Elective single embryo transfer (eSET)-the Scandinavian perspective

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High multiple birth rate!

Glyptoteket Copenhagen

Incidence of multiple pregnancies in ART
IVF/ICSI in Europe 2003, ESHRE report*

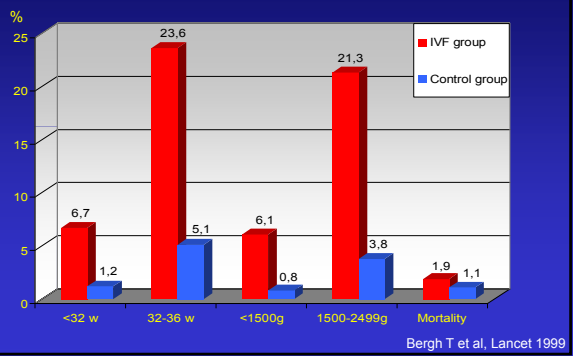
	%	Range,%
Singletons	76.7	59.6 – 88.1
Twins	22.0	11.8– 38.3
Triplets	1.1	0.0 – 4.4
Quadruplets (41 cases)		
Multiple birth babies	38.4	

*frozen embryo replacement exluded

Nyboe Andersen et al. Hum Reprod, 2007

Children born after IVF in Sweden 1982-1995

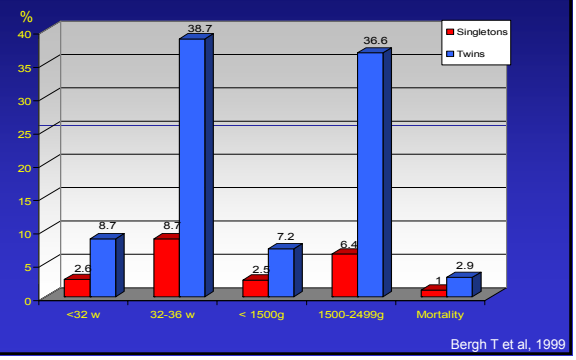
(n=5 856) Obstetric outcome



Bergh T et al, Lancet 1999

Children born after IVF in Sweden 1982-1995

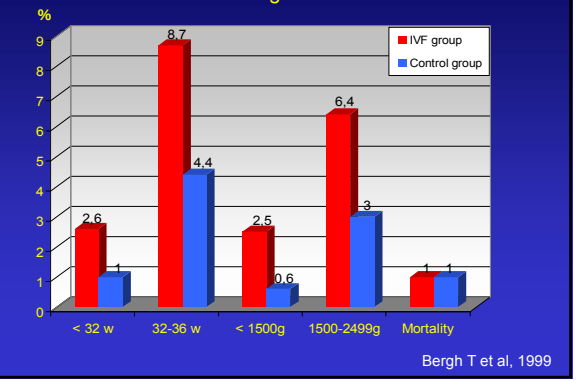
Obstetric outcome in singletons and twins



Bergh T et al, 1999

Deliveries after IVF in Sweden, 1982-1995

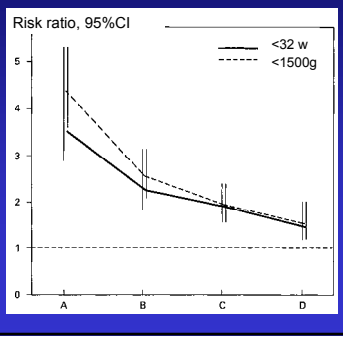
Obstetric Outcome in Singletons



Bergh T et al, 1999

Deliveries after IVF in Sweden, 1982-1995

Risk ratios for preterm delivery <32 weeks and very low birth weight <1 500g in IVF singletons



Stratification
A year of delivery
B year of delivery, maternal age, parity
C year of delivery, maternal age, parity and infertility
D year of delivery, maternal age, parity and duration of infertility when known

Bergh et al, Lancet 1999

Congenital Malformations in Children born after IVF/ICSI in Sweden (ICD 8, 9, 10) 1982-1997 (n=9 111)

	%	OR*	95% CI
All IVF children	5.6	1.47	1.34-1.61
IVF singletons	4.7	1.25	1.07-1.46
IVF multiples	6.3	1.08	0.93-1.25

*stratification for year of birth

Ericson and Källén, Hum Reprod, 2001

Congenital Malformations in Children born after IVF/ICSI in Sweden (n=9 111)

OR for any malformation diagnosis in MBR

Stratification	OR	95% CI
Year of birth	1.47	1.34-1.61
Also maternal age and parity	1.39	1.25-1.54
Also number in birth	1.18	1.06-1.32
Also known period of infertility	0.89	0.74-1.06

Ericson and Källén, Hum Reprod, 2001

Congenital Malformations in Children born after IVF/ICSI in Sweden , 1982-2001(n=16,280)

OR for any malformation diagnosis in SMBR

Stratification	OR	95% CI
Year of birth	1.42	1.32-1.52
Also maternal age and parity	1.39	1.29-1.49
Singletons	1.30	1.20-1.41
Multiple births	1.02	0.91-1.25
Also known period of infertility	1.05	0.95-1.16

Källen B et al.Birth defect research 2005;73:162-169

Neurological sequelae in children born after IVF

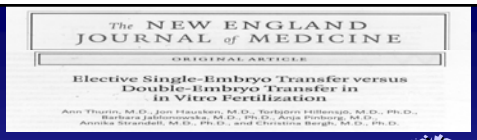
Cerebral Palsy

	n	/1000	OR (95% CI)
All IVF children	31	5.5	3.7 (2.0-6.6)
Singletons	12	3.7	2.8 (1.3-5.8) [1]
Twins	15	7.3	1.1 (0.6-2.0) [2]
Triplets	4	10.9	
Quads	0	0	
Controls		1.5	

[1] *vs* spontaneous singletons

[2] *vs* spontaneous twins

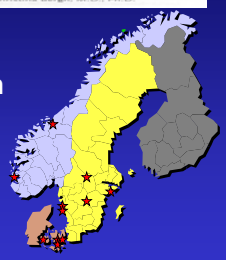
Strömberg et al, Lancet 2002


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Elective Single-Embryo Transfer versus Double-Embryo Transfer in in Vitro Fertilization

1. **Equivalence concerning live birth**
2. **Reduction multiple gestation**



Results

	SET (1 + 1)	DET (2+0)	p-value	95 % CI for the diff
N	330	331		
Live births, n (%)				
- only fresh	91 (27.6)	142 (42.9)	<0.001	
- only thawed	29 (16.4)			
- spontaneous	8			
- Cumulative	128 (38.8)	142 (42.9)		-3.4 – 11.6

Thurin et al, New Engl J Med, 2004

	eSET	DET	p-value
Multiple live births, n (%)	1 (0.8)	47 (33.1)	<0.001

Thurin et al, New Engl J Med, 2004

Neonatal outcome; gestational age of live born children

	SET cumulative n=129	DET n=189	p-value
Days; mean (SD)	276 (16.7)	265 (26.0)	<0.0001
Low gestational age (<37 weeks) n (%)	15 (11.6)	55 (29.1)	0.002
Very low gestational age (<32 weeks) n (%)	3 (2.3)	14 (7.4)	0.07

Thurin-Kjellberg et al, Hum Reprod, 2006

Birth weight of live born children

	SET cumulative n=129	DET n=189	*p-value*
Gram; mean (SD)	3439 (721)	2938 (850)	<0.0001
Low birth weight (<2500g) n (%)	10 (7.8)	52 (27.5)	<0.0001
Very low birth weight (<1500g) n (%)	5 (3.9)	14 (7.4)	0.23

Thurin-Kjellberg et al, Hum Reprod 2006

Severe neonatal complications, requiring neonatal ward (n,%)

	SET n=129	DET n=189	DET twins n=96
Prematurity	12 (9.3)	47 (24.8)	40 (41.6)
Low birth weight	10 (7.8)	43 (22.8)	37 (38.5)
Respiratory disorders	11 (8.5)	24 (12.7)	20 (20.8)
Neurological complications	2 (1.6)	6 (3.2)	4 (4.2)
Sepsis or pneumonia	5 (3.9)	8 (4.2)	4 (4.2)
Blood disorders	3 (2.3)	8 (4.2)	5 (5.2)
Retinopathy	0	4 (2.1)	3 (3.1)
Neonatal dead	0	2	2*

*Three more intrauterine deaths before gw 28.

Bergh C, RBMonline 2007

Severe neonatal complications, requiring neonatal ward (n,%)

	SET n=129	DET n=189	DET twins n=96
”Mean”/child	0.36	0.81	1.28

Bergh C, RBMonline 2007

Elective single embryo transfer vs double embryo transfer; results from randomized controlled studies

Author, year	n	PR SET	DR	Twin n	PR DET	DR	Twin
Gerris, 99	53	38.5	n.a.	1	74.0	n.a.	30.0
Martikainen, 01	144	32.4	29.7	1	47.1	40.0	39.3
Thurin, 04	661	28.5	27.6	1	43.8	42.4	33.1
Lukassen, 05	107	37.0	26.0	0	47.0	36.0	37.0
v Montfoort,06	308	21.4	na	0	40.3	na	21.0
Total	**1273**	**28.4**	**27.7**	**1.8**	**45.0**	**41.6**	**31.0**

eSET vs DET; results from observational studies of fresh cycles (cleaved embryos)

Author, year	n	PR SET	DR	Twin	PR DET	DR	Twin
Vilska,99	816	29.7	24.3	0	29.4	n.a.	23.9
Tiitinen,03	1494	34.4	27.2	1.6	36.7	26.9	27.6
Gerris,0	1152	35.1	n.a.	0.9	36.2	n.a.	35.3
De Sutter,03	2898	28.2	n.a.	0.6	31.7	n.a.	30.4
Gerris,04	367	40.3	37.4	0	40.4	36.6	30.8
Martikainen,04	1111	34.7	27.9	0.9	31.8	n.a.	n.a.
v Montfoort,05	521	35.1	31.5	0	34.6	29.0	23.0
Saldeen, 05	340	45.5	na	-	34.7	na	19.5
Veleva, 06	920	33.1	26.0	0	29.9	21.9	17.7
Total	**9619**	**34.3**	**28.7**	**0.6**	**33.0**	**26.7**	**28.3**

Revision 2003-01-01 of the legislation (the law concerning in vitro fertilization 1998:711)

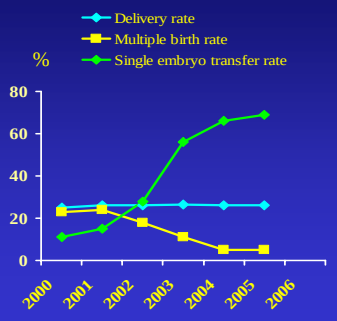
Guidelines

1§ After IVF should normally only one embryo be transferred.

Advices

If the risk for twin pregnancy is regarded low two embryos can be transferred.

Delivery rate, multiple birth rate and single embryo transfer rate in Sweden 2000-2006



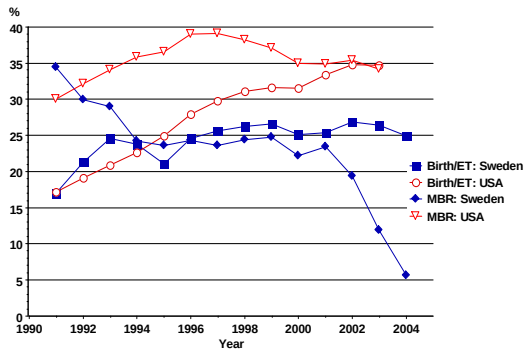
Karlström and Bergh, 2008

Number of ETs, percentage of SET, delivery and multiple birth rates in different age cohorts in Sweden, year 2000 and 2004.

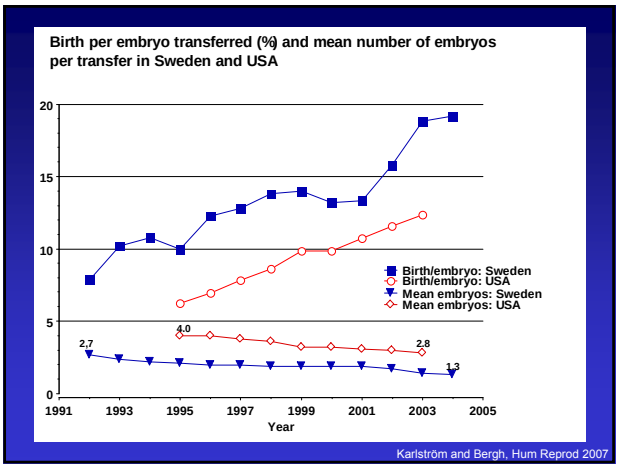
Age	Number of ET		SET (%)		Delivery rate (%)		MBR (%)	
	2000	2004	2000	2004	2000	2004	2000	2004
<30	965	1211		82,7	32,3	31,0	25,3	4,0
30-34	2424	2937		76,5	30.0	29,7	25,0	6,0
35-37	1596	2005		69,8	22,8	24,0	18,5	5,6
38-39	**771**	**1032**		**49,9**	**17,3**	**17,9**	**15,8**	**5,4**
40-41	**469**	**603**		**38,3**	**14,5**	**12,9**	**10,3**	**7,7**
>41	361	348		26,1	5,8	10,3	6,2	13,9
total	6586	8136	12,6	67,4	25,1	25,0	22,2	5,7

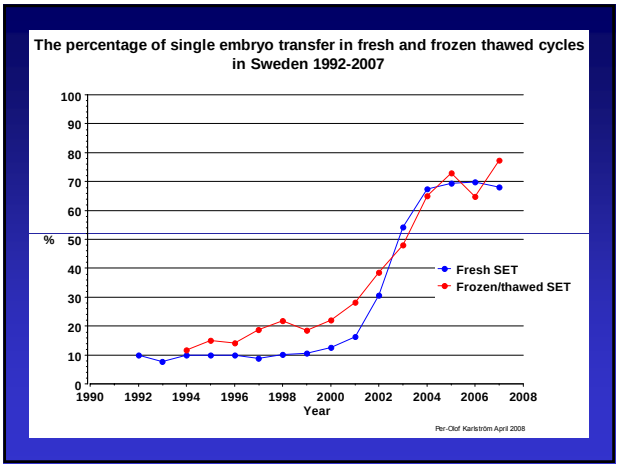
Karlström and Bergh, Hum Reprod 2007

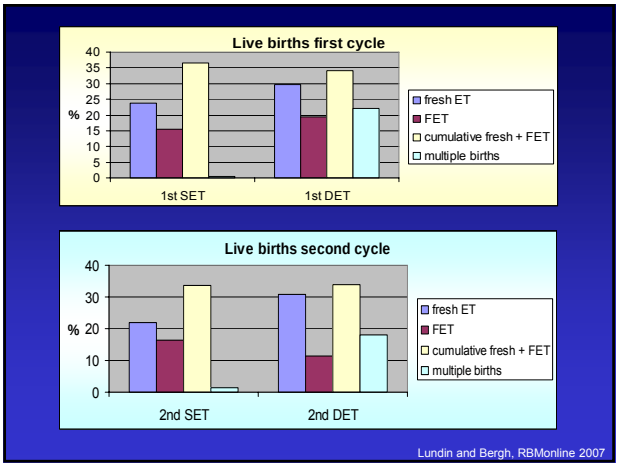
Birth per embryo transfer (%) and MBR in Sweden and USA



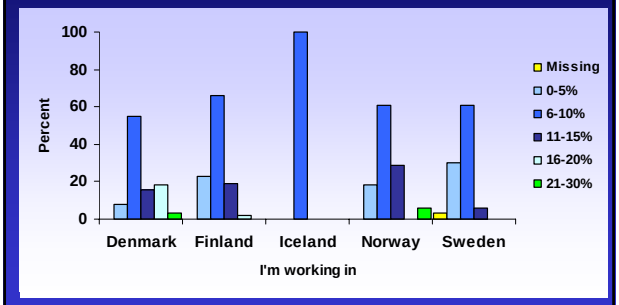
Karlström and Bergh, Hum Reprod 2007


Birth per embryo transferred (%) and mean number of embryos per transfer in Sweden and USA
20
15
10
5
0
1991
1993
1995
1997
1999
2001
2003
2005
Year
Birth/embryo: Sweden
Birth/embryo: USA
Mean embryos: Sweden
Mean embryos: USA
2.7
4.0
2.8
1.3
Karlström and Bergh, Hum Reprod 2007


The percentage of single embryo transfer in fresh and frozen thawed cycles in Sweden 1992-2007
100
90
80
70
60
%
50
40
30
20
10
0
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
Year
Fresh SET
Frozen/thawed SET
Per-Olof Karlström April 2008

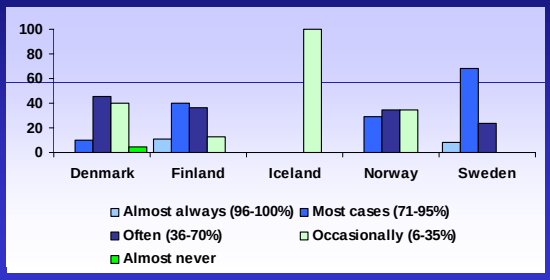

Live births first cycle
40
35
30
25
%
20
15
10
5
0
1st SET
1st DET
fresh ET
FET
cumulative fresh + FET
multiple births
Live births second cycle
40
30
%
20
10
0
2nd SET
2nd DET
fresh ET
FET
cumulative fresh + FET
multiple births
Lundin and Bergh, RBMonline 2007

An acceptable rate (%) of twin pregnancy after ART is



Bergh et al, Acta Obstet Gynecol Scand 2007

I recommend eSET (elective Single Embryo Transfer) to my patients



Bergh et al, Acta Obstet Gynecol Scand 2007

Health economy and SET

	SET delivery/child	DET delivery	DET child
Total costs maternal-neonatal (Euro)	23.984	28.712	21.505
+ costs for loss of productivity (Euro)	28.172	34.408	25.806
Per randomized woman	9.309	12.318	

Thurin Kjellberg et al, Hum Reprod 2006

Results

		SET		DET	p-value
	n	mean	n	mean	
Total cost for pediatric health care (Euro)	128	2445	142	5551	<0.0001
Sum		807036		1837355	

Health economy; cost-effectiveness analysis

- ICER (incremental cost-effectiveness ratio)
- The difference in cost is divided by the difference in effect

- 73 307 Euro per extra delivery with live-born child in the DET group
- Including also productivity losses, ICER 91 702 Euro

Fiddelers A et al, Hum Reprod Update 2007

Study	Effects (%)SET/DET	Costs per effect (Euros)	ICER (DET vs SET)
Health care perspective			
Thurin, 06	38.8/42.9	24399/29200	74634
Thurin, 06	27.6/42.9	27627/28651	30571
Lukassen, 05	25.9/35.8	13059/14378	17804
Fiddelers, 06	20.8/39.6	27450/16460	8399

Predictive factors for live birth in cryopreservation single embryo transfer cycles

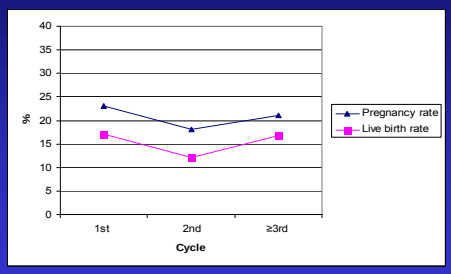
371 women, 622 cryopreservation SETs

	Live birth	Pregnancy
Blastomere survival rate	X	X
No of previous cycles	X	X
IVF vs ICSI	X	
No of embryos thawed		X

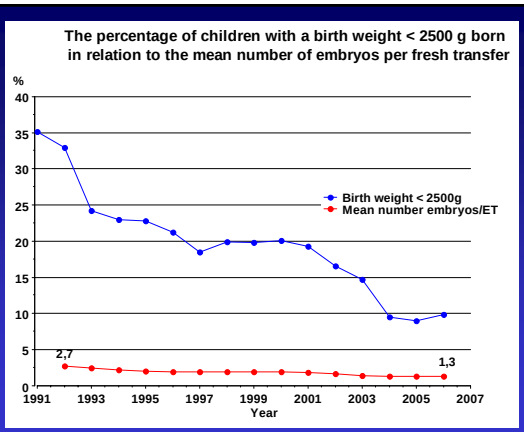
Olivius C et al 2008

Live birth after 1st, 2nd or > 3rd cryopreservation SET from the same egg retrieval

(371 women, 622 cryopreservation SETs)

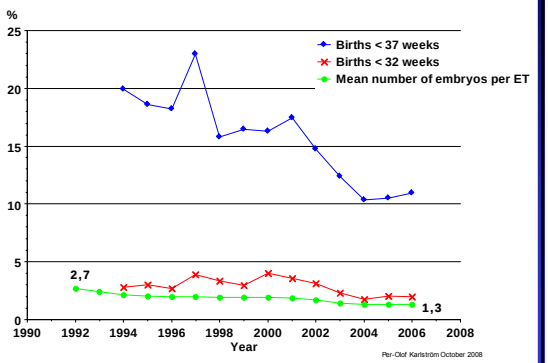


Olivius C et al 2008

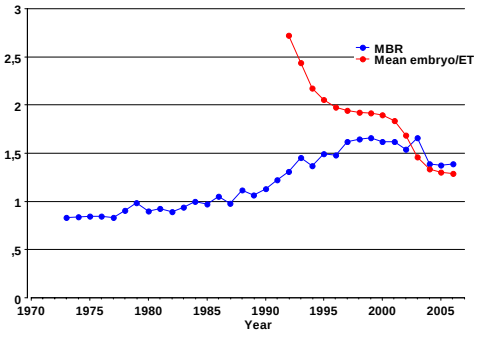


from Karlström 2008

The percentage of births before 32 and 37 weeks of gestational age in relation to the mean number of embryos transferred in fresh cycles



Total national multiple birth rate (%) in relation to the mean number embryo transferred



Summary

RCT

SET vs DET:
- ✓ Significantly/clinically lower live birth rate
- ✓ Reduces the multiple birth rate dramatically
- ✓ Costeffective?

SET+frozen vs DET:
- ✓ Live birth rate not substantially lower
- ✓ SET reduces severe maternal and neonatal complications
- ✓ SET seems costeffective in comparison to DET

Observational& Registry

SET vs DET:
- ✓ Similar live birth rate
- ✓ Reduces the multiple birth rate dramatically
- ✓ Reduces preterm and low birth weight