Simposio 6: Time-lapse ¿A dónde podemos llegar?

Coordinador: Lidia Cantú | Uruguay y Ricardo Azambuja | Brasil

09:00 - 09:20 Time-lapse e IA en la selección embrionaria: perspectivas y resultados -

Edson Borges Jr.

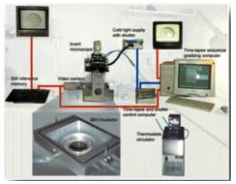
Fertility Medical Group

Instituto Sapientiae

FERTILITY

Instituto Sapientiae

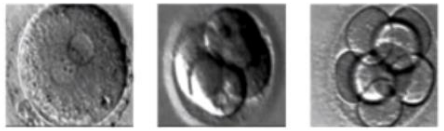
History of « modern » TLT



Single-point morphological assessment

1997[1] **2011[2]** **2020**

D3 culture **Blastocyst culture**



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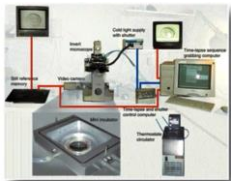
[2]Meseguer et al. *Hum Reprod.* 2011;**26**:2658–2671.

History of « modern » TLT

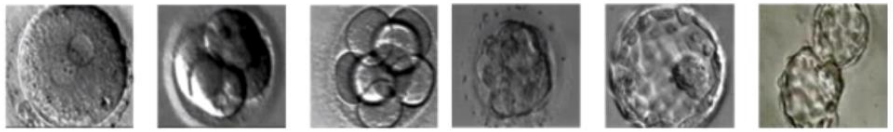


Single-point morphological assessment

Continuous embryo monitoring

1997[1] **2011[2]** **2020**

D3 culture **Blastocyst culture**



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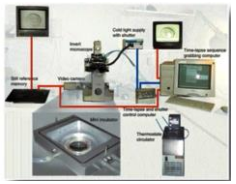

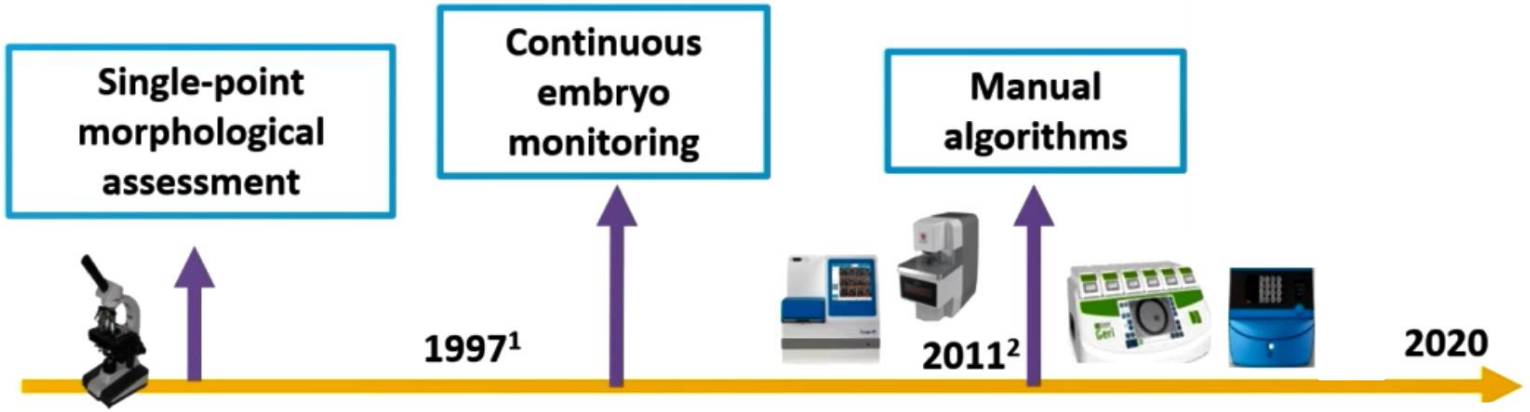

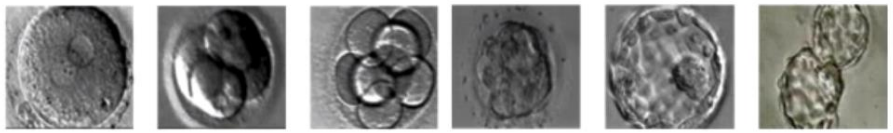

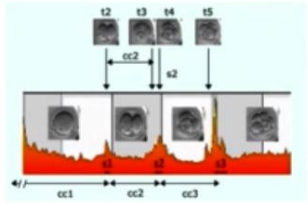

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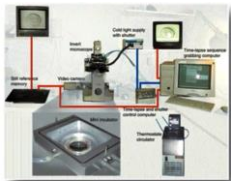

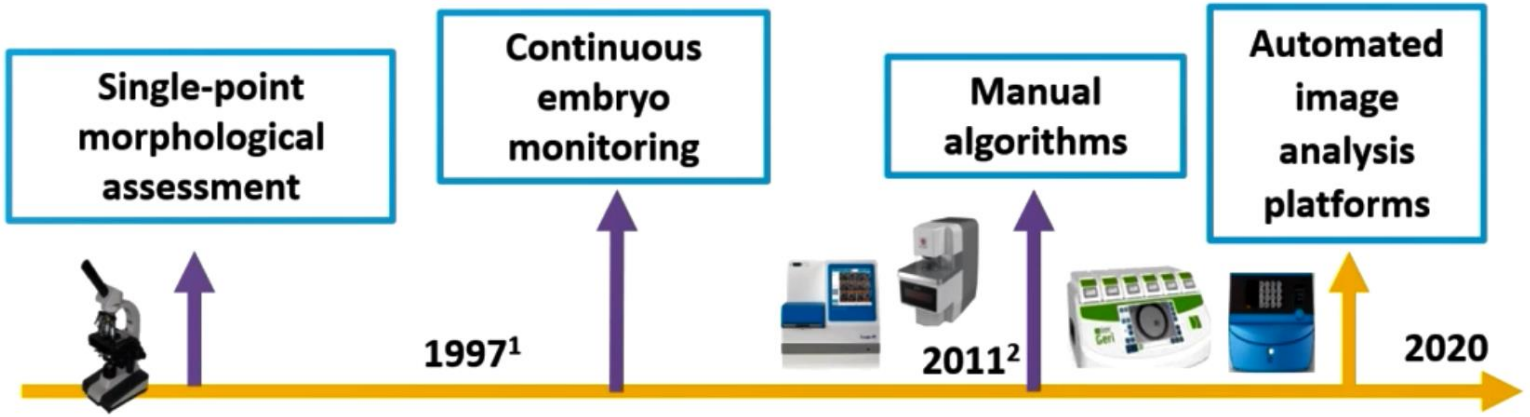

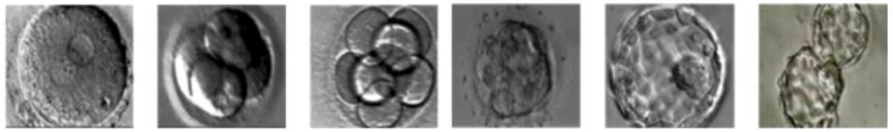

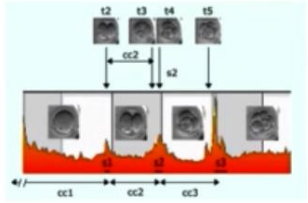

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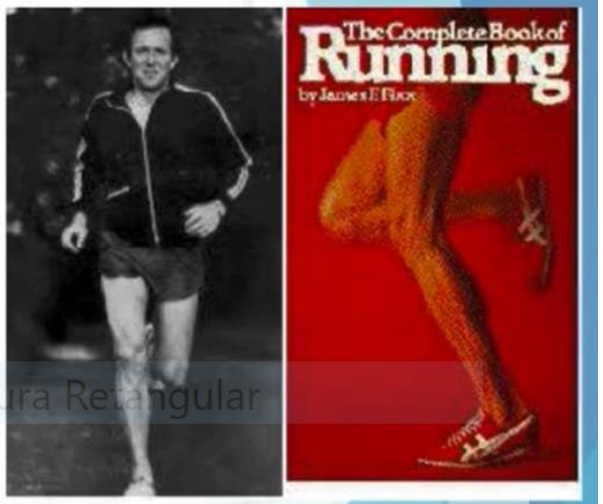
Morphokinetics and what we do not see!

- Winston Churchill
- Drank
- Smoked Cigars
- Overweight

- Roger Bannister
- The first man to run the 4 minute mile
- Exercised frequently

- Jimmy Fixx
- Started America's fitness revolution, popularizing running



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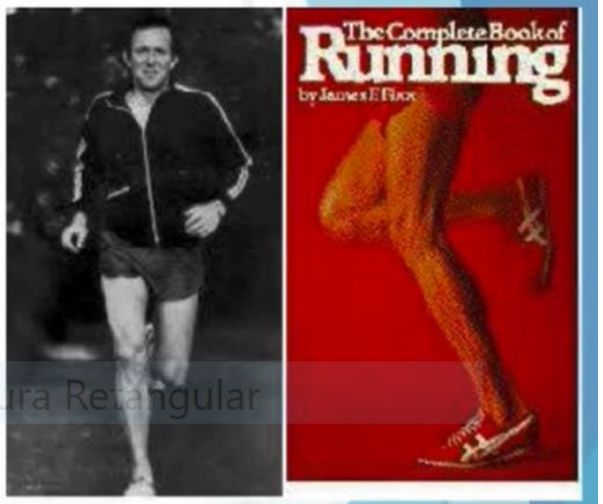

Who lived the longest?

Morphokinetics and what we do not see!

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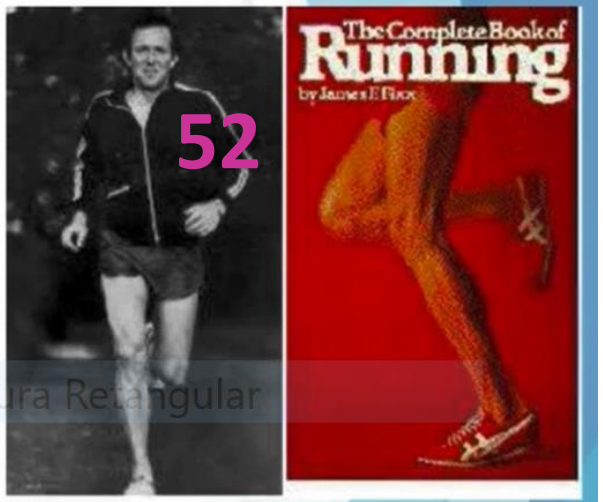
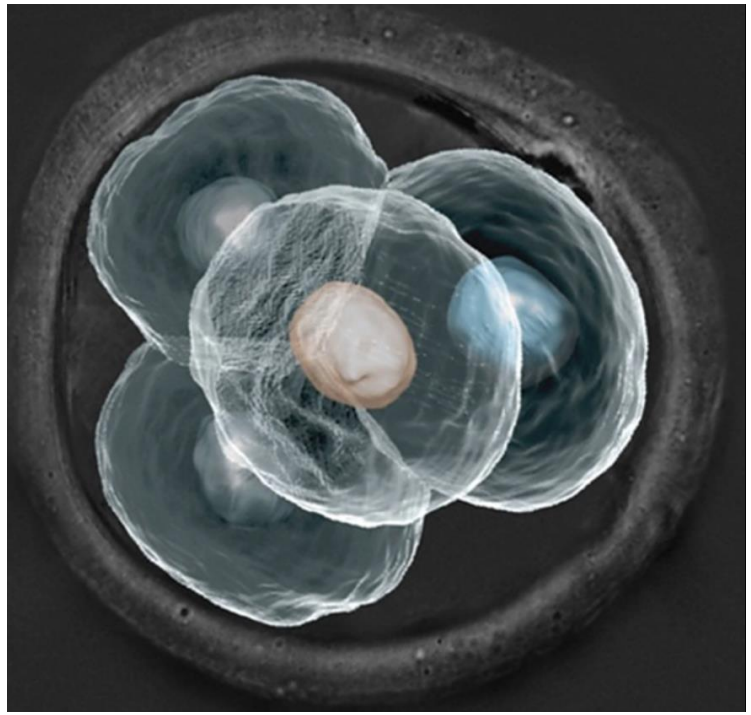


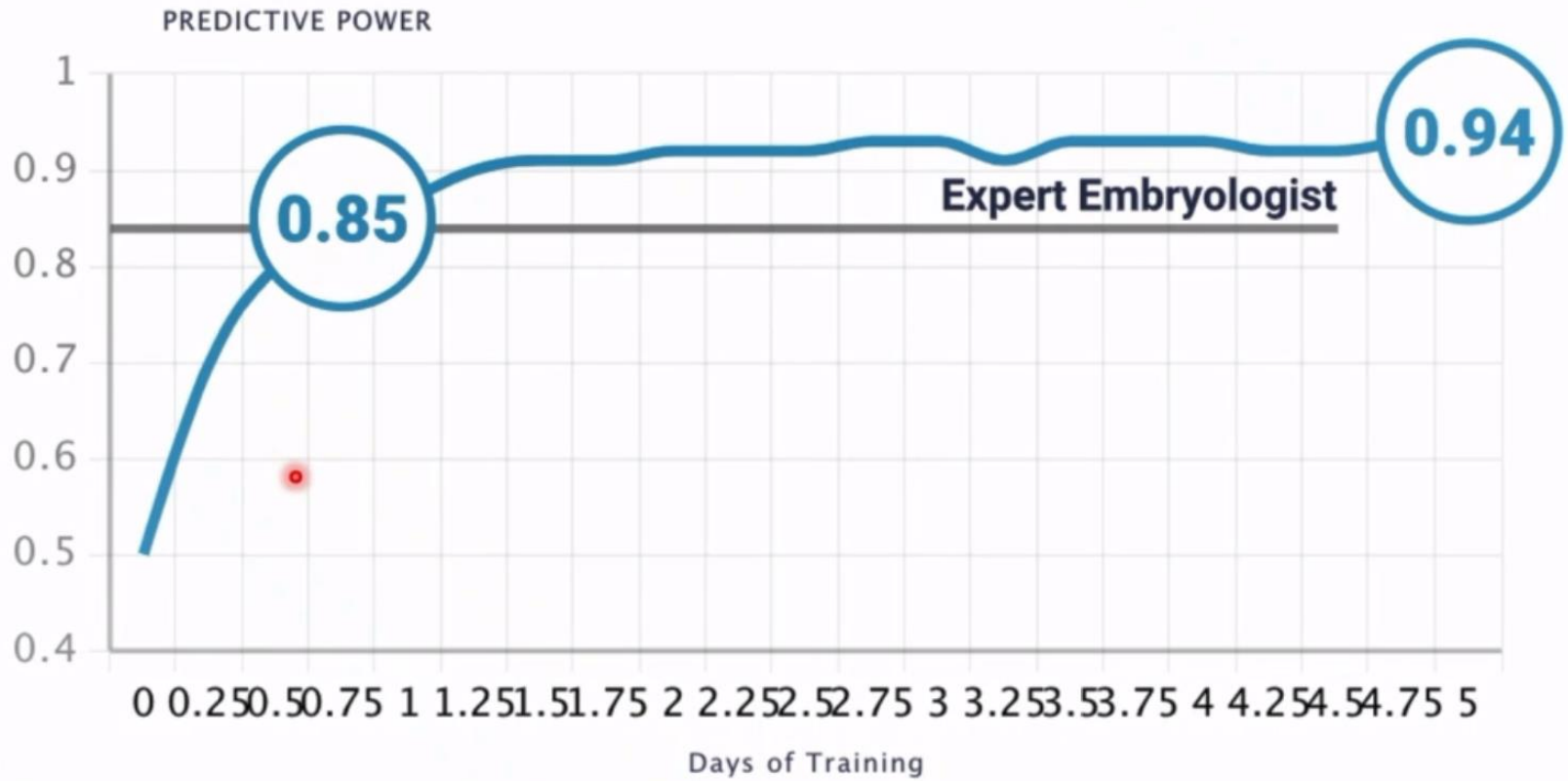
Who lived the longest?

IA and deep learning – embryo evaluation



FERTILITY

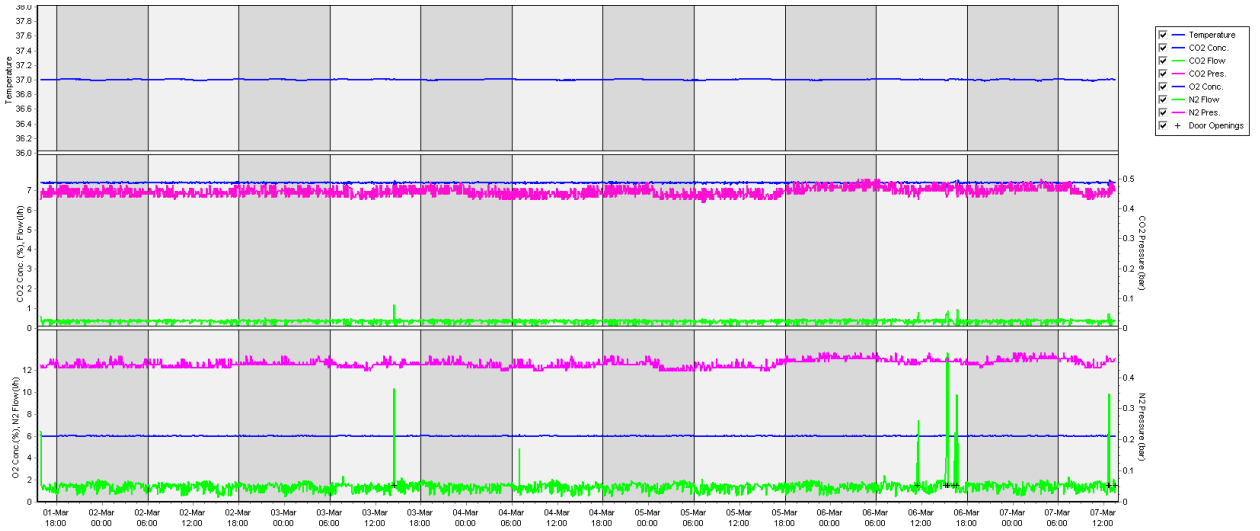
AI technology **exceeded expert human embryologists after only one day** of training



FERTILITY

EMBRYOSCOPE

AMBIENTE DE CULTIVO SEGURO PARA OS EMBRIÕES



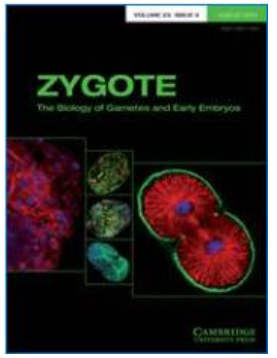
- Temperatura
- CO_2 / O_2
- pH
- VOC
- Coleção de imagens
- Alarme

Summary | Alarms | Warnings | Log | Other

Variable	Unit	Average	Min	Max	StdDev	Set-Point
Temperature	C	37.00	36.98	37.02	0.007	37.0
CO2 Concentration	%	7.38	7.25	7.46	0.032	7.4
CO2 Flow	l/h	0.36	0.01	0.60	0.096	0.0
CO2 Pressure	bar	0.46	0.42	0.50	0.016	0.0
O2 Concentration	%	6.01	5.97	6.15	0.011	6.0
N2 Flow	l/h	1.38	0.45	6.45	0.361	0.0
N2 Pressure	bar	0.44	0.42	0.48	0.013	0.0

FERTILITY

Improved embryonic development and utilization rates with EmbryoScope: a within-subject comparison versus a benchtop incubator



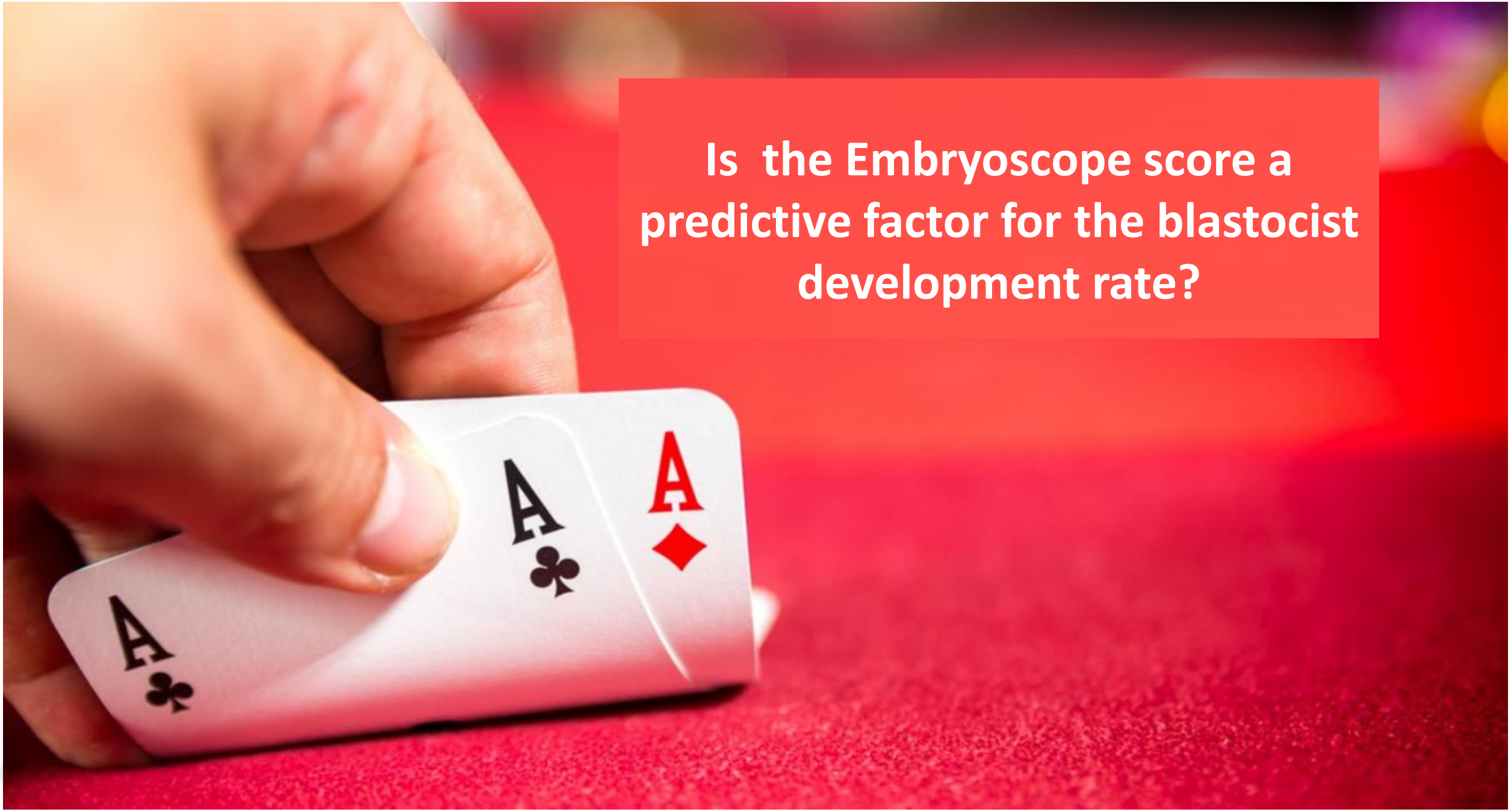
Edson Borges Jr. *et al,* 2022

doi:10.1017/S0967199422000077

Table 2. Comparison of embryonic development between Control and TLI groups using GzLM followed by Bonferroni post hoc test

Variables	Control group ($n = 71$)	TLI group ($n = 71$)	*P*-value
Normal fertilization (%)	74.8 ± 2.7 (69.6–80.1)	77.4 ± 2.7 (72.2–82.6)	0.499
Abnormal fertilization (%)	6.2 ± 1.5 (3.1–9.2)	6.8 ± 1.5 (3.8–9.8)	0.767
Non-fertilization (%)	16.8 ± 2.1 (12.7–20.8)	11.9 ± 2.1 (7.8–15.9)	0.098
Oocyte degeneration post injection (%)	2.2 ± 1.3 (0.22–4.7)	3.9 ± 1.3 (1.4–6.3)	0.352
Day-2 non-cleavage (%)	3.8 ± 0.2 (3.3–4.3)	1.1 ± 0.1 (0.9–1.3)	<0.001
Cleavage (%)	85.3 ± 1.2 (83.0–87.7)	84.2 ± 1.3 (81.7–86.8)	0.521
Day-5 embryos (%)	62.4 ± 1.0 (60.5–64.3)	86.4 ± 1.1 (84.2–88.6)	<0.001
Blastocyst development (%)	40.9 ± 1.1 (38.8–43.1)	55.6 ± 1.3 (53.1–58.1)	<0.001
Frozen blastocyst (%)	31.8 ± 0.8 (30.3–33.3)	37.0 ± 0.9 (35.2–38.9)	<0.001
OUR	40.7 ± 1.0 (38.8–42.7)	50.2 ± 1.1 (48.0–52.4)	<0.001
EUR	52.4 ± 1.1 (50.3–54.7)	66.6 ± 1.2 (64.3–68.9)	<0.001

Note: Values are means ± standard error (95% confidence interval). EUR: embryo utilization rate; GzLM: generalized linear models; OUR: oocyte utilization rate; TLI: time-lapse imaging.

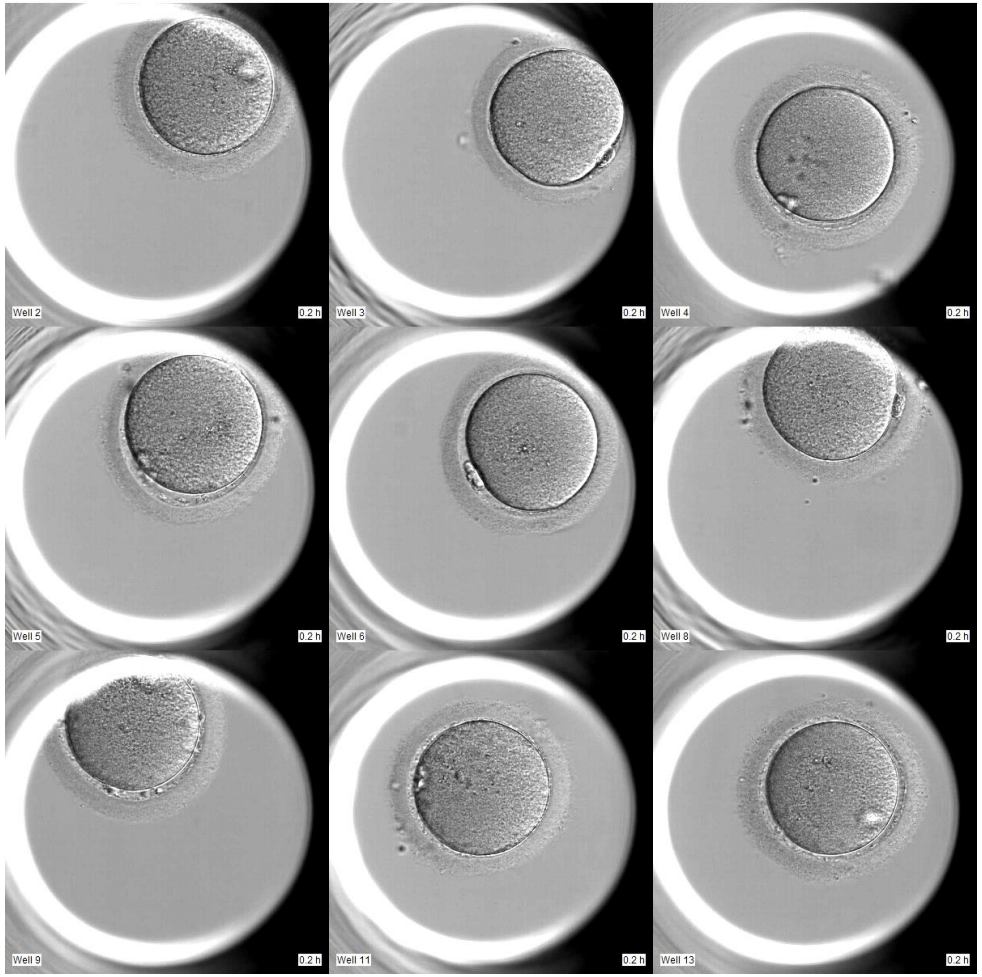

Is the Embryoscope score a predictive factor for the blastocist development rate?

Embryoscope FERTILITY

- 427 ciclos
- 372 pacientes

✓3.020 ovócitos cultivados
✓2.398 2PN (79,4%)
✓1.488 blastocistos: *62,1% 2PN*

❑ 2018: *49,9% 2PN*



FERTILITY


Is the Embryoscope score correlated with pregnacy rate?

EmbryoScope FERTILITY

ICSI e OVODON					
Variáveis	Convencional (n=764)		Embryoscope (n=119)		p
	Média	DP	Média	DP	
Taxa de fertilização (%)	76,5	25,0	74,4	26,5	0,255
Taxa de blastocisto (%)	**59,2**	25,0	**66,0**	25,4	**0,003**
Embriões transferidos (n)	**2,0**	0,6	**1,2**	0,9	**<0,001**
Taxa de implantação (%)*	**24,5**	37,3	**36,4**	42,2	**0,006**
Taxa de gestação (%)*	**34,6**		**55,7**		**<0,001**
Taxa de aborto (%)*	**19,5**		**12,3**		**0,001**

FERTILITY

EmbryoScope FERTILITY

Resultado clínico estratificado por idade	n=504		n=681		
Até 35 anos					
	Convencional (n=182)		**Embryoscope (n=181)**		**p**
	Média	**DP**	**Média**	**DP**	
Taxa de implantação (%)	41.9	5.5	29.8	6.3	0.147
Taxa de gestação (%)	51.6		38.3		0.166
Taxa de aborto (%)	16.1		27.8		0.329
36 a 39 anos					
	Convencional (n=182)		**Embryoscope (n=275)**		**p**
	Média	**DP**	**Média**	**DP**	
Taxa de implantação (%)	29.7	4.9	24.4	4.4	0.421
Taxa de gestação (%)	32.9		37.3		0.576
Taxa de aborto (%)	12.5		7.4		0.542
≥ 40 anos					
	Convencional (n=140)		**Embryoscope (n=225)**		**p**
	Média	**DP**	**Média**	**DP**	
Taxa de implantação (%)	11.1	4.2	21.0	4.5	**<0.001**
Taxa de gestação (%)	14.1		28.8		**0.045**
Taxa de aborto (%)	31.3		32.0		0.915

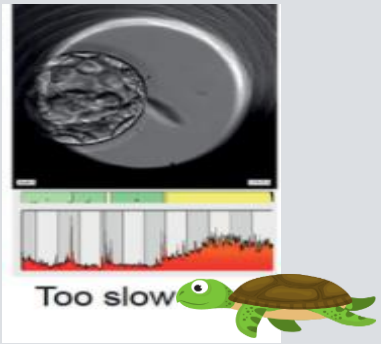
FERTILITY

EmbryoScope FERTILITY

KIDscore D5	≤ 2,5	2,6 – 5,0	5,1 – 7,5	> 7,5
Taxa de Implantação (%)	24,0[a]	27,3[b]	31,4[c]	37,2[d]

a ≠ b ≠ c ≠ d, p < 0,001
General linear model, função Log linear, distribuição Poison

FERTILITY



DNA fragmentation can interfere with the speed and pattern of cell divisions

FERTILITY

Morphokinetic parameter comparison between embryos from couples with high or low sperm DNA fragmentation index

Amanda Souza Setti, M.Sc.,[a,b] Daniela Paes de Almeida Ferreira Braga, Ph.D.,[a,b] Patricia Guilherme, M.Sc.,[a] Rodrigo Provenza, B.Sc.,[a] Assumpto Iaconelli Jr., M.D.,[a,b] and Edson Borges Jr., Ph.D.[a,b]

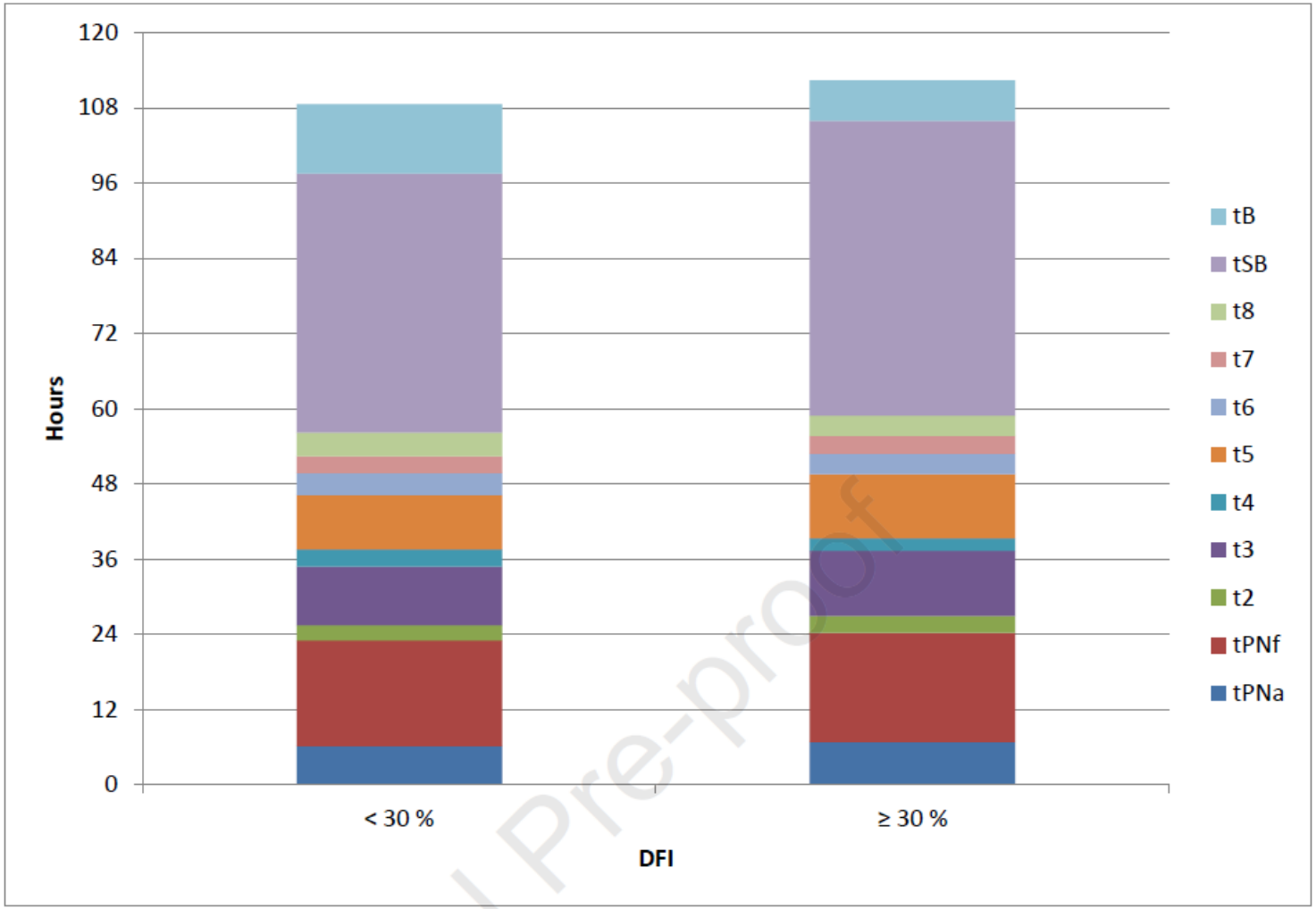
[a] Fertility Medical Group, Av. Brigadeiro Luis Antonio, São Paulo, Brazil; and [b] Sapientiae Institute – Centro de Estudos e Pesquisa em Reprodução Humana Assistida, Rua Vieira Maciel, São Paulo, Brazil

F&S Science (2021), doi: https://doi.org/10.1016/j.xfss.2021.10.001

- 118 patients, 978 zygotes, ICSI cycles, idiopathic male factor
- Morphokinetic markers: time to pronucleus, appearance and disappearance (tPNa and tPNf), time to two (t2), three (t3), four (t4),five (t5), six (t6), seven (t7), and eight cells (t8), and time of onset (tSB) and blastulation (tB).
- Low (<30%) or high (≥30%) DFI (sperm DNA fragmentation index
- Mixed generalized linear models adjusted for potential confounders, followed by *post hoc* Bonferroni test

FERTILITY

Table 2. Results from multivariate linear regression analysis followed by Bonferroni post hoc for the comparison of embryo morphokinetics between DFI groups (n=978)



F&S Science (2021), doi: https://doi.org/10.1016/j.xfss.2021.10.001

Morphokinetic markers

FERTILITY

Use of epididymal spermatozoa in ICSI cycles impacts the morphokinetic of embryos: lessons of time-lapse system

Borges E. *et al* (submitted)

Cohort → **January /2019 – December/2020** → **Embryos in TLS up to D5**

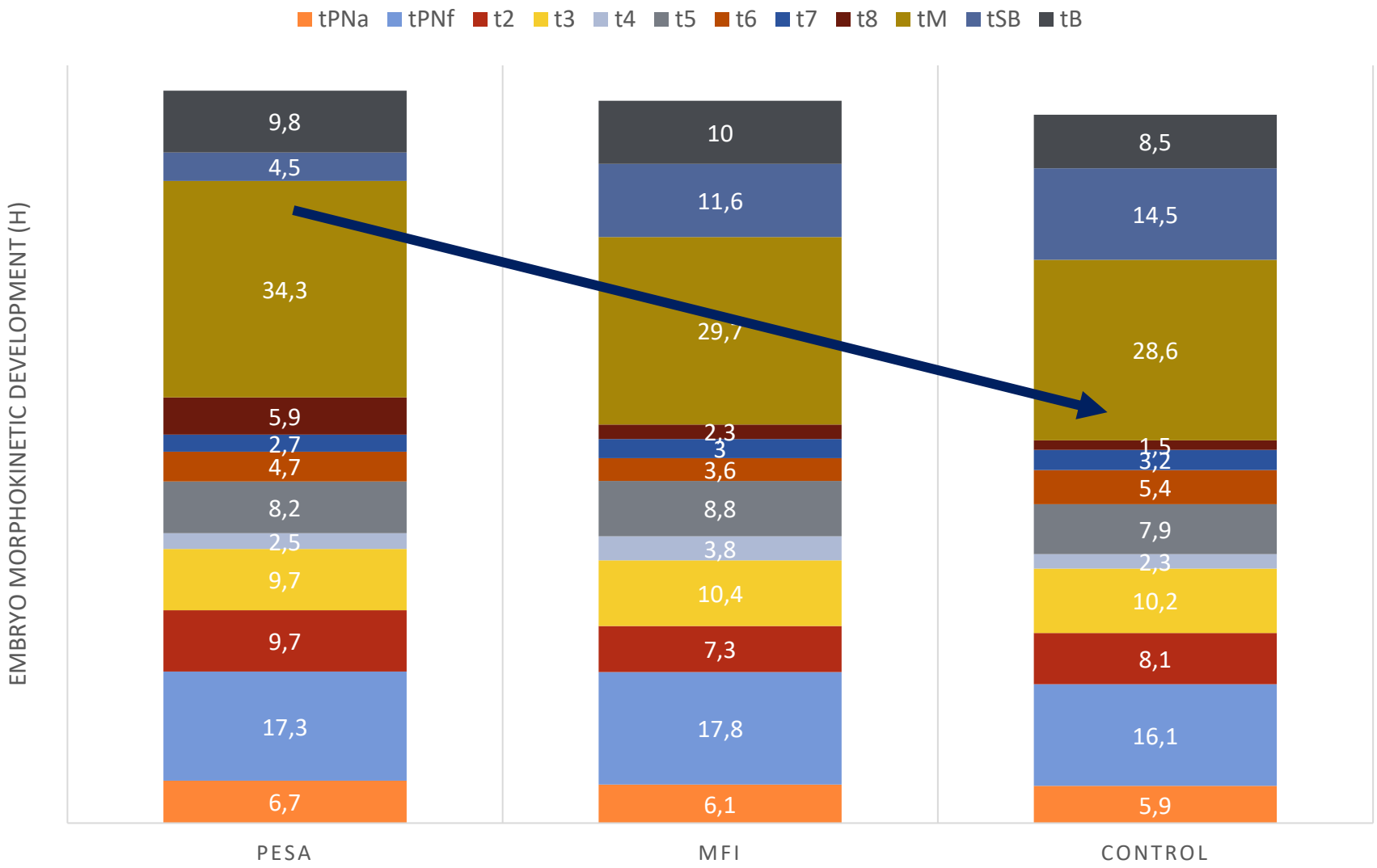
96 ICSI cycles

806 embryos

Pairing by maternal and paternal age, number of eggs retrieved and OCE protocol

- **PESA** 32 cycles 276 embryos
- **Idiopathic MF** 32 cycles 284 embryos
- **CONTROL** 32 cycles 246 embryos

FERTILITY


tPNa
tPNf
t2
t3
t4
t5
t6
t7
t8
tM
tSB
tB
EMBRYO MORPHOKINETIC DEVELOPMENT (H)
9,8
4,5
34,3
5,9
2,7
4,7
8,2
2,5
9,7
9,7
17,3
6,7
10
11,6
29,7
2,3
3
3,6
8,8
3,8
10,4
7,3
17,8
6,1
8,5
14,5
28,6
1,5
3,2
5,4
7,9
2,3
10,2
8,1
16,1
5,9
PESA
MFI
CONTROL

FERTILITY

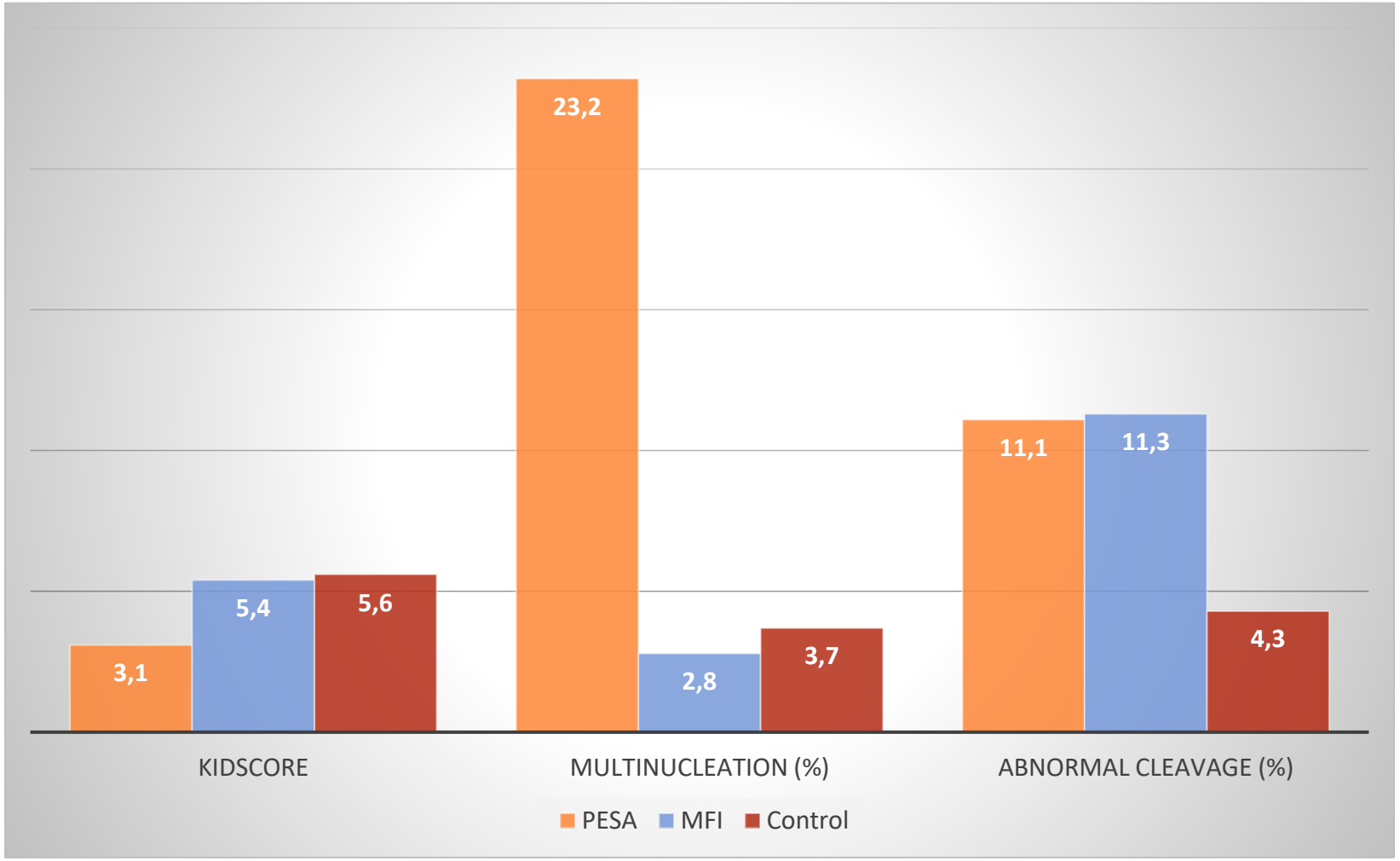
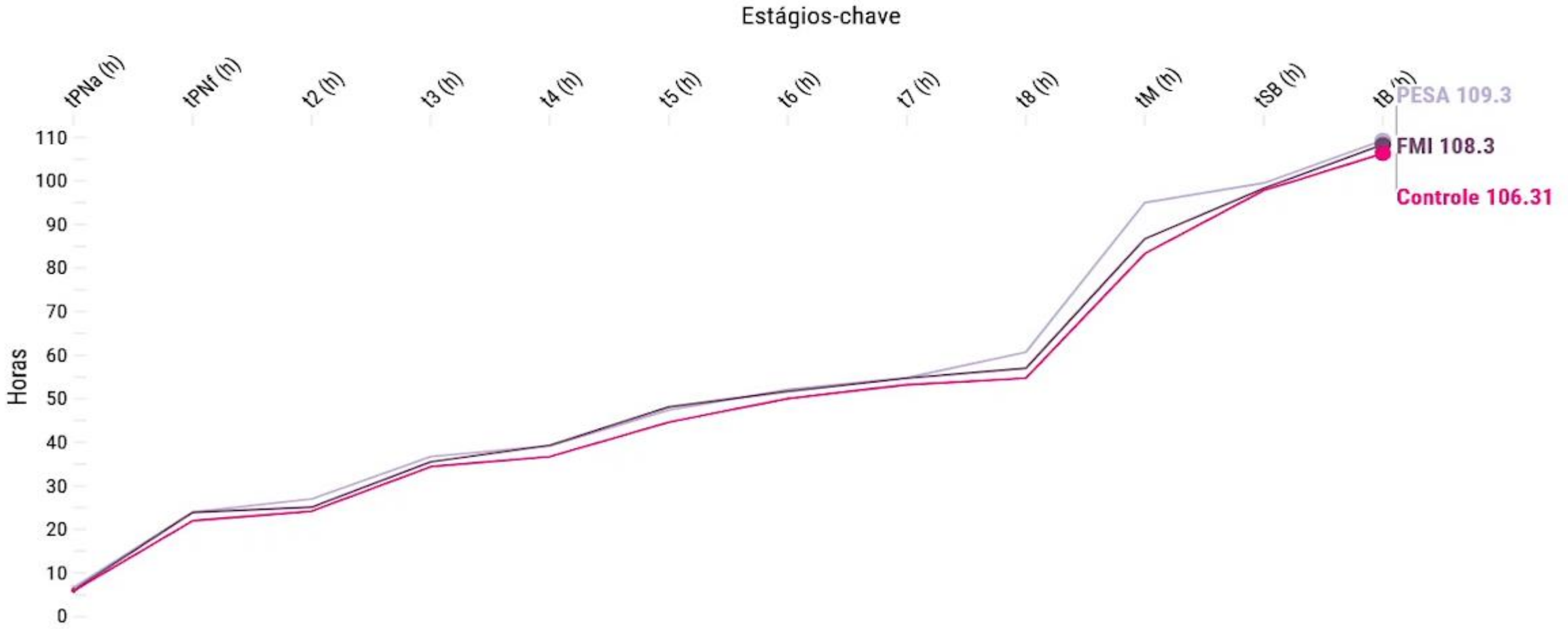


Figure 3. A comparison of KIDScore, and incidences of multinucleation and abnormal cleavage patterns in PESA, MFI and Control groups.

Note: KIDScore – known implantation diagnosis, PESA – percutaneous epididymal sperm aspiration, MFI – male factor infertility.

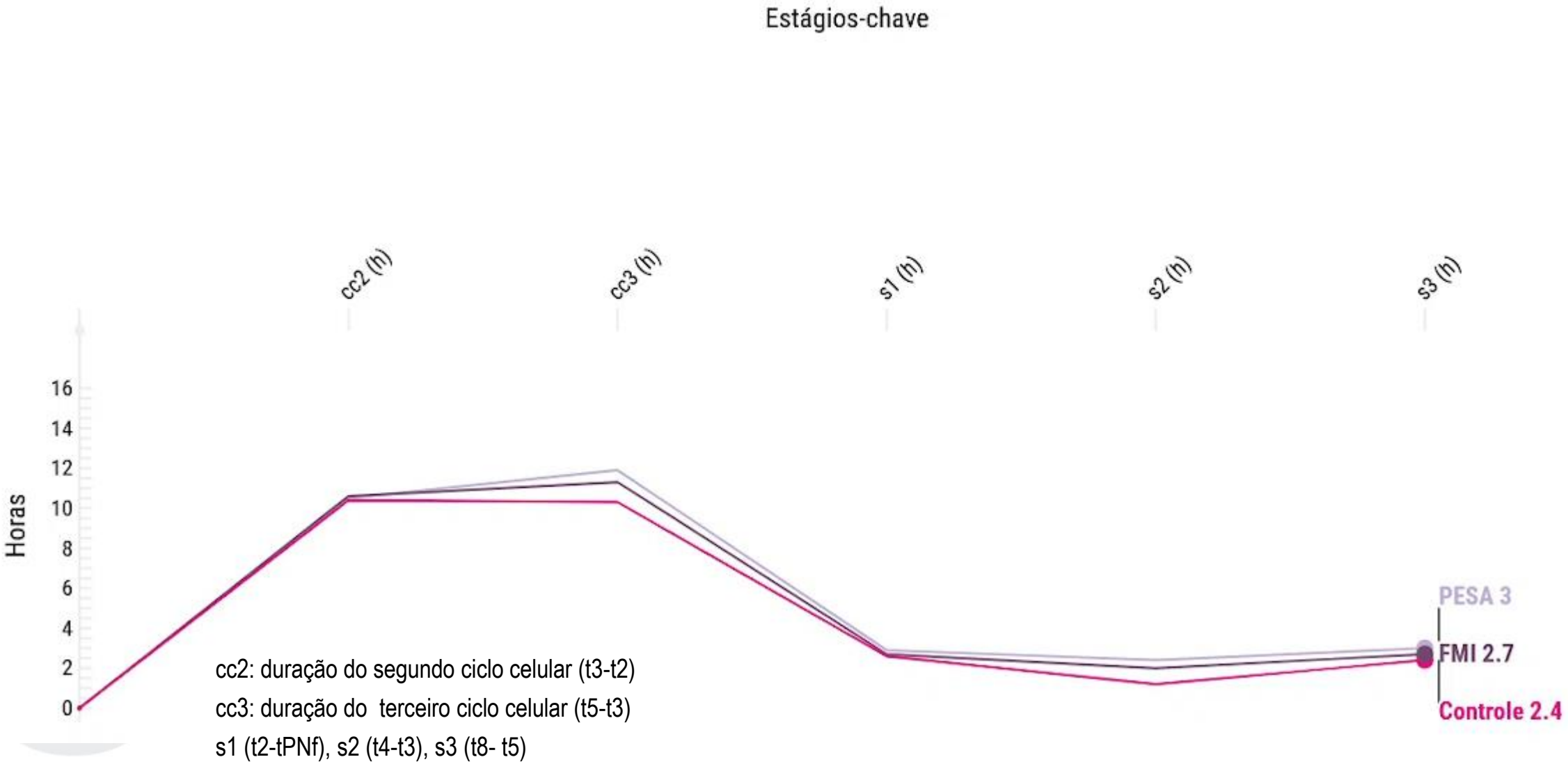
FERTILITY

Behavior of embryos from the PESA, IFM and Control groups in relation to early and late morphokinetics events



FERTILITY

Behavior of embryos from the PESA, FM and Control groups in relation to cell cycles and synchronous divisions



Received: 31 March 2021 | Revised: 29 July 2021 | Accepted: 30 July 2021

DOI: 10.1111/and.14211

ORIGINAL ARTICLE

First International Journal of Andrology
aNDROLOGIa
WILEY

Early and late paternal contribution to cell division of embryos in a time-lapse imaging incubation system

Amanda Souza Setti[1,2] | Daniela Paes de Almeida Ferreira Braga[1,2] | Livia Vingris[3] | Assumpto Iaconelli Jr.[2,4] | Edson Borges Jr.[2,4]

FERTILITY

RESULTS

First International Journal of Andrology
ANDROLOGIA
Early and late paternal contribution to cell division of embryos in a time-lapse imaging incubation system

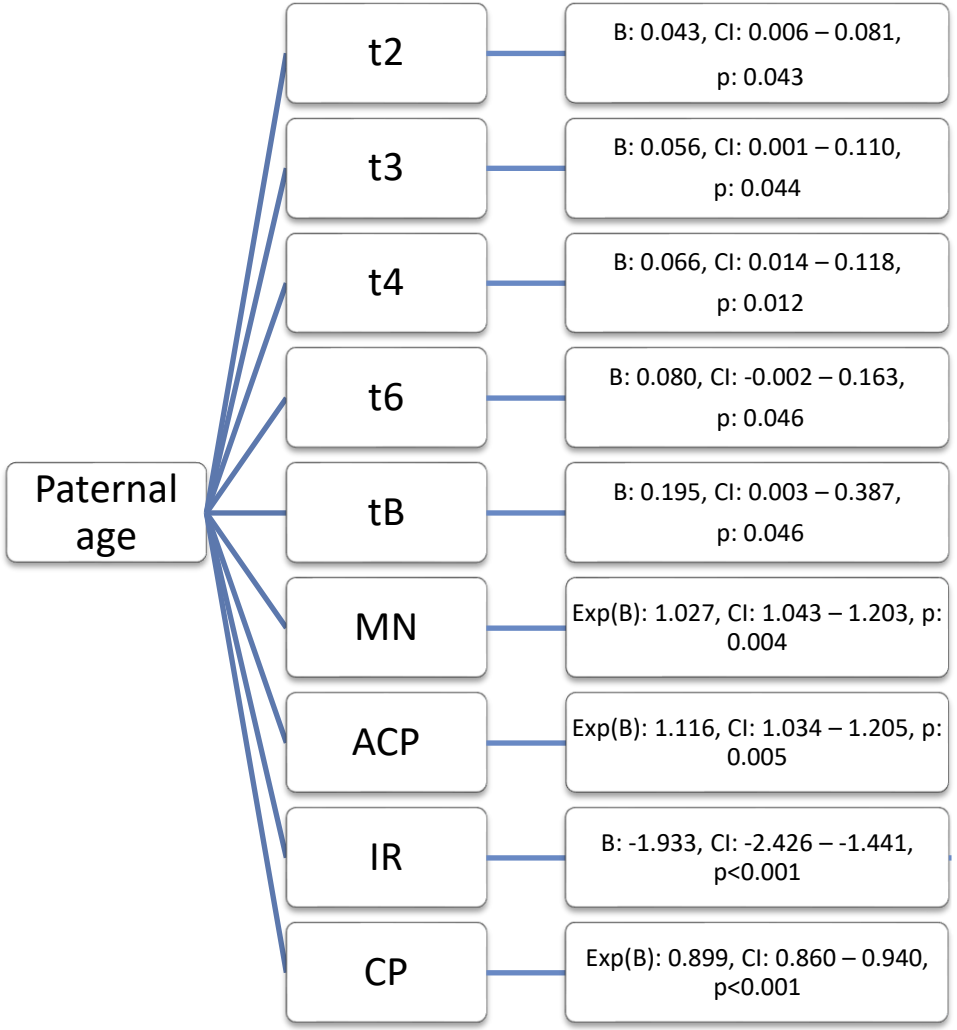
Variable	Mean ± SD
Semen analysis	
Male age (years)	41.3 ± 6.8
Ejaculatory abstinence length (days)	3.2 ± 2.5

FERTILITY

RESULTS

First International Journal of Andrology
ANDROLOGIA

Early and late paternal contribution to cell division of embryos in a time-lapse imaging incubation system



FERTILITY

Table 3. Results from regression analysis for the influence of oocyte maturity rate on embryo morphokinetics (n=3368 embryos)

Morphokinetic parameters (h)	B	95% CI	p-value
tPNa	0.053	0.045 – 0.061	<0.001
tPNf	0.081	0.070 – 0.093	<0.001
t2	0.076	0.064 – 0.087	<0.001
t3	0.070	0.056 – 0.084	<0.001
t4	0.070	0.055 – 0.084	<0.001
t5	0.083	0.063 – 0.102	<0.001
t6	0.066	0.047 – 0.086	<0.001
t7	0.076	0.055 – 0.098	<0.001
t8	0.064	0.040 – 0.087	<0.001
tSB	0.090	0.014 – 0.165	0.020
tB	0.043	0.011 – 0.075	0.009
s1	-0.001	-0.004 – 0.003	0.725
s2	0.001	-0.008 – 0.009	0.887
s3	0.004	-0.015 – 0.0240	0.649
cc2	-0.003	-0.013 – 0.007	0.510
cc3	0.018	0.005 – 0.031	0.007

Note: Values are means ± standard deviation, unless otherwise noted. h – hours, B – Beta coefficient, CI – confidence interval, tPNa – timing to pronuclei appearance, tPNf – timing to pronuclei fading, t2 – timing to two cells, t3 – timing to three cells, t4 – timing to four cells, t5 – timing to five cells, t6 – timing to six cells, t7 – timing to seven cells, t8 – timing to eight cells, tSB – timing to start blastulation, tB – timing to blastulation, s1 – timing to complete t2-tPNf synchronous divisions, s2 – timing to complete t4-t3 synchronous divisions, s3 – timing to complete t8-t5 synchronous divisions, cc2 – duration of the second cell cycle (t3-t2), cc3 – duration of third cell cycle (t5-t3).

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ELSEVIER

ARTICLE

High oocyte immaturity rates affect embryo morphokinetics: lessons of time-lapse imaging system

Amanda Setti[1,2,*], Daniela Braga[1,2], Patricia Guilherme[1], Assumpto Iaconelli Jr.[1,2], Edson Borges Jr.[1,2]

FERTILITY

High oocyte immaturity rates impact embryo morphokinetics: Lessons of time-lapse imaging system

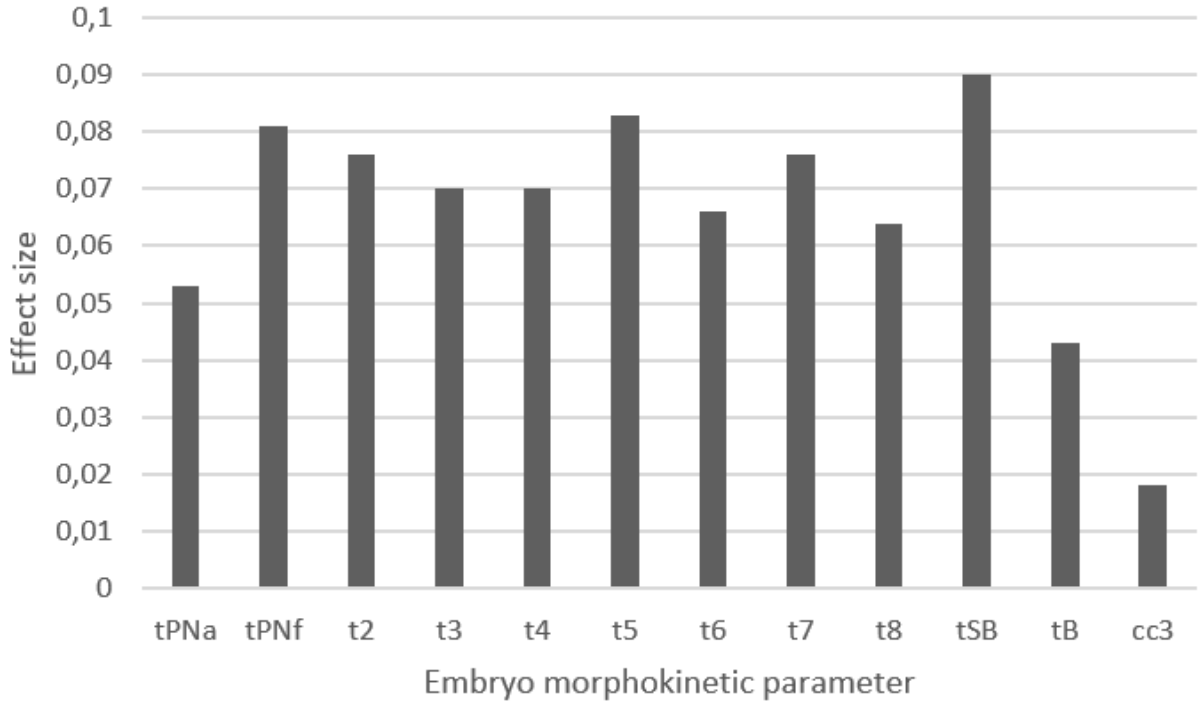

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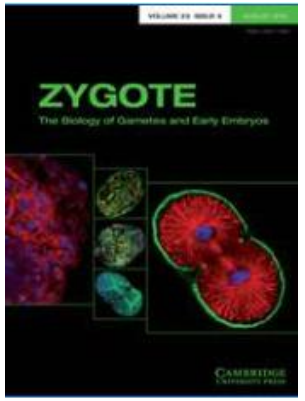
Figure 2. Illustration of cumulative delayed morphokinetic development in MII inseminated oocytes derived from cohorts with high proportion of immature sibling oocytes.

Table 3. Results from regression analysis for the influence of serum AMH concentration levels on embryo morphokinetics (n=114 cycles and 902 embryos)

Morphokinetic parameters (h)	B	95% CI	p-value
tPNa	0.251	-0.315 – 0.816	0.385
tPNf	-0.047	-0.071 – -0.024	<0.001
t2	-0.028	-0.056 – 0.001	0.057
t3	-0.070	-0.102 – -0.039	<0.001
t4	-0.080	-0.114 – -0.046	<0.001
t5	-0.075	-0.123 – -0.028	0.002
t6	-0.105	-0.147 – -0.064	<0.001
t7	-0.120	-0.165 – -0.075	<0.001
t8	-0.170	-0.220 – -0.119	<0.001
tSB	-4.898	-12.208 – 2.412	0.189
tB	-0.153	-0.224 – -0.082	<0.001
s1	-0.274	-0.686 – 0.137	0.191
s2	-0.009	-0.027 – 0.009	0.344
s3	-0.086	-0.129 - -0.044	<0.001
cc2	-0.041	-0.062 – -0.019	<0.001
cc3	-0.005	-0.036 – 0.025	0.739



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(accepted)

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Figure 1. Illustration of faster embryo morphokinetic development according to increased serum AMH concentration levels

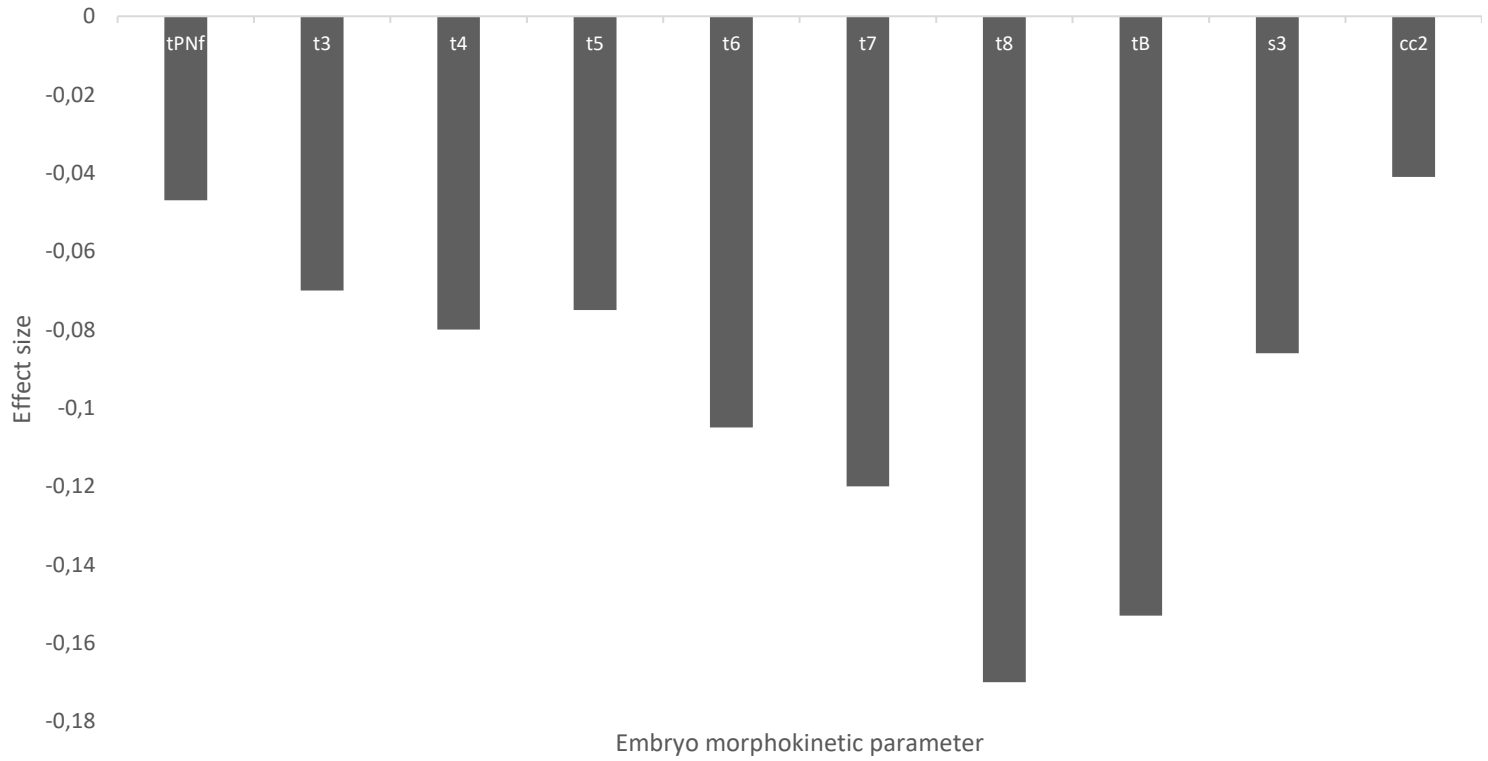

Figure 2. Illustration of the predictive value of AMH on embryos' KIDScore ranking (p=0.023)

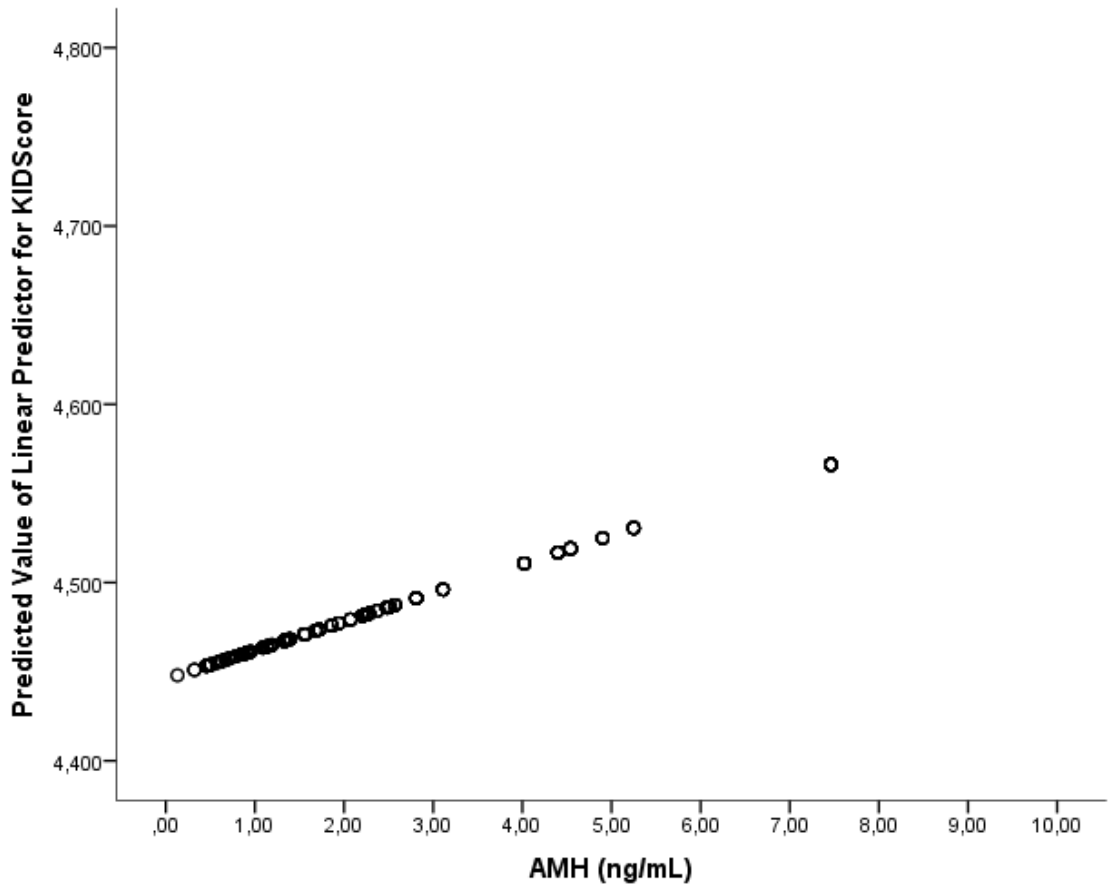

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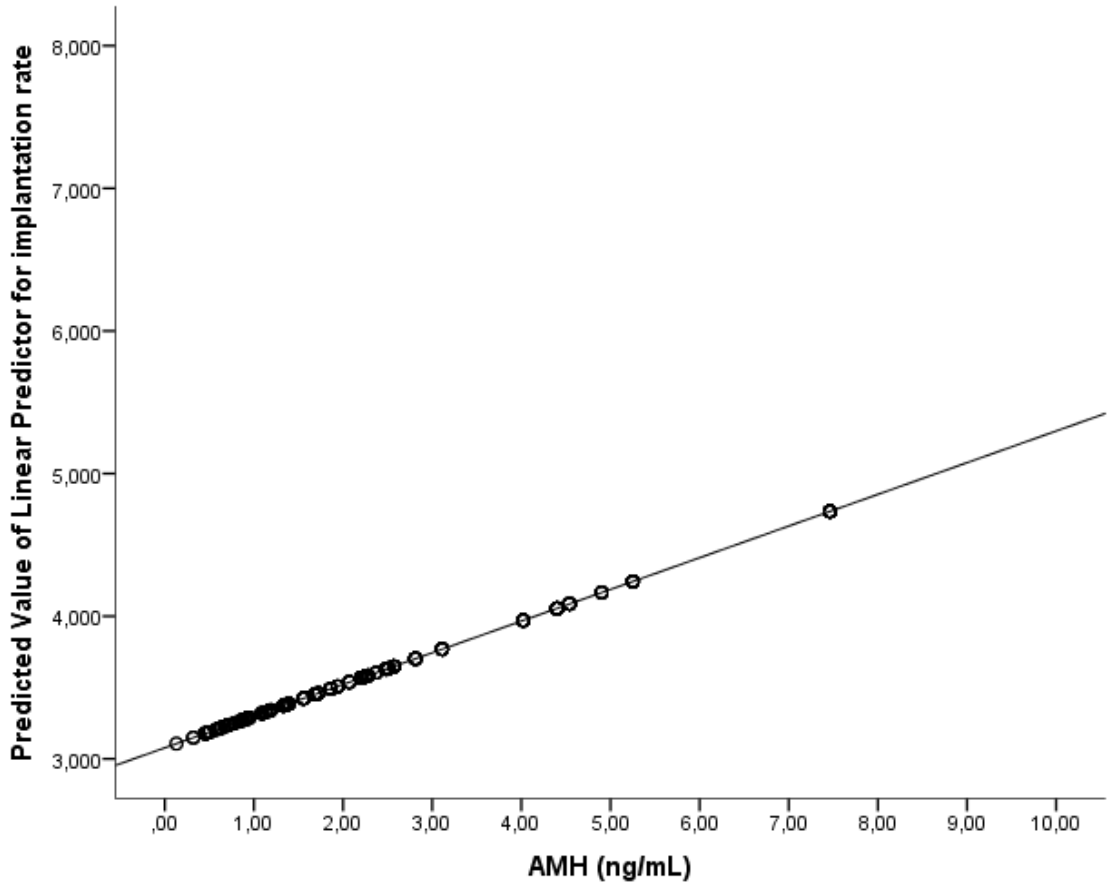
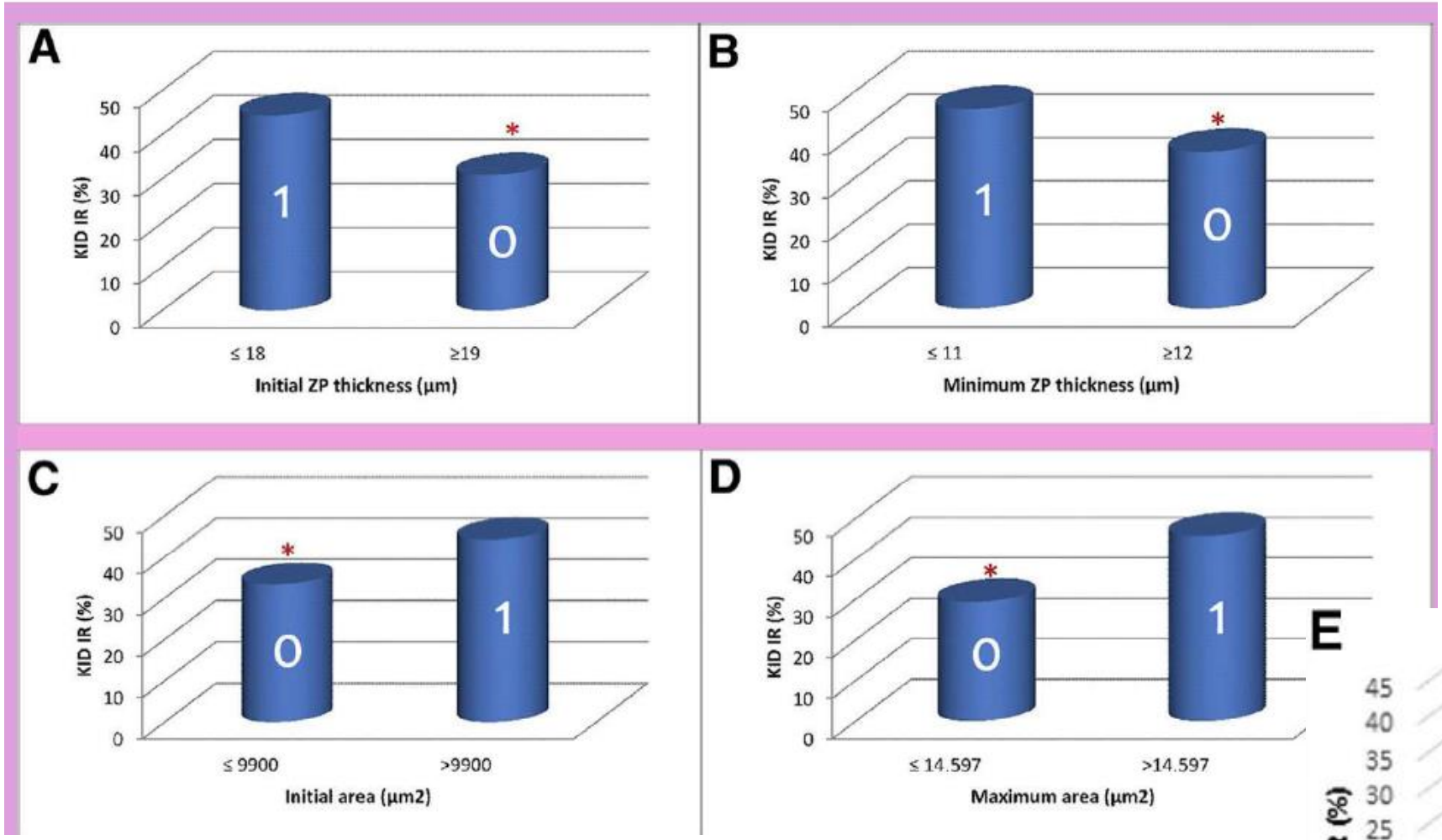
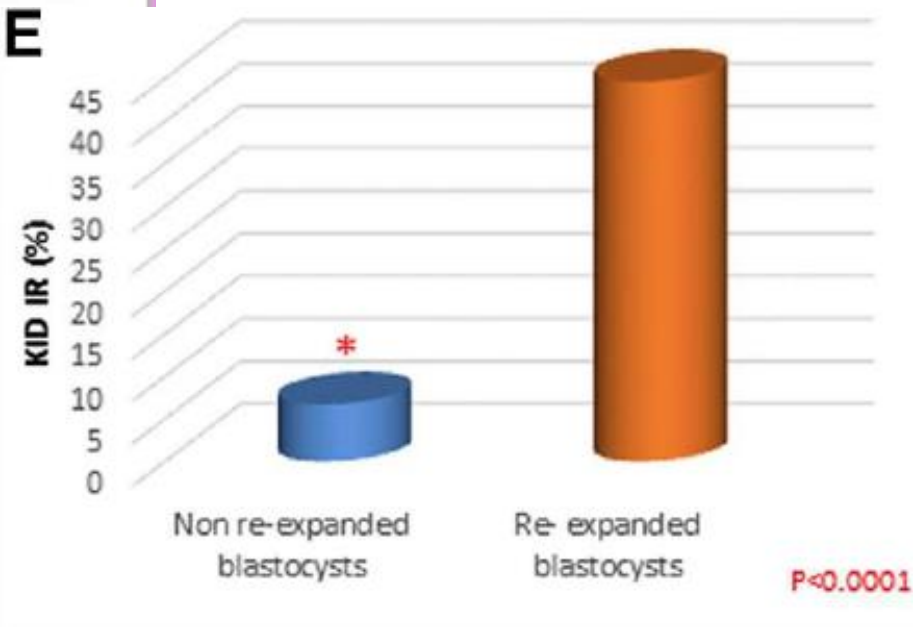
Figure 3. Illustration of the predictive value of AMH on embryos' implantation rate (p<0.001)



FERTILITY

Use of the EMBRYOSCOPE in Thaw Embryos





Score: 0 = < implantation rate| 4 = > implantation rate

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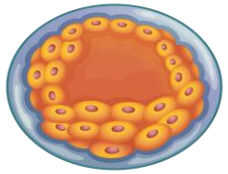
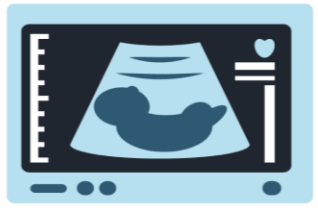




FERTILITY

Blastocyst thaw - EmbryoScope (Fertility)

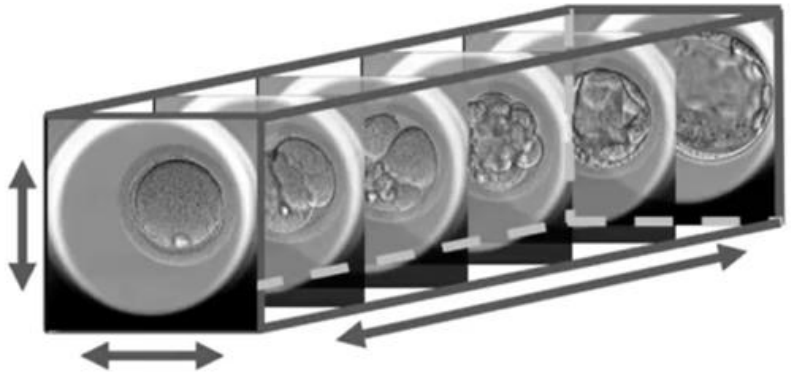
182 embryos transfer

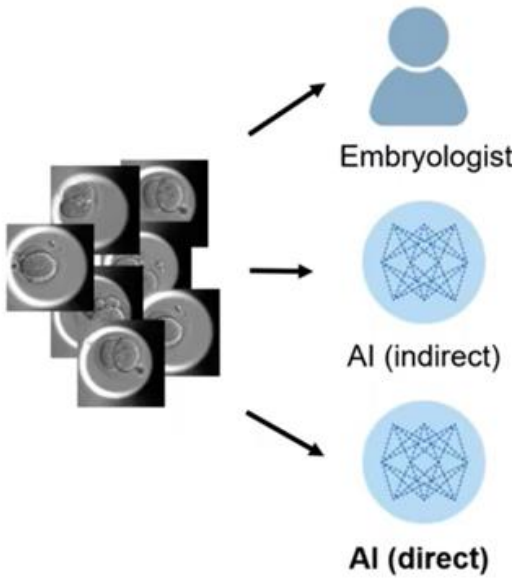
- ***Post-thaw initial and final blastocyst zona pellucida thickness were negatively associated with implantation*** (B: -0.024, CI: -0.029 - -0.018, p<0.001, and B: -0.025, CI: -0.031 - -0.020, p<0.001, respectively).

- ***Implantation rates were significantly different when cut-off values of 0 or 1 (threshold 11µm) were attributed to final ZP thickness*** (0: 27.7% ± 0.4 vs. 1: 33.8% ± 0.7, p<0.001).

- ***Post-thaw final blastocyst area was positively associated with implantation*** (B: 0.011, CI: 0.007 - 0.015, p<0.001).

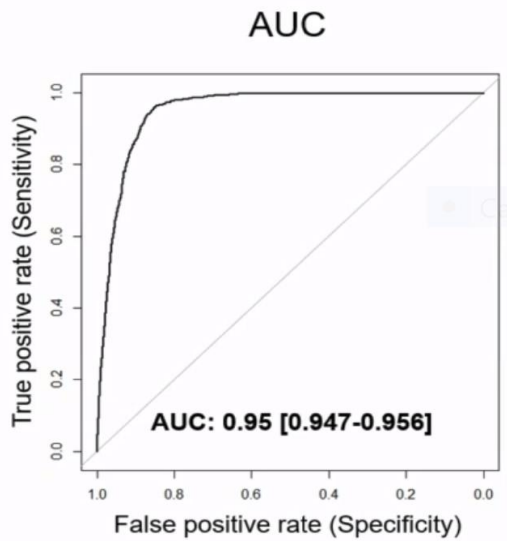
- ***Implantation rates were significantly different when cut-off values of 0 or 1 (threshold 14.597 µm^2) were attributed to final area*** (0: 27.7% ± 0.4 vs. 1: 33.8% ± 0.7, p<0.001)



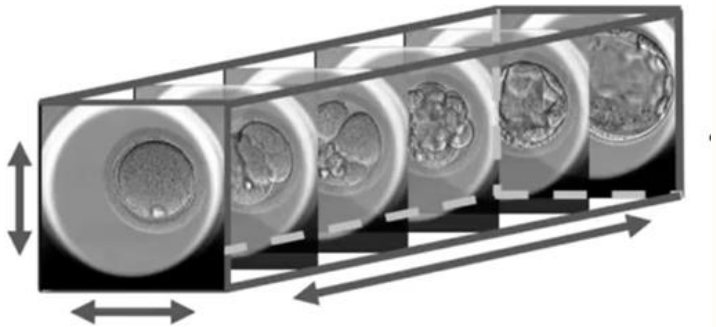


EVALUATING iDASCORE

iDASCORE	Test
Clinics	18
Embryos	17.249
Positive fetal heartbeat	661
Negative fetal heartbeat	1.551
Discards	15.037



FERTILITY



Embryos

Make a Decision

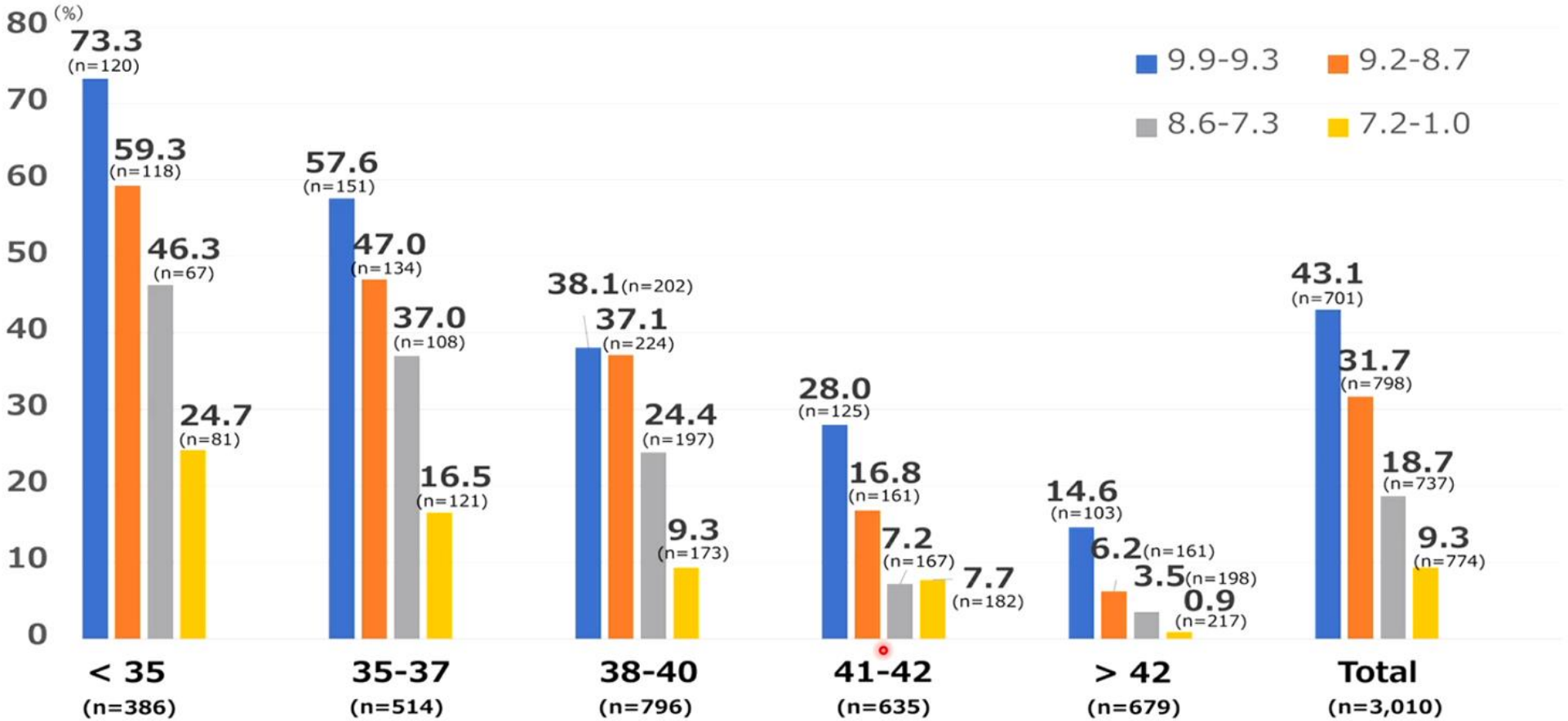
Finalise

Embryo	Score	Fresh ○ All ●	Pronuclei	Decision
AA-1	9.0			
AA-2	8.9			
AA-4	8.9			
AA-6	8.2			
AA-7	6.7			
AA-8	8.9			
AA-9	9.5			✓
AA-10	8.9			

FERTILITY

European Society of Human Reproduction and Embryology

The correlation between LB rates and each iDAScore group stratified by SART maternal age groups.



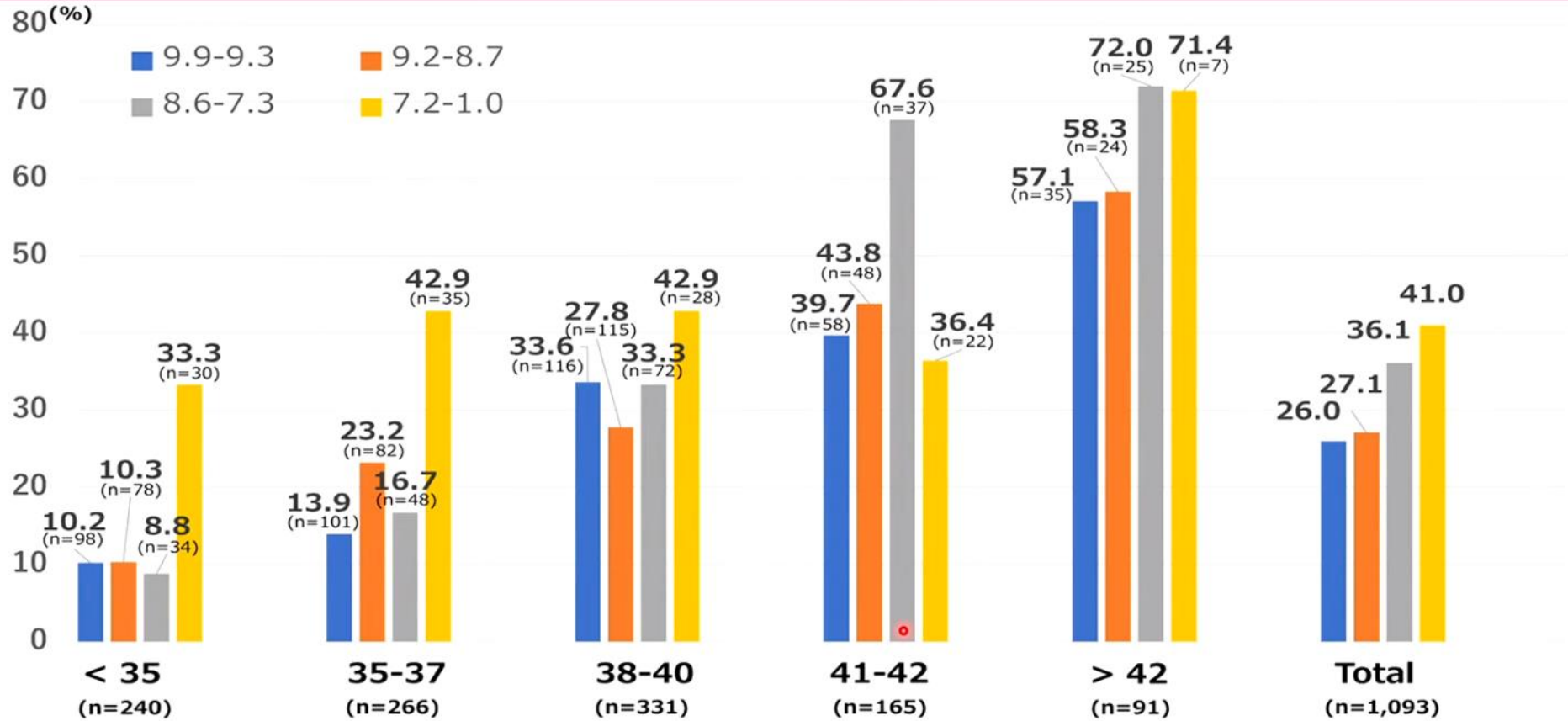
In each maternal age group, LB rates significantly decreased when the iDAScore group decreased ($P<0.05$)

Kato Ladies Clinic

Journal of Assisted Reproduction and Genetics (2022) 39:2089–2099
https://doi.org/10.1007/s10815-022-02562-5

European Society of Human Reproduction and Embryology

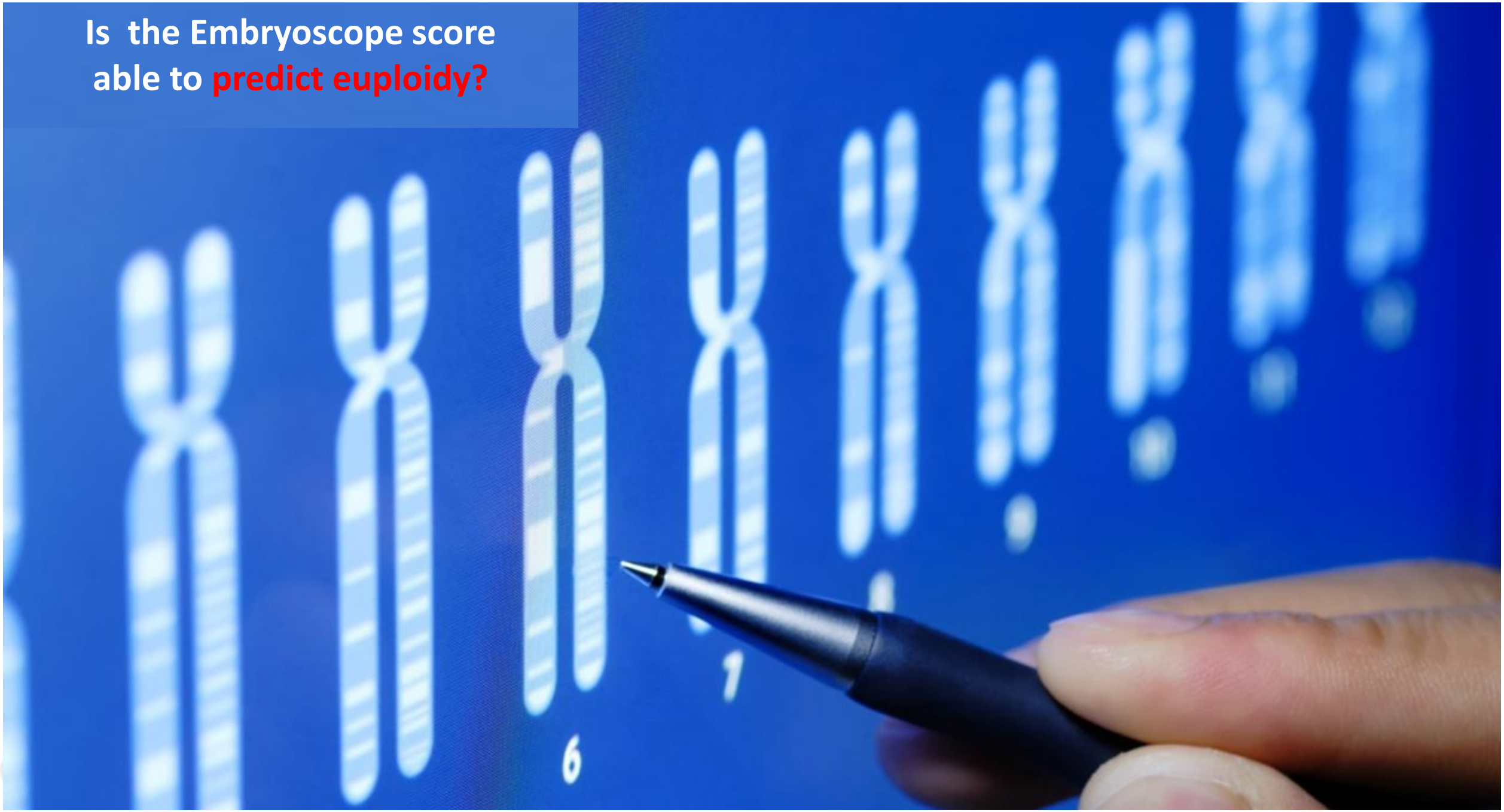
The correlation between miscarriage rates and each iDAScore group stratified by maternal age



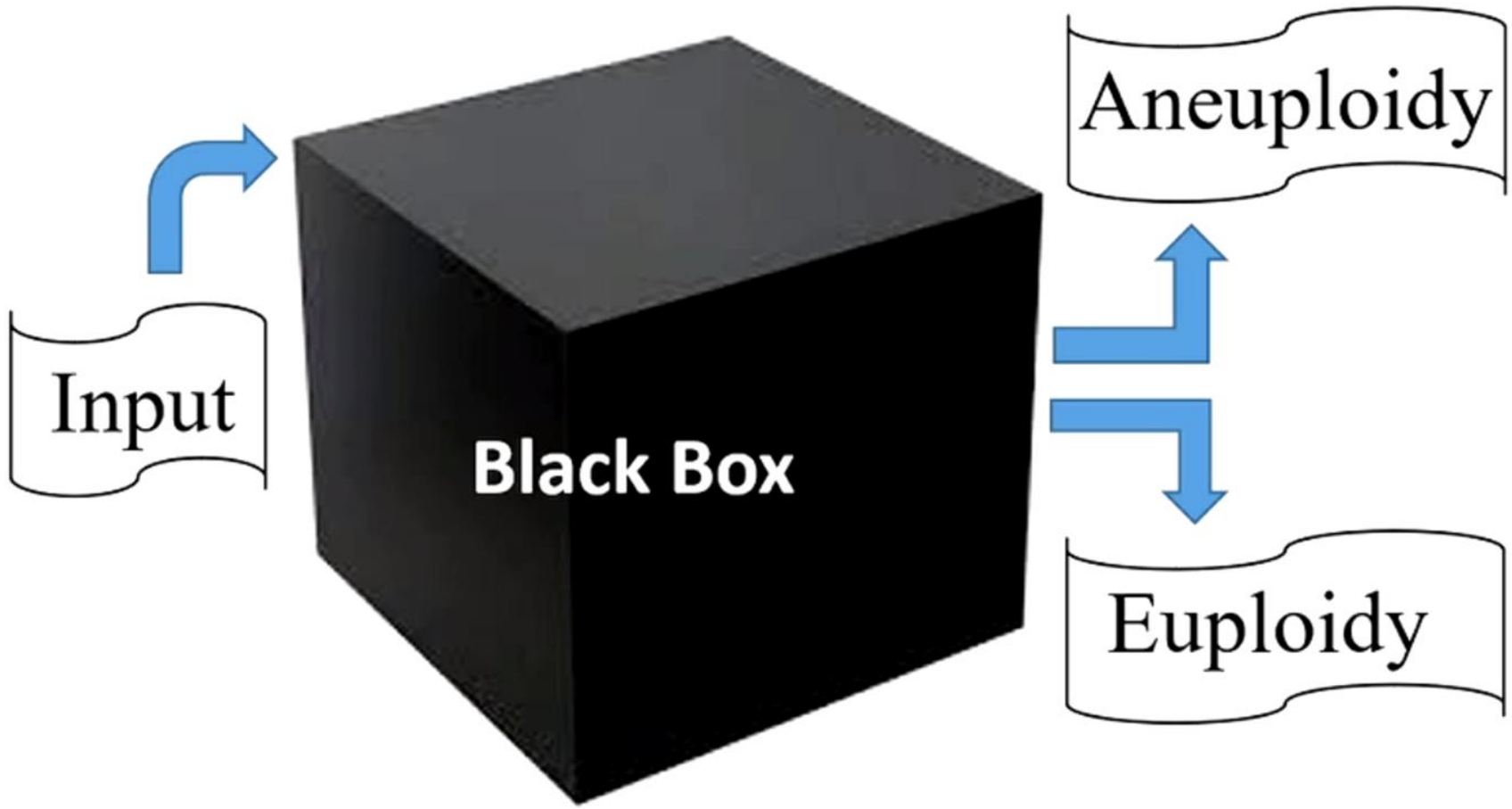
TM rates significantly increased progressively with decreasing iDAScores, except in the 38–40 year-old group and >42 years-old group (P<0.05).

Journal of Assisted Reproduction and Genetics (2022) 39:2089–2099
https://doi.org/10.1007/s10815-022-02562-5

Is the Embryoscope score able to predict euploidy?



- Noninvasive PGT: Current Status



FERTILITY

Time-lapse monitoring: an adjunct tool to select embryos for preimplantation genetic testing

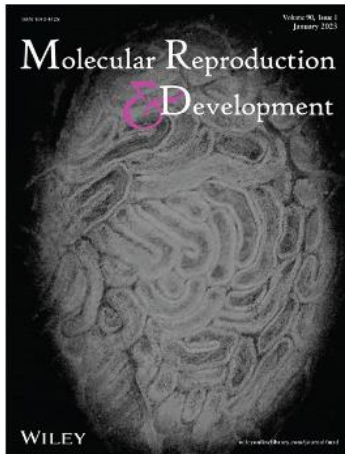


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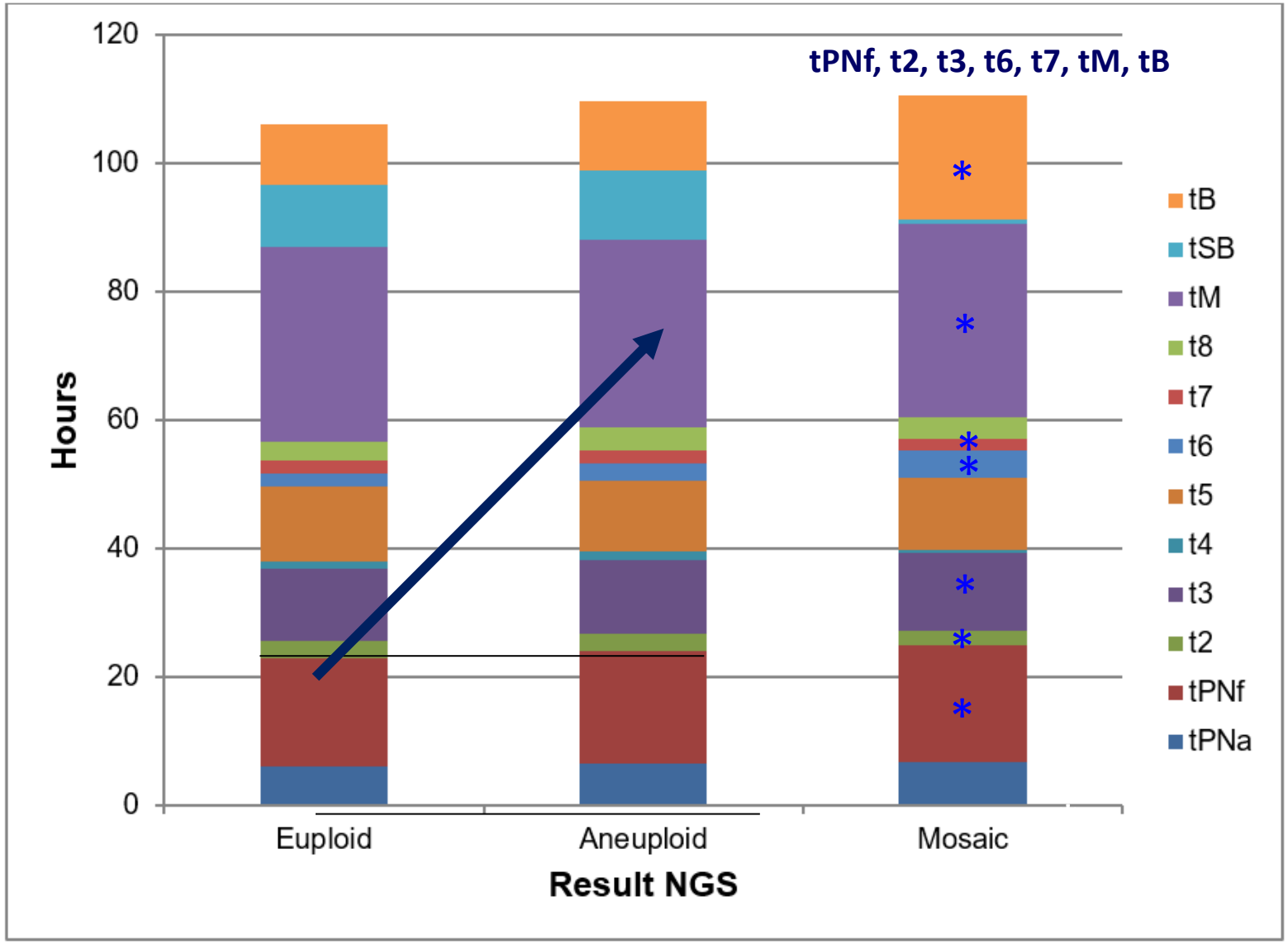
Table 1: General characteristics of patients and laboratory ICSI cycle outcomes (n=316)

		Mean	Std. Deviation
Female age (years)		38.3	3.4
Male age (years)		40.2	5.5
Total dose of FSH	Follitropin alfa (IU)	2615.7	799.2
	Follitropin delta (µg)	152.8	34.7
Oestradiol level on hCG trigger (pg/mL)		2127.9	2104.2
Follicles (n)		13.1	8.6
Retrieved oocytes (n)		10.0	7.1
Oocyte yield (%)		76.8	17.0
Mature oocytes (n)		7.7	5.9
Mature oocyte rate (%)		77.4	19.2
Fertilization rate (%)		77.7	19.0
Blastocyst development (%)		53.6	31.4

Note: ICSI – intracytoplasmic sperm injection; FSH– follicle stimulating hormone; hCG – human chorionic gonadotropin



FERT

Figure 1: A comparison of the cumulative morphokinetic development of euploid, aneuploidy and mosaic embryos.

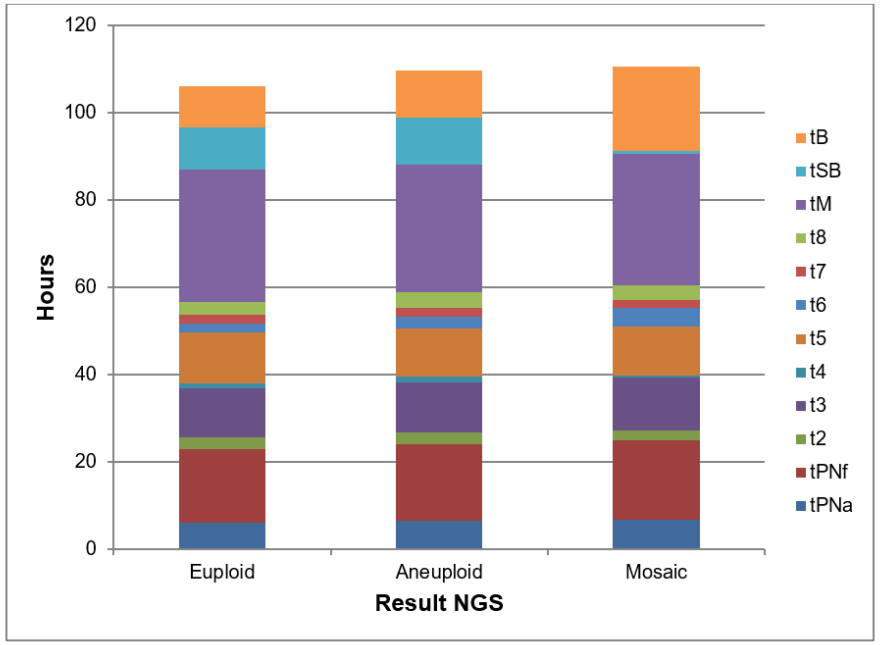


Figure 1: A comparison of the cumulative morphokinetic development of euploid, aneuploidy and mosaic embryos.

Morphokinetic data	Euploid embryos (n=352)	Aneuploid embryos (n=593)			Mosaic embryos (n=22)			p-value
KIDScore day 5	6.52±0.13[a]	5.54±0.10[b]	-0.97	-1.30 - -0.64	4.62±0.49[a.b]	-1.89	-2.89 - -0.88	< 0.001

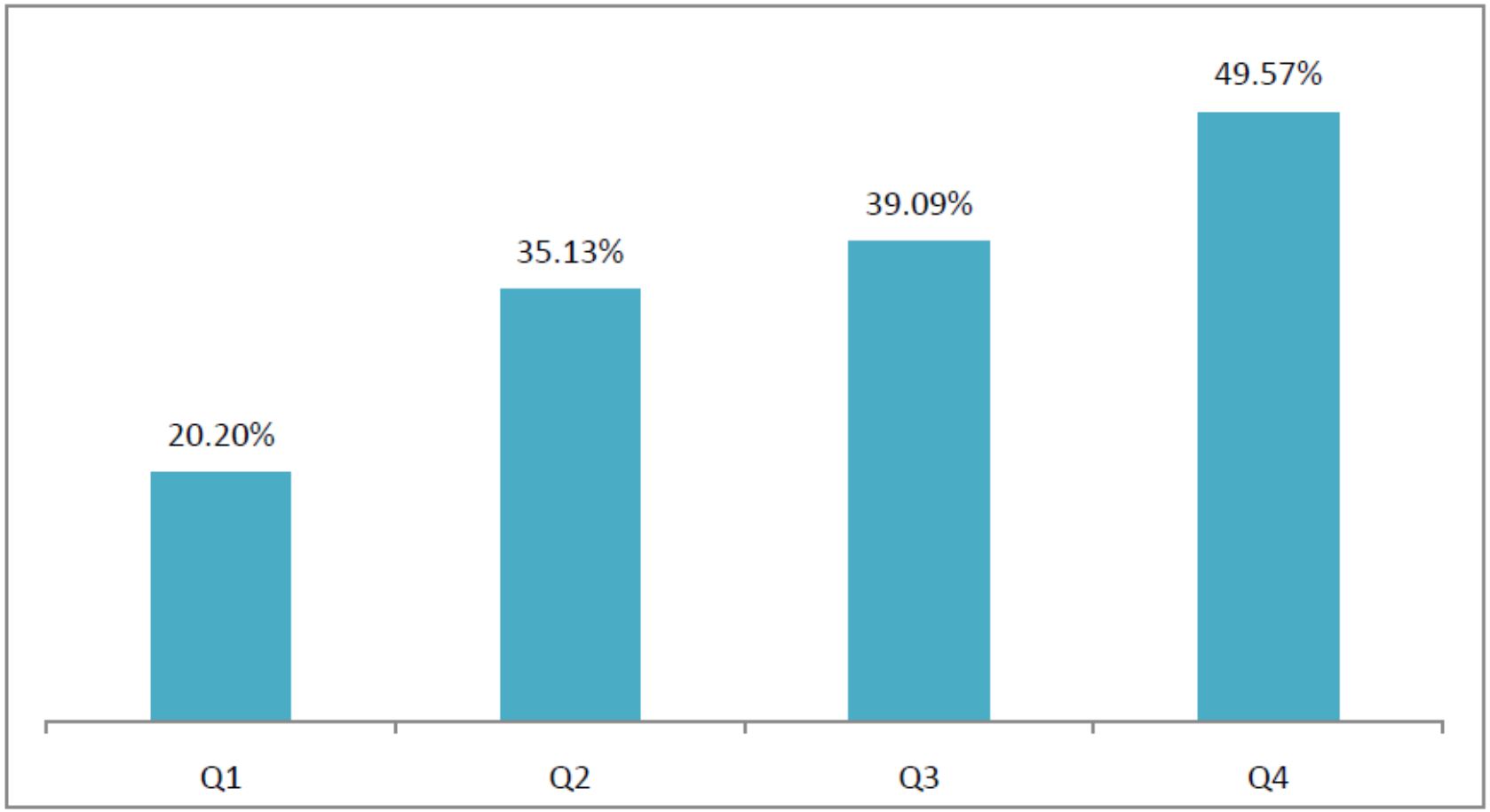


Figure 2: Distribution of the percentage of euploid embryos into the KIDScore D 5 categories, Q1 ≤3.9, Q2, between 4 and 5.6, Q3 between 5.7 and 7.5, and Q4 ≥7.6

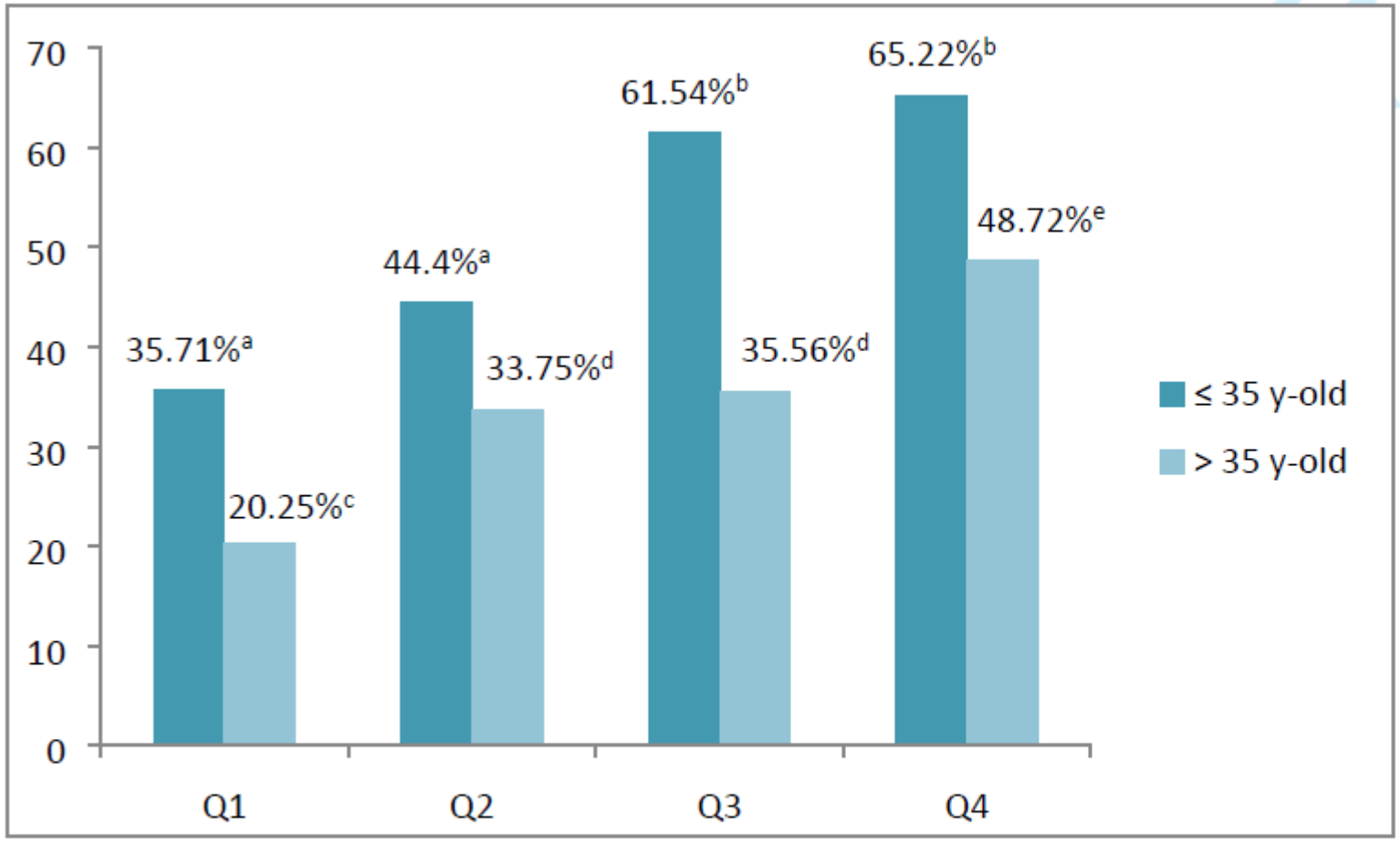


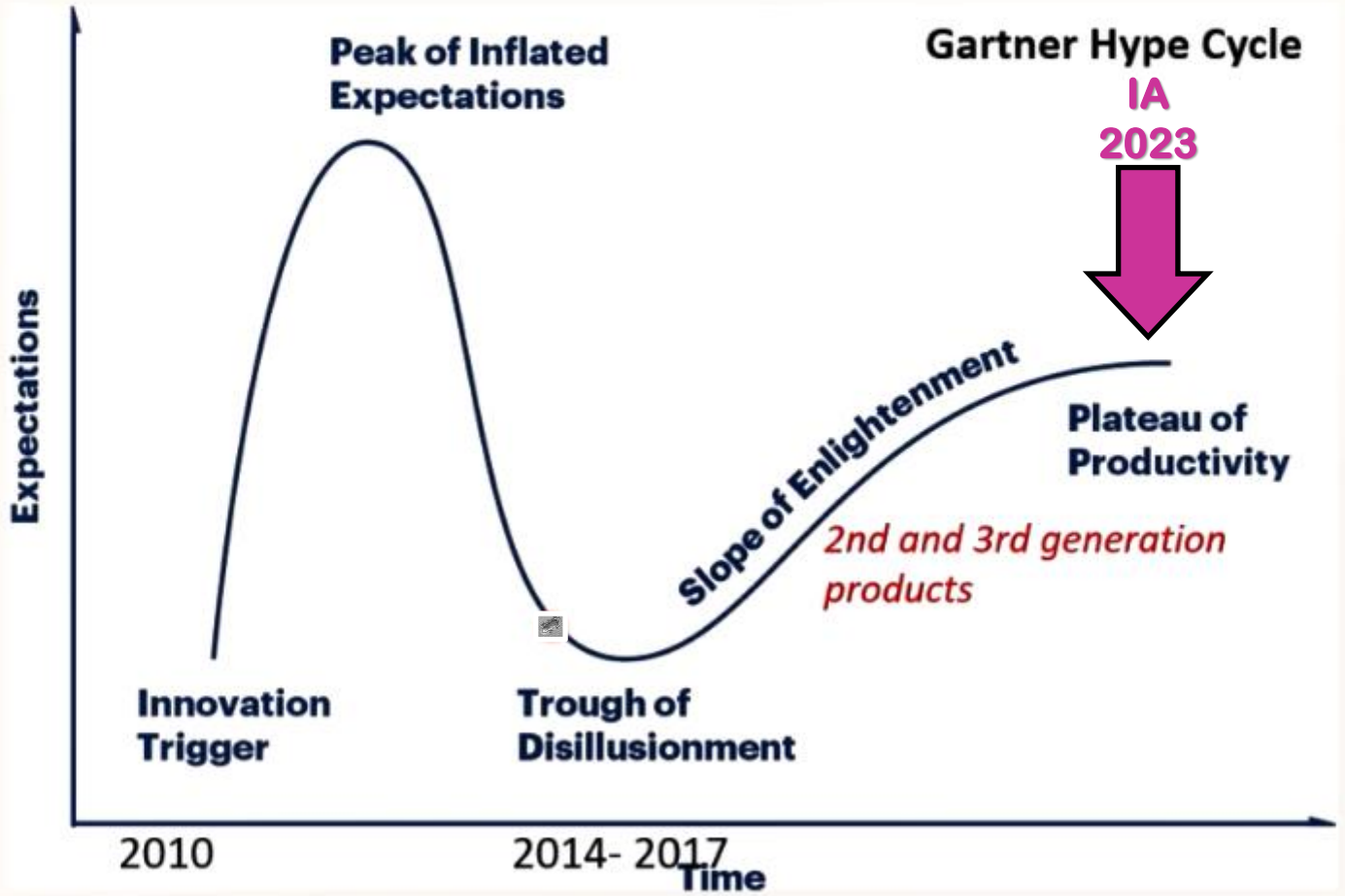
Figure 3: The distribution of the chance of being euploid according with the KIDScore D 5 category: Q1 ≤3.9, Q2 between 4 and 5.6, Q3 between 5.7 and 7.5, and Q4 ≥7.6. a≠b≠c≠d≠e.

Time lapse technology (TLT) – Ideal automation partner

From past to future...

Gartner Hype cycle

Five key phases of a technology's life cycle



Embryo through the lens: from time-lapse cinematography to artificial intelligence

Elnur Babayev, M.D. and Eve C. Feinberg, M.D.

Northwestern University Feinberg School of Medicine, Chicago, Illinois

https://doi.org/10.1016/j.fertnstert.2019.12.001

Brackett BG. In vitro fertilization of rabbit ova: time sequence of events. Fertil Steril 1970;21:169–76.

"Once a new technology rolls over you, if you're not part of the steamroller, you're part of the road."

—Stewart Brand

FERTILITY

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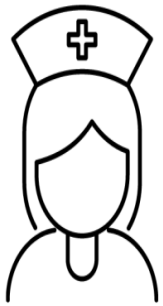

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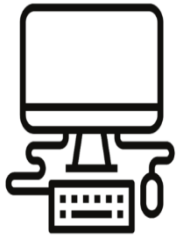

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Gracias!

Obrigado!

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