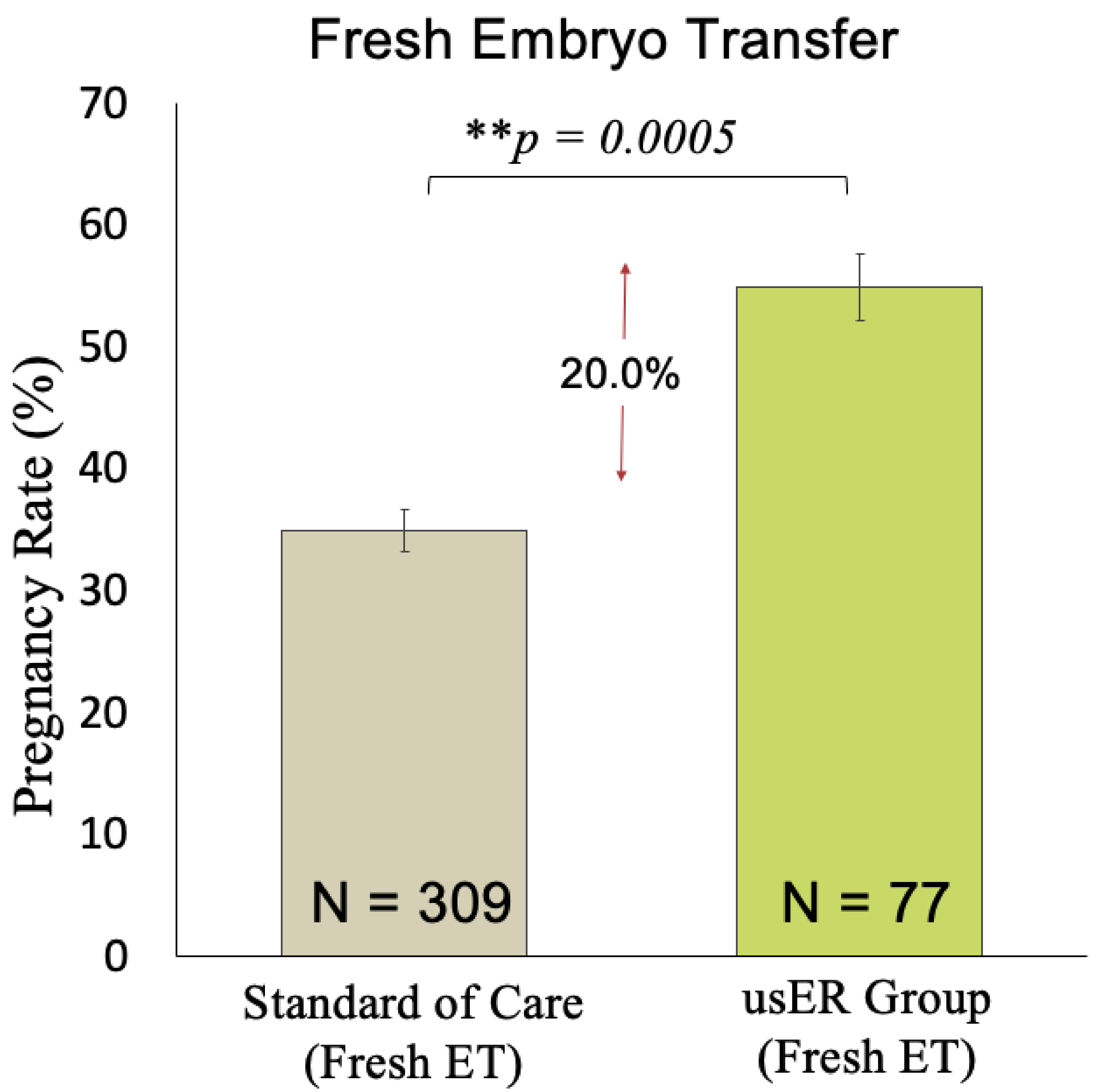


For both groups:
Fresh ET = ~ 24 %
Frozen ET = ~ 76 %

Pierson HE et al. (2022) J Fertilization: IVF World Wide, 9(6)6: 248

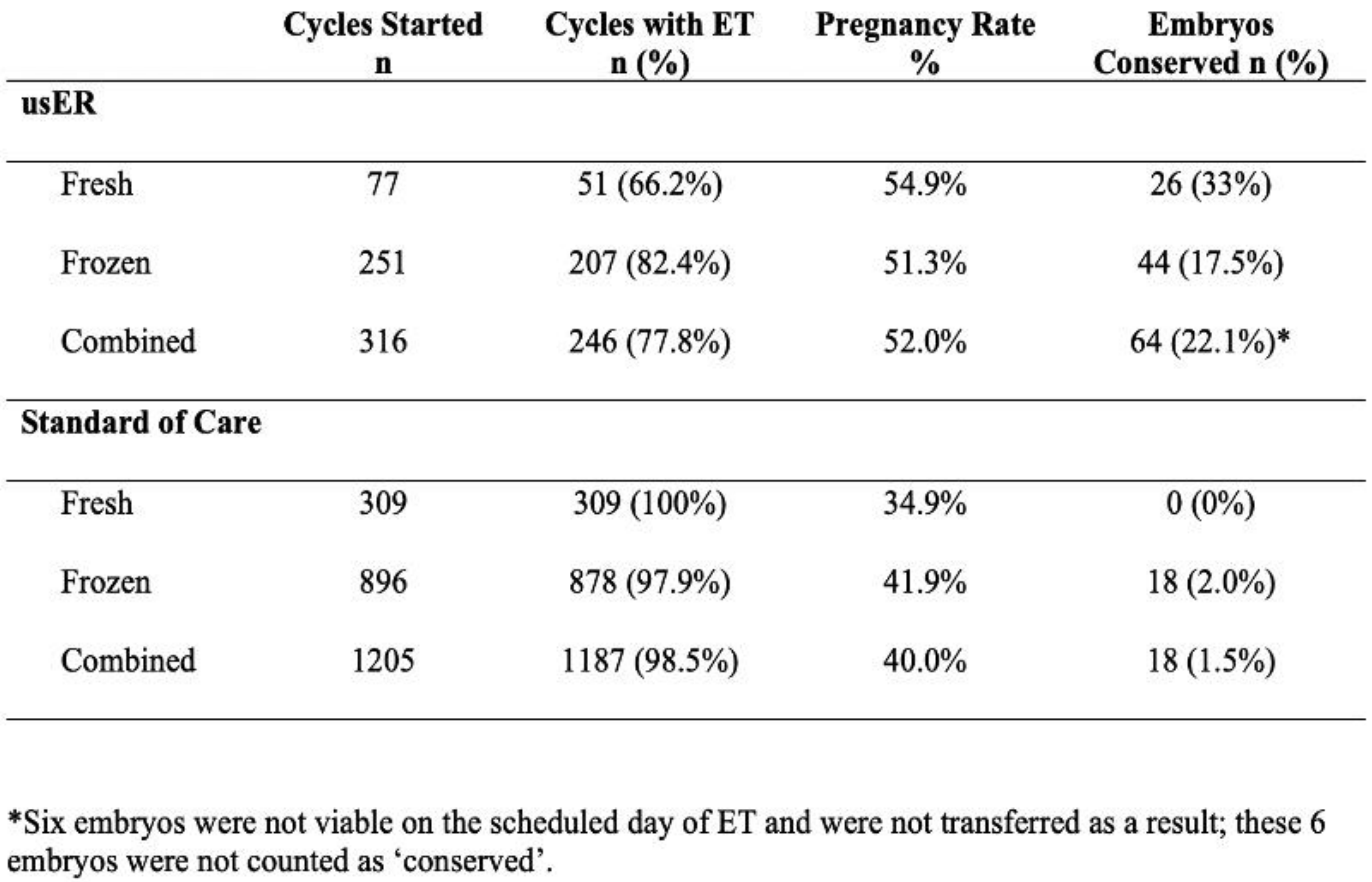
usER testing increased pregnancy rates in both fresh and frozen embryo transfer cycles





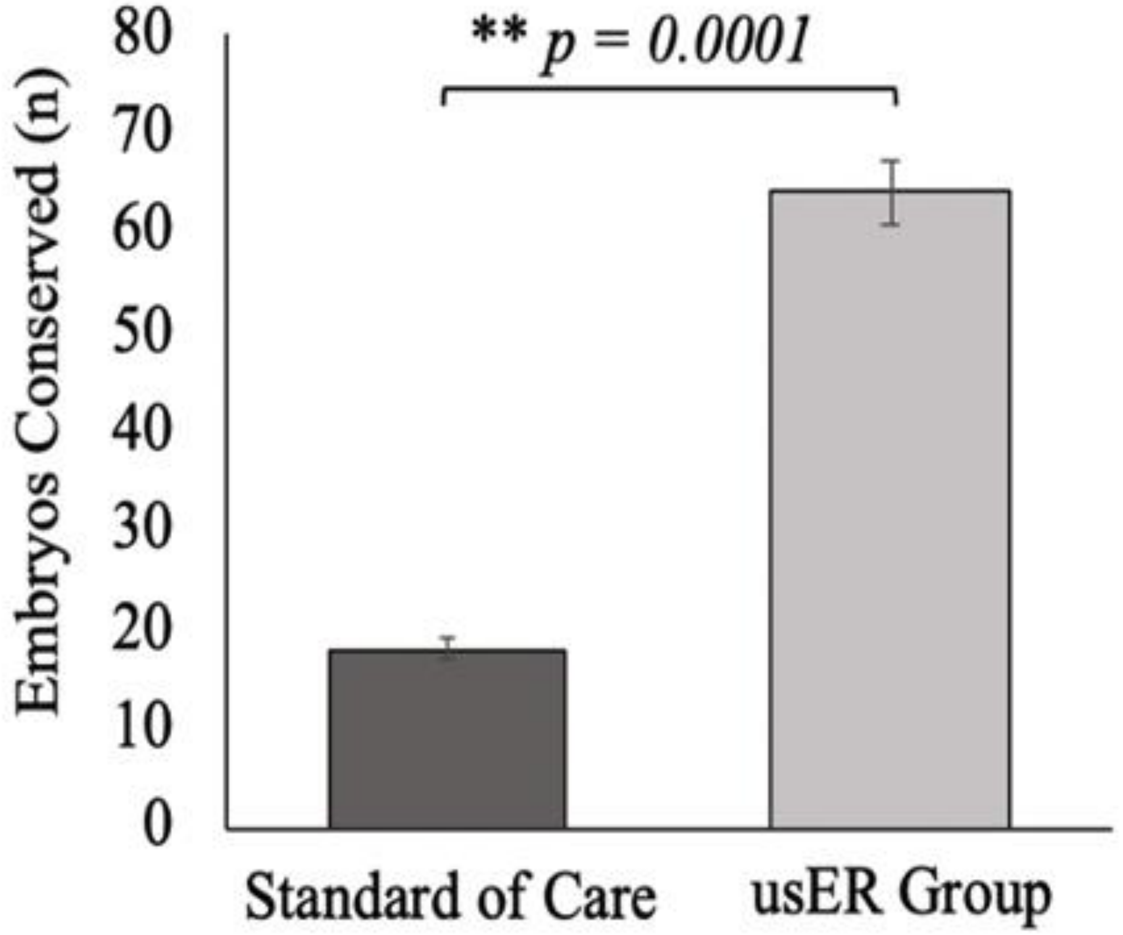
Pierson HE et al. (2022) J Fertilization: IVF World Wide, Vol. 9 Iss.6 No: 248

Routine usER testing facilitates conservation of embryos



	Cycles Started n	Cycles with ET n (%)	Pregnancy Rate %	Embryos Conserved n (%)
usER				
Fresh	77	51 (66.2%)	54.9%	26 (33%)
Frozen	251	207 (82.4%)	51.3%	44 (17.5%)
Combined	316	246 (77.8%)	52.0%	64 (22.1%)*
Standard of Care				
Fresh	309	309 (100%)	34.9%	0 (0%)
Frozen	896	878 (97.9%)	41.9%	18 (2.0%)
Combined	1205	1187 (98.5%)	40.0%	18 (1.5%)

*Six embryos were not viable on the scheduled day of ET and were not transferred as a result; these 6 embryos were not counted as 'conserved'.



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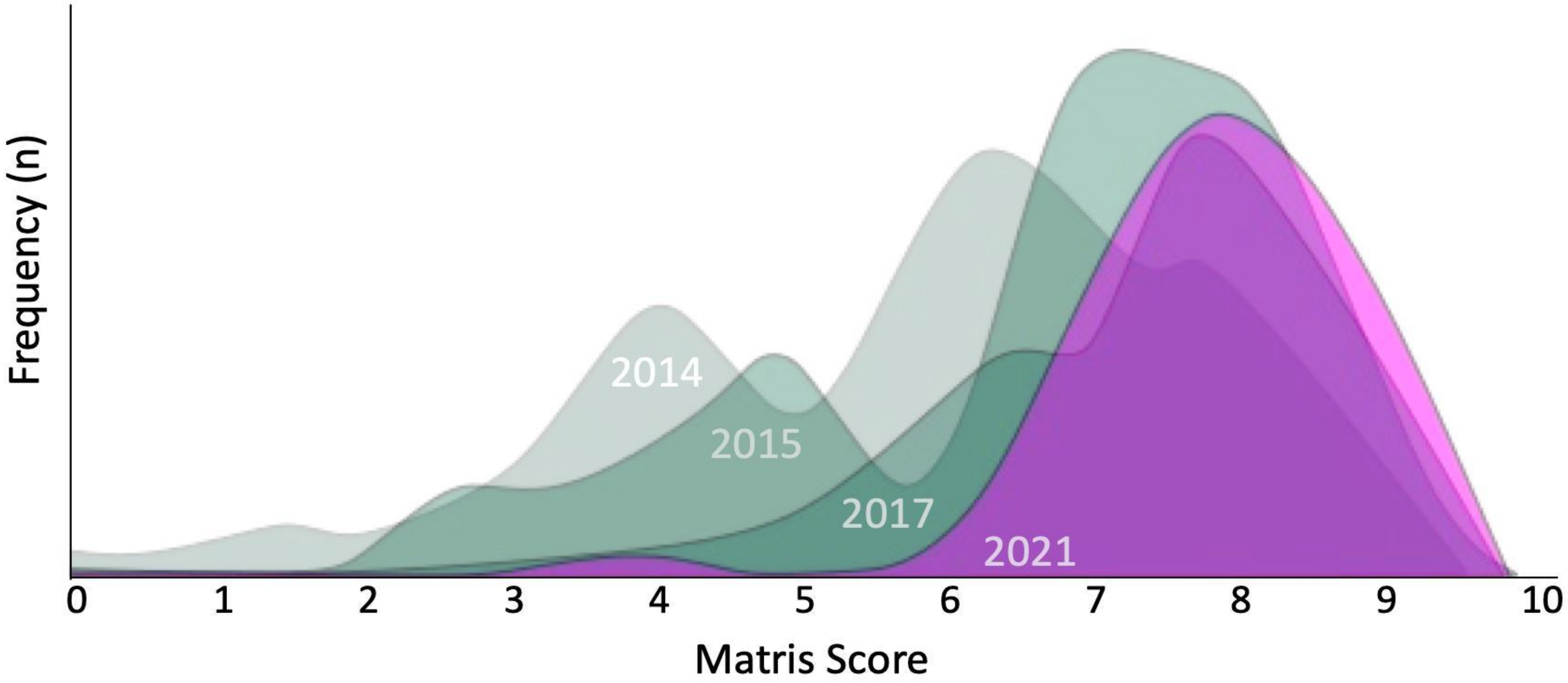
Routine usER use facilitates protocol refinement



Take Home Messages

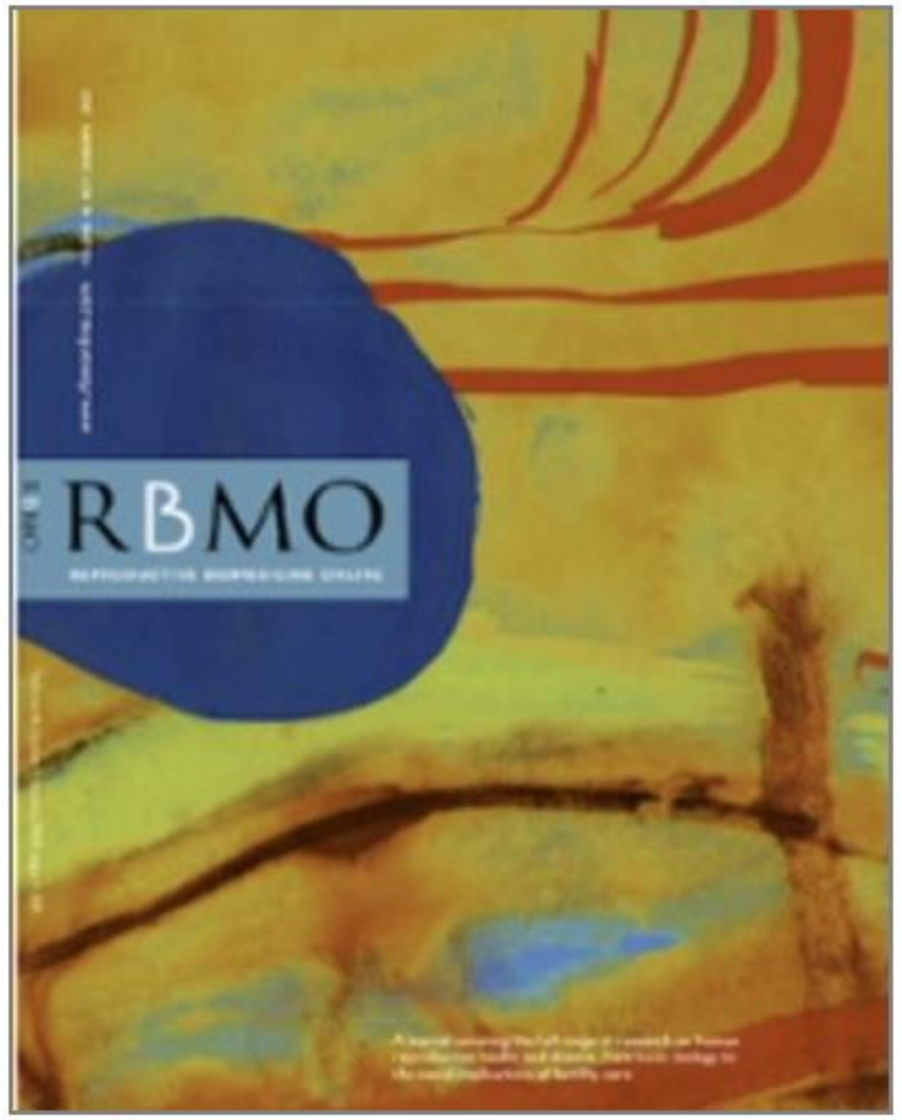
- usER is a real-time per-cycle tool to assess endometrial receptivity
- Approximately 25 % of first cycles will be recommended for deferral
- Chart review analysis of patient population (N = 2274) demonstrates that usER accurately identifies low-probability cycles
- Chart retrospective review (N=1521 cycles) showed significantly higher pregnancy rates among cycles selected for transfer with usER
- Embryos deferred from transfer into deficient endometrial environments may be conserved for future transfers
- Routine utilization of usER testing provides significant improvement to patient outcome

Integration of embryo quality into the equation.

ELSEVIER

Dear Dr. Pierson,

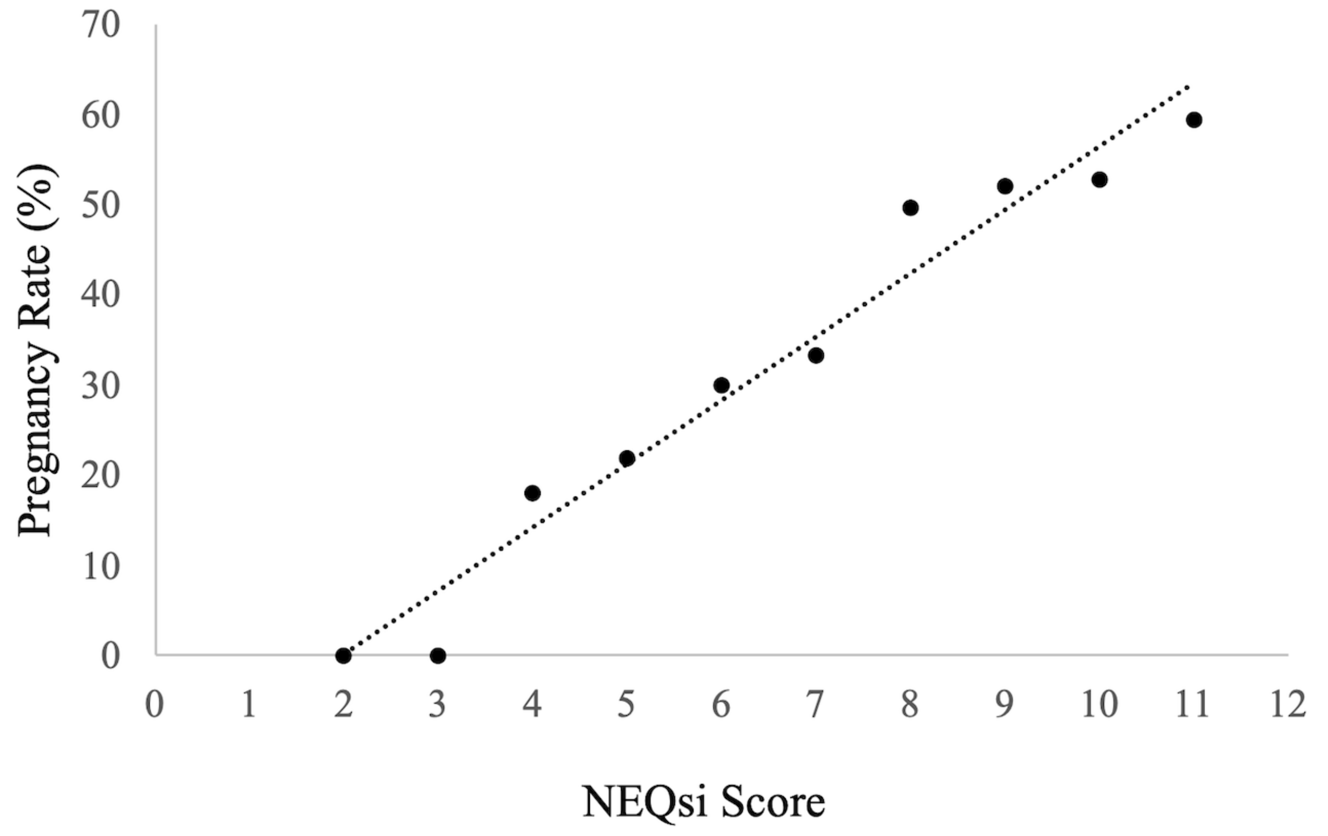
Your article *A novel system for rapid conversion of Gardner embryo grades to linear scale numeric variables* will be published in Reproductive BioMedicine Online.



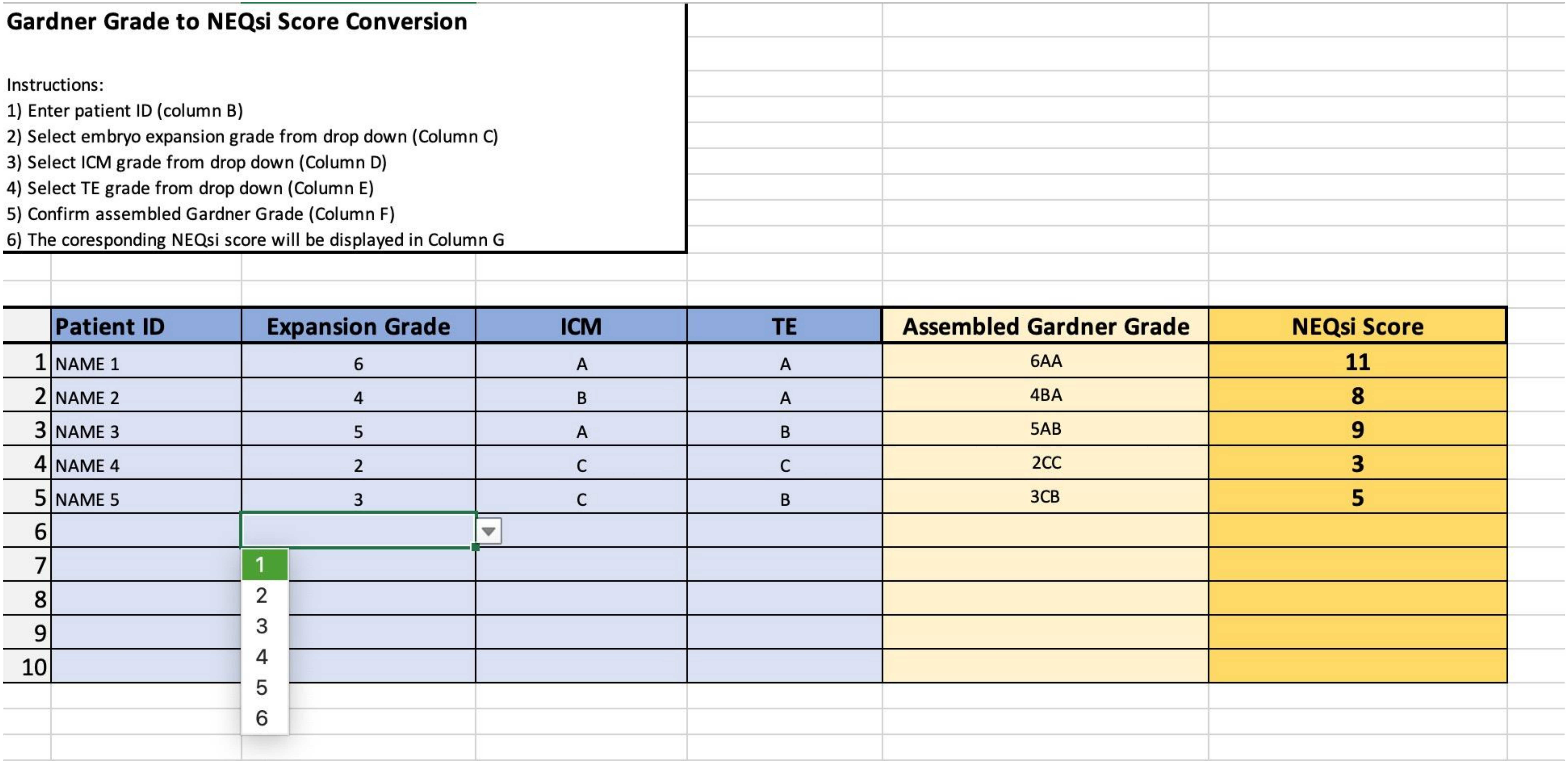
NEQsi Work-Flow

Process Step	Action	Example Embryo (6AA)
Step 1:	Retain number from Gardner's grade.	6
Step 2:	Conversion of letter portion of score.	AA = +5
Step 3:	Summation of results of steps 1 and 2. *Gardner # + AlphaCon = NEQsi Score*	6 + 5 = NEQsi score 11

AlphaCon		2nd Letter		
		A	B	C
1st Letter	A	AA +5	AB +4	AC +3
	B	BA +4	BB +3	BC +2
	C	CA +3	CB +2	CC +1



Pierson H, Invik J, Meriano J, Pierson RA (2023) RBMO *In Press*.



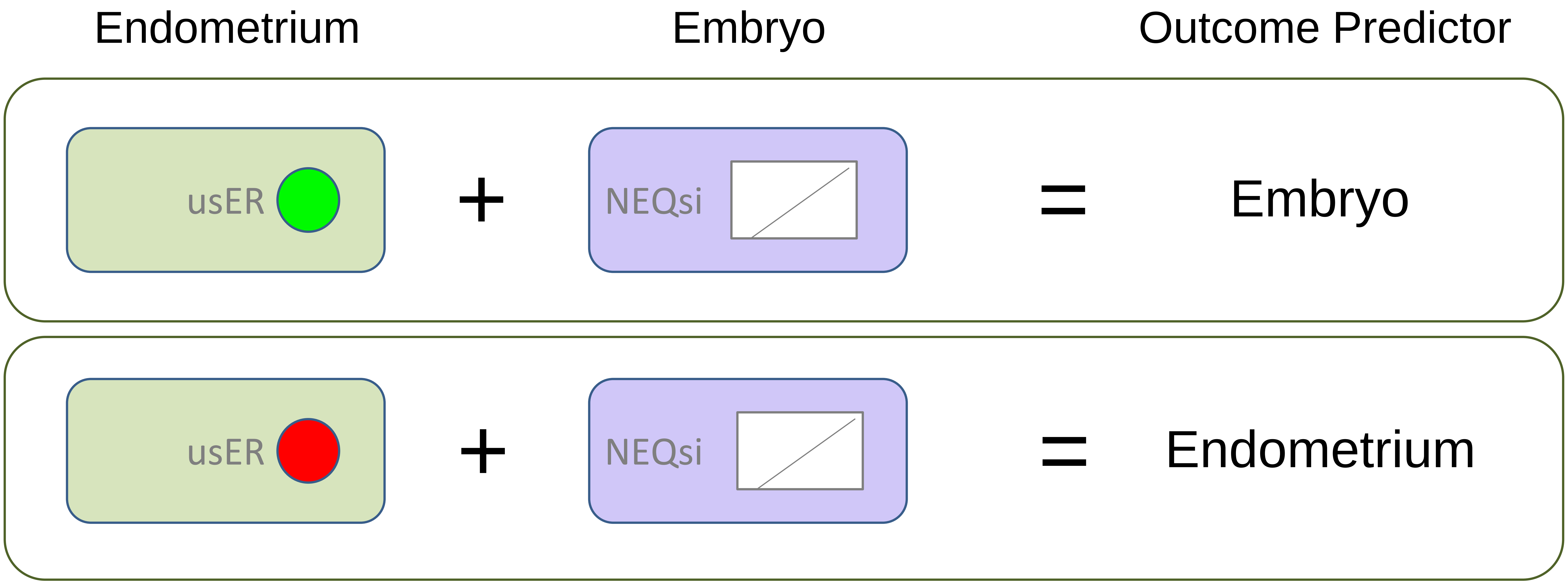
Gardner Grade to NEQsi Score Conversion

Instructions:

1) Enter patient ID (column B)
2) Select embryo expansion grade from drop down (Column C)
3) Select ICM grade from drop down (Column D)
4) Select TE grade from drop down (Column E)
5) Confirm assembled Gardner Grade (Column F)
6) The coresponding NEQsi score will be displayed in Column G

	Patient ID	Expansion Grade	ICM	TE	Assembled Gardner Grade	NEQsi Score
1	NAME 1	6	A	A	6AA	**11**
2	NAME 2	4	B	A	4BA	**8**
3	NAME 3	5	A	B	5AB	**9**
4	NAME 4	2	C	C	2CC	**3**
5	NAME 5	3	C	B	3CB	**5**
6						
7						
8						
9						
10						

Linking Embryo Quality and Endometrial Receptivity…



Endometrium		Embryo		Outcome Predictor
usER 🟢	+	NEQsi	=	Embryo
usER 🔴	+	NEQsi	=	Endometrium

Data driven decisions help clinics to respond to policy decisions and increase the quality of patient care

$$\left| f(x) \right|$$

Quality Embryo +

Receptive Endometrium +

Transfer Efficiency.

THANK YOU

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