

Vanishing Twin and its consequences



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VANISHING TWIN PHENOMENON



Disappearance of one of two gestational sacs or
embryos after documented foetal activity is known
(Landy and Keith, 1998)

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INTRODUCTION



- Up to 5% of a birth cohort is born after IVF
- 22.7% ART twin deliveries in Europe in 2004 (Nyboe Andersen et al., HR 2008)
- IVF singletons have poorer obstetric outcome than naturally conceived singletons

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Obstetric outcome in IVF singletons



OR (95%CI)	Helmerhorst*	Jackson*
	<i>Br Med J, 2004</i>	<i>Am J Obs Gyn, 2004</i>
No	5.361	12.283
<2500 g	1.7 (1.5-1.9)	1.8 (1.4-2.2)
<1500 g	3.0 (2.1-4.4)	2.7 (2.3-3.1)
<37 weeks	2.0 (1.8-2.3)	2.0 (1.7-2.2)
<32 weeks	3.3 (2.0-5.3)	-
SGA	1.4 (1.2-1.7)	1.6 (1.3-2.0)
Mortality	1.7 (1.1-2.6)	2.2 (1.6-3.0)

(*Controlled for maternal age and parity)

IVF SINGLETONS *Malformations*

(Hansen, Hum Reprod Update, 2004)

Studies	All	Selected
n	15	6
OR (95%CI)	1.3 (1.2-1.5)	1.4 (1.2-1.5) (maternal age, parity)

(Källén, Birth Defects Research, 2005)

n	16.280
OR (95%CI)	1.4 (1.3-1.5) (maternal age, parity)
Adj.OR (95%CI)	1.1 (1.0-1.3) (+ years of infertility)

IVF SINGLETONS *Cerebral palsy*

	Lidegaard Hum Rep 2005	Strömberg Lancet 2002	Källén Fertil Steril 2005
N	6052	5680	16.280
OR (95%CI)*	1.8 (1.2-2.8)	2.8 (1.3-5.8)	1.9 (1.4-2.6)
OR (95%CI)**	-	-	1.1 (0.7-1.8)

*Adj. Maternal age, parity, child year of birth

**Adj. +Years of infertility

Why higher risks in IVF singletons?

- **Controlled ovarian hyperstimulation**
- **IVF methods**
- **Subfertility**
 - Prematurity and low birth weight
 - Neonatal mortality
 - Malformations
- **Number of gestational sacs/foetuses**

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ART

- **Ovarian stimulation**
 - Oocytes
 - Endometrium
 - Luteal phase
 - Early pregnancy
- **IVF laboratory procedures**

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Subfertility and obstetric outcome

- **Subfertility correlates with adverse outcome**
(Henriksen, OG 1997; Pandian, HR 2001; Basso, HR 2003; Thomson, OG 2005; Zhu, BMJ 2006)
- **Time-to-pregnancy >12 months and preterm birth**
(Basso, HR 2003)

Primiparas: Untreated OR 1.4 (1.1-1.7)

Multiparas: Untreated OR 1.6 (1.2-2.1)

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Subfertility and mortality

- **TTP >12 months and perinatal deaths**

(Draper, Lancet 1999)

- No treatment AOR 3.3 (1.6-6.8)
- Treatment AOR 2.7 (1.5-4.7)

- **TTP >12 months and neonatal deaths**

(Basso, BMJ 2005)

- No treatment AOR 3.3 (1.5-7.5)
- Treatment AOR 2.3 (0.9-5.8)

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Subfertility and malformations

- **SC singletons of infertile couples vs. singletons of fertile couples**
Hazard ratio 1.20 (95% CI 1.07 to 1.35)

- **ART singletons vs. singletons of fertile couples**
Hazard ratio 1.39 (95% CI 1.23 to 1.57)

- **Congenital malformations increased with increasing "time to pregnancy"**

(Zhu et al., BMJ 2006)

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THE VANISHING TWIN IN ART

- **GA and BW was inversely related to the initial number of gestational sacs in 5962 ART singletons irrespective of the final birth number**

(Dickey et al., AJOG, 2002)

- **15% of IVF singleton births began as higher order gestations and to a large part this could explain the increased risk of preterm birth**

(Dickey et al., HR 2004)

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THE VANISHING TWIN IN ART

- Increasing no of gestational sacs in early pregnancy was associated with a higher risk of preterm birth in singleton pregnancies

(Lancaster et al., ESHRE 2004)

- 6.377 IVF singletons were more likely to have low BW in pregnancies, if more than one foetal heart was present at early UL

(Schieve et al., NEJM 2004)

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Consequences of vanishing twins in IVF/ICSI

- Retrospective Danish cohort study 1995-2001
- Multi-centre study (11 fertility clinics)
- 72% of all IVF/ICSI cycles in Denmark
- Singleton and twin pregnancies 8 weeks
- The National Medical Birth Register and The National Patient Register

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COHORTS



Cohort	n	
Singleton	5237	
Twins	3678	
Survivor	642	
Early (<8 weeks)	424 (66%)	} Singleton survivors 10.4% (611/5848)
Intermediate (≥8 weeks)	187 (29%)	
Late (stillborn)	31 (5%)	

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Consequences of vanishing twins in IVF/ICSI

(Hum Reprod 2005, 20; 2821-9)

	Survivors	Singletons	p-value
n	642	5237	
Birth weight, g	3264 ±795	3442 ± 662	<0.001
Gestational age	38.9 ±3.4	39.5± 2.6	<0.001
NICU, days (mean)	15.5	11.4	0.01
NICU, >7 days (%)	46.5%	38.5%	0.05
n (per 1000)			
Mortality <1 år	10 (15.6)	24 (4.6)	0.001
Neu. sequelae	11 (17.1)	95 (18.1)	0.9
Cerebral palsy	5 (7.8)	22 (4.2)	0.2

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Consequences of vanishing twins in IVF/ICSI

(Hum Reprod 2005, 20; 2821-9)

Outcome	OR (95%CI)*
BW <2500g	1.7 (1.2; 2.2)
BW <1500g	2.1 (1.3; 3.6)
GA<37 weeks	1.3 (1.0; 1.7)
GA<32 weeks	2.3 (1.4; 4.0)
Neu. sequelae	0.8 (0.4; 1.6)
Cerebral palsy	1.9 (0.7; 5.2)

*OR adjusted for age, parity and treatment method

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VANISHING TWINS

"Time of vanish"



	Early (<8.weeks)	p	Intermediate (≥8.weeks)	p	Late (Stillborn)
Live born, n	424		187		31
Birth weight	3365±695	<0.001	3185±867	<0.001	2178±940
Gestational age	39.4±2.6	<0.001	38.5±4.1	<0.001	34.3±4.8
Mortality <1 year (per 1000)	1 (2.4)	<0.001	8 (42.8)	0.8	1 (32.3)

(Hum Reprod 2005, 20; 2821-9)

VANISHING TWINS

Neurological sequelae



	Early (<8 wks) (N=424)	Intermediate (≥8 wks) (N=187)	Late (stillborn co-twin) (N=31)	Spearman correlation (r)*	P
No. (per 1000)					
Cerebral palsy	3 (7.1)	2 (10.7)	0	-0.008	0.85
Neurological sequelae	4 (9.4)	5 (26.7)	2 (64.5)	-0.09	0.022
All neurological diagnoses	14 (33.0)	15 (80.2)	3 (96.8)	-0.109	0.006

*Spearman correlation coefficient (r) for ordinal data

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Small-for-gestational age (SGA)



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Vanishing twins and SGA

- Crowding of gestational sacs
- Lack of appropriate sites for implantation
- Vaginal bleeding
- Unfavourable foetal nourishment

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Small for gestational age (SGA)

- Small for gestational age
~ Birth weight <10th percentile
- Term infants (>37 weeks) with
birth weight <2500 g



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SGA in IVF singletons after a vanishing twin

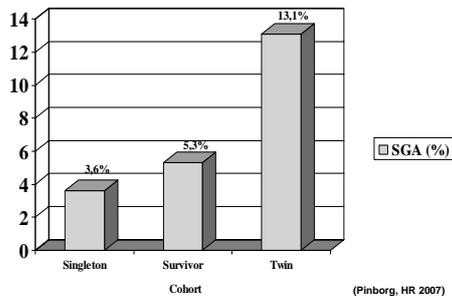
N (%)	SGA		non-SGA	All
Singletons	186 (3.6%)		5012 (96.4%)	5198 (100%)
Survivors	33 (5.3%)	p=0.04	592 (94.7%)	625 (100%)
<8 wks	16 (3.8%)	r = -0.1	402 (96.2%)	418 (100%)
≥8 and <22 wks	14 (7.7%)		169 (92.3%)	183 (100%)
≥22 wks	3 (12.5%)	p<0.02	21 (87.5%)	24 (100%)

(Hum Reprod 2007, 22, 2707-14)

SGA = small for gestational age
r = Spearman correlation coefficient

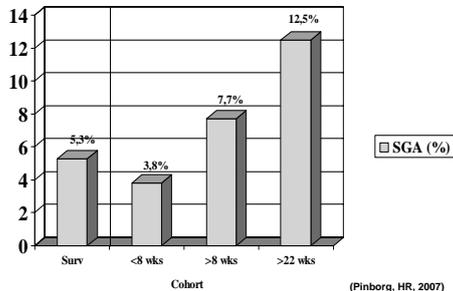
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SGA (%) in IVF singletons



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SGA (%) in IVF singletons



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(Pinborg, HR, 2007)

SGA in IVF singletons after a vanishing twin

- SGA in the survivor cohort: OR 1.5 (95%CI 1.0-2.2) ($p=0.04$)
- SGA babies increased with increasing gestational age at onset of vanish ($r = -0.1$, $p<0.02$)
- In multiple logistic regression vanish of co-twin was the only predictor of SGA: OR 2.1 (95%CI 1.0-4.3)
(Maternal age, parity, child gender)
- Similar results shown for term infants with BW<2500 gram

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CEREBRAL PALSY

“Vanishing embryo syndrome” Hvidtjørn D, HR 2005

- 9.444 IVF children and 395.025 non-IVF children
The risk of cerebral palsy was higher in pregnancies, where the number of gestations at delivery was less than the number of embryos originally transferred
Cox regression: HRR 2.3 (95% CI 1.0;5.3)

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CEREBRAL PALSY

Anand D, Twin Research 2007
229 children (92 singletons, 180 twins and 33 survivors)

1 year of age, Griffiths scale
2 twins with CP
2 vanishing twins with CP
0 singletons with CP
Vanishing twins vs. Singletons

Cerebral palsy: RR 6.1 (95%CI 1.5-8.3) p = 0.03

Mental development scores: No significant differences

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Obstetric outcome in SET singletons

De Sutter et al., HR 2006

404 SET singletons & 431 DET singletons, Retrospective 2000-2004

Adjustment: Age, parity, cycle no, treatment indication, ART method, embryo characteristics, gender

- **BW: DET: 3204 ± 618 gram vs. SET: 3324 ± 510 gram (P<0.01)**
- **Low birth weight: OR 3.4 (1.9-6.1)**
- **Preterm birth: OR 1.8 (1.1-2.9)**

De Neubourg HR 2006; Thurin HR 2006
• **Higher BW in SET than DET singletons**

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Outcome in SET singletons

Poikkeus et al., HR 2007

269 SET singletons, 230 DET singletons, 15037 SC singletons
1997-2003

Retrospective

Adj: Maternal age, parity, socio economic status

Similar findings in SET and DET singletons

SET vs. SC singletons:

Preterm birth: OR 2.9 (2.0-4.2)
Low birth weight: OR 2.0 (1.2-4.0)

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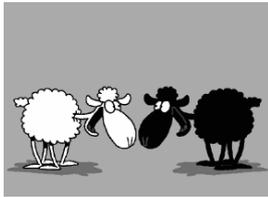
TAKE HOME MESSAGES



- Vanishing twins are seen in 10% of IVF singletons
- SGA ↑ prematurity ↑ LBW ↑ Mortality ↑
- Cerebral palsy ↑ ?
- The higher risk the higher gestational age at “vanish”
- Obstetric outcome in SET singletons ↑

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Another argument for elective single embryo transfer



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