Recurrent Implantation Failure: Where Evidence Meets Ambiguity

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Disclosure(s)

No Financial Disclosures

Objectives

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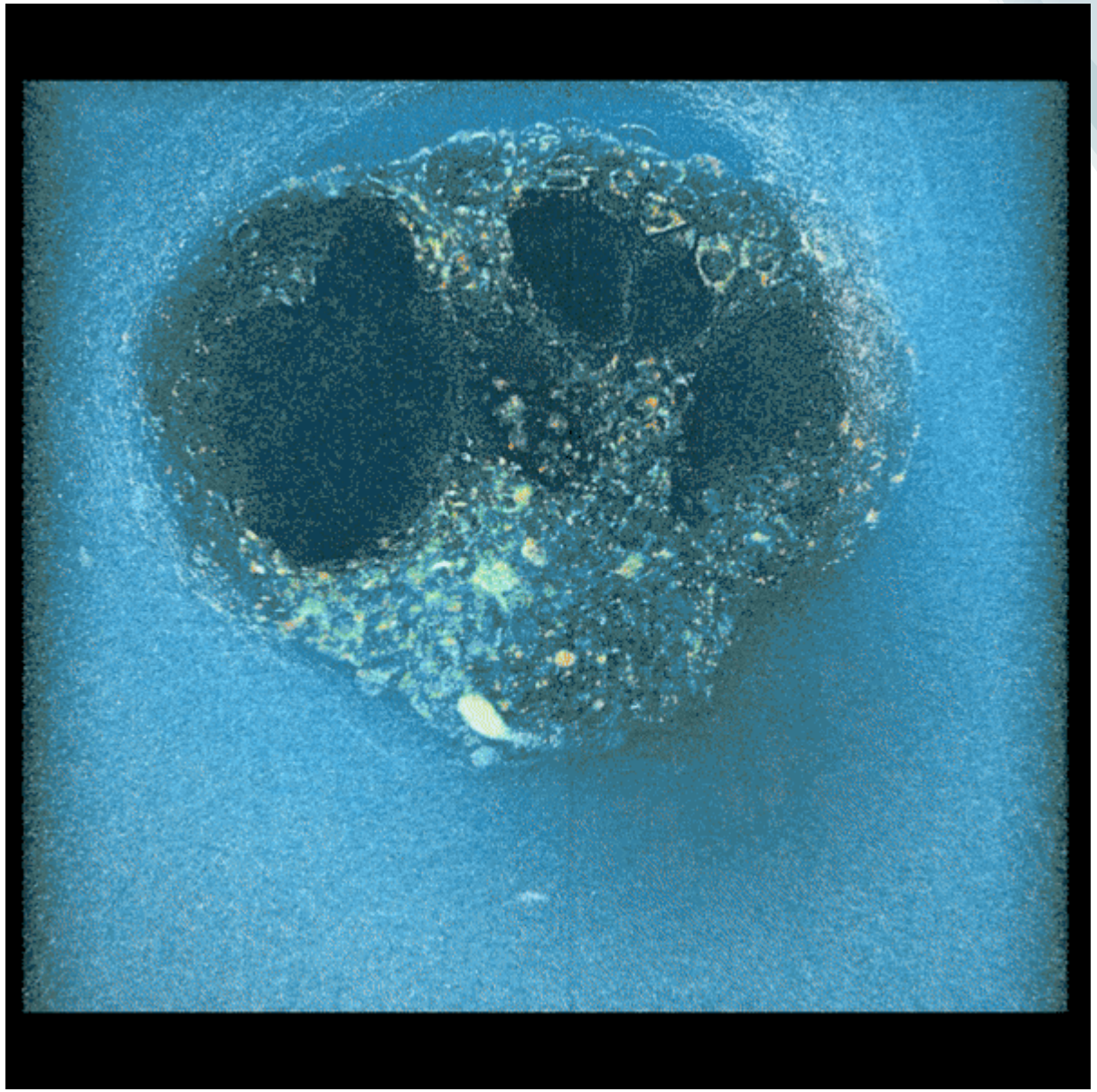
- To define recurrent implantation failure (RIF) using current consensus and understand challenges with the variability in existing definitions.
- Understand key factors that contribute to implantation failure.
- Employ evidence-based interventions for the management of RIF.



Godeau et al. Science Advances. 2025

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Definition

Implantation

Defined as attachment and penetration of a blastocyst into the endometrium

Several factors

(blast transfer, ultrasound guidance, etc)

have led to increased implantation rates

Zegers-Hochschild et al. F&S 2017

Recurrent Implantation Failure (RIF)

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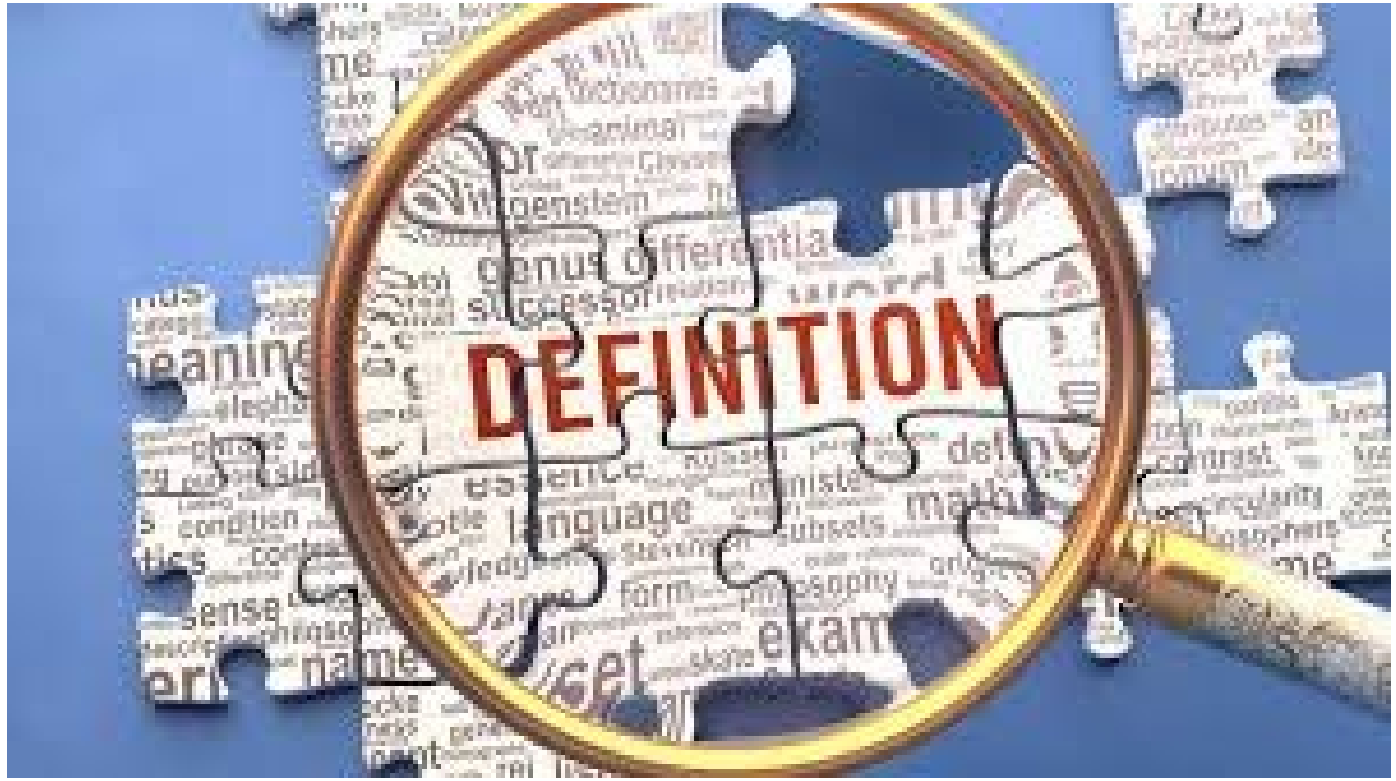
- A group who may be at risk of unsuccessful implantation following multiple embryo transfers has been defined
- …and redefined
- …and redefined…



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A Review of Previously Used Definitions

Wilton	2003	≥10 Cleavage Stage Embryos	No PGT
Coulam	2006	≥8 Cleavage Stage Embryos	No PGT
Coulam	2008	≥8 Cleavage Stage Embryos	No PGT
Goodman	2008	≥8 Cleavage Stage Embryos	No PGT
Sauer	2010	≥8 Cleavage Stage Embryos	No PGT
Coulam	2008	≥4-6 Cleavage Stage Embryos	No PGT
Firouzabadi	2009	≥5 Cleavage Stage Embryos	No PGT
Coulam	2006	≥4 Blastocyst Embryos	No PGT

Lugano Writing Group

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- A group of esteemed authors met in 2022 to discuss RIF

- RIF should be defined based on failure to achieve a gestational sac on US

Pirtea et al. F&S. 2021

Lugano (cont.)

- The consensus was to assign the diagnosis of RIF if patient failed:
  - at least 3 euploid embryo transfers
  - or the equivalent number of unscreened embryos, adjusted to age

TABLE 2

Estimation model for of the number of unscreened good-quality embryos needed to be equivalent to 3 successive euploid embryo transfers and achieve a 95% chance of sustained implantation on the basis of the observed aneuploidy rate (20).

Age (y)	Observed aneuploidy rate	No. of untested blastocysts to achieve a 95% chance of sustained implantation
<35	20%	4
35–37	30%	5
38–40	50%	7
41–42	70%	13
≥43	85%	27

Recurrent implantation failure. Fertil Steril 2023.

Recurrent implantation failure. F&S. 2023

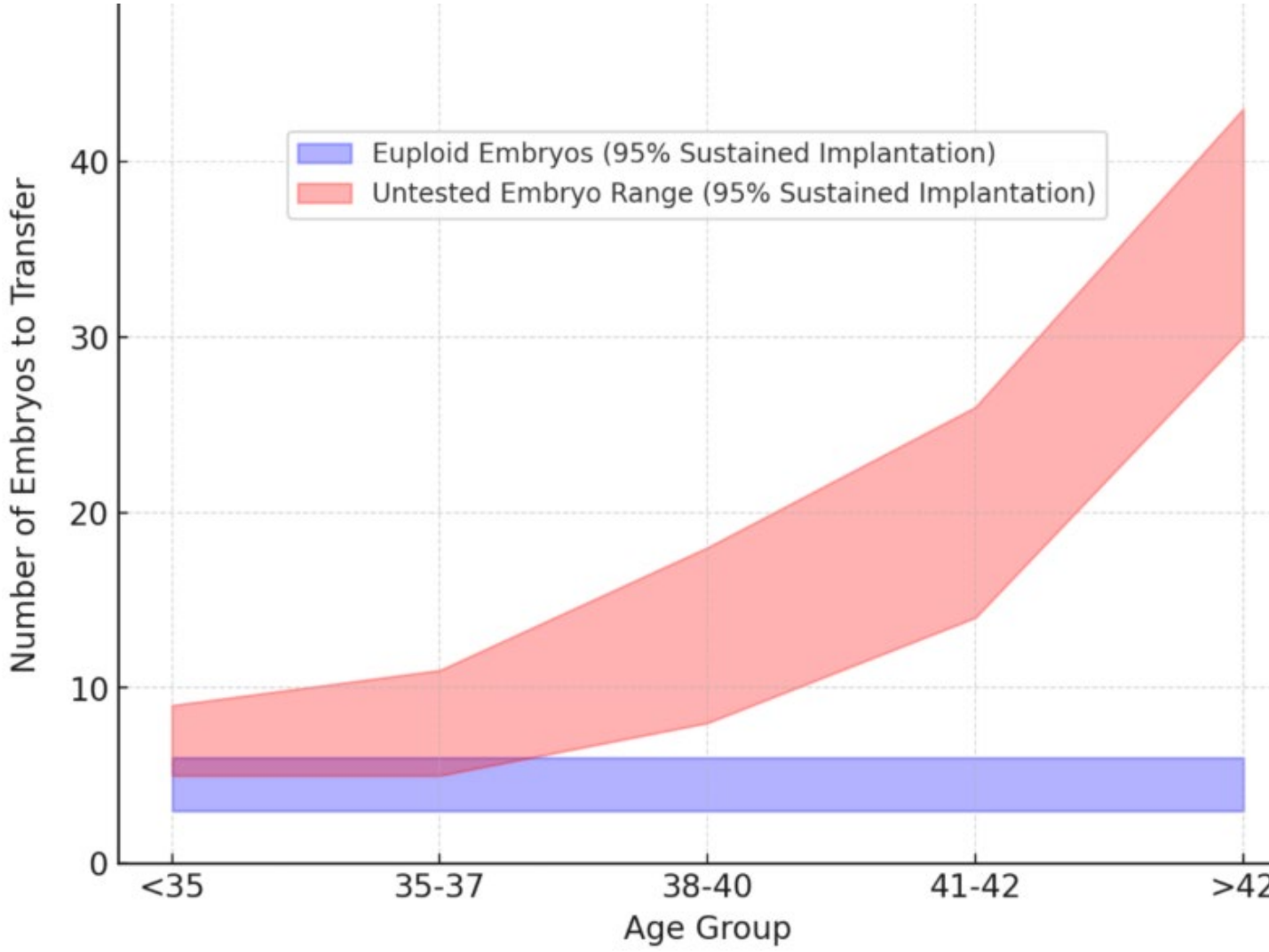
ASRM Definition

- Why a 2nd definition?
  - The definition established by ASRM greatly mirrors the Lugano writing group, and agrees with several factors (impact of age, risk of aneuploidy)
  - Implantation definition differs
- As recurrent pregnancy loss studies are now defined including biochemical pregnancies, our team greatly felt the definition should include only **negative HCG level cycles**

Zegers-Hochschild et al. F&S 2017

ASRM Definition

- RIF should be defined as the failed implantation of the estimated number of good-quality blastocysts to achieve a 95% cumulative chance of a **positive pregnancy test.**



Pirtea et al. F&S. 2023
Gill et al. Hum Reprod.2024
Ata et al. F&S. 2021
Franasiak et al. F&S. 2014

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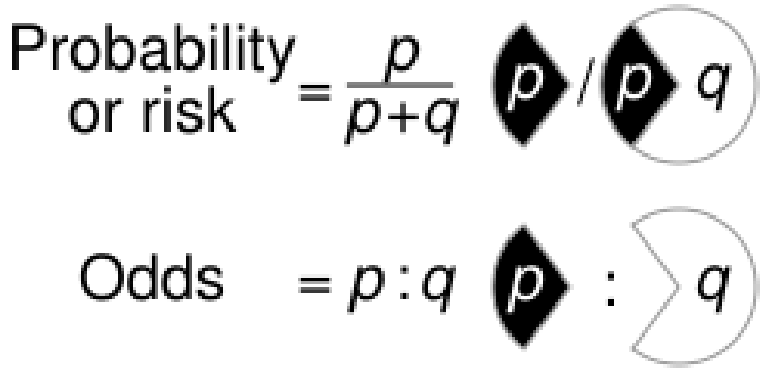
Implantation and euploidy rates were derived from studies of PGT-A with comprehensive chromosome analysis published until 2021. The estimates are merely theoratical and actual cumulative implantation rate may differ for each patient.	
I want to use my own data for euploidy rate	No
Age of woman at the time of oocyte collection	Euploidy rate
<35	0.65
35-37	0.55
38-40	0.35
41-42	0.25
>42	0.08
Euploid blastocyst implantation rate	0.6
RIF calculator	
VARIABLES	VALUES
Age category	<35
Were the blastocysts known to be euploid?	Yes, embryos were known to be euploid
Total number of blastocysts transferred	4
Threshold of expected cumulative implantation rate for diagnosing RIF (%)	95
Expected cumulative implantation rate (%)	95.899375
Patient status	Patient may have recurrent implantation failure

When a woman has received blastocyst which were derived from oocytes collected at different ages and/or blastocysts some underwent PGT-A and some not, expected cumulative implantation rates can be calculated separately for each scenario, i.e., using different age brackets, and blastocyst euploidy status (known euploid or untested), and the figures can be summed up to calculate expected cumulative implantation rate for that patient.

Ata et al. F&S. 2021

DOES RIF EXIST?

- Several studies have suggested that this may be a statistical aberration- that with enough treatment- all patients would conceive



- These studies often restrict the populations studied to well-screened patients, with normal endometrial measurements

Pirtea et al. Fert Stert. 2023
Gill et al. Hum Reprod. 2024

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Factors Affecting Implantation

Non-Modifiable Cycle Factors

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- Age
- Endometrium
- Day of Blastulation
- Blastocyst Progression
- Morphology

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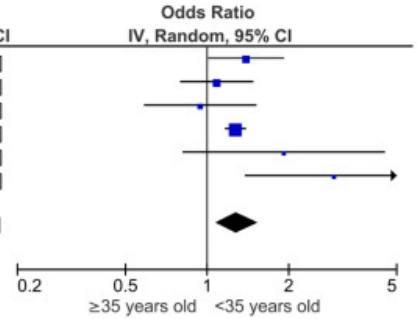
A

Study or Subgroup	<35 years old Events	Total	≥35 years old Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Harton et al 2013	134	233	209	424	18.7%	1.39 [1.01, 1.92]
Irani et al 2019	125	227	296	558	19.6%	1.08 [0.80, 1.48]
Munne et al 2019	75	152	62	122	10.9%	0.94 [0.59, 1.52]
Reig et al 2020	2368	3789	2488	4386	41.8%	1.27 [1.16, 1.39]
Whitney et al 2014	45	53	88	118	4.0%	1.92 [0.81, 4.53]
Yan et al 2021	452	577	16	29	5.0%	2.94 [1.38, 6.27]
Total (95% CI)		**5031**		**5637**	**100.0%**	**1.29 [1.07, 1.54]**
Total events	3199		3159			

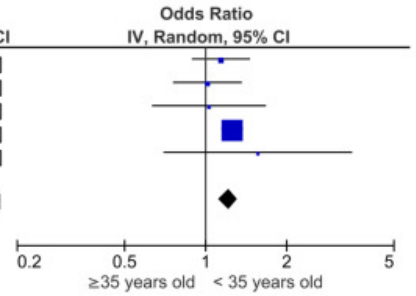
Heterogeneity: Tau² = 0.02; Chi² = 8.40, df = 5 (P = 0.14); I² = 40%
Test for overall effect: Z = 2.74 (P = 0.006)



B

Study or Subgroup	<35 years old Events	Total	≥35 years old Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Harton et al 2013	192	413	276	638	10.7%	1.14 [0.89, 1.46]
Irani et al 2019	144	255	345	615	7.6%	1.02 [0.76, 1.36]
Munne et al 2019	92	152	73	122	2.8%	1.03 [0.63, 1.67]
Reig et al 2020	2592	3789	2778	4386	77.9%	1.25 [1.14, 1.37]
Whitney et al 2014	64	73	132	161	1.0%	1.56 [0.70, 3.50]
Total (95% CI)		**4682**		**5922**	**100.0%**	**1.22 [1.12, 1.32]**
Total events	3084		3604			

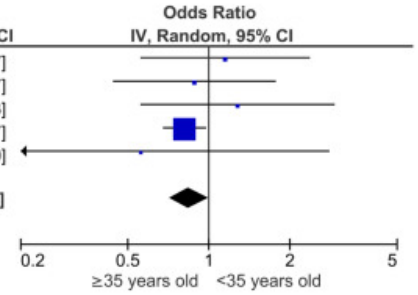
Heterogeneity: Tau² = 0.00; Chi² = 2.94, df = 4 (P = 0.57); I² = 0%
Test for overall effect: Z = 4.74 (P < 0.00001)



C

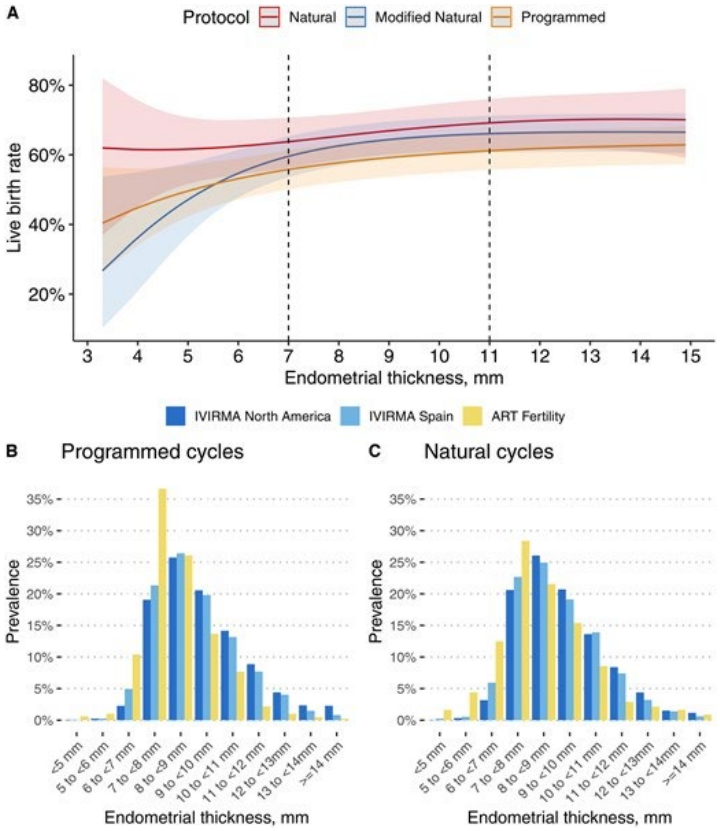
Study or Subgroup	<35 years old Events	Total	≥35 years old Events	Total	Weight	Odds Ratio IV, Random, 95% CI
Harton et al 2013	14	148	19	228	5.4%	1.15 [0.56, 2.37]
Irani et al 2019	12	136	32	324	5.8%	0.88 [0.44, 1.77]
Munne et al 2019	17	92	11	73	4.1%	1.28 [0.56, 2.93]
Reig et al 2020	224	2592	290	2778	83.7%	0.81 [0.68, 0.97]
Whitney et al 2014	2	47	7	95	1.1%	0.56 [0.11, 2.80]
Total (95% CI)		**3015**		**3498**	**100.0%**	**0.84 [0.71, 1.00]**
Total events	269		359			

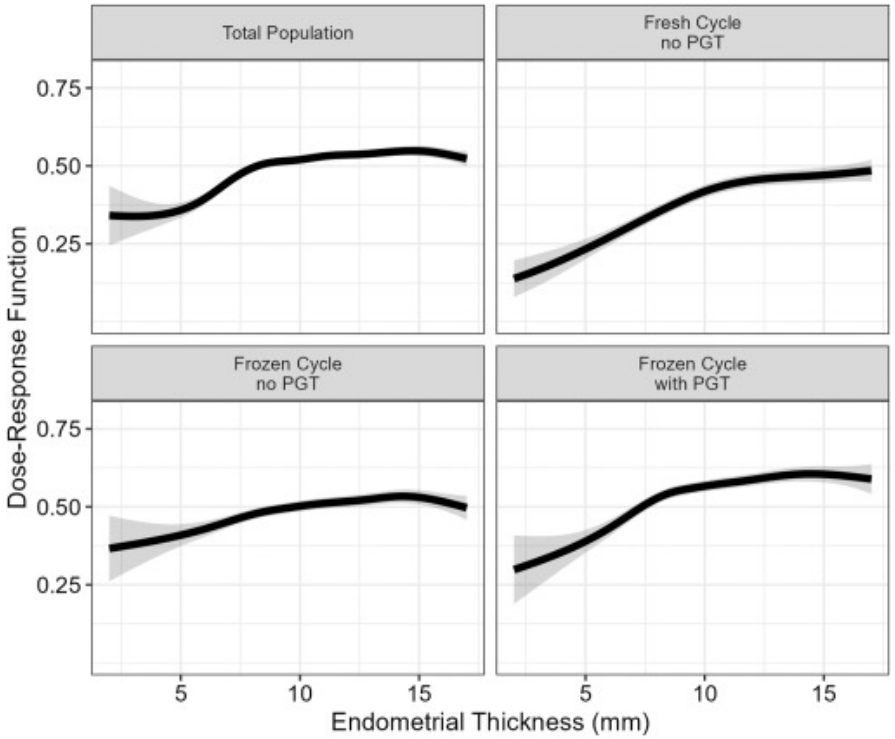
Heterogeneity: Tau² = 0.00; Chi² = 2.10, df = 4 (P = 0.72); I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)



Vitagliano et al. Fert Stert. 2023

Effect of Endometrial Measurement





Gingold et al. Fert Stert. 2025

Genovese et al. Hum Reprod 2025.

Day 5 vs 6…7?

Fig. 3 Euploidy rate by maternal age and day of biopsy

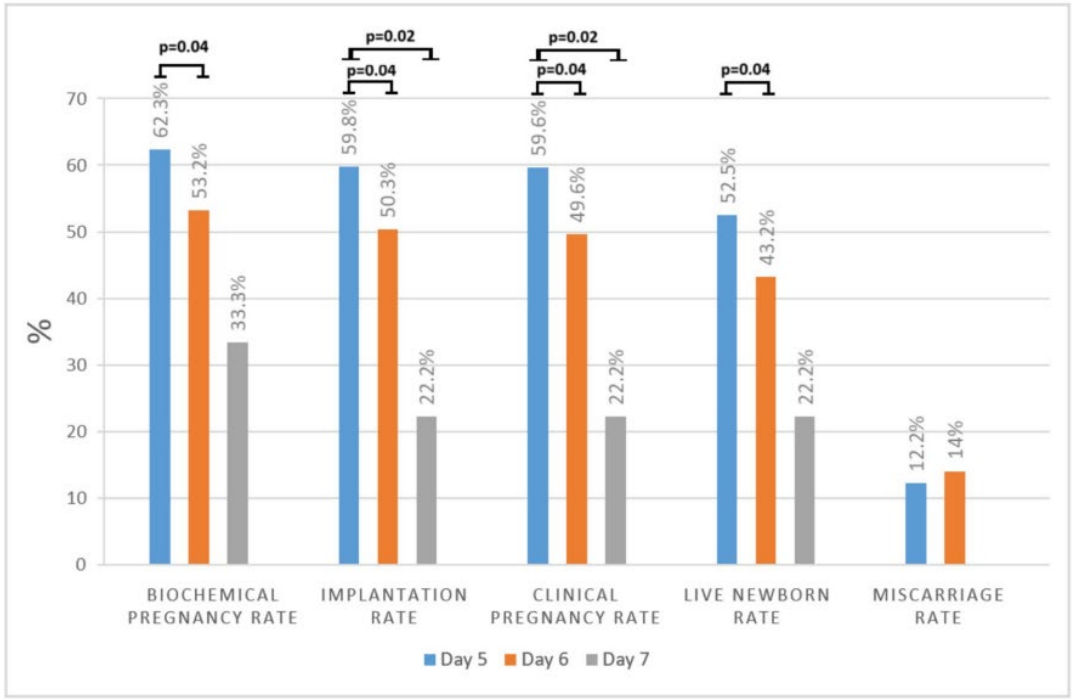


Table 2 Clinical outcomes following transfer of a euploid embryo biopsied on day 5 or day 6

	Day 5 biopsy ($N=353$) Referent	Day 6 biopsy ($N=198$)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Implantation rate	247 (70.0)	125 (63.1)	0.90 (0.80, 1.02)	n/a
Miscarriage rate	26 (7.4)	14 (7.1)	0.96 (0.51, 1.79)	0.98 (0.52, 1.83)
Ongoing pregnancy rate	231 (65.4)	112 (56.6)	0.86 (0.75, 1.00)	0.87 (0.75, 1.00)
Live birth rate*	137/220 (62.3)	61/123 (49.6)	**0.80 (0.64, 0.98)**	**0.81 (0.65, 1.00)**

Values represent *n* (%)

*Live birth data available for embryo transfers prior to May 1, 2021. Missing due to loss to follow-up prior to May 1, 2021 (day 5 biopsy = 1)

Relative risks adjusted for patient age and BMI

n/a = adjusted statistics were not performed since implantation rate was calculated as a pooled effect estimate

Of note, the 95% CI for adjusted RR for live birth rate is 0.65–0.996, which is significant. The unadjusted RR and Adjusted RR for ongoing pregnancy rate are not significant (95% CI for both: 0.75–1.003)

Gordon et al. JARG 2022
Abarca-Rodriguez et al. JARG 2025

Day 5 vs 6 continued

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TABLE 1
Baseline demographic, embryological, and genetic data of cycles included in the study

Baseline data	United States	European	*P* value
Demographic data			
Participants, n	6951	4382	-
Stimulation cycle procedures, n	7564	4555	-
Embryo transfer procedures, n	9828	5487	-
Mean female age at the time of stimulation cycle (SD)	35.0 ± 4.1	36.5 ± 5.6	<.001
Mean female age at the time of embryo transfer (SD)	35.4 ± 4.0	38.8 ± 3.9	<.001
BMI female, mean (±SD)	26.8 ± 5.9	23.2 ± 4.1	<.001
AMH (ng/mL), mean (±SD)	3.8 ± 4.1	2.6 ± 3.6	<.001
Endometrial thickness, mean (±SD)	9.3 ± 1.8	9.2 ± 4.4	.18
Cycle data			
Retrieved oocyte(s), mean (±SD)	17.7 ± 11.2	13.7 ± 7.2	<.001
MII oocyte(s), mean (±SD)	13.5 ± 8.7	11.2 ± 5.7	<.001
2PN zygote(s), mean (±SD)	11.2 ± 7.4	8.6 ± 4.6	<.001
Biopsied embryo(s), mean (±SD)	5.8 ± 3.8	4.5 ± 2.9	<.001
Embryological data			
Day 5, % (95% CI)	38.2% (37.3%–39.2%)	74.1% (73.0%–75.3%)	<.001
Day 6, % (95% CI)	57.9% (56.9%–58.9%)	25.5% (24.3%–26.6%)	
Day 7, % (95% CI)	3.9% (3.5%–4.3%)	0.4% (0.3%–0.6%)	

Gill et al. AJOG. 2025 (online)

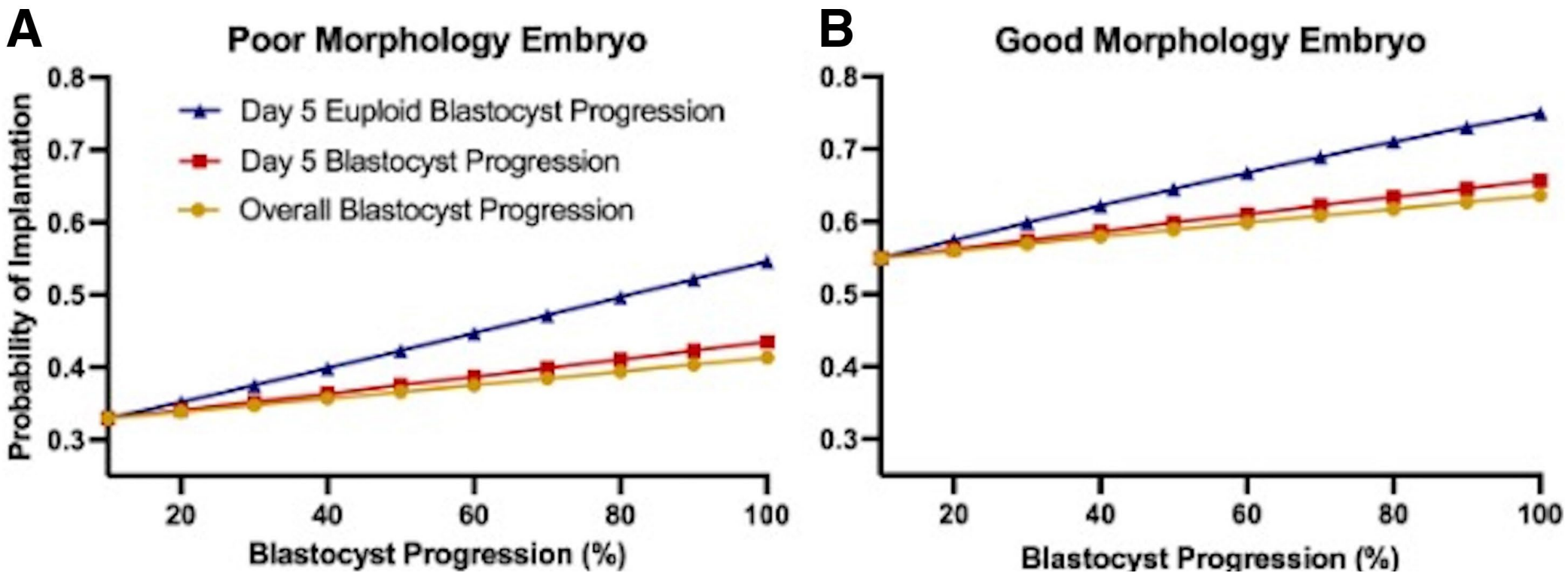
Table 5. Pregnancy outcomes in live birth cycles, stratified by the female age and day of cryopreservation.

Female age (years)		Day 4	Day 5	Day 6	Day 7	P-value
<35	ET cycles, n	9	656	226	6	
	Live birth, n (%)	7 (77.8)[a]	401 (61.1)[a]	64 (28.3)[b]	0 (0)[b]	<0.0001
35–37	ET cycles, n	14	839	298	10	
	Live birth, n (%)	6 (42.9)[a,b]	389 (46.4)[b]	68 (22.8)[a]	1 (10.0)[a]	<0.0001
38–40	ET cycles, n	15	1147	431	13	
	Live birth, n (%)	7 (46.7)[a]	384 (33.5)[a]	74 (17.2)[b]	0 (0)[b]	<0.0001
41–42	ET cycles, n	6	817	403	18	
	Live birth, n (%)	2 (33.3)[a]	169 (20.7)[a]	20 (5.0)[b]	1 (5.6)[a,b]	<0.0001
>42	ET cycles, n	9	709	481	29	
	Live birth, n (%)	1 (11.1)[a,b]	57 (8.0)[a]	16 (3.3)[b]	1 (3.5)[a,b]	0.0079

ET: embryo transfer.
[a,b] Different superscript letters indicate a significant difference at $P < 0.05$.

Coticchio et al. Human Reproduction 2023.

Does Blastocyst progression rate matter?



Huang et al. Fert Stert. 2025

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TABLE 2 DISTRIBUTION OF EMBRYO MORPHOLOGY AND DAY OF BIOPSY

	Primary analysis (n = 229 embryos)	Secondary analysis (n = 203 embryos)
Day 5 good (AA/AB/BA)	48 (21)	42 (21)
Day 5 fair (BB/CB)	86 (38)	74 (36)
Day 5 poor (BC/CC)	33 (14)	30 (15)
Day 6 good (AA/AB/BA)	3 (1)	2 (1)
Day 6 fair (BB/CB)	17 (7)	15 (7)
Day 6 poor (BC/CC)	42 (18)	40 (20)

Data are given as n (%).

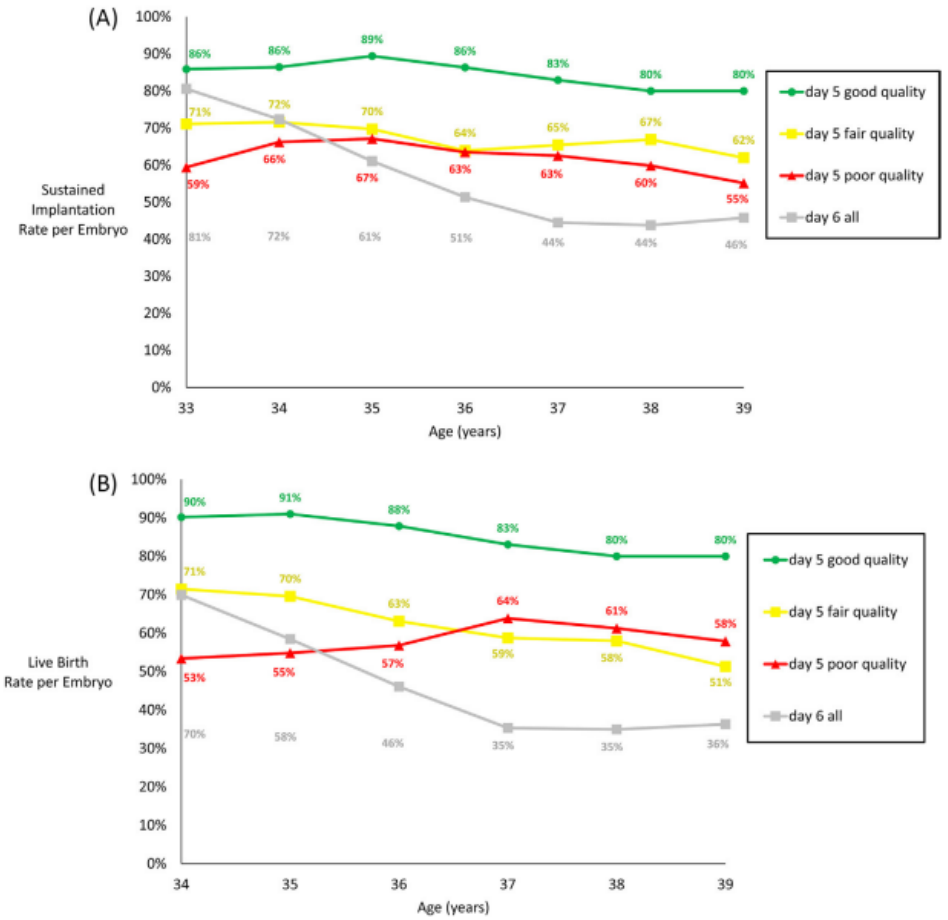
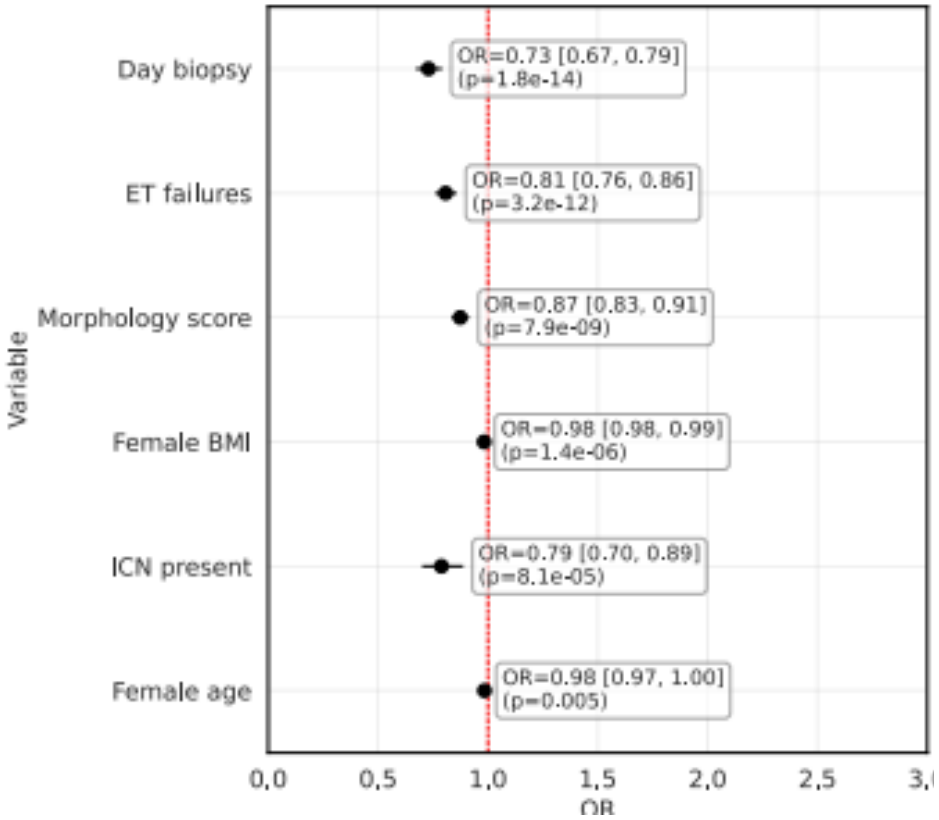


FIGURE 2 (A) Primary analysis of best-fit sustained implantation rates per embryo and (B) secondary analysis of best-fit live birth rates per embryo. Nine-year moving age groups are used for data analysis. Linear interpolation is used to centre the outcome rates on each integer of age.

Awadalla et al. RBMO 2021

Morphology (and Day) continued

A



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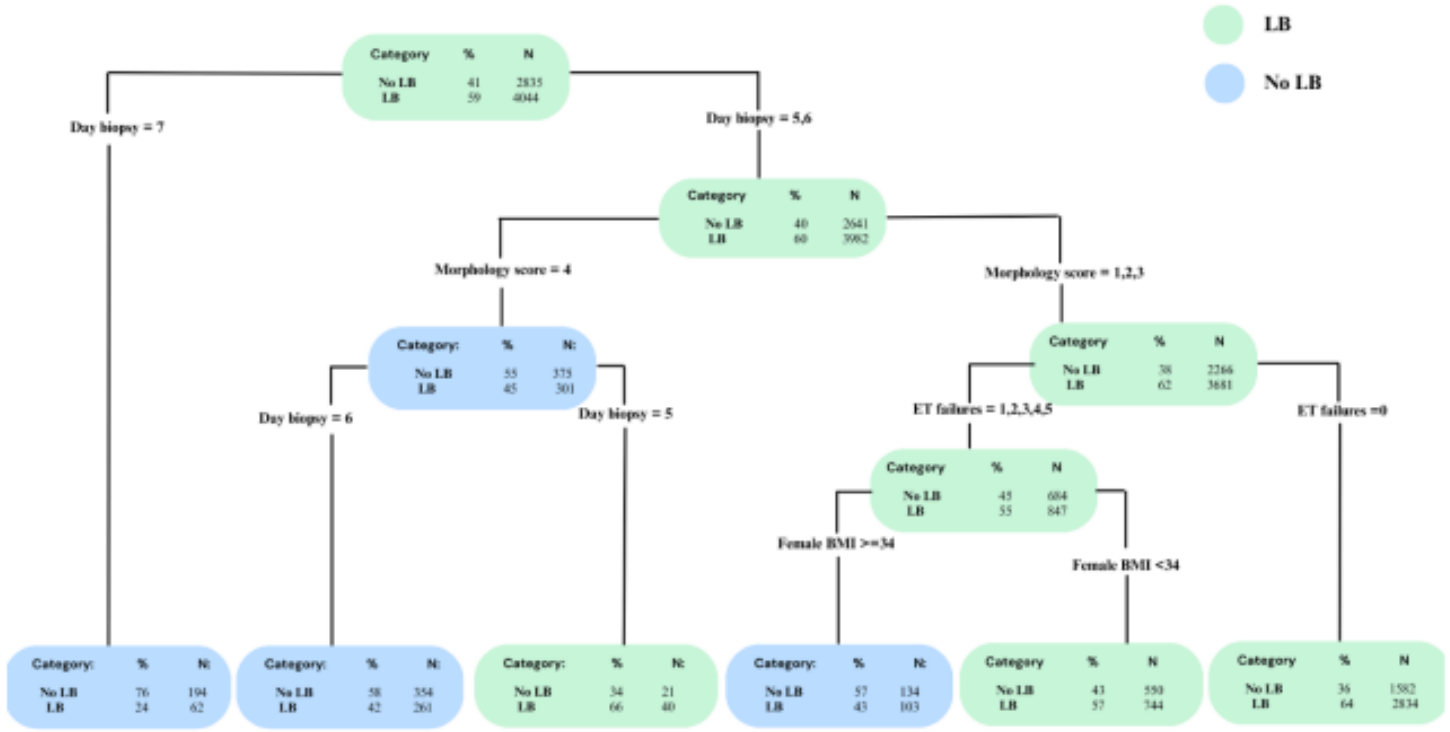

Gill et al. AJOG. 2025 (online)

Summary of Risks

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- Age affects implantation, even of euploid embryos
- Try to optimize size of endometrial lining- at least to 6mm, but higher increases success
- Counsel patients on possible decreased success on day 6-7 embryos, low blast progression
- Morphology matters- even in euploidy (Good >Fair and Poor?)

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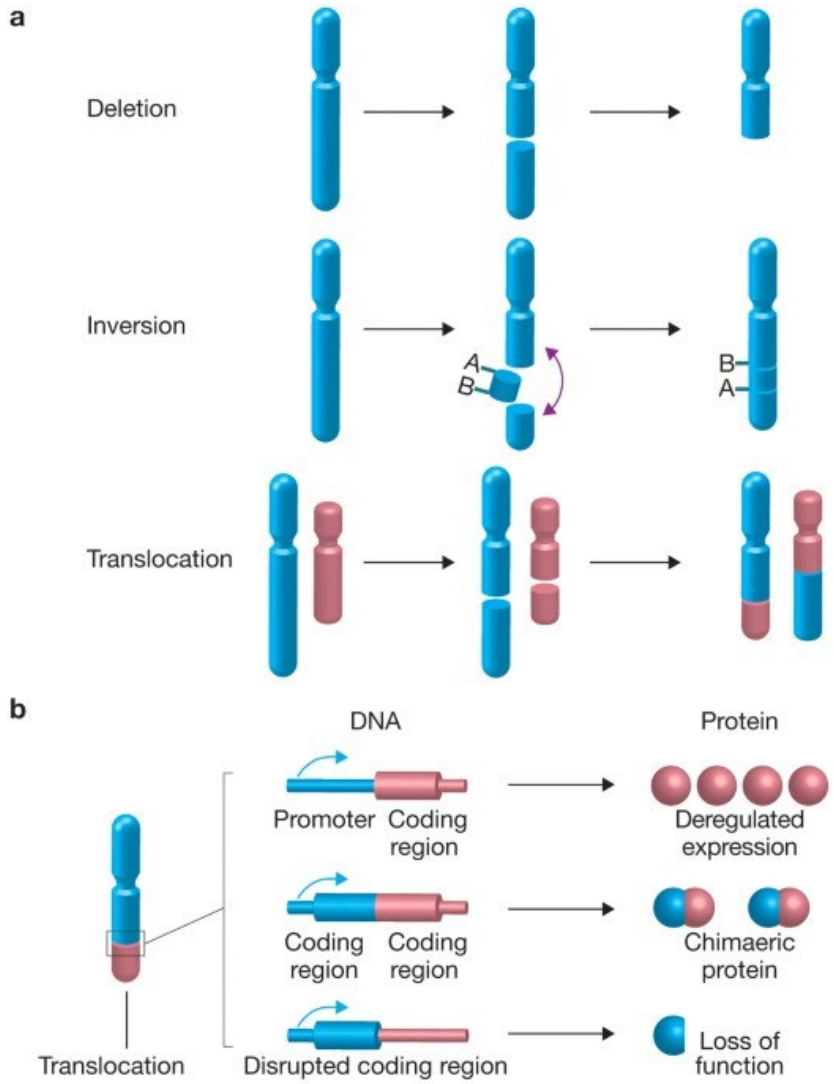
Possible Interventions for RIF

PGT-A

- Aneuploidy is a known cause of treatment failure
- No study has demonstrated a benefit of PGTA in RIF
- Consider this with shared-decision making with patients- but its not evidence based

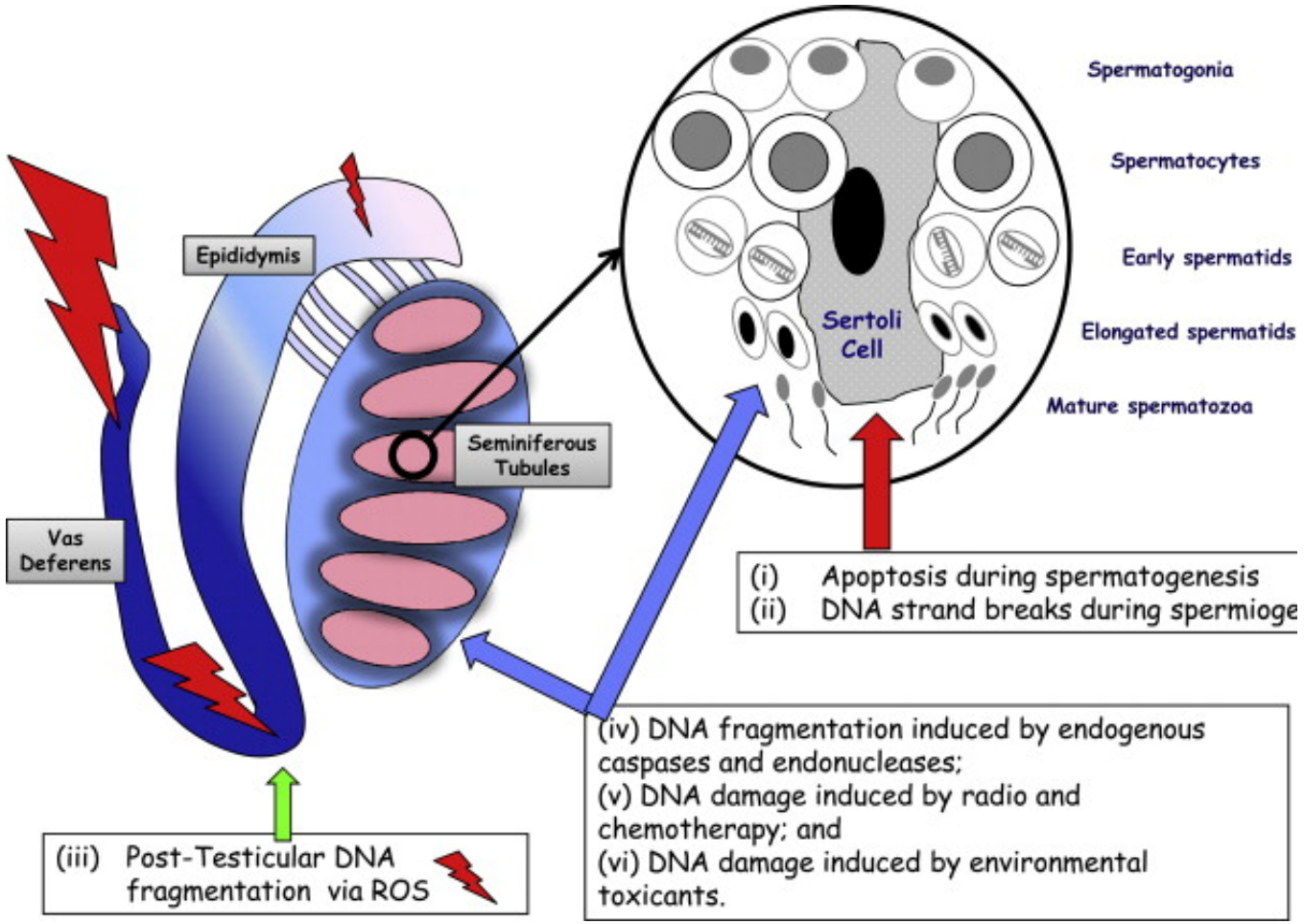
Parental Chromosome Abnormalities



Raziel et al. Fert Stert. 2002
Va Dijk. Hum Reprod Update. 2020
Stern et al. Hum Reprod. 1999
Coughlan et al. J Obstet Gynaecol. 2013

Sperm DNA Frag

- Small study suggested no benefit of testing DNA fragmentation in RIF patients.
- There are changes to possible treatment and testing.
- There is no current data to suggest a role for this testing in RIF patients.



Sakkas et al. Fert Stert. 2010

Cavity (Re)Evaluation

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- Endometrial cavity evaluation prior to embryo transfer is a well-established
- Treat the pathology!
- There is conflicting data on repeating cavity evaluation for RIF patients.
- Reasonable to consider this (no data that HSC is superior)

Difficult Transfers

ASRM PAGES

Performing the embryo transfer: a guideline

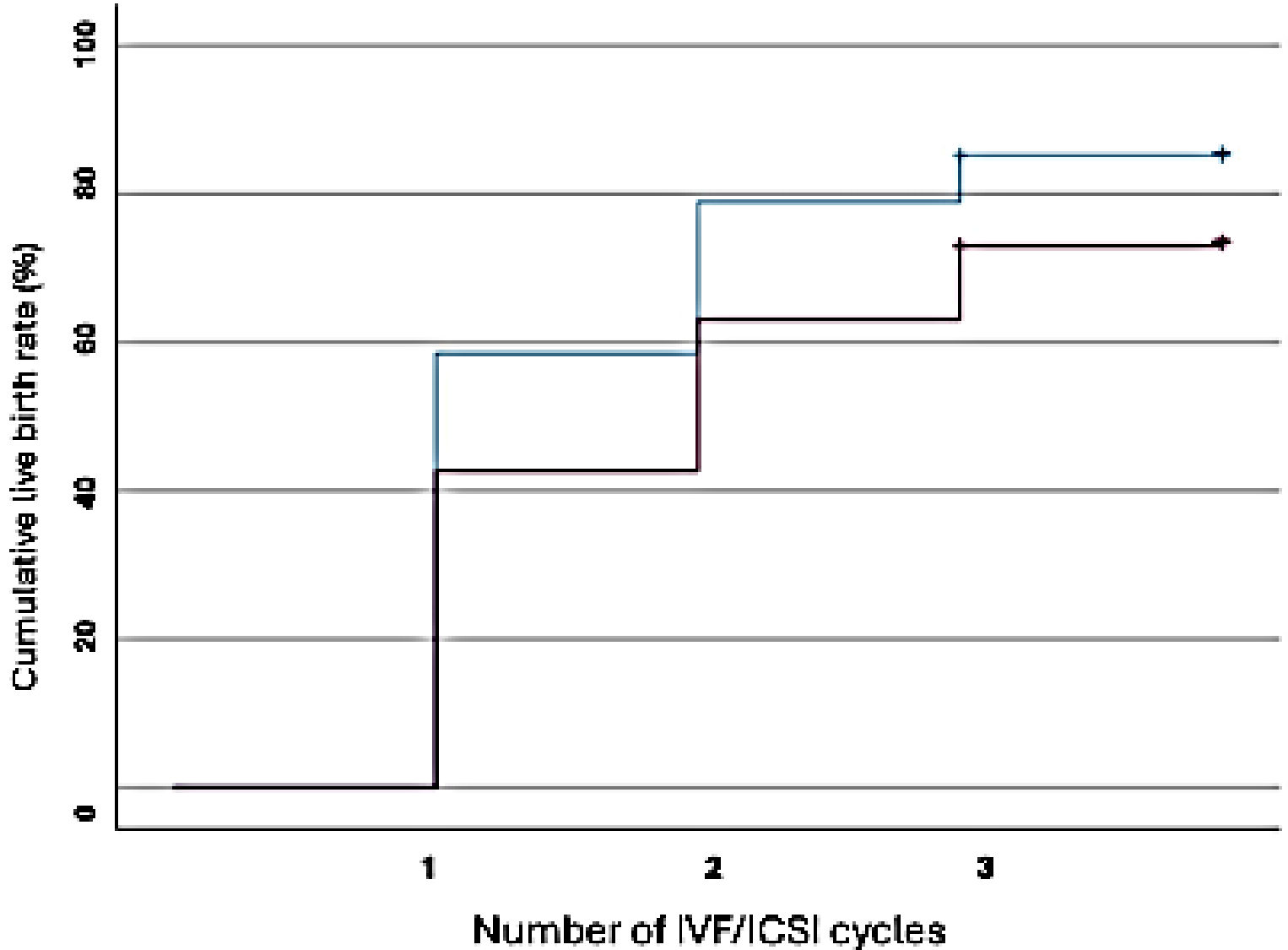
Practice Committee of the American Society for Reproductive Medicine

The following interventions are supported by the literature for improving pregnancy rates:

- Abdominal ultrasound guidance for embryo transfer
- Removal of cervical mucus
- Use of soft embryo transfer catheters
- Placement of embryo transfer tip in the upper or middle (central) area of the uterine cavity, greater than 1 cm from the fundus, for embryo expulsion
- Immediate ambulation once the embryo transfer procedure is completed

Practice Committee. Fert Stert. 2017
Galati et al. Sci Rep. 2023

Endometriosis and Adenomyosis



Alson et al. Human Reprod. 2025

Endometriosis and Adenomyosis

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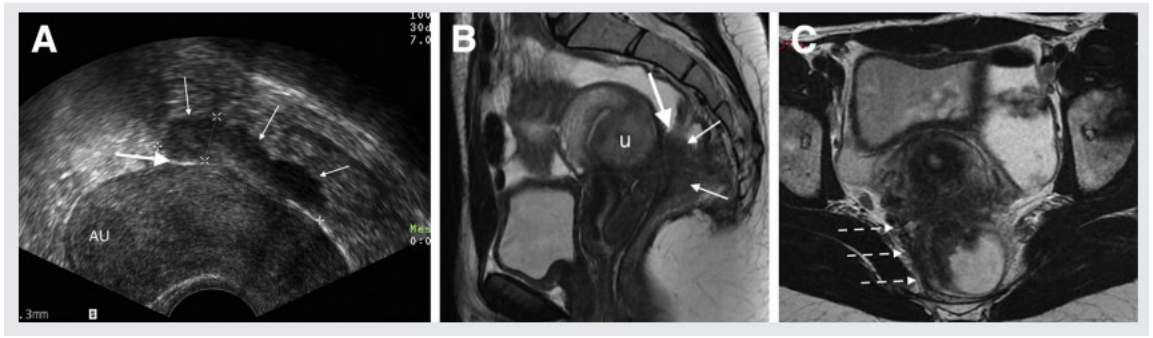
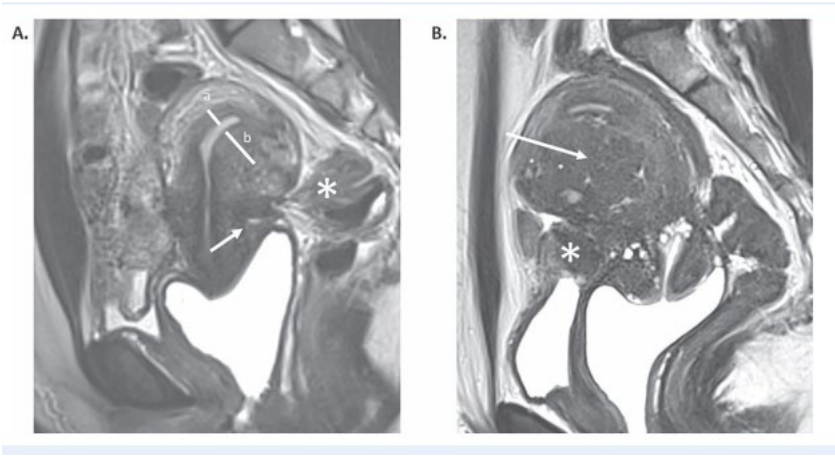
- Diagnosis modalities have evolved- yet surgical diagnosis remains the gold standard.
- Women with endo and infertility benefit from GnRH agonist or surgery.
- Reasonable to extrapolate this to RIF? adenomyosis?

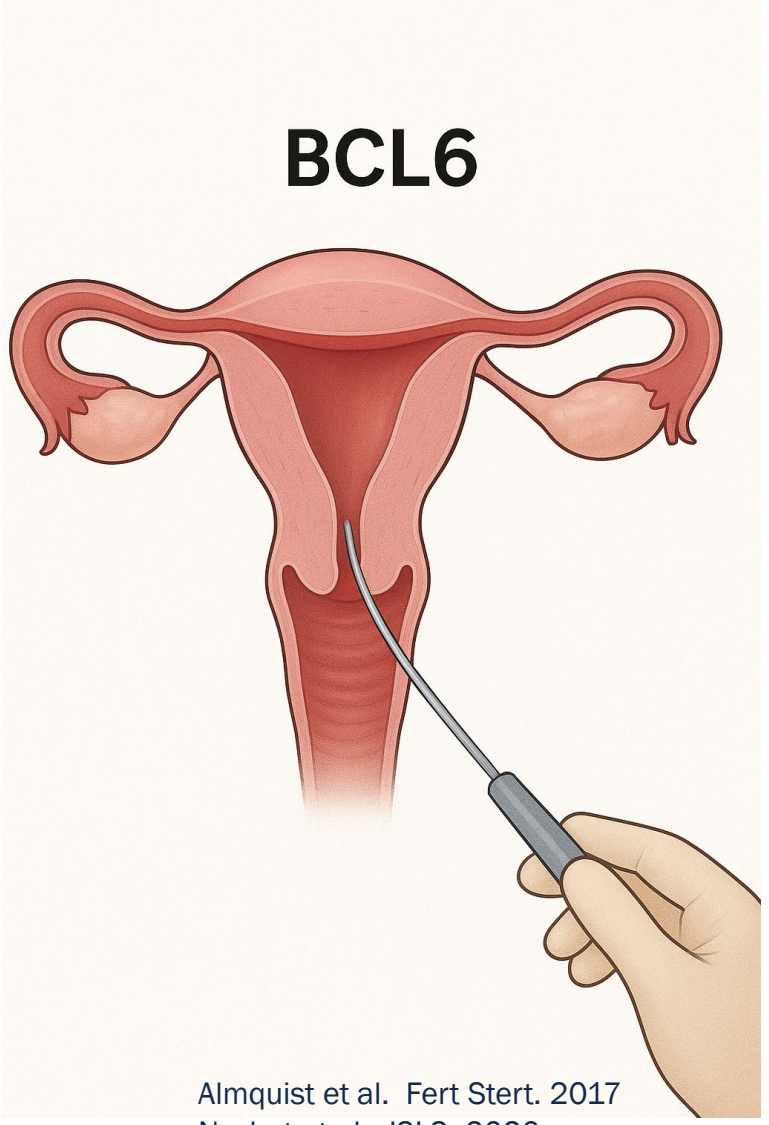




Bazot et al. Fert Stert. 2017
Chapron et al. Hum Reprod. 2020
Hodgson et al. Fert Stert. 2020

BCL6 Testing

- BCL-6 is known oncogene thought to be upregulated with endometriosis
- Testing for endometrial presence on BCL-6 has been marketed as a method to detect endometriosis, PR, CE
- A positive test prompts consideration of hormonal suppression



Almquist et al. Fert Stert. 2017
Nezhat et al. JSLS. 2020

BCL-6 for RIF?

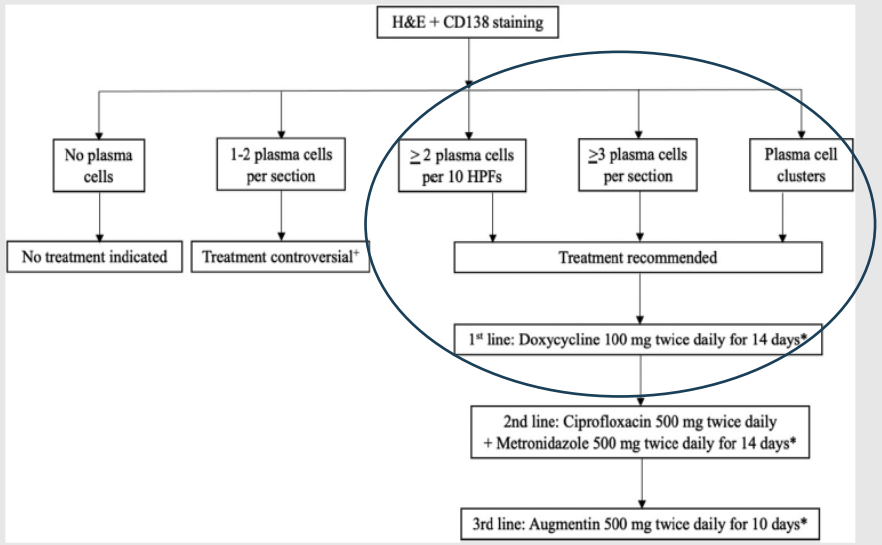
- One study suggested high correlation with a + BCL-6 and laparoscopy, and higher LBR with treatment
- Does progesterone interfere with BCL-6?
- A small case-control demonstrated no association with +BCL-6 and increased IR/LBR
- Given conflicting data on BCL6- its not ready for RIF primetime.

Likes et al. JARG. 2019
Huang et al. Fert Stert. 2023
Klimczaket al. Fert Stert. 2022

Chronic Endometriosis

- Chronic endometritis has long been studies as a possible cause of RIF
- Like RIF- little agreement on diagnostic criteria of CE
- Systematic review- antibiotics and TOC?
- Luteal biopsy

FIGURE 1



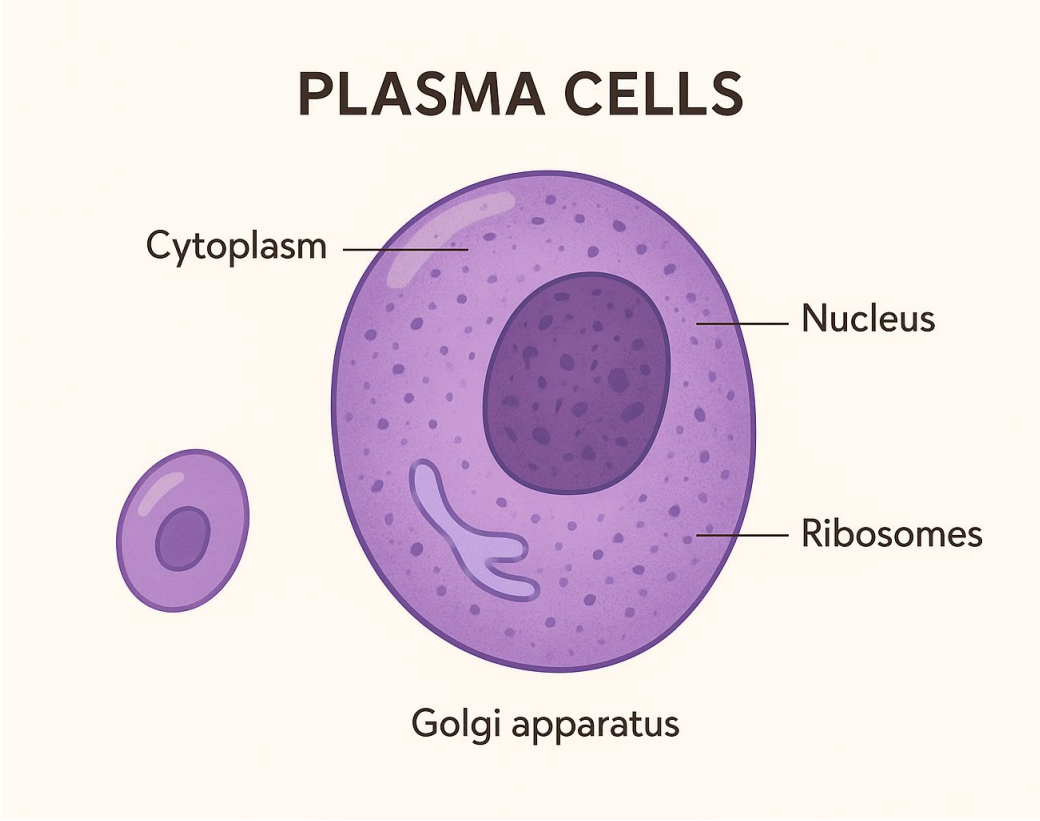
Algorithm for Evaluation and Treatment of Chronic Endometritis. CD138 staining is used as a guide to identify plasma cells and treatment is performed on the basis of plasma cell counts using criteria as outlined. +Consider in the setting of risk factors for chronic endometritis, *Test-of-cure recommended after completion of treatment. H&E = hematoxylin and eosin; CD138 = immunohistochemical staining for syndecan-1; HPFs = high powered fields.

Strug. Chronic endometritis and fertility. F S Rev 2024.

Vitagliano et al. Diagnostics. 2022
Cheng et al. JARG. 2022
Strug. F S Rev. 2024

Chronic Endometritis

- Taken together, the data suggests it reasonable to test CE in RIF patients
- Antibiotic treatment is warranted
- Studies lack true consensus on a test of cure



Strug. F S Rev. 2024

Endometrial Receptivity for Implantation failure

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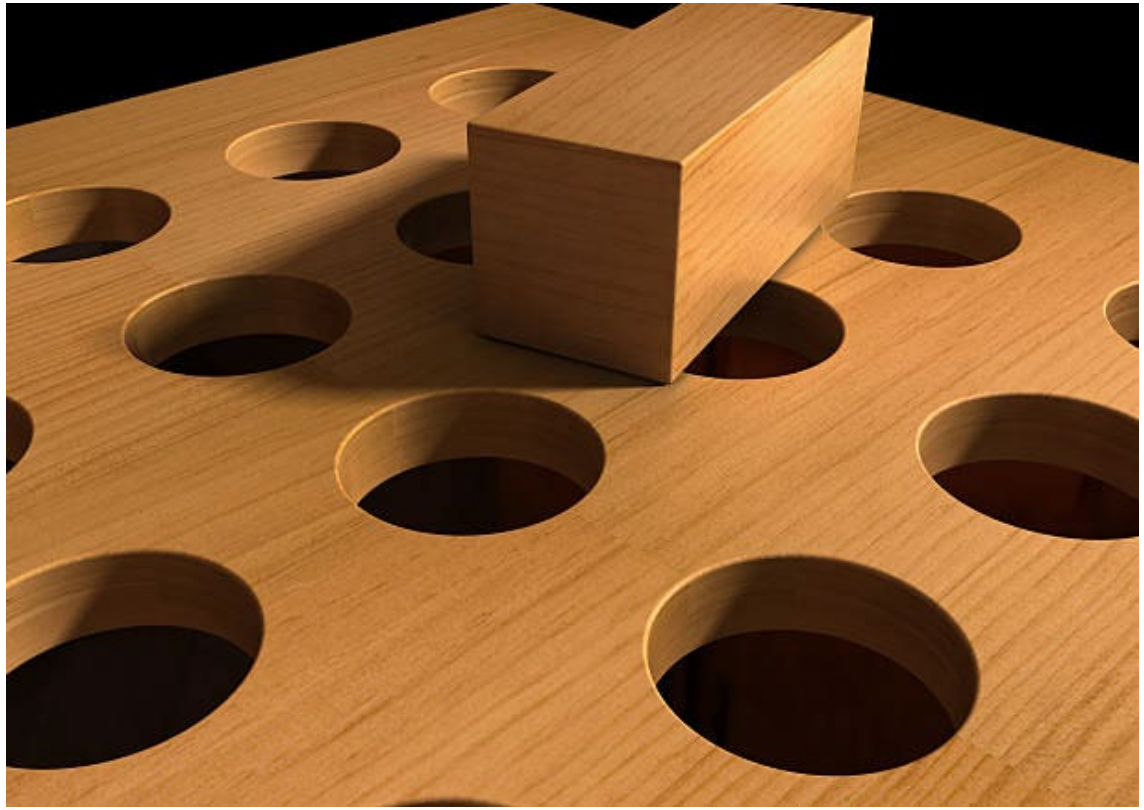
- Two randomized controlled trials have demonstrated no improvement in LBR with endometrial receptivity testing
- A secondary analysis demonstrated an AUC of 0.52 as a test to diagnose implantation failure
- BUT- they did not include women with >2 failed transfers

Simon et al. RBMO 2020
Doyle et al. JAMA 2022
Chae-Kim et al. F&S 2023

Analyses of Endometrial Receptivity in RIF

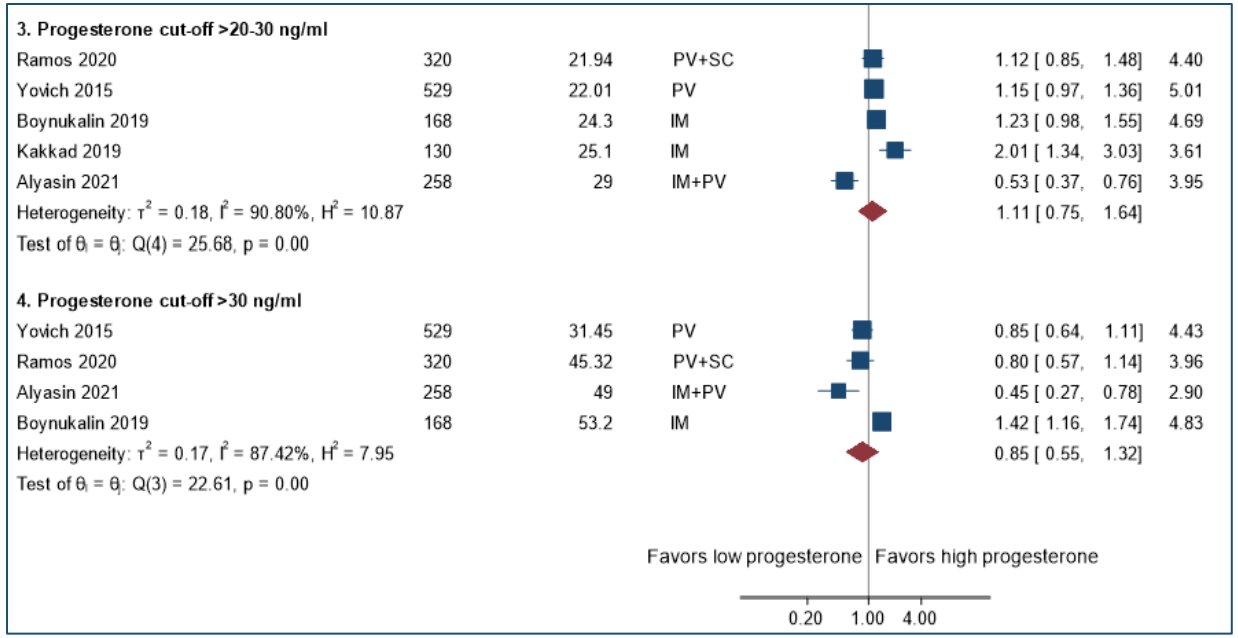


- Studies (as expected) vary with RIF definition
- A meta-analysis of studies that used >2 previous failures demonstrated no benefit of test in next transfer.
- “personalized” --- maybe is time to weigh this test and growing data vs our vow to do no harm

Arian et al. F&S 2023
Raff et al. F&S 2022

Testing Progesterone Levels

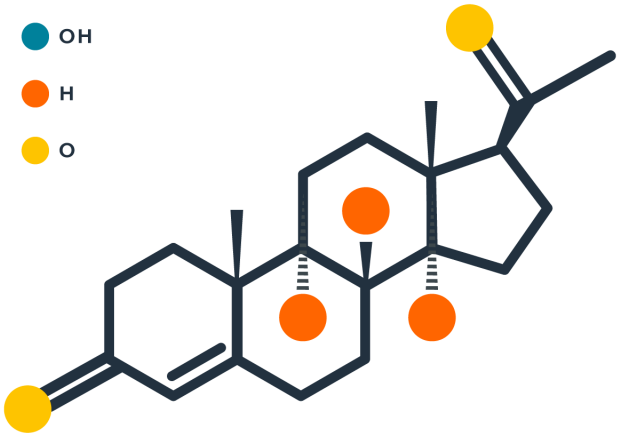
- A large meta-analysis suggested progesterone levels may impact FET success
- Only 3 of the studies included IM progesterone use with varying outcomes



Melo et al. Fert Stert. 2021

Progesterone

- For frozen embryos- data from the Devine et al RCT demonstrates PIO IM (at least q3) is superior
- Interestingly, this study measured P4 levels 2 weeks after FET
- Finding the vaginal progesterone only cohort was more likely to have progesterone levels below 9 ng/ml when compared to IM cohorts



PROGESTERONE

Devine et al. Fert Stert. 2021

Immunomodulators/Add-Ons

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- One RCT looked at installation of G-CSF into endometrial cavity in RIF patients- no difference in outcomes
- PRP- several studies have been performed, but to date- do not suggest a role in RIF patients
- Other add-ons (lovenox/heparin, IVIG, TNF-alpha inhibitors) also have not demonstrated efficacy in RIF patients

Kalem et al. Sci Rep. 2020.
Katsika et al. Hum Reprod. 2025.
Santiago et al. Reprod Biol. 2021

Diet/Smoking/Weight loss

- Smoking has previously been demonstrated to decrease implantation rates
- Studies suggest obese women have decreases in implantation and live birth as BMI rises
- Three RCTs have demonstrated that weight loss for these patients does not increase chance of success in fertility treatments
- More work is needed (GLP1)- but little data is present for these items with regards to RIF

Practice Committee ASRM. Fertil Steril. 2021
Practice Committee ASRM. Fertil Steril. 2024

Clinical Scenario	Possible Testing/Intervention	Considerations
Testing and treatment to consider after detailed history and review of IVF cycles when RIF is suspected		
Structural causes	Endometrial cavity assessment with SHG, hysteroscopy (HSC), or 3D US.	Imaging studies (SHG and 3D US) offer ability to screen for pelvic abnormalities (i.e. hydrosalpinx), while HSC may offer concomitant treatment of pathology and co-testing for CE.
Genetic	Parental karyotypes for structural chromosomal rearrangements	
Inflammatory	Testing and treatment for chronic endometritis	May be considered, although evidence is inconclusive for improvement in live birth rate and cannot routinely recommend.
	GnRH agonist or aromatase inhibitor estradiol suppression in women with endometriosis or adenomyosis	May be considered, although evidence is inconclusive and cannot routinely recommend.
Not currently recommended		
Sperm	DNA fragmentation	Lack of evidence showing improvement in live birth in RIF population.
Endometrial	Endometrial receptivity panels	Lack of evidence showing improvement in live birth in RIF population.
	BCL-6 testing	Lack of evidence showing improvement in live birth in RIF population.
	Endometrial scratching	Lack of evidence showing improvement in live birth in RIF population.
Immunologic	IVIG	Lack of evidence showing improvement in live birth rate in RIF population.
	G-CSF	Lack of evidence showing improvement in live birth rate in RIF population.
	Heparin or Lovenox	Lack of evidence showing improvement in live birth rate in RIF population.

Future of RIF

- Debating of definition likely to continue- but closer to agreed definition?
- Research is needed!
- Or perhaps- we will circle back to the possibility this diagnosis doesn't exist?

Acknowledgements

- Task Force for ASRM RIF CO:
  - Dr. Jessica Lentscher, MD
  - Dr. Edward McClellan, MD
  - Dr. Austin Schirmer, MD
  - Dr. Erica Wang, MD MAS
  - Dr. Bo Yu, MD
- ASRM Practice Committee


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