



Antti Perheentupa, MD, PhD **Reproductive Medicine and Andrology** Dept of Obstetrics and Gynecology **Turku University Hospital** FINLAND

Int@FedFertilitvSoc

www.iffs-reproduction.org 🈏 @IntFertilitySoc 📑

Disclosures

- Chief of Department, Gyn outpatient, Infertility, Andrology at Department of Ob & Gyn, Turku University Hospital
- Ass. Professor in Reproductive Medicine, Univ of Turku
- Chairman, Finnish Fertility Society, board member in NFS
- Chairman Scientific Committee of NFOG
- IFFS Executive board, communications director
- Private practice Aura Clinic, Andrology consultant for Inova
- Founding shareholder of Forendo Pharma Ltd
- Board member Finnish OB & GYN Research Foundation
- Congress planning, lecturing, congress participation (Gedeon-Richter, Merck, MSD, Ferring)

A successful ET

- One of the most critical steps in IVF treatment is the embryo transfer – extensive literature supports it's importance to the overall IVF success
- studies have consistently shown that IVF pregnancy rates vary by the clinician performing the transfer
- the transfer of a good-quality euploid embryo does not ensure a successful implantation or pregnancy
- standard protocol to optimize results

A successful ET – easy ET

 delivery of the best available embryo atraumatically to the optimal location in the uterine cavity without disturbing the uterus / endometrium

• minimal embryo stress

a difficult transfer

- easy (or intermediate) ETs have a higher PR (1.7 fold) than difficult transfers
- The difficulty of a transfer is subjective: time consuming requires firmer catheter causes discomfort involves additional instrumentation
- Difficult transfers stimulate uterine contractions ?

4 techniques for ET (ASRM)

• Direct transfer: the catheter is loaded with the embryo and the transfer is performed without a prior trial

• Trial followed by transfer: a catheter is used immediately before the actual transfer. It is passed just through the internal os. The actual transfer is then performed after the embryo is loaded

• Afterload transfer: the inner sheath & outer sheath are held together (1 cm of the tip extending through the sheath) while traversing the cervical canal. Once the inner catheter has passed the internal os, the outer sheath is positioned at the top of the cervix. Inner catheter is loaded and and the embryo threaded into the endometrial cavity

A successful ET



Schoolcraft F & S 2016

A successful ET – use of ultrasound

in 3969 patients trans-abdominal US compared with clinical touch:

OR for ongoing / live birth rate 1.64 (CI 1.35 – 1.99; 28.6 % vrs. 19.8%)

ectopic pregnancy rate overall (792 women) was 2.40%. No difference TA-US vrs. CT: 1.64% vrs. 3.29% (OR 0.52, CI 0.21-1.28)

 miscarriage rate overall was 10.58% (945 pregnancies) - 9.61% vrs 11.76% (TA-US vrs CT; OR 0.76, CI 0.50-1.15)



Cozzolino et al RBM Online 2018

successful ET – soft catheter

Study ID			RR (95% CI)	Events, soft	Events, firm	% Weight
McDonald 2002 van Weering 2002 Overall			1.44 (1.10, 1.89) 1.32 (1.08, 1.60) 1.36 (1.16, 1.59)	96/324 173/639 269/963	67/326 135/657 202/983	34.49 65.51 100.00
.5	Firm i	Soft	2			

ASRM Embryo transfer guideline F & S 2017

ET – fellows vs. attending physicians

TADLEO				
Outcome	Attending physicians n = 760	Fellows n = 104	ıde OR i% CI)	Adjusted OR (95% CI)
Clinical pregnancy	292 (38%)	40 (38%)	0 (0.66—1.53)	1.10 (0.71-1.71)
Live birth	239 (31%)	35 (34%)	0 (0.59—1.40)	0.99 (0.63—1.55)
Multiple birth	48 (6%)	7 (7%)	3 (0.41–2.12)	1.05 (0.45-2.44)
Values represent n (%) or C)R (95% Cl). ORs adjı	usted for maternal a	d number of high quali	ity embryos transferred.

Eaton. Live birth rates following embryo transfer by fellows vs attending physicians. Am J Obstet Gynecol 2014.

Eaton et al 2014 AJOG

ASRM evidence based recommendations

- abdominal ultrasound guidance
- removal of cervical mucus
- prefer soft catheters
- embryo placement in the upper or middle area of the uterine cavity (more than 1 cm from the fundus)
- no bed rest or immobilization

ASRM - no proof of benefit

- acupuncture
- analgesics, massage, anesthesia, whole system-traditional Chinese medicine
- prophylactic antibiotic
- waiting / resting after the embryo transfer

Suggested protocol

- review earlier transfers, trial transfer (choose catheter)
- patient in lithotomy position, bladder full
- abdominal ultrasound visualization of uterus & cervix
- speculum clear mucus choose catheter (soft)
- easy case directly transfer with a loaded catheter
- otherwise afterload transfer to minimize delay
- US guided placement 1.5 2.0 cm from fundus
- check the delivery of embryo) = empty catheter
- no immobilization
- make notes for the future ETs

Transmyometrial embryo transfer

 may be used in patients with severe cervical stenosis (congenital cervical atresia)

•typically the procedure is performed using an endovaginal probe

 a special needle with a stylet is attached to the needle holder is inserted transmyometrially and under Sonographic guidance into the endometrial cavity.

- the stylet is removed and a transfer catheter with the embryo is passed through the needle.
- painful and difficult reserve for extreme cases

Transmyometrial embryo transfer



Figure 1 Image of the transmyometrial embryo transfer showing the perpendicular insertion of the Towako needle and deposition of the embryo (bright echo) in the centre of the endometrial cavity.

Multiple pregnancy is a complication of ART

• multiple pregnancy rate remains at a level (>15%) most consider unacceptable given the associated clinical risk to mothers and babies as well as the cost of neonatal care

 given the clear benefits of elective single embryo transfer eSET should be the default and DET the exception that requires evaluated (written?) justification

 several countries have ensured eSET practice through legislation / reimbursement - dramatic decrease in MPs

Harbottle et al 2015 Hum Fertil

eSET compared to DET

- in RCTs comparing eSET with DET live birth rate is reduced unless an effective program for the use of subsequent frozen embryo is available
- a meta analysis of 8 RCTs eSET vs. DET (McLernon 2010) cumulative LBR from 2 eSET (fresh + frozen) day 2/3 transfer not significantly lower than that from a single DET 38 % vs. 42 %
- with an effective cryopreservation program cumulative success rates of eSET at least match those of DET

Does it work ?

- Quebec introduced eSET legislation in 2010 aiming at eSET in every treatment cycle. Multiple ET only when justified (case by case) by the physician
- first 3 mos (5 centres; 1353 cycles) CPR of 32% / ET (vs earlier 43%), 50% eSET. MPR 25.6% -> 3.7%
- central funding ensured implementation
- cumulative PRs (fresh + frozen) nearly equal to the DET
- dramatic changes in MPRs with / without legislation
 SWE legislation / Finland no legislation MPR < 5%

Bissonnette et al 2011, Velez et al 2013

Selection of embryos for eSET

- robust embryo selection is crucial clinical embryologist
- pronuclear assessment (number, position, size, alignment)
- cleavage stage embryo (cell #, size, fragmentation)
- blastocyst assessment: higher implantation rate most viable embryos less embryos to be transferred



better temporal synchronization embryo – endometrium increased risk of monozygotic twinning





Importance of cryopreservation

- A functioning cryoprogramme is crucial to maximize the cumulPRs
- •Similar CPRs with SET and DET (41 vs 46%) of vitrified blastocysts and reduced risk of ectopic pregnancy 1.2 vs 4.4% as well as significantly increased risk of twinning in DET 16 vs 2% (Yanaihara et al 2008)
- recent data indicates that the impaired endometrial receptivity of fresh transfer is not observed in natural FET.
- in Scandinavia 32% of all ART pregnancies from FET (FIN 45%)

Effect of # of quality embryos

- 739 cycles eSET results in women < 36 y old
- fresh transfer LBR 29.2% cumulative LBR 51.3%
- twin rate was 3.4 %
- having two (OR 1.73) or <a>> 3 top embryos (OR 2.66) ->
 higher odds for live birth in both fresh and frozen ET
- with top embryo cumLBR 40.2% vs <u>></u>3 64.1%
- LB from fresh transfer -> 20.4% at least one child from frozen ET.
- Women with >3 top embryos have a good chance of having more than one child per ovum pick-up

Are age limits justified ?

 results of fresh ET (n= 1224) and frozen ET (n=828) in women 36-39 y of age

	PR %	LBR %	cumLBR	cTwinR%
• 335 eSET, TOP embryo	33.1	26.0	41.8	1.7
• 110 nt-eSET non-TOP	19.1	15.5		4.8
 194 compulsory SET 	19.6	14.4		0
• 585 DET	29.9	21.9	26.7	16.6

- miscarriage rate similar in all
- eSET policy can be efficiently applied in 36-39 y old women reducing the MPRs i.e. improving the safety.

Are age limits justified ?

Table III Outcomes in eSET and DET groups.

	eSET (n = 264)	DET (n = 364)	P-value
Fresh cycle			
Clinical pregnancy (%)	62 ^a (23.5)	71 ^b (19.5)	0.228
Live birth (%)	36 (13.6)	40 (11.0)	0.315
Miscarriage (%)	24 (37.5)	26 (36.1)	0.735
Twins (%)	0 (0)	3 (7.5)	0.135
Cumulative results			
Clinical pregnancy (%)	98 (37.I)	88 (24.2)	< 0.00 I
Live birth (%)	60 (22.7)	48 (13.2)	0.002
Twins ^c (%)	4 (6.7)	4 (8.3)	0.726

^aOne pregnancy ended in induced abortion and one pregnancy outcome was unknown.

^bFive pregnancies were ectopic.

^cAll twins in the eSET group were from frozen embryo transfer cycles.

• eSET (n= 264) DET (n=364) Were compared with in women 40-44 y old age

 represent a well functioning
 IVF unit with experience and a good cryopreservation program

Sufficient patient counseling

- Patients need robust, detailed information to help them make an informed decision about eSET.
- many patients perceive patients selection in eSET unfair and view the risk of twins from DET acceptable.
- required additional treatments are regarded by some burdensome and unnecessary.
- women fail to recognize the social impact of having twins
- emphasizing tangible benefits e.g. improved long-term the well-being of the offspring

Decision and policy makers need to be properly informed of eSET implications -> improved reimbursement.

Selection of patients for DET

- continued focus on minimizing MBRs from IVF treatment through an effective, dynamic eSET strategy
- when embryo quality is poor, clinics should consider the transfer of two embryos.
- eSET rates, selection criteria, MBRs should be audited. Dynamic strategy means that the policy is adjusted so that MPR is lowered while LBR remains good (own results).

Conclusions

• appropriate implementation will decrease the MPR significantly without compromising the CPR.

- cryopreservation and embryo selection MUST be optimized to ensure favorable cumulative PR
- embryo quality is paramount in deciding eSET vs DET
- legislation and reimbursement appear to be effective in changing the policy
- patient counseling is key to eSET policy compliance

This presentation made possible, in part, with the generous nonrestricted educational grant support from our sponsor for this

workshop:





2019 WORLD CONGRESS

Transforming the Frontiers of Human Reproduction



www.iffs-reproduction.org



f Int@FedFertilitySoc

Lightless winter- nightless night



of embryos to transfer

TABLE 1

Recommendations for the limit to the number of embryos to transfer.

	Age (y)					
Prognosis	< 35	35–37	38–40	41–42		
Cleavage-stage embry	OS ^a					
Euploid	1	1	1	1		
Other favorable ^b	1	1	≤ 3	≤ 4		
All others	≤ 2	≤ 3	≤ 4	≤ 5		
Blastocysts ^a						
Euploid	1	1	1	1		
Other favorable ^b	1	1	≤ 2	≤ 3		
All others	<u>≤</u> 2	≤ 2	≤ 3	≤ 3		

^a See text for more complete explanations.

^b Other favorable = Any ONE of these criteria: *Fresh cycle*: expectation of 1 or more highquality embryos available for cryopreservation, or previous live birth after an IVF cycle; *FET cycle*: availability of vitrified day-5 or day-6 blastocysts, euploid embryos, 1st FET cycle, or previous live birth after an IVF cycle.

Please note: Justification for transferring additional embryos beyond recommended limits should be clearly documented in the patient's medical record.

ASRM. Limits on number of embryos to transfer. Fertil Steril 2017.

embryos to transfer

- individual programs using own data regarding patients characteristics and the number of embryos transferred with the goal of maintaining pregnancy rates and minimizing multiple gestations.
- favorable prognosis: young age, one or more high-quality embryos for cryopreservation, euploid embryos, previous life birth

ASRM patients with a favorable prognosis - eSET

- patient of any age transfer of an euploid embryo
- patients under the age of 35, irrespective of embryo stage
- patients between 35 37 strong consideration