Recent Developments on the Transmission of Human Life

19 to 21 January 2023

Berlin, Germany

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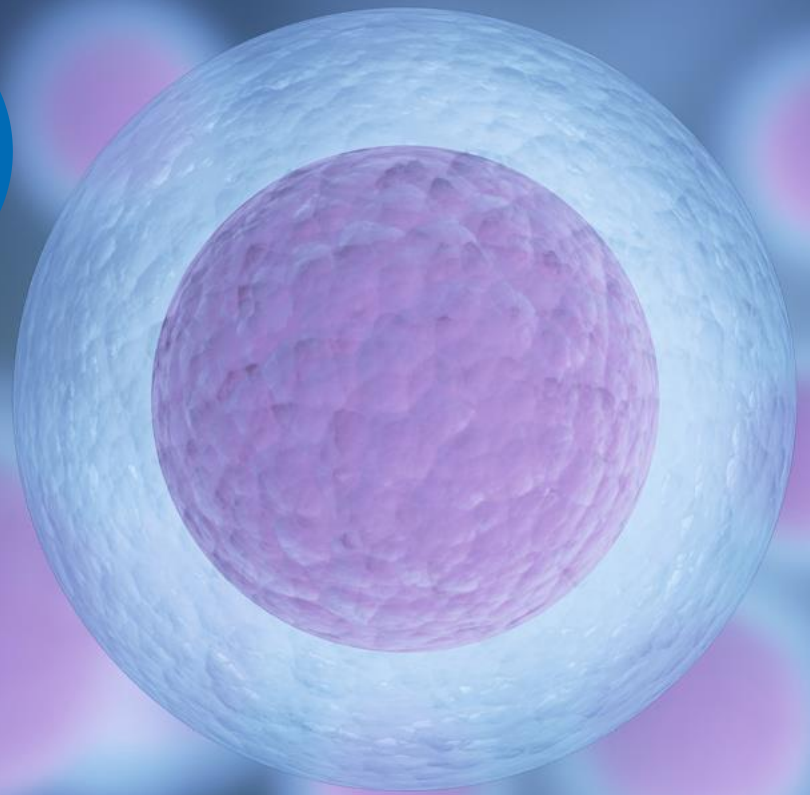
Recent Developments on the Transmission of Human Life

How to manage difficult embryo transfers.

Prof. Paolo Emanuele Levi Setti



Full Professor of Obstetrics and Gynecology, Humanitas University
Director and Chair, Department of Gynecology,
Division of Gynecology and Reproductive Medicine, Fertility Center,
IRCCS - Humanitas Research Hospital.

Faculty Disclosure

I have no potential conflict of interest to declare.

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viable embryo

receptive endometrium

optimal ET technique

- It is estimated that a **poor ET** technique may be responsible for **30%** of all IVF failures *(Cohen J, ASRM 1998)*
- Despite the apparent simplicity of the ET, difficult transfers **are frequent** and have been shown to **significantly** decrease PR *(Kava-Braverman, F&S 2016)*.

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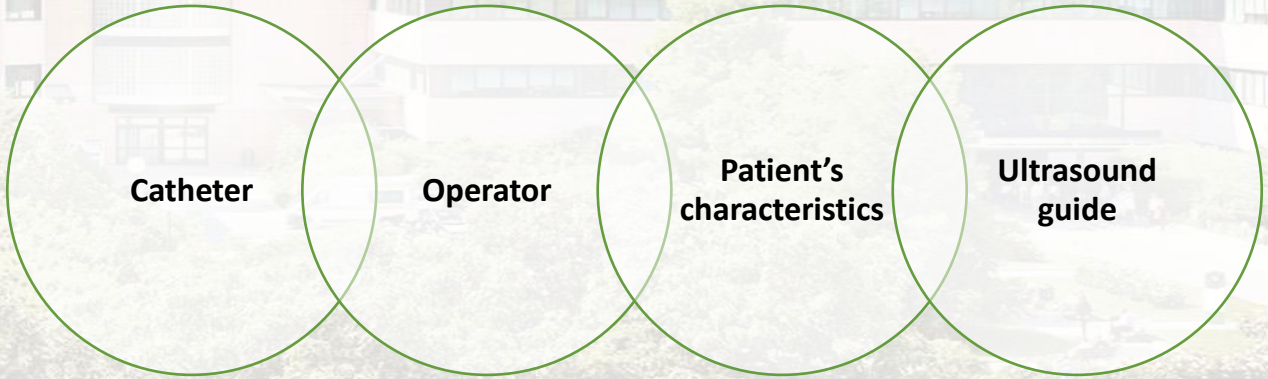
Difficult embryo transfer: outline

- Definition
- Clinical relevance
- Variables involved



- Simulators usefulness

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What is a difficult transfer?

There is no universal definition of difficult ET, which makes an accurate comparison of studies even more difficult.

Study	Study type, location and size	Intervention	Inclusion and exclusion	Embryo transfer	Markers of difficult transfer	Outcomes	NOS
Bodri (2008)	Spain, single centre RCT, $n=330$	Transabdominal ultrasound versus transvaginal	Fresh IVF donor cycles	Day 2 or 3 transfer with soft catheter, full bladder for TA, unclear for TV	Longer, more difficult, repeat transfer or use of dilator. Any amount of blood	Clinical pregnancy rate, ongoing pregnancy rate, miscarriages	7
Drakeley (2008)[a]	UK-based, single centre RCT, $n=2276$	Ultrasound-guided versus clinical touch	All IVF and ICSI cycles using fresh and frozen embryos	Variety of soft catheters, "comfortably full" bladder. Day of transfer unclear	Use of outer sheath, stylet or tenaculum	Clinical pregnancy rate	7
Eskander (2008)	Saudi Arabia, single centre RCT, $n=373$	Ultrasound-guided versus clinical touch	Fresh IVF cycles with good-quality embryos	Day 3 transfer with Sydney catheter and full bladder	Blood and mucus on catheter tip	Clinical pregnancy rate	7
Karande (2002)	USA, single centre, quasi-RCT, $n=251$	Cook Echotip™ versus Wallace catheter	Not stated. Fresh, frozen and donor embryo IVF cycles	Day 3 transfer with soft catheter, full bladder and ultrasound-guidance	Blood on catheter tip	Clinical pregnancy rate	7
Mansour (1990)	Egypt, single centre, quasi-RCT, $n=168$	Mock transfer prior to IVF cycle	Not stated. Fresh IVF cycles	Day 2 transfer with Wallace, Craft or metal catheter. No ultrasound	Required "manipulations and strong push" or use of the metal catheter	Clinical pregnancy rate	7
Rhodes (2007)	USA, single centre RCT, $n=99$	Cook™ versus Wallace™ catheter	Fresh IVF and ICSI cycles. Less than 40 years old, BMI 20–35, first cycle of IVF	Day 3 transfer with mock transfer at time of transfer. Moderately full bladder/use of ultrasound not clear	"Tinge", moderate, or extensive blood on or in the catheter	Clinical pregnancy rate	7
Rhodes (2005)	USA, single centre, prospective cohort study, $n=205$	To determine factors instrumental in ART outcome	Fresh IVF and ICSI cycles. Less than 40 years old, BMI 20–35, first cycle of IVF	Day 3 transfer with soft catheter and mock transfer at time of transfer. Moderately full bladder, ultrasound used in some transfers	"Tinge", moderate, or extensive blood on or in the catheter	Clinical pregnancy rate	7
Shaker (1993)[b]	UK-based, single centre retrospective cohort study, $n=398$	To assess ease of transfer and pregnancy rate	None stated. All cycles included	Unclear	Anything other than a smooth and direct insertion	Clinical pregnancy rate	7
Shaker (1993)[b]	UK-based, single centre RCT, $n=120$	Sublingual GTN 3 min prior to transfer versus placebo	First cycle of IVF	Transfer with Wallace catheter and empty bladder	Use of outer sheath, tenaculum or uterine sound, or a need to fill the bladder	Clinical pregnancy rate	7
Spandorfer (2003)	USA, single centre retrospective cohort study, $n=2263$	To identify which factors influence pregnancy outcome	IVF cycles with fresh embryos	Day 3 transfer with Wallace catheter and mock transfer. Ultrasound was not used	Required manipulation, multiple attempts, force, dilatation, or resulted in trauma	Clinical pregnancy rate	7

Philip J et al, Europ J Obst Gynecol Reprod Biol 2013

What is a difficult transfer?

- Use of an outer catheter sheath
- Use of malleable stylet
- Use of tenaculum
- Use of hysterometer
- Resistance to embryo expulsion
- Presence of blood and/or mucus in the catheter after withdrawal
- Longer procedure

And more…

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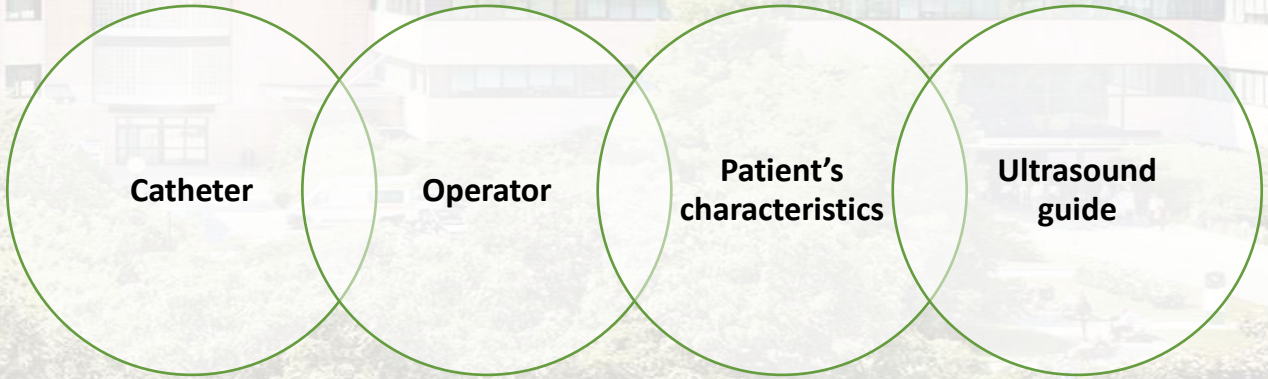
Difficult embryo transfer: outline

- Definition
- Clinical relevance
- Variables involved



- Simulators usefulness

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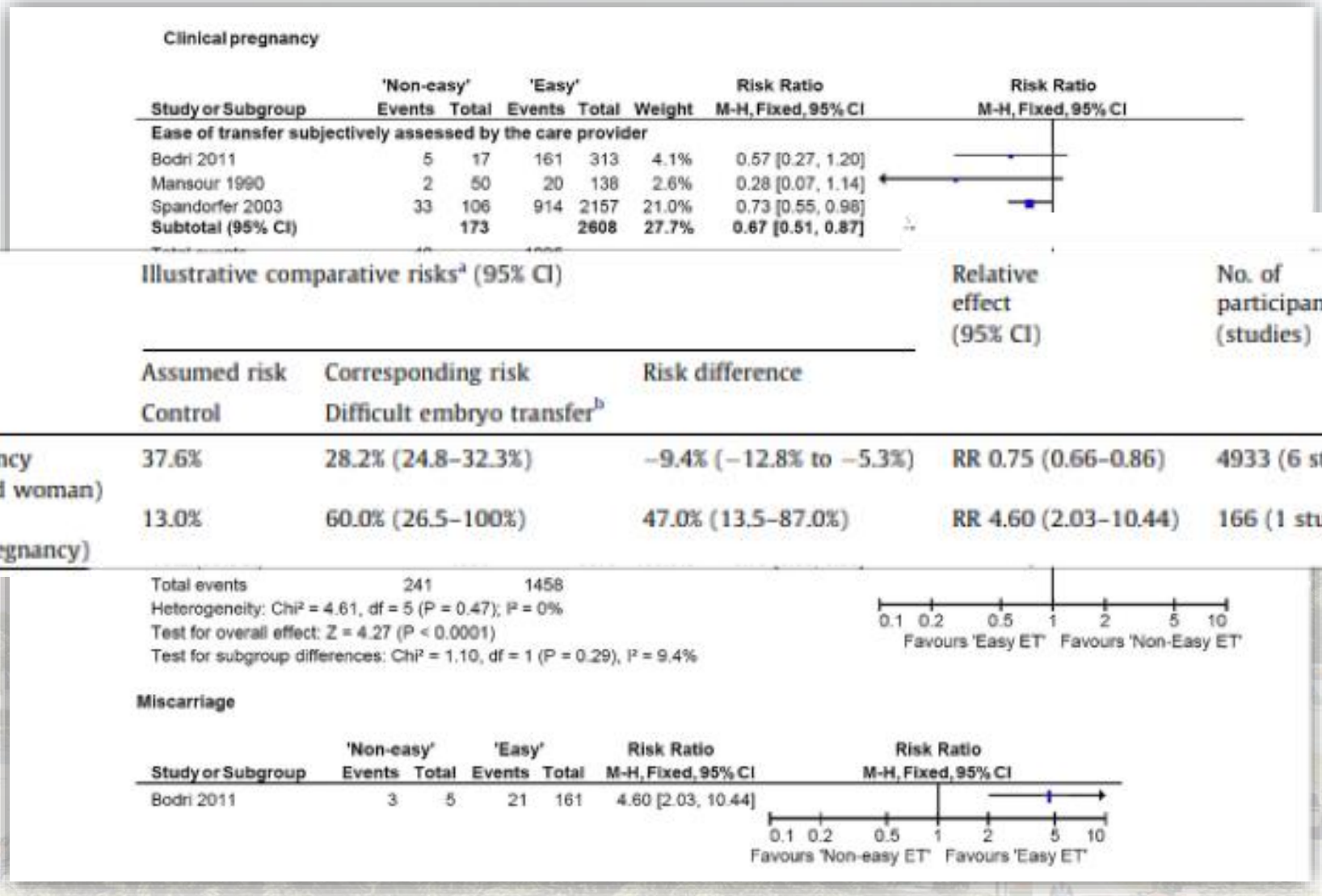
Difficult embryo transfer compromises success

Forest plots for clinical pregnancy and miscarriage: comparison between ‘Non easy’ versus ‘Easy’ embryo transfers.



Illustrative comparative risks[a] (95% CI)				Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Difficult embryo transfer[b]	Risk difference			
Clinical pregnancy (per allocated woman)	37.6%	28.2% (24.8–32.3%)	−9.4% (−12.8% to −5.3%)	RR 0.75 (0.66–0.86)	4933 (6 studies)	⊕⊕⊕⊖ low[c]
Miscarriage (per clinical pregnancy)	13.0%	60.0% (26.5–100%)	47.0% (13.5–87.0%)	RR 4.60 (2.03–10.44)	166 (1 study)	⊕⊖⊖⊖ very low[d]

Philip J et al, Europ J Obst Gynecol Reprod Biol 2013

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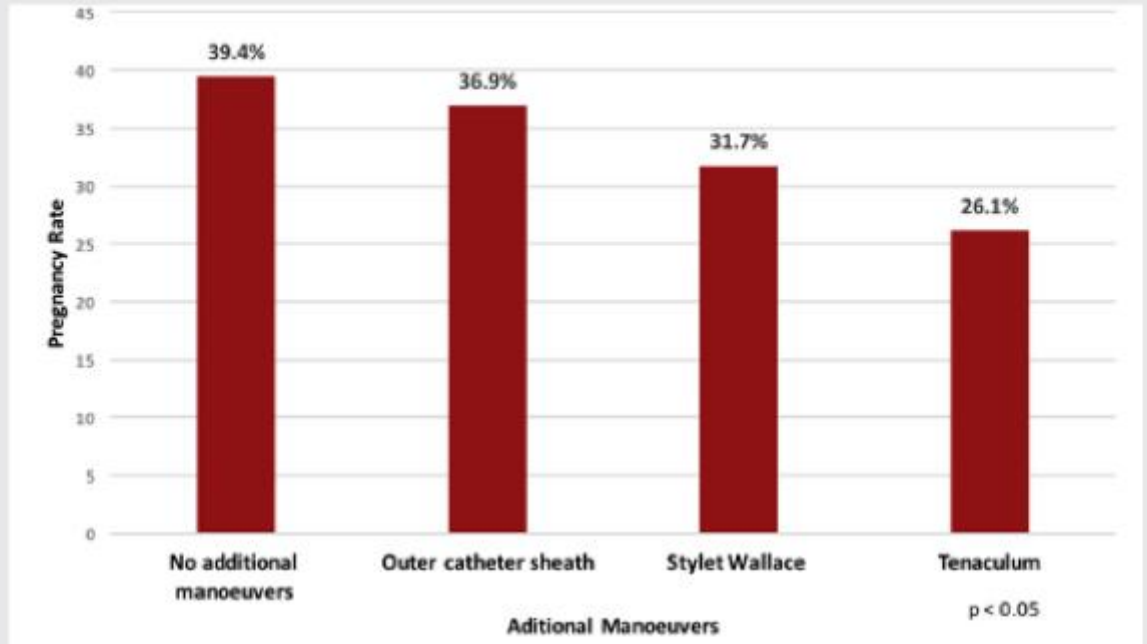
Difficult embryo transfer compromises success



	CPR (%)	OR (95 CI)		Adjusted OR* (95 CI)	
No additional manoeuvers	39.4	1	-	1	-
Outer catheter sheath	36.9	0.87	(0.77 - 0.99)	0.89	(0.79 - 1.01)
Stylet Wallace	31.7	0.68	(0.59 - 0.78)	0.71	(0.62 - 0.81)
Tenaculum	26.1	0.47	(0.32 - 0.71)	0.54	(0.36 - 0.79)

Clinical pregnancy rate and OR of CPR with additional maneuvers. *Adjusted OR for ART (IVF/ICSI in fresh embryo transfer or frozen–thawed embryo transfer), number of transferred embryos, the day of ET, physicians who performed the ETs, embryo quality, and the interaction between age and technique.

Difficult ET significantly reduces the CPR from **38.2% to 27.1% (P<.001**) and the LBR from **28.0% to 19.0%** (P<.001).

Kava-Braverman, Fertil Steril 2016

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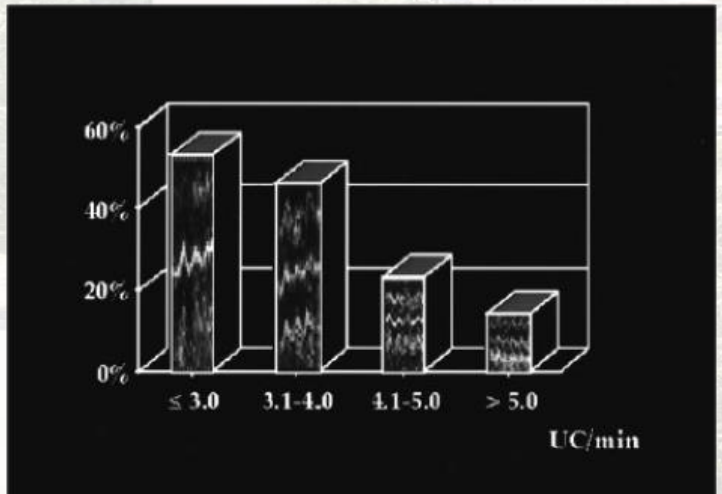
Why does difficult ET compromise implantation?

Main hypothesis

Endometrial lesion

Uterine contractions



Bulletti&deZiegler, Curr Opin Obster Gynecol 2006

Marconi G, Fertil Steril 2003

Stepwise decrease in clinical pregnancy rates from the lowest to the highest uterine contraction (UC) frequency groups.

Franchin R, Human Reprod 1998

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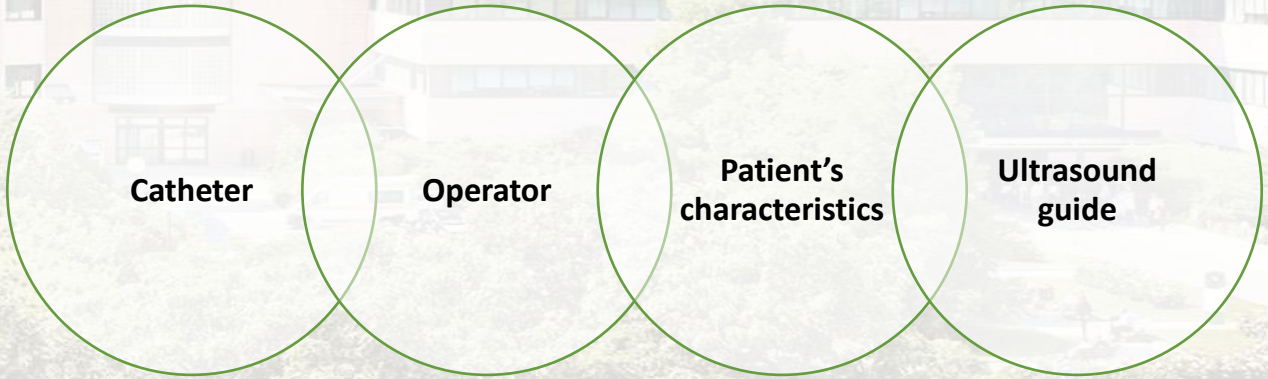

- Simulators usefulness

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Variables involved: ET catheters

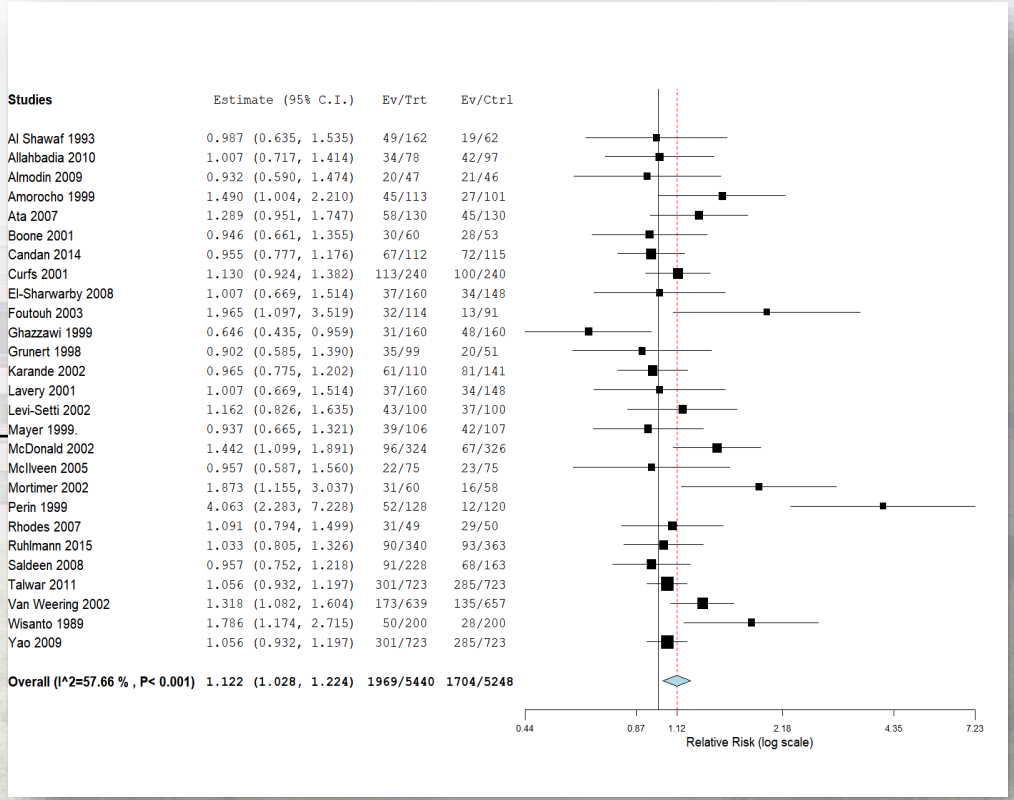
Catheters League

Soft catheter

VS

Hard catheter

27 RCTs



CPR primary outcome
No RCT evaluating difficult ET rate

Tyler B et al, Human Reprod Update 2022

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Variables involved: ET catheters

Catheters League

Direct technique

VS

Afterload technique

1 RCT

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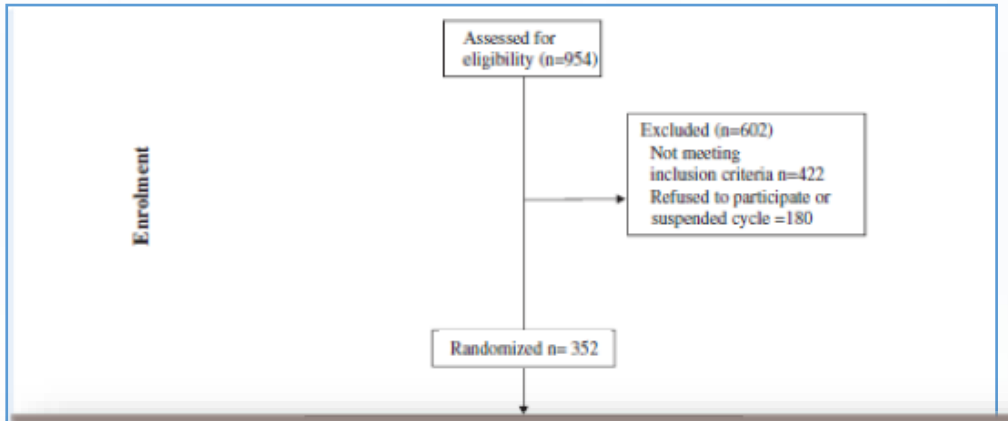
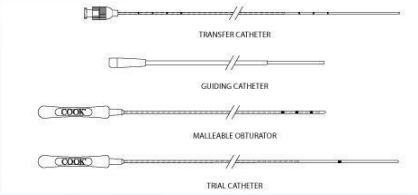
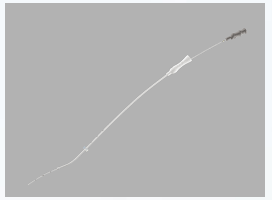
Direct vs Alterload tecniques on the rate of difficult ETs



- Patients < 38 years of age
- BMI between 18 and 28
- Only d5-d6 frozen blastocyst
- Excuded ICSI-TESE and PGT-A cycles





		Protocol	
		Direct	Afterload
Transfer	Simple	Straight-forward advancing of the preloaded inner catheter through the cervix, the internal os and the uterine cavity up to the site of embryo release	Straight-forward advancement of the outer catheter through the cervix up to the internal os followed by advancement of the inner loaded catheter to the site of embryo release
	Difficult	Advancement of the outer sheath, multiple attempts, use of force, required manipulation, use of a stylet or tenaculum, dilatation, or use of a different catheter	Required manipulation, multiple attempts, use of force, use of a stylet or tenaculum, dilatation, or use of a different catheter

Levi-Setti et al, Human Reprod 2021

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Direct vs Alterload tecniques on the rate of difficult ETs

	ALL CYCLES	Direct	Afterload	OR (95% CI)	P
N	352	176	176		
Difficult transfers	85 (24.1%)	68 (38.6%)	17 (9.7%)	0.17 (0.09–0.30)	<0.001
Average rate of difficult transfers per operator % (SD)	22.5 (14.5)	36.1 (23.4)	8.6 (8.2)		<0.001
Range of difficult transfer per operator (%)	0-43.8	0-77.8	0-25.0		
Biochemical pregnancies	21 (6.0%)	8 (4.5%)	13 (7.4%)	1.67 (0.68–4.15)	0.368
Viable intrauterine pregnancies	159 (45.2%)	74 (42.0%)	85 (48.3%)	1.29 (0.85–1.96)	0.239
Implantation rate % (SD)*	46.0% (51.6)	43.2% (51.9)	48.9% (51.3)		0.265
Ectopic Pregnancies	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Miscarriages	32 (20.1%)	16 (21.6%)	16 (18.8%)	0.84 (0.39–1.83)	0.661
Terminations of pregnancy	2 (1.3%)	0 (0.0%)	2 (2.4%)		0.499
Deliveries	125 (35.7%)	58 (33.1%)	67 (38.3%)	1.25 (0.81–1.94)	0.315

*One set of twins occurred in each group (live births) and one more twin pregnancy occurred in the direct group (miscarriage). Twins are considered as two implantations.

Primary outcome

Secondary outcomes

Levi-Setti et al, Human Reprod 2021

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Direct vs Alterload tecniques on the rate of difficult Ets - Operator's role

Levi-Setti et al, Human Reprod 2021

Mantel–Haenszel analysis of operator total number of transfers performed and difficult transfers

Operator ID	Total no. of procedures	No. difficult transfers	OR (95% CI)	P
1	27	5	0.44 (0.04–4.94)	0.492
2	18	2	0	
3	20	5	0	
4	8	0	NC	
5	57	17	0.12 (0.02–0.56)	0.001
6	27	7	0.27 (0.04–1.93)	0.160
7	15	1	0	
8	2	0	NC	
9	9	3	0.25 (0.01–6.69)	0.371
10	5	2	0	
11	18	5	0.08 (0.00–1.62)	0.031
12	27	7	0.27 (0.04–1.93)	0.160
13	27	2	0.92 (0.05–17.39)	0.957
14	20	8	0.03 (0.00–1.16)	0.002
15	21	9	0.25 (0.02–3.19)	0.248
16	20	4	0.33 (0.03–3.60)	0.342
17	16	7	0.20 (0.02–2.19)	0.143
18	15	1	0	
Total	352	85		

Stratifying operators by their number of procedures performed and their rate of difficult transfers no statistically significant results were found (test of homogeneity of ORs, P¼0.954)

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Direct vs Alterload tecniques on Pregnancy Rate

Retrospective study
Same population of the RCT
6-year period
8,189 single blastocyst transfers

- CPR of **afterload group** resulted significantly higher compared to direct group
  (44.69% versus 41.65%, OR 1.13, 95% CI 1.02-1.25, p=0.017)
- The rate of difficult transfers two-thirds lower
  (9.06% versus 26.85%, OR 0.27, 95% CI 0.24-0.31, p<0.001)

Interaction between technique and difficult ET on CPR. Reference value: direct easy ET (OR=1)

	OR (95% CI)	P value
Afterload easy ET	0.97 (0.82-1.14)	0.685
Afterload difficult ET	0.85 (0.67-1.08)	0.197
Direct difficult ET	0.62 (0.49-0.77)	<0.001

- Afterload technique showed the same CPR of an easy transfer performed with the direct method, no matter whether the ET was easy or difficult.
- For afterload method the presence of a difficult ET was not a limit, concerning the direct one, in case of difficulty, the CPR was reduced.

Cirillo et al, under review RBM

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Direct vs Alterload tecniques on Pregnancy Rate - Operator's role

Interaction between technique and difficult ET among different operators

	All cycles	Afterload	Direct	OR (95% CI)	p
N	8,189	6,189	2,000		
Difficult transfers	1098 (13.41%)	561 (9.06%)	537 (26.85%)	0.27 (0.24-0.31)	<0.001
Average rate of difficult transfers per operator % (SD)	13.4 (34.0)	8.6 (28.0)	26.6 (44.2)		<0.001
Range of difficult transfer per operator %	1.9-25.3	0.8-20.5	3.8-45.4		

The afterload technique, facilitating the procedure, improved the operator performance in term of PR and has a shorter learning curve.

Cirillo et al, under review RBM

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Direct vs Alterload tecniques on Pregnancy Rate - Operator's role

Human Reproduction, Vol.35, No.2, pp. 275–282, 2020
Advance Access Publication on February 25, 2020 doi:10.1093/humrep/dez290

human reproduction ORIGINAL ARTICLE *Embryology*

The human factor: does the operator performing the embryo transfer significantly impact the cycle outcome?

F. Cirillo[1], P. Patrizio[2], M. Baccini[3], E. Morenghi[4], C. Ronchetti[1], L. Cafaro[1], E. Zannoni[1], A. Baggiani[1], and P. E. Levi-Setti[1,*]

- PR is influenced by the operators who perform the embryo transfer
- Experience does not assure proficiency for everyone

Afterload protocol seems to lead to a higher homogeneity in difficult transfer rate and consequently to a global improvement of the outcomes.

Cirillo et al, under review RBM

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Anatomical causes of difficult embryo transfer

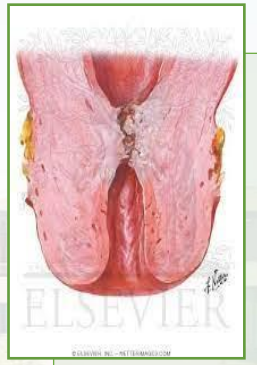
Garzo et al, Clin Obstet Gynecol 2006

Lasso et al, Human Reprod 1999

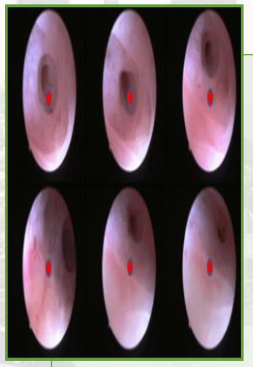
Franchin et al, Human Reprod 1998

Larue et al, J Gynecol Obstet 2017

Severe anteflaction/retroflexion



Cervical stenosis



Contraction of the internal os

Others: synechiae, histhmocele, polyps, myomas

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Anatomical causes of difficult embryo transfer

Anatomical characteristic	EET	DET	*P*-value[a]	DET		*P*-value[a]
	Total (*n* = 151)	Total (*n* = 155)		diffET (*n* = 100)	vdiffET (*n* = 55)	
Uterine position, n (%)						
Anteversion 3	17 (11)	40 (26)	<0.01	24 (24)	16 (29)	NS
Anteversion 2	84 (56)	85 (55)	NS	54 (54)	31 (56)	NS
Angle 0	38 (25)	14 (9)	<0.001	11 (11)	3 (5)	NS
Retroversion	12 (8)	16 (10)	NS	11 (11)	5 (9)	NS
Cervical canal, n (%)						
Direct						
Tortuous						
Very tortuous						
T + VT						
Presence of cervical cry						
Presence of IO contract						
Presence of other cause						

Anteversion 3 and 2 repre

[a] Between group compa

Larue et al, J G

	Univariable		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
Female age at transfer	1.00 (0.92–1.08)	0.969		
Female age at cryopreservation	1.02 (0.94–1.11)	0.575		
Female BMI	0.99 (0.90–1.09)	0.904		
Years of infertility	0.91 (0.81–1.03)	0.133	–	
Active smoking	0.96 (0.51–1.78)	0.894		
Myomas	0.32 (0.12–0.83)	0.019	0.30 (0.11–0.80)	0.017
Previous surgery on uterine cavity	2.46 (1.23–4.91)	0.011	2.56 (1.19–5.50)	0.016
Afterload	0.17 (0.09–0.30)	<0.001	0.16 (0.09–0.30)	<0.001

Levi-Setti et al, Human Reprod 2021

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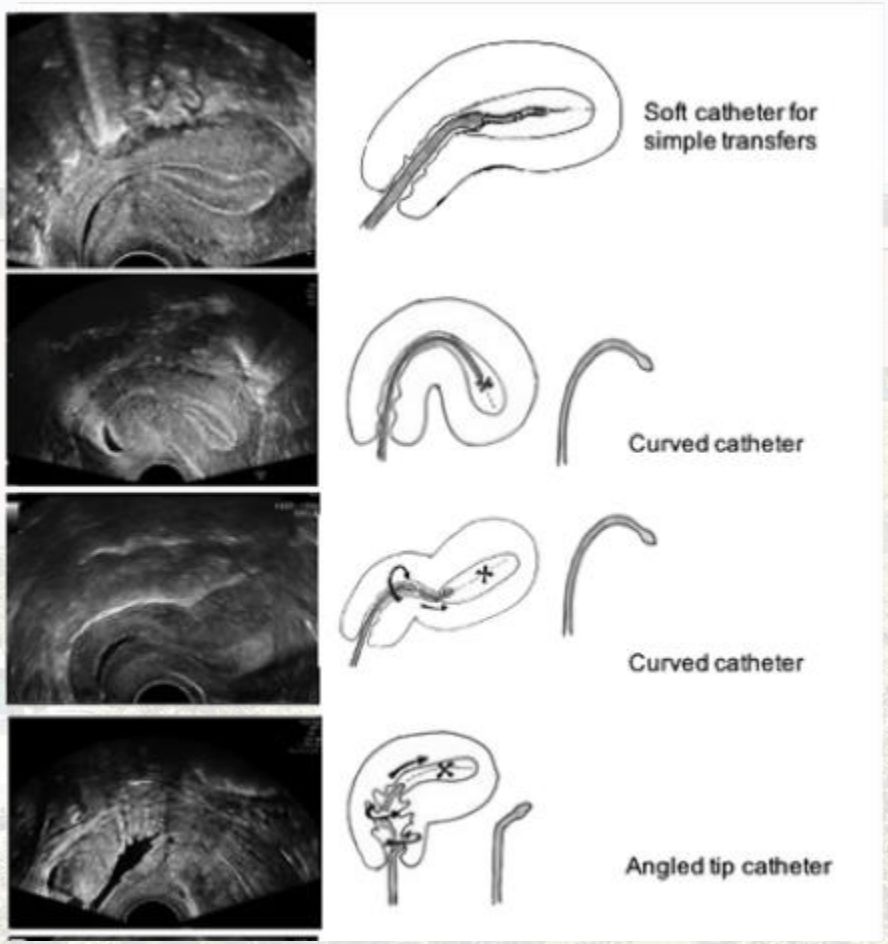
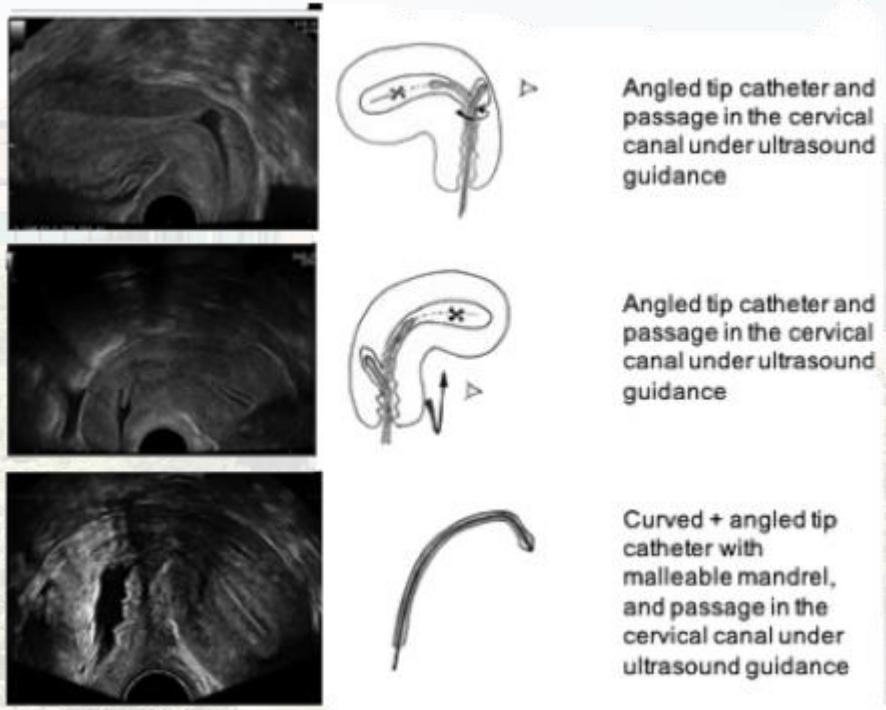
Evaluation of a strategy for difficult embryo transfers from a prospective series of 2,046 transfers

Fertil Steril Rep 2020

Lionel Larue, M.D., Ph.D.,[a] Laure Bernard, M.D.,[a] Julie Moulin, M.D.,[a] Anne Massari, M.D.,[a] Nino-Guy Cassuto, Ph.D.,[b] Dominique Bouret, M.D.,[b] and Gwenola Keromnes, M.D.[a]

[a] Centre de Fertilité - Groupe Hospitalier Diaconesses Croix Saint Simon, Paris, France, and [b] Laboratoire Dr





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Variables involved: use of ultrasound

ET under ultrasound guidance > ET guided by clinical touch

24 RCTs – data on CPR and LBR

Transvaginal ultrasound guidance = Transabdominal ultrasound guidance

7 RCTs – data on CPR and LBR

3D ultrasound guidance = 2D ultrasound guidance

1 RCT – data on CPR

Tyler B et al,Human Reprod Update 2022

When there is poor ultrasound visualization, the CPR diminishes significantly!

Kava-Braverman, Fertil Steril 2016

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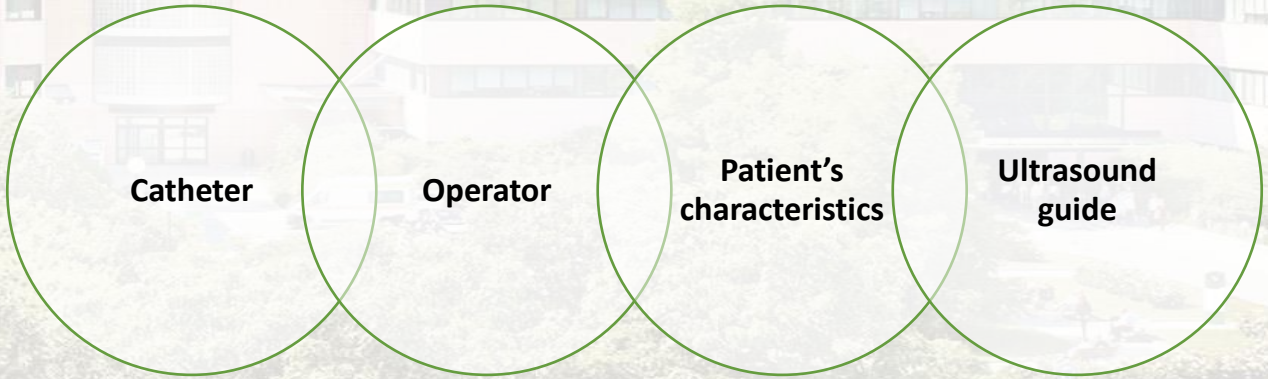

- Simulators usefulness

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Training for embryotransfer

HUMANITAS FERTILITY CENTER

Fellows training programm

75 procedures with support of a senior
At least 100 procedures autonomously

(based on ESHRE/EBCOG fellowship logbook)

- Only 44% of US Reproductive Endocrinology and Infertility (REI) fellowship trainees performed embryo transfers. *(McQueen et al, Fertil Steril 2020)*
- 21% of trainees performed no embryo transfers *(Segars&Thomas, Fertil Steril 2021)*

logical answer = **simulation**

acquisition of skills in challenging situations

Embryo Transfer Certificate Course

Two-day simulation workshops using four different uterine models
five direct transfers
five afterload transfers

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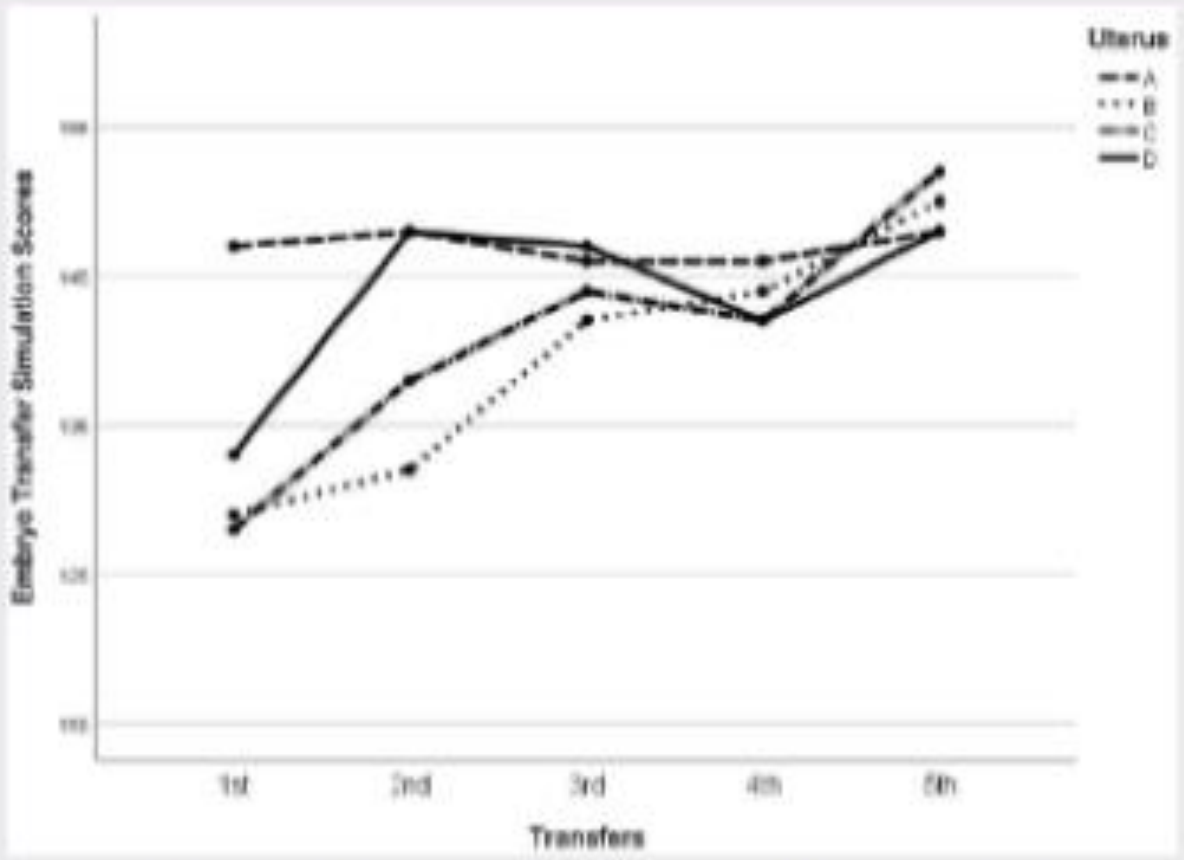
Simulation training for embryo transfer on the rate of difficult ETs



Comparison of simulation scores for the first through fifth transfers of the different uteri for the afterload technique.

Ramaiah. Simulation training for embryo transfer. Fertil Steril 2020.

Uterus A is a straight forward transfer with an axial uterus and a straight, but short, cervical canal.

Uterus B presents an anteflexed uterus with a canal that initially points downward and then points upward with theanteflexion.

Uterus C has a torturous cervical canal.

Uterus D presents a ridge at the upper posterior cervical canal across from which a false passage arises.

The ET simulation scores (degree of ease) for fellows using the uterine B, C and D models showed a progressive and significant increase across the five afterload ETs.

In addition to skill acquisition, trainee confidence also significantly improved

Ramaiah S et al,Fertil Steril 2021

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Simulation training for embryotransfer on Pregnancy Rate

A simulated embryo transfer cannot take the place of a live embryo transfer, just as a flight simulator cannot teach a pilot to fly!

Embryo transfer simulation improves pregnancy rates and decreases time to proficiency in Reproductive Endocrinology and Infertility fellow embryo transfers

Heitman R et al,Fertil Steril 2017

Embryo transfer training in fellowship: national and institutional data

NO learning curve when pregnancy rate was the outcome

McQueen et al, Fertil Steril 2013

….a correlation between improvement in skills and pregnancy outcome associated with the curriculum remains to be demonstrated.

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Interventions to optimize embryo transfer technique

- Soft catheter
- Afterload technique
- Identification of anathomical variants
- Use of ultrasound
- Simulation training

Bladder fullness
Three RCTs
(Mitchell et al., 1989; Lewin et al., 1997; Lorusso et al., 2005)
NO differences

Pressure on cervix
Two RCTs
(Mansour, 2005; Amui et al., 2011)
NO differences

Pump regulated transfer Vs Manual
One RCT
(Caanen et al., 2016)
NO differences

Cervical mucus removal
Six studies
(Ruhlman et al, 1999; Soroka et al, 1999; Glass et al, 2000; Berkkanoglu et al, 2006; Visschers et al, 2007; Moini et al, 2011)
NO differences

Tyler B et al,Human Reprod Update 2022

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Take home messages

Difficult ETs are associated with lower CPR.

Progressive decline in CPR as the level of the ET difficulty increases.

Few RCTs - No difficult ET rate as primary outcome.

Difficult standardization.

The positive effect of afterload technique on CPR is mediated by its ability to reduce difficult transfers.

Training in the ET and routine analyses of performance are important measures to standardize ET.

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Recent Developments on the Transmission of Human Life

How to manage difficult embryo transfers.

Paolo Emanuele Levi Setti

Thanks for your attention

Full Professor of Obstetrics and Gynecology, Humanitas University
Director and Chair, Department of Gynecology,
Division of Gynecology and Reproductive Medicine, Fertility Center,
IRCCS - Humanitas Research Hospital.