The number of embryos to transfer: the result of a double dialogue

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Single versus multiple embryo transfer

What is the challenge?

Consider the extremes

Always all embryos transferred
- Very high pregnancy rates
- Very high multiple rates: disaster

Always one embryo transferred
- Only monozygous multiples (1%)
- Depressingly low pregnancy rates

Balance between extremes

Always all embryos transferred

Always one embryo transferred

Very high PR
Very high MR

Only MZ multiples
Low PR

A matter of:
- embryo assessment
- clinical judgement
- common sense
- societal values, norms and perceptions
- financial constraints

TYPES OF SINGLE EMBRYO TRANSFER

- COMPULSORY SET
  = cSET
- MEDICALLY INDICATED SET
  = mSET
- ELECTIVE SET
  = eSET

Medical SET:
(Vilska et al., 1999, Hum Reprod)

Absolute contraindications for twin pregnancy

- (1) Congenital anomalies of the uterus
- (2) Isthmic insufficiency
- (3) Bad obstetrical history (loss of previous twin, severe prematurity)
- (4) Diabetes mellitus
- (5) Severe systemic disease

Relative contraindications for twin pregnancy

- (1) Prenatal diagnosis indications
- (2) Explicit wish of the patients
- (3) Single women
- (4) Lesbian women

Elective SET
= prevention of complications due to twins & multiples = also “medical”

Maternal Morbidity

Multiple (n=44,674) vs singleton pregnancy (n=165,188)

	RR (95% CI)
Pre-eclampsia	2.8 (2.7-2.9)
Gestational diabetes	1.1 (1.9-1.2)
Myocardial infarction	**3.7 (2.3-5.8)**
Heart failure	**12.9 (2.7-62.3)**
Venous thromboembolism	**2.7 (2.0-3.5)**
Pulmonary oedema	**7.1 (4.5-11.3)**
Post partum haemorrhage	1.9 (1.8-1.9)
Caesarean delivery	2.2 (2.1-2.2)
Hysterectomy	2.3 (1.7-3.2)

Walker et al, BJOG, 2004

My hypothesis: the number of embryos to transfer is the result of a double dialogue:

one between physician and embryologist

one between physician and patient

This holds for both fresh & frozen ETs

The dialogue physician - embryologist

What do we need for a rational ET policy?

Assessment of the patient	Decision algorithm of the embryo(s)
• The ideal candidate for SET: 1. Young woman (<35 years old) 2. First or second attempt 3. With a choice of embryos to transfer/freeze 4. Preferably no tubal disease	• A ranking system of D2-D3 embryos • A ranking system of D5 embryos

The mathematical approach

Trade-off of the probability of no pregnancy versus a multiple pregnancy as the number of embryos transferred increases,

assuming a 10% implantation rate

1 embryo transferred:

* P_{one}= 10%
* P_{mult} = 0%
* P_{none} = 90%

3 embryos transferred:

* P_{one} = 27.5%
* P_{mult} = 2.5%
* P_{none} = 70%

Martin and Welch, FS 1998

Trade-off of the probability of no pregnancy versus a multiple pregnancy as the number of embryos transferred increases, assuming a 30% implantation rate

1 embryo transferred:

* P_{one} = 30%
* P_{mult} = 0%
* P_{none} = 70%

3 embryos transferred:

* P_{one} = 44%
* P_{mult} = 22%
* P_{none} = 34%

Martin and Welch, FS 1998

Trade-off of the probability of no pregnancy versus a multiple pregnancy as the number of embryos transferred increases, assuming a 50% implantation rate

1 embryo transferred:

* P_{one} = 50%
* P_{mult} = 0%
* P_{none} = 50%

2 embryos transferred:

* P_{one} = 50%
* P_{mult} = 25%
* P_{none} = 25%

Martin and Welch, FS 1998

	IR(%)	n embr	P_{one}	P_{mult}	P_{none}
	5	19	0.38	0.25	0.38
	10	9	0.39	0.23	0.39
	15	6	0.40	0.22	0.38
	20	4	0.41	0.18	0.41
	25	3	0.42	0.16	0.42
	30	3	0.44	0.22	0.34
	35	2	0.46	0.12	0.42
	40	2	0.48	0.16	0.36
One TQE	**40**	**1**	**0.40**	**0.00**	**0.60**
	45	2	0.50	0.20	0.30
	50	1	0.50	0.00	0.50

Pregnancy outcomes at various implantation rates if the number of embryos transferred is selected to maximize the P(singl. pregn.)

The laboratory findings

Characteristics of a top quality embryo

- **4 or 5 blastomeres on day 2.**
- **7 or more blastomeres on day 3.**
- **Not more than 20% fragmentation.**
- **No observed multinucleation ever.**

Ongoing implantation rate = ~40%

Van Royen et al. Human Reproduction, 2345-2349, 1999
Van Royen et al. Human Reproduction, 326-332, 2001

Fragment.	N bl D2	N bl D3	Implanted fraction (%)	N embryos
2	4	10	50.0	10
1	4	8	44.2	547
2	4	9	41.7	24
2	4	8	40.4	193
1	4	9	37.5	40
1	5	10	36.4	22
2	5	10	35.7	14
1	5	8	32.4	34
1	5	9	31.1	45
1	2	7	29.4	17
1	2	8	29.2	24
1	2	6	28.6	14
2	5	9	28.6	42
1	6	10	27.3	11
2	2	8	27.3	11
1	4	7	24.8	101
2	5	7	23.8	21
2	4	7	20.7	58
1	3	7	20.0	10
1	4	10	20.0	25

Embryo characterisation: Ranking of implantation potential of embryos with 1-to-1 documented outcome on the basis of day 2/3 morphology

The implantation potential of human embryos is not a categorical variable (top versus non-top = a useful simplification) but a continuous variable ranging between 0-50% for the "best" (= "least bad") embryos.

Total: 1704 SETs of embryos, all without MNB's, at least 10 embryos in each group

Non-morphokinetic assessment of embryo implantation potential

1. The –omics
2. PGS
3. Time-lapse video-assessment

Predicted ongoing pregnancy rate

Blastocyst and expansion	Inner cell mass	Trophectoderm	Ongoing pregnancy (%)
4–5	A	A	48
4–5	A	B	45
4–5	A	C	44
4–5	B	A	42
4–5	B	B	38
4–5	B	C	37
4–5	C	A	35
4–5	C	B	32
4–5	C	C	31
3	A	A	25
3	A	B	22
3	A	C	21
3	B	A	20
3	B	B	18
3	B	C	17
3	C	A	16
3	C	B	14
3	C	C	14
2	-	-	12
1	-	-	6

Van den Abbeel E et al. RBM Online, in press, 2013

The clinical experience

Fresh cycle eSET vs DET: live birth

	eSET N = 677	DET N = 676	OR (95% CI)	P-value
Live birth	27%	42%	0.50 (0.40, 0.63)	< 0.001
			0.46 (0.36, 0.58)*	< 0.001*
Multiple live birth	2%	29%	0.04 (0.01, 0.13)	< 0.001

* Adjusted for duration & cause of infertility, female's age, BMI, & parity, use of ICSI, no. of embryos available for transfer, & day of transfer

All 8 trials included

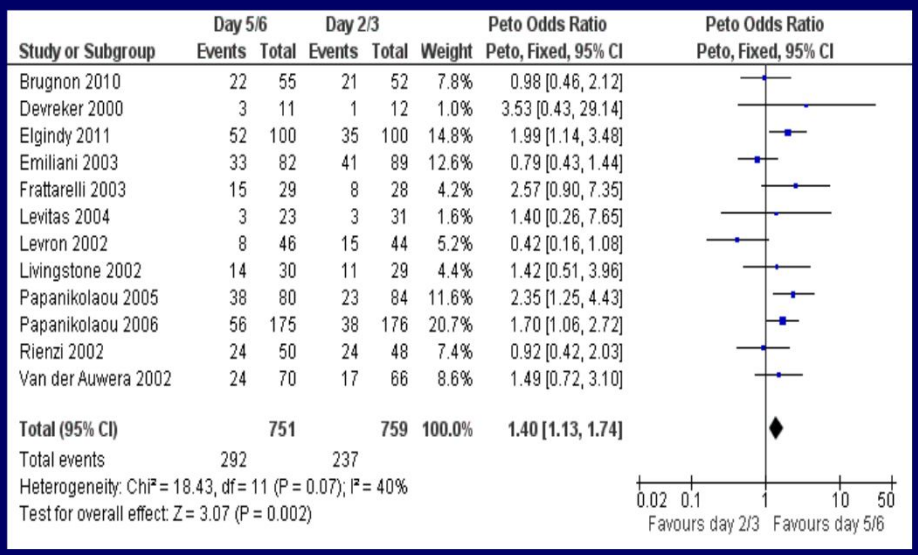
Fresh & frozen eSET vs fresh DET: livebirth

	eSET N = 350	DET N = 353	OR (95% CI)	P-value
Live birth	38%	42%	0.83 (0.61, 1.12)	0.22
			0.85 (0.62, 1.15)*	0.29*
Multiple live birth	1%	32%	0.02 (0.00, 0.13)	< 0.001

* Adjusted for duration & cause of infertility, female's age, BMI, & parity, use of ICSI, no. of embryos available for transfer, & day of transfer

2 trials included

Live birth rate per couple: Cleavage stage & Blastocyst transfer (Glujovski et al, 2012, Cochrane review)



Blake et al.,Cochrane Review, 2007

BELGIAN REIMBURSEMENT REGULATION

- Six IVF/ICSI cycles (= oocyte harvests) reimbursed in a life-time
- 1182€ per cycle for laboratory costs (gamete procurement and handling)
- Including cryocycles
- Up to the age of 43 years

Linked to a rational transfer strategy

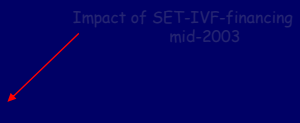
≤ 36 years	>36 - ≤39 years	> 39 years
1st trial ever or 1st trial after previous IVF/ICSI-delivery: always one fresh embryo; 2nd trial: one embryo if of sufficient quality; two if of insufficient quality; ≥3rd trial: maximum 2 embryos	1st and 2nd trial: maximum 2 embryos; ≥3rd trials: maximum 3 embryos.	No maximum number of embryos to transfer is dictated

CRYOCYCLES: 1 or 2 embryos

COUNTRY LEVEL (BELGIUM)

Data on twin pregnancies in Flanders

- Evolution of twin pregnancies as a % of total pregnancies in Flanders (SPE)



- Evolution of twin pregnancies as a function of the origin of the pregnancy in Flanders (SPE)

EUROPE

Assisted reproductive technology in Europe, 1997-2006: results generated from European **registers by ESHRE**

The European IVF-monitoring (EIM) Consortium, for the European Society of Human Reproduction and Embryology (ESHRE)

Main CPI's for fresh IVF + ICSI 1997-2008

IVF/ICSI	nETs	%1e	%2e	%3e	%≥4e	nDEL	%twin	%trip	CPR/OPU		CPR/ET	
N countries		x2	+50%	-50%	1/7		-20%	1/3	IVF	ICSI	IVF	ICSI
2008 N=36	**315.287**	**22.4**	**53.2**	22.3	2.1	**73.024**	**20.7**	1.0	28.5	28.7	32.5	31.9
2007 N=33	264022	21.4	53.4	22.7	2.5	72493	21.3	1.0	**29.1**	28.6	**32.8**	**33.0**
2006 N=32	222354	22.1	57.3	**19.0**	**1.6**	58725	20.8	0.9	29.0	**29.9**	32.4	**33.0**
2005 N=30	236480	20.0	56.1	21.5	2.3	47966	21.0	**0.8**	26.9	28.5	30.3	30.9
2004 N=29	225480	19.2	55.3	22.1	3.3	45128	21.7	1.0	26.6	27.1	30.1	29.8
2003 N=28	234142	15.7	55.9	24.9	3.5	47212	22.0	1.1	26.1	26.5	29.6	28.7
2002 N=25	203877	13.7	54.8	26.9	4.7	42827	23.2	1.3	26.0	27.2	29.5	29.4
2001 N=23	189549	12.0	51.7	30.8	5.5	37467	24.0	1.5	25.1	26.2	29.0	28.3
2000 N=22	171301	12.1	46.7	33.3	6.8	36066	24.4	2.0	24.7	26.6	28.4	28.7
1999 N=22	132979	11.9	39.2	39.6	9.3	25085	24.0	2.2	24.2	26.1	27.7	27.9
1998 N=18	141251	11.5	37.2	42.0	9.4	22859	23.9	2.3	23.2	24.8	27.0	26.8
1997 N=18	103125	11.5	35.9	38.3	14.2	24516	25.6	3.3	NA	NA	26.1	26.4

The dialogue physician - patient

Future considerations

- Indications that too high progesteron rise prior to OPU/ET decrease implantation potential of endometrium: segmentation? Bosch E *et al.* Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for *in vitro* fertilization: analysis of over 4000 cycles. *Hum. Reprod.* 25, 2092-2100 (2010).
- Indications that implantation in natural endometrium performs better than in stimulated endometrium: segmentation?
- Data from SART, ESHRE, ICMART, Japan indicate lower incidence of EUP in FRET cycles than in fresh cycles: segmentation? Ishihara O *et al. Frozen-thawed blastocyst transfer reduces ectopic pregnancy risk: an analysis of single embryo transfers in Japan. Fertil. Steril. 95, 1966)9 (2011).*

FRET can always be SET, issue is only TTP: segmentation?

The third dialogue?

embryologist - patient

Heavy load transfer

- One of the major flaws in the Belgian “model” is the absence of a link between strict embryo morphology and the number of embryos (to be) replaced
- Due to:
  - Lack of strict criteria adopted by all IVF-labs
  - Lack of conviction both from patients and doctors to implement SET widely

Consequence of this flaw

- SET has (rightly) become the standard for those patients where it was intended for (twin prone)
- It has so much become the standard of care that the other side of the spectrum (never pregnant prone) tends to be forgotten
- These are two different problems with little overlap (few multiples in poor prognosis patients once they happen to conceive)
- Hence: the risk exists that we undertreat the poorest prognosis patients

Distribution of multiple pregnancies according to age (BELRAP)

	<36 yoa	>36-<40 yoa	>40-<43 yoa	>43 yoa	TOTAL
1-tons	2227	509	148	5	2889
2-ns	266	97	20	2	385
3-lets	6	1	2	0	9
TOTAL	2499	598	170	7	

24/394 = 6%

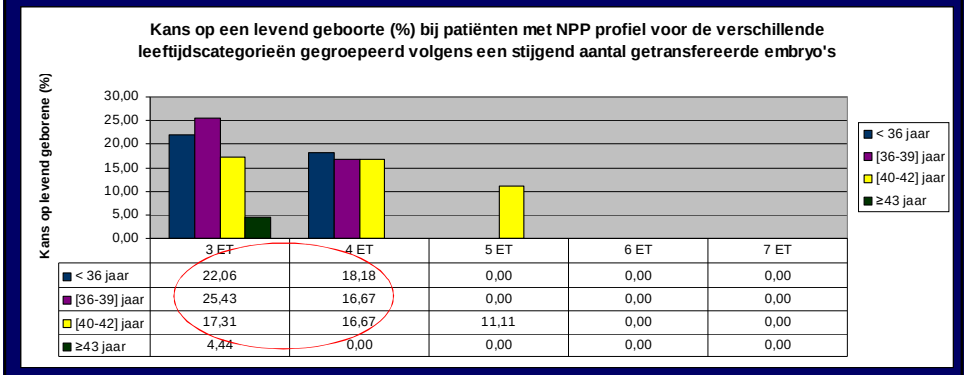
Underlying reason: Chance for live birth per embryo transferred decreases with age (BELRAP 2007)

Rational conclusion: replace more embryos per ET

Is there a place for heavy load embryo transfer?

Or are we all “SET”?

Retrospective observational data



	3 ET	4 ET	5 ET	6 ET	7 ET
< 36 jaar	22,06	18,18	0,00	0,00	0,00
[36-39] jaar	25,43	16,67	0,00	0,00	0,00
[40-42] jaar	17,31	16,67	11,11	0,00	0,00
≥43 jaar	4,44	0,00	0,00	0,00	0,00

BELRAP data*

Age group	<36	36-<40	40-<43	>43
Rank of trial	≥7	≥7	≥7	≥7
N deliveries/OPU	173/989	116/672	39/405	7/194
1/2/3	138/34/0	92/23/0	32/6/1	5/2/0
Percentage births/OPU	17.4	17.3	9.6	3.6

We do not know the number of embryos transferred but it can be assumed that it has been 3 or 4 in many cases

Ergo: BELRAP cijfers stemmen overeen met UGent ervaring

* BELRAP report: www.belrap.be/Public/Reports.aspx

"CONCLUSION"

A reasonably high total pregnancy rate can be obtained (12.7%) per fresh attempt in the "never pregnant prone" in whom HLT is performed

In the youngest group the figure may be as high as 20% LB/OPU

The absolute number of multiples in this subpopulation of NPP patients is low