

**VANISHING TWIN, ECTOPIC PREGNANCY,
PREGNANCY LOSS AND GESTATIONAL
DISEASE AFTER IVF**



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Ectopic Pregnancy in IVF

- Ectopic pregnancy rate 2-8%
- Heterotopic pregnancy 1%
- Do IVF enhance EP?
- US data 2000: IVF-EP 2.1% vs. SC-EP 2.0%
- France 1999: IVF-EP 3.4%, ICSI-EP 1.9%

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**Risk factors for
Ectopic Pregnancy**

Spontaneous conception

Previous EP
Pelvic inflammatory disease
Tubal disease or surgery
Smoking
Age >35 years

IVF

Specific ART procedure
Female health characteristics
Embryo implantation potential

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Ectopic pregnancy

- US data 1999-2001
- 94.118 ART pregnancies
- 2.1% EP rate
- Tubal pathology (+ hydrosalpinx 4.2% vs. 3.0% without HS)
- ZIFT-EP rate 3.6%
- Donor oocytes-EP rate 1.4%
- Tubal factor infertility OR 2.0 (95%CI 1.7-2.4)
- Endometriosis OR 1.3 (95%CI 1.0-1.6)
- Non-tubal factors female infertility OR 1.4 (95%CI 1.2-1.6)
- Previous live-birth OR 0.6 (95%CI 0.5-0.7)
- High-implantation potential <3 embryos OR 0.7 (95%CI 0.5-0.9)

(Clayton HB, Obstet Gynecol 2006, 107, 595-604)

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Other possible risk factors

- Blastocyst transfer (Milki 2003)
- Assisted hatching ? (Clayton 2006; Jun 2004)
- Frozen embryo replacement ? (Keegan 2006)
- Deep fundal transfer ?
- Higher transfer volume ?
- Multiple embryo transfer ?

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Ectopic pregnancy

- Retrospective 1998-2003
- OPR: Fresh 2688 and FER 285
- Only 5% with primary tubal factor
- Aggressive management of tubal disease
- Overall EP rate 0.9% equal after fresh and FER
- EP increased after 2000 where blastocyst transfer became routine

(Keegan DA, Fertil Steril 2007, 88, 734-6)

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Ectopic pregnancy



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Ectopic Pregnancy in IVF

- Laparoscopic salpingectomy in hydrosalpinges enhances the success of IVF (Strandell 2000; Johnson 2002)
- ART do not increase the risk of EP, however specific characteristics of the female patients do

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Pregnancy loss

- True SA rate 10-20%
- Slightly higher after IVF (Ezra and Schenker 1995; Simon 1999)
- Higher maternal age (Andersen 2000)
- Aneuploidy increases with maternal age >35 years (Abdalla 1993; Fretts 1995)

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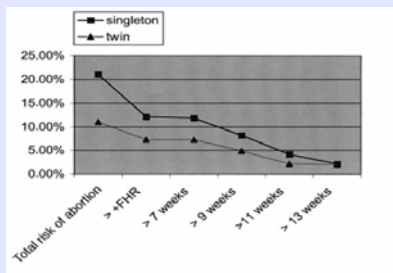
Pregnancy loss in IVF

- 1200 singleton and 397 twin pregnancies
- Miscarriage singleton pregnancies 21.7%
- Fetal death after fetal heart beat 12.2%
- Spontaneous abortions in twins 17.1%
(12.1% vanishing twins and 5.0% miscarriage)

(Tummers; Hum Reprod 2003)

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Risk of SA per fetal sac



(Tummers, HR 2003)

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Total risk of SA per fetal sac in relation to maternal age

Age	Singleton	Twin	P
≤35 years	19.8 (201/1015)	9.5 (67/704)	<0.001
>35 years	28.6 (59/185)	18.8 (17/90)	<0.02
P	<0.0009	<0.003	

(Tummers, Hum Reprod 2003)

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Pregnancy loss



No of pregnancies	One viable +one vanish 453	One viable foetus 5661	Two viable foetuses 2137
Miscarriage ≤12 wks	14 (3.1%)	251 (4.4%)	14 (0.7%)
Miscarriage > 12 wks	13 (2.9%)	131 (2.3%)	61 (2.8%)
Miscarriage	1 (0.2%)	9 (0.2%)	0 (0)
Miscarriage, all	28 (6.2%)	391 (6.9%)	75 (3.5%)

(Pinborg et al., HR 2005)

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Gestational disease after IVF

- Metaanalysis
- 12283 IVF singletons + 1.9 mill SC singletons
- Placenta praevia ↑ OR 2.9 (1.5-5.4)
- Gestational diabetes ↑ OR 2.0 (1.4-3.0)
- Preeclampsia ↑ OR 1.6 (1.2-2.0)

(Jackson, Obstet Gynecol 2004)

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Gestational disease after IVF

- Multivariate logistic regression analysis
- 36062 singletons: SC 32286, ovulation induction 1222, IVF 554

Ovulation induction	IVF
• Placental abruption ↑	Placental abruption ↑
• Fetal loss >24 wks ↑	Placenta praevia ↑
• Gestational diabetes ↑	PI hypertension ↑
	Preeclampsia ↑

(Shevell, Obstet Gynecol 2005)

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Gestational disease after IVF in Sweden

(Källen et al., BJOG 2005)

- All women having IVF in Sweden 1982-2001
- 13.261 births and 12.186 women
- Pre-eclampsia: OR 1.63 (95%CI 1.53-1.74)
- Placental abruption: OR 2.17 (95%CI 1.74-2.72)
- Placenta praevia: OR 3.65 (95%CI 3.15-4.23)
- Bleeding + vaginal del: OR 1.40 (95%CI 1.38-1.50)
- PROM OR 2.54 (95%CI 2.34-2.76)
- Thromboembolism OR 1.2 (95%CI 0.53-2.7)

(Adj. For year of birth, maternal age, parity, smoking)

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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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Why higher risks in IVF singletons?

- IVF/ICSI methods
- Subfertility
 - Prematurity and low birth weight
 - Neonatal mortality
 - Malformations
- Number of gestational sacs/foetuses

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Subfertility and adverse outcome

- **Subfertility correlates with adverse outcome**
(Henriksen, OG 1997; Pandian, HR 2001; Basso, HR 2003; Thomson, OG 2005; Zhu, BMJ 2006)
- **Perinatal mortality and time-to-pregnancy >12 months**
(Draper, Lancet 1999; Basso, HR 2005)
- **Malformations in SC singletons of infertile couples vs. fertile couples: HRR 1.2 (95%CI 1.07-1.35)** (Zhu, 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)
- **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%)
Intermediate (≥8.weeks)	187 (29%)
Late (stillborn)	31 (5%)

Singleton survivors
10.4% (611/5848)

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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)	<i>p</i>	Intermediate (≥8.weeks)	<i>p</i>	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 (<i>r</i> *)	<i>P</i>
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

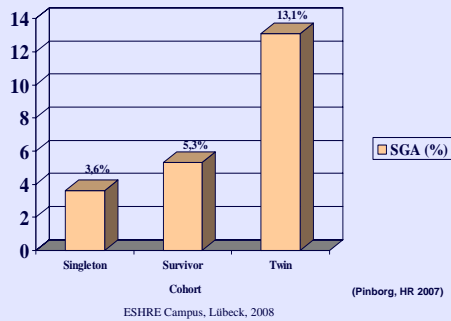
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Vanishing twins & SGA

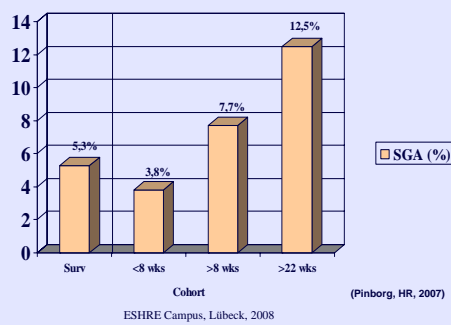


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SGA (%) in IVF singletons



SGA (%) in IVF singletons



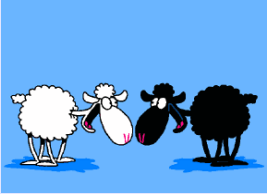
TAKE HOME MESSAGES



- 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 eSET singletons ?

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**Another argument for
elective single embryo transfer**



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