Risk of congenital anomalies in children born after frozen embryo transfer with and without vitrification

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The outline of the lecture

- Background
- Finnish study by Sari Pelkonen;
- Conartas study Preliminary results
- Slow freezing vs. vitrification
- Conclusions

Background

- >6 million children born after IVF in the world
- first child after frozen/thawed embryo replacement (FER) born in 1984

  Zeilmaker et al., Fertil Steril, 1984
- 0.2 – 6.1 % of the national birth cohorts in Europe in 2012

  Calhaz-Jorge et al., Hum Reprod, 2016
- the proportion of FER transfers compared with fresh transfers 34,5% in Europe in 2012 (large variation)

  Calhaz-Jorge et al., Hum Reprod, 2016
- eSET increasing, ”freeze-all” increasing

Perinatal outcome, ART vs. spontaneously conceived singletons

	aOR
Very preterm birth	2.3 - 3.3
Very low birth weight	1.8 - 3.0
Small for gestational age	1.4 - 1.6
Perinatal mortality	1.7 - 2.2

Helmerhorst et al., 2004, Jackson et al., 2004, McGovern et al., 2004, McDonald et al., 2009

Subfertility ”TTP” > 1 year

	aOR (95 % CI)
Low birth weight	1.8 (1.2- 2.7)
SGA	1.2 (1.1- 1.4)
Preterm delivery	1.5 (1.2- 1.8)
Malformation	1.2 (1.1- 1.4)
Neonatal mortality	3.3 (1.5-7.5)

Henriksen Obstet Gynecol 1997; Draper, Lancet 1999; Pandlan, HR 2001; Basso HR 2003; BMJ 2005; Zhu BMJ 2006, Obst Gynecol 2007;

Risk of malformations in ART

- increased in ART children compared to SC, no change over time (Henningsen, 2017, submitted)
- the major challenges:
  - sufficient sample size (malformations rare events, data on elective terminations lacking)
  - complexity of both the exposure and the outcome, differences in data collection
  - difficulties of grouping embryological heterogeneous malformations

Background

- studies on the obstetric and pediatric outcome of pregnancies after FET are limited
- the health of the children born after FET has been similar compared to the children born after fresh ET
- FET singletons have higher birth weight than fresh ET singletons

Frydman et al.,1989; Heijnsbrock et al., 1995, Wada et al., 1994; Sutcliffe at al.,1995a,b; Olivennes et al.,1996; Bonduelle et al., 1998; Bergh et al.,1999; Aytoz et al.,1999; Wennerholm et al.,1997, 2000, Shih et al., 2008

Congenital malformations, FET vs Fresh ET, older studies

	Fet vs Spont, aOR	Fet vs ivf/icsi, aOR
Pinborg , HR 2010	0.83 (0.73-1.31)	0.92 (0.71- 1.19)
Davies, NEJM 2012	1.08 (0.76-1.53), Fet-ivf 1.10 (0.65-1.85), Fet-icsi	
Olson, FS 2005		0.40 (0.15-1.11)
Belva, HR 2008		0.81 (0.44-1.48), Fet-ivf 1.96 (1.31-2.91), Fet-icsi
Källen, HR 2010		1.01 (0.76- 1.33), Fet-icsi

Perinatal outcome of children born after frozen embryo transfer: the Finnish cohort study 1995-2006.

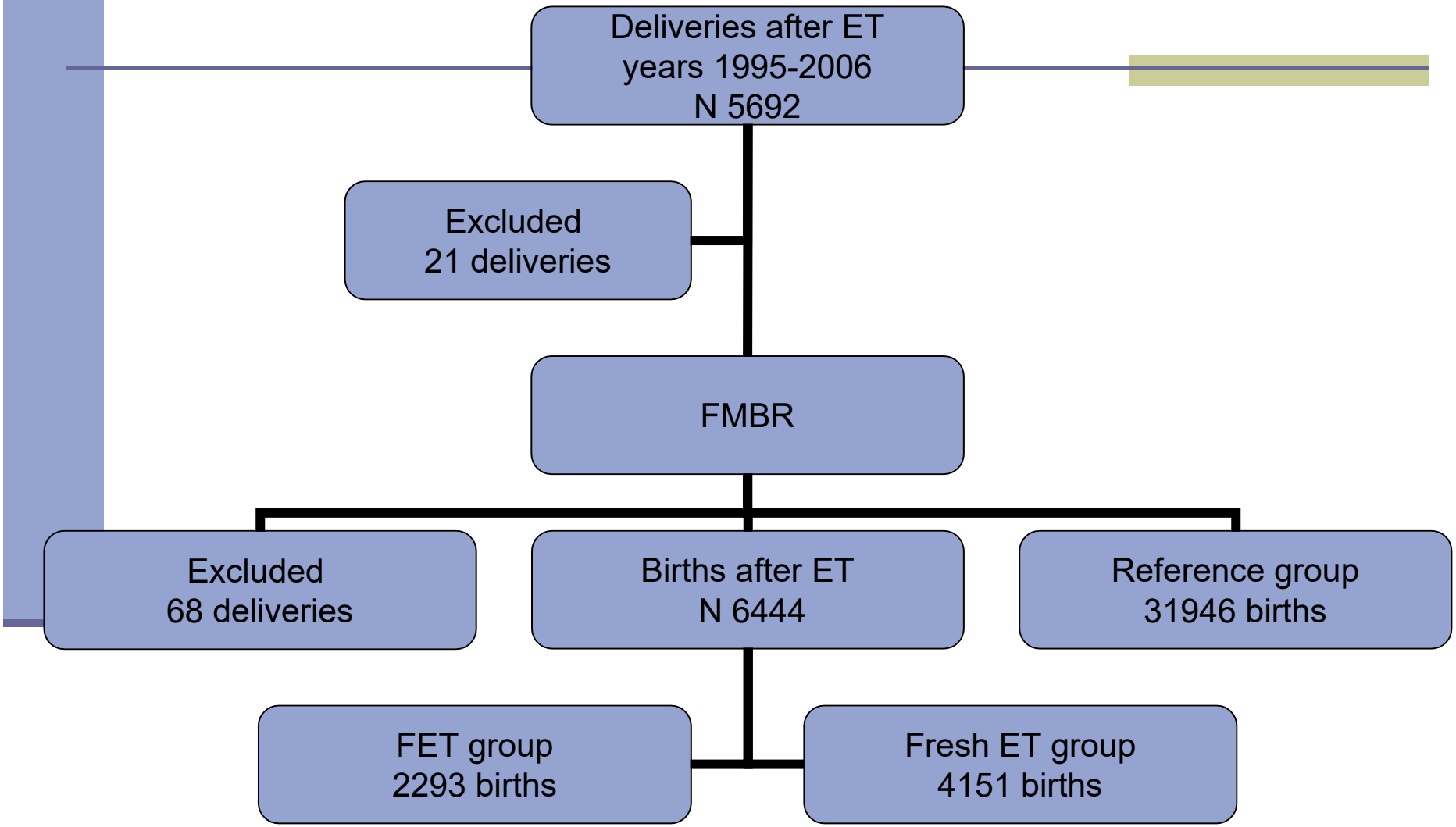
Pelkonen et al. Hum Reprod 2010; 25(4):914-23.

- Registry based cohort study
- ET treatments leading to delivery in 1995-2006
  - University hospitals and

    Family Federation clinics

    in Helsinki and Oulu
- Reference group
  - 10% random sample of mothers from Finnish Medical Birth Register (FMBR) with spontaneus pregnancies matched for the year of the delivery and mother`s place of residence

Flowchart


Deliveries after ET
years 1995-2006
N 5692
Excluded
21 deliveries
FMBR
Excluded
68 deliveries
Births after ET
N 6444
Reference group
31946 births
FET group
2293 births
Fresh ET group
4151 births

human reproduction ORIGINAL ARTICLE *Infertility*

Perinatal outcome of children born after frozen and fresh embryo transfer: the Finnish cohort study 1995–2006

S. Pelkonen[1,7], R. Koivunen[2], M. Gissler[3,4], S. Nuojua-Huttunen[2], A.-M. Suikkari[5], C. Hydén-Granskog[6], H. Martikainen[1], A. Tiitinen[6], and A.-L. Hartikainen[1]

	Fet n=1852	Fresh ET n=3298	Spont n=29 885	p-value
Age, mean (±SD)	34.2 (4.1)	33.7 (4.2)	30.0 (5.4)	*. ** <0.0001
Nulliparity, %	55.5	72.2	41.3	*, ** <0.0001
Socioeconomic position, %				* 0.249 ** <0.0001
Upper white collar	31.7	29.5	20.8	
Lower white collar	43.5	43.6	38.1	
Blue collar	9.3	10.0	12.7	
Other	15.5	16.8	28.4	
Smoking during pregnancy, %	6.9	6.9	15.1	*0.309, ** < 0.0001

*Fet vs Fresh ET
**Fet vs Spont

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human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Major congenital anomalies in children born after frozen embryo transfer: a cohort study 1995–2006

S. Pelkonen[1,*], A.-L. Hartikainen[1], A. Ritvanen[2], R. Koivunen[3], H. Martikainen[1], M. Gissler[2,4], and A. Tiitinen[5]

	FET n	Fresh ET n	P[b]	OR[c]	CL 95%
Singleton births, all	1830	2942			
Singleton births with CA	**77**	**132**	**0.647**	**0.94**	**0.70 – 1.25**
%	**4.2%**	**4.5%**			
All organ systems affected:					
Central nervous system	1	5	0.274	0.32	0.04 – 2.75
Eye, ear, face and neck	2	9	0.168	0.36	0.08 – 1.65
Cardiac	27	36	0.459	1.18	0.71 – 1.94
Other circulatory system	1	3	0.583	0.54	0.06 – 5.15
Respiratory system	3	2	0.319	2.41	0.40 – 14.46
Cleft palate and cleft lip	6	7	0.562	1.38	0.46 – 4.11
Digestive system	5	6	0.627	1.34	0.41 – 4.40
Urogenital	15	21	0.681	1.23	0.64 – 2.36
Musculoskeletal system	16	25	0.929	0.83	0.43 – 1.64
Integument (skin, hair and nails)	2	7	0.319	0.46	0.10 – 2.21
Chromosomal anomalies	10	10	0.283	1.61	0.67 – 3.88
Other congenital anomalies	3	8	0.449	0.60	0.16 – 2.27

Major congenital anomalies, %

	FET			Fresh ET			Spont		
	Cases (n)	Children (n)	%	Cases (n)	Children (n)	%	Cases (n)	Children (n)	%
Singletons	77	1830	**4,2**	132	2942	**4,5**	974	31243	**3,2**
Twins	17	448	4,00	50	1194	4,5	24	694	3,
Triplets	1	15	6,67	2	15	6,67	0	9	0,00
Terminated pregancies	13			20					
Total			**4,7**			**4,9**			

Major congenital anomalies, %

	FET-IVF	IVF	FET-ICSI	ICSI	Spont
	%	%	%	%	%
Singletons	**3,9**	**4,2**	**5,1**	**5,0**	**3,2**
Twins	3,50	3,67	4,48	5,20	3,5
Triplets	6,7	11,1	0,00	0,00	0,00

Major congenital anomalies, Fet / Fresh vs Spont , singletons

	All		Boys		Girls	
	aOR*	95% CL	aOR*	95% CL	aOR*	95% CL
Spont	1.00		1.00		1.00	
Fet	1.21	0.95-1.54	1.27	0.91-1.76	1.14	0.79-1.64
Fresh ET	1.27	1.04-1.55	1.41	1.09-1.83	1.10	0.81-1.50

*Adjusted for child's year of birth, maternal age, parity, and SES

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human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Major congenital anomalies in children born after frozen embryo transfer: a cohort study 1995–2006

S. Pelkonen[1,*], A.-L. Hartikainen[1], A. Ritvanen[2], R. Koivunen[3], H. Martikainen[1], M. Gissler[2,4], and A. Tiitinen[5]

Singletons with CAs	n	OR	95% CL	aOR [b]	95 % CL
Fresh ET	132	1.00		1.00	
FET	77	0.94	0.70 – 1.25	0.95	0.71 – 1.27
Organ systems affected					
Cardiac [c]					
Fresh ET	37	1.00		1.00	
FET	27	1.18	0.71 – 1.94	1.15	0.69 – 1.89
Urogenital					
Fresh ET	21	1.00		1.00	
FET	16	1.23	0.64 – 2.36	1.32	0.69 – 2.51
Musculoskeletal					
Fresh ET	25	1.00		1.00	
FET	13	0.83	0.43 – 1.64	0.83	0.43 – 1.64
Chromosomal anomalies					
Fresh ET	10	1.00		1.00	
FET	10	1.61	0.67 – 3.88	1.57	0.65 – 3.79

Adjusted parity, ses, child´s year of birth and maternal age

Conclusion; slow freezing

- Children born after FET have a similar risk of developing major CAs as children born after fresh ET
- aOR 0.95; 0.71-1.27;
- but we need knowledge on the effect of:
  - new culture media or cryoprotectants,
  - blastocyst culture
  - vitrification
- and updated, good quality research databases

Material and methods

Study group:

6 647 singletons born after FER (DK, N, SW)

Control group 1:

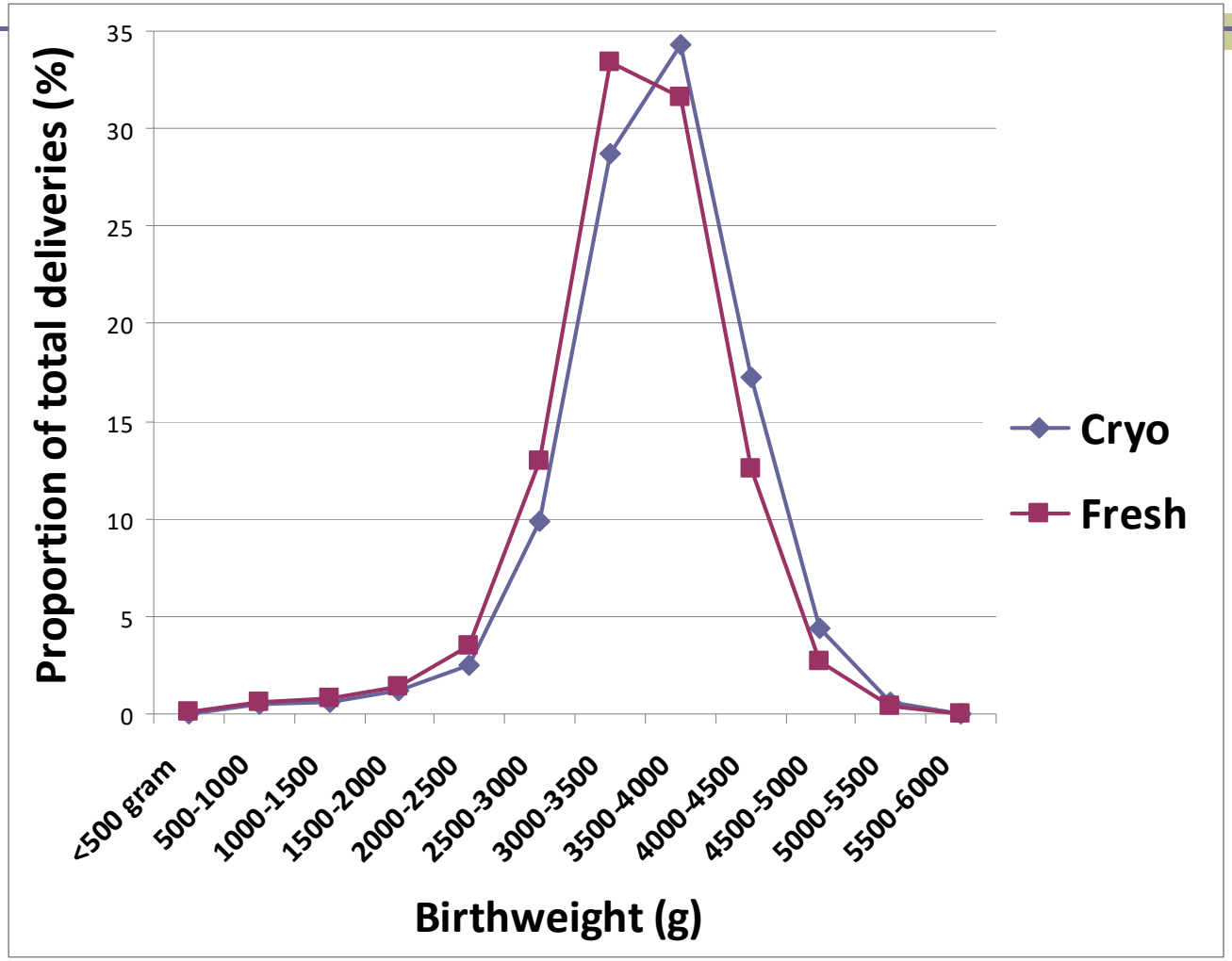
42 242 singletons born after fresh IVF/ICSI (DK, N, SW)

Control group 2:

288 542 SC singletons (DK, N, SW)

Wennerholm et al; Hum Reprod 2013

Birthweight (500 gram intervals) in IVF/ICSI singletons: FER and fresh IVF

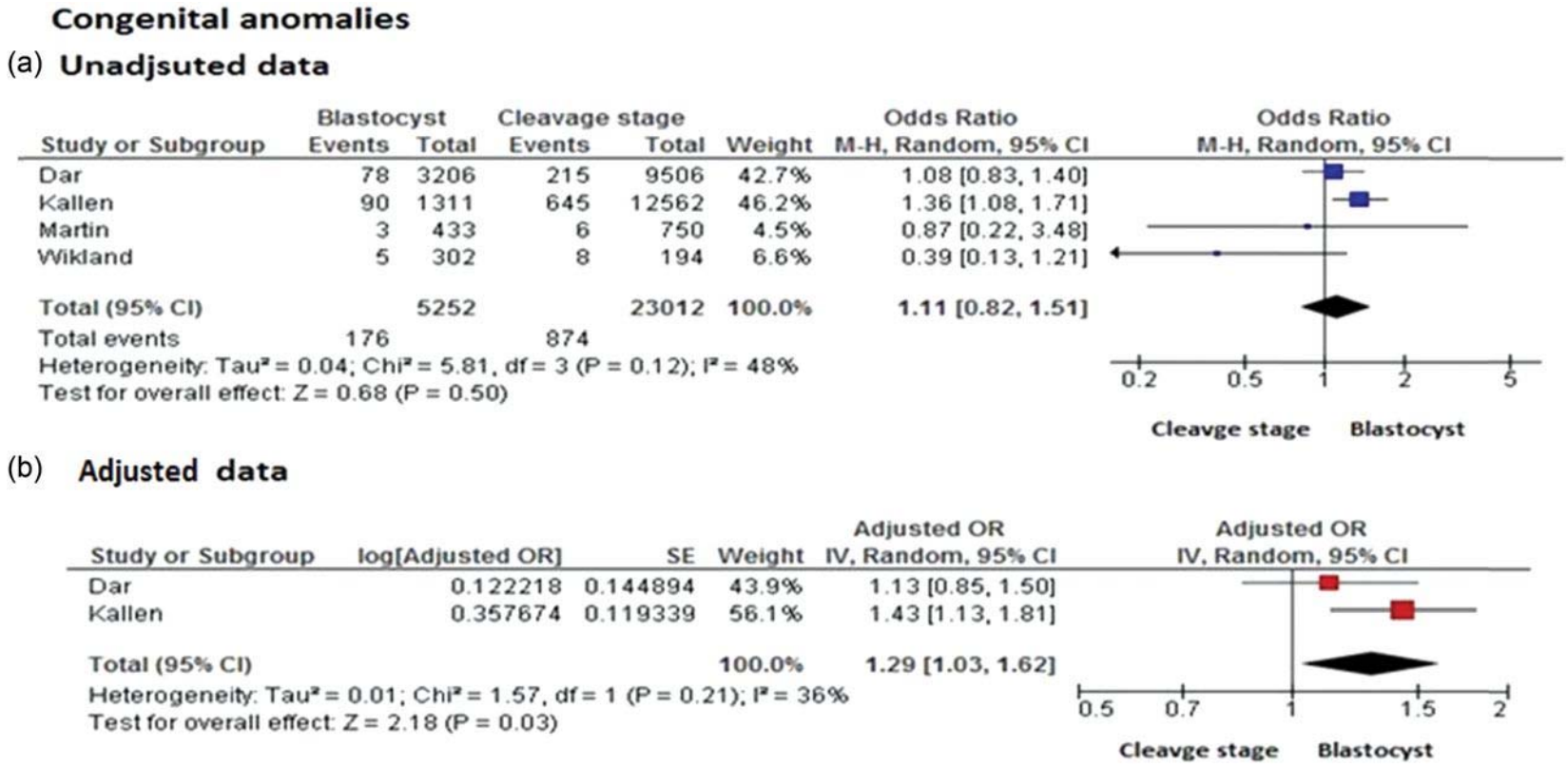


Wennerholm et al, HR 2013

Cryopreservation and fetal growth

- selection of better quality embryos?
- selection of women?
  - but a higher mean birth weight after cryopreservation persists also in sibling studies Henningsen et al., Fertil Steril, 2011
- natural cycles are more favorable than controlled ovarian hyperstimulation?
- epigenetic modifications?
- effect on malformations??

Meta-analysis of blastocyst versus cleavage stage embryo transfer for congenital anomalies.



S. Dar et al. Hum. Reprod. Update 2014;20:439-448

human reproduction update

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human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Neonatal health including congenital malformation risk of 1072 children born after vitrified embryo transfer

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Congenital malformations

- the rate of major malformations: 2.6% (vitrified transfer) vs 2.8% (fresh transfer) in liveborns
- the rate of total malformations (including stillborns and terminated pregnancies) 3.4% vs 3.9%
- conclusion: comparable congenital malformation rate

Major malformations: OR adj 0.91 (95%CI 0.47-1.78)

Table V Unadjusted and adjusted ORs for neonatal characteristics in singletons and twins following vitrified embryo transfer compared with fresh embryo transfer.

Neonatal outcome	Singletons		Twins	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Low birthweight	0.83 (0.59–1.1)	0.76 (0.457–1.28)	0.44 (0.24–0.79)	0.53 (0.20–1.44)
Small-for-gestational age	0.62 (0.45–0.87)	0.55 (0.34–0.90)	0.62 (0.40–0.96)	0.46 (0.20–1.04)
Large-for-gestational age	2.22 (0.77–6.44)	1.85 (0.42–8.06)	/	/
Preterm delivery	1.08 (0.80–1.43)	0.91 (0.57–1.43)	1.02 (0.74–1.41)	1.40 (0.74–2.66)
Perinatal death	0.94 (0.39–2.26)	0.97 (0.40–2.36)	0.35 (0.12–1.04)	0.37 (0.12–1.10)
Major congenital malformations	0.93 (0.53–1.63)	0.91 (0.47–1.78)	0.87 (0.04–19.6)	0.88 (0.15–4.96)

Adjusted for treatment variables (number of embryos transferred and embryo stage at vitrification/transfer: cleavage-stage or blastocyst) and maternal characteristics (age, BMI, parity, smoking and pregnancy-induced hypertensive disorder).

Conclusions

- Children after FET have similar perinatal outcome as children after fresh ET or the outcome is even better
- Studies (until now) provide evidence of the safety of FET
- It is important to give good information for the couples