The vanishing twin: a major determinant of infant outcome in IVF singleton births

This article attempts to assess the frequency of vanishing twins in assisted reproductive and spontaneously conceived pregnancies, including in-vitro fertilization (IVF), and its impact on the live-born surviving twin.

As early as in 1945 Stoeckel suggested that twins are more often conceived than born. This was based on the presence of a fetus papyraceus, but he also proposed that twin material could be reabsorbed following early death without leaving any trace. Ultrasound has later confirmed such events, characterized as the 'vanishing twin' phenomenon, which has also been called spontaneous reduction. The routine use of ultrasonography has since proved that spontaneous reduction is a relatively frequent event. As in-vitro fertilization (IVF) has been a major contributor to the worldwide increase in twin birth rates, these procedures have also increased the number of singletons born after a vanishing twin pregnancy. This review will focus on the frequency of vanishing twins in assisted reproductive and spontaneously conceived pregnancies and the short- and long-term consequences for the surviving fetus.

Pathological considerations

Several explanations have been proposed to account for the phenomenon of the vanishing twin. In 1979 it was postulated that a collection of blood seen during pregnancy termination represented earlier sonographic finding of a second sac that had been adjacent to a 6-week viable gestation, which was pathologically confirmed afterwards (Finberg and Birnholz, 1979). Subsequent publications have documented more convincing histological findings from the fetal surface of placenta including well-defined cysts or sacs, degenerated chorion villi, fibrin deposition or fibrinoid degeneration, placental nodules or plaques, embryonic remnants, and macerated or stunted fetuses (Landy and Keith, 1998).

The cause of the vanishing twin phenomenon has been explained by chromosomal abnormalities in one of the twins including trisomy 9 and 16, triploidy, tetraploidy and sex discrepancies (Landy and Keith, 1998). Tharapel et al (1989) suggested that trisomy 16 cells arose from residual villi belonging to a trisomic co-twin that never developed. The vanishing twin phenomenon could theoretically be responsible for iso-immunization developing during a pregnancy in which a rhesus-positive fetus disappears and a rhesus-negative twin continue in a previously unsensitized rhesus-negative mother (Landy et al, 1986).

Early pregnancy disappearance appears to involve resorption and/or formation of a blighted ovum, but the exact pathophysiological mechanism is still unclear.

Diagnosis and frequency

Transvaginal sonography has provided detailed information about early resorption in multiple gestations. However, the assessed incidence of vanishing conceptions depends on both the experience of the sono-grapher and the ultrasound equipment used, and there is a possibility of both exaggeration and underestimation of the true incidence. Normal early embryonic structures such as amniotic cavity, chorionic sac, yolk sac, extraembryonic coelom and also subchorionic haemorrhage or hydropic changes in chorion villi can be misinterpreted as additional gestational sacs (Landy and Keith, 1998). In 1998 Landy and Keith reviewed the pertinent studies published since 1990 to determine the frequency of resorption in first trimester in assisted reproductive technology (ART) *vs* spontaneous pregnancies after early sonography had shown either two sacs or fetuses. These results and more recent studies on the frequency of spontaneous reductions in ART and spontaneous conceived pregnancies are listed in *Table 1*.

Table 1. Outcome of pregnancies after two fetuses or two sacs observed by ultrasonography in first trimester

		Pregnancy outcome				
Early sonography		No	Twins	Singleton	Spontaneous abortion	Reference
Two sacs	ART	549	63.9%	26.8%	9.3%	Dickey et al (2002)*
		317	64%	27.1%	8.8%	Landy and Keith (1998)*
	Non-ART	37	40.5%	40.5%	19%	Landy and Keith (1998)*
Two fetuses	ART	2137	87.7%	8.8%	3.5%	Pinborg et al (2005)†
		397	82.9%	12.1%	5.0%	Tummers et al (2003)*
		261	64.8%	23.7%	11.5%	La Sala et al (2004b)*
		213	57.3%	38%	4.7%	Landy and Keith (1998)*
	Non-ART	41	82.9%	7.3%	9.8%	Landy and Keith (1998)*

*Outcome of pregnancy in second trimester. † Outcome of pregnancy at birth

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The rate of spontaneous reduction in ART pregnancies after two sacs had been observed in early pregnancy varied from 26–27% and after two fetuses from 9–38%. The wide range of frequencies of spontaneous reduction is attributable first to the difficulties in the diagnosis of a spontaneous reduction, second that early ultrasonography was performed at different gestational weeks and third that pregnancy outcome was recorded either after the first trimester or at birth. It is puzzling, however, that in the study by Landy and Keith the spontaneous reduction rate in ART pregnancies was higher when two fetuses were diagnosed (38%) than if two sacs were observed (27%). On the other hand, in spontaneous pregnancies, after identification of two sacs sonographically, loss of one twin could be expected in 40.5% and if two fetuses were seen in only 7.3% (Landy and Keith, 1998). However, the authors emphasized that interpretations should be cautious, as the number of spontaneous pregnancies were very limited compared with the number of ART pregnancies. More importantly, the majority of patients with spontaneous conceptions underwent early ultrasonography because of vaginal bleeding or other high-risk conditions and at different gestational weeks. The authors also stated that disappearance of gestational sacs or fetuses occurs with a higher frequency the earlier the gestational age (Landy and Keith, 1998). In some ART units the first sonography is performed as early as 4 weeks after embryo transfer, whereas the most common routine is to perform the first sonography 5 weeks after.

The proportion of singletons being survivors of a vanishing twin pregnancy among spontaneously conceived children could theoretically be calculated to be approximately 0.5%, based on the assumption that a similar proportion of gestations vanish in spontaneously conceived twin gestations and that the twin birth rate is 1.0% (Imaizumi, 1998). However, precise estimates demand large prospective studies with repeated ultrasound examinations.

In the first study on the outcomes of vanishing twin ART pregnancies Dickey et al (2002) found that 26.8% of ART pregnancies with two gestational sacs at early ultrasound (gestational week 6–7) ended up with only one fetus continuing at 12 weeks. Additional later analysis showed that 15% of singleton births following IVF began as a higher order gestation (Dickey et al, 2004).

In 2003 Tummers and colleges analysed the outcome of 1200 singleton and 397 twin IVF/ICSI (intracytoplasmic sperm injection) pregnancies. These were followed by transvaginal ultrasound every second week throughout the first trimester from before week 7. Of pregnancies with two gestational sacs 12.1% ended with a vanishing twin, 5.1% with a complete miscarriage and 82.8% were ongoing (Tummers et al, 2003).

A Danish multicentre cohort study from 1995 to 2001, on 8542 clinical IVF pregnancies detected by week 7 sonography, found that 10.4% of live-born IVF/ICSI singletons originated from a twin gestation in early pregnancy (Pinborg et al, 2005). A study from the national register of assisted conception in Australia and New Zealand showed that 6.0% of singleton IVF babies were born after two gestational sacs at early pregnancy, but no information of gestational age at early sonography was provided (Lancaster, 2004).

In summary 10–15% of ART singletons have been born after an initial twin gestation in the early pregnancy. The corresponding figure among spontaneously conceived children is theoretically in the order of 0.5%, but no solid data on spontaneous children are available.

Short and long-term outcome

Obstetric complications

Disappearance of a fetus or a gestational sac is reported to be associated with vaginal bleeding or spotting, and the clinical presentation of bleeding seems to coincide with the vanishing process (Landy and Keith, 1998).

Since early pregnancy scans are not routinely done in spontaneously conceived pregnancies, the majority of studies on outcomes of vanishing twins are in ART pregnancies, where clinical practice includes an early ultrasound scan around 5 weeks after embryo transfer. However, the implementation of nuchal translucency scans in week 10–14 provides new possibilities of evaluating the outcome of vanishing twins in spontaneously conceived pregnancies.

In IVF pregnancies more studies have shown that the higher the number of gestational sacs the higher the obstetric risks, irrespective of the final birth number (Dickey et al, 2002; Schieve et al, 2002; Lancaster, 2004). Dickey et al found that after spontaneous reduction with two initial gestational sacs, the average length of gestation for singleton births was shortened by 3 days ($P<0.05$) (Dickey et al, 2002). Furthermore, the average birth weight for singletons without spontaneous reduction was 3360 g compared with 3200 g in singletons with loss of one gestational sac ($P=0.002$). Lancaster (2004) found that birth <37 weeks occurred in 13.7% of singletons with initially one gestational sac and in 18% with two initial gestational sacs and birth <32 weeks occurred in 3.3% of singletons with initially one gestational sac and in 6.3% with two initial gestational sacs.

A large American cohort study on 18 408 singletons demonstrated that with one initial live gestation 12.6% were born with low birth weight (LBW) (<2500 g) *vs* 17.6% if two live fetuses had been present in early pregnancy (Schieve et al, 2004)(*Table 2*).

In 499 IVF singletons, La Sala et al (2004a) found similarly that the percentage of preterm and very preterm births was higher in pregnancies with two initial fetuses compared with pregnancies where only one fetus was present initially (*Table 2*).

The results from the previous studies are in accordance with a Danish multicentre cohort study, where survivors of a vanished co-twin carried a 2.3-fold increased risk of very preterm birth (<32 weeks), a 2.1-fold increased risk of very low birth weight (<1500 g) and a mortality rate that was three-fold increased (Pinborg et al, 2005). Disappearance

of a co-twin was sub-divided into early (<8 weeks), intermediate (8–22 weeks) and late (>22 weeks) vanish and birth weight and gestational age were found to be inversely correlated to onset of spontaneous reduction in pregnancy, the later onset the worse the outcome.

In the European data from 2001 a sizeable number of fetal reductions (*n*=397) were recorded (Nyboe Andersen et al, 2005). As most countries presented no or very limited information on fetal reductions, the number of fetal reductions performed in Europe is probably much higher. In a meta-analysis of three studies comparing 107 women with multifetal reduction to twins *vs* 102 women conceiving twins either spontaneously or by ART, gestational age and perinatal mortality were similar in the two groups (Dodd, 2004). No studies on fetal reduction of twins to singletons are available as the vast majority of fetal reductions are performed in high-order multiple pregnancies. Even though the results of the meta-analysis on fetal reduction are reassuring, the findings of poorer obstetric outcome in singletons from ART pregnancies with spontaneous reduction, and the poorer outcome the later in pregnancy that the reduction occurs indicates that fetal reduction also carries a risk for the outcome of the remaining fetus. Therefore fetal reduction, if not avoidable, should be performed as early in pregnancy as possible.

In summary, IVF singletons born after an initial presence of two gestational sacs or fetuses have a higher risk of preterm birth than IVF singletons born after one initial gestational sac or fetus. However, studies on obstetric outcome in spontaneously conceived singletons from vanishing twin pregnancies are missing.

Neurological sequelae

Knowledge of the long-term consequences for the singleton survivor of a vanished co-twin is sparse. In an Australian study on spontaneously conceived twins born in the 1980s identified from the Western Australian cerebral palsy (CP) register, the prevalence of CP was 96.2 per 1000 in twins who survived to 1 year after in-utero death of a co-twin, 15 times higher than for twins who were both live born (6.4/1000), and 60 times higher than for live-born singletons (1.6/1000) (Petterson et al, 1993). They also found that pregnancies in which intrauterine death of a co-twin occurred were associated with a 10% greater risk of CP.

Late intrauterine death of one twin has considerable influence on the risk of CP and mortality in the surviving co-twin in spontaneous twin pregnancies (Pharoah and Adi, 2000; Scher et al, 2002). Pharoah found that the live-born co-twin of a fetus that died in utero was at a 20-fold increased risk of cerebral impairment compared with the general twin risk (Pharoah et al, 2000) and Scher et al (2002) found a 4-fold increased risk of CP in twin survivors of a stillborn co-twin. These data relate to death of a co-twin in the third trimester. To the authors' knowledge, only the Danish multicentre cohort study describes the risk of CP in twins surviving an earlier disappearance of a co-twin (Pinborg et al, 2005).

Table 2. The frequency of preterm birth (<37 gestational weeks) or very preterm birth (<32 gestational weeks) in IVF singletons after either one or two gestational sacs/embryos had been present at early sonography

		Gestational age				
		<37 weeks		<32 weeks		
		No. fetuses/sacs		No. fetuses/sacs		
Early sonography	N	2	1	2	1	Reference
Fetuses	5879	13.2%‡	9.0% ‡	3.8% ‡	1.3%‡	Pinborg et al (2005)*
	499	19.3%	16.7%	4.8%	2.7%	La Sala et al (2004a)*
Sacs	20 063	18.0% §	13.7% §	6.3% §	3.3% §	Lancaster (2004)†
	4823	11.4% §	8.4% §	4.5% §	1.4% §	Dickey et al (2002)†

IVF = in-vitro fertilization. * Number of embryos; † Number of sacs; ‡ $P < 0.001$; § Statistically significant, no *P*-value available

The Danish survey revealed that the overall incidence rate of CP was 8.2% (5/611) in singletons with a vanished co-twin and 4.2% (95/5237) in singletons with an initial singleton gestation, implying a nearly two-fold increased risk of CP in singleton survivors of a vanished co-twin (odds ratio = 1.9, 95% confidence interval = 0.7–5.2). It also revealed a significant correlation between gestational age at onset of spontaneous reduction and development of neurological sequelae (*Table 3*). The Danish study comprised 72% of all IVF/ICSI cycles performed in Denmark between 1995 and 2001 with outcome on more than 8000 clinical pregnancies including 642 singleton survivors of a vanished co-twin. Despite demonstrating a positive correlation between onset of vanish and neurological sequelae, the number of vanishing twins was too low to make specific estimates for single diseases such as CP.

Discussion

In 2001 IVF children accounted for about 1–4% of newborns in Europe and this figure is still increasing (Nyboe Andersen et al, 2005). Two meta-analyses have agreed that IVF singletons have 2–3-fold increased risk of preterm birth, low birth weight and perinatal mortality compared with spontaneously conceived singletons (Helmerhorst et al, 2004; Jackson et al, 2004). This increased risk is limited to singletons as IVF twins have similar outcomes to their spontaneously conceived counterparts (Helmerhorst et al, 2004; Pinborg et al, 2004). Further it has been documented in three Scandinavian studies based on national register data that the risk of CP was also increased by a factor of 2–3 in IVF singletons (Strömberg et al, 2002; Källen et al, 2005; Lidegaard et al, 2005).

Some researchers have argued that the excess risk is caused by the underlying infertility of couples seeking treatment rather than the treatment per se (Pandian et al, 2001; Basso and Baird, 2003). However, a contributing explanation to the adverse short- and long-term outcome in IVF singletons is that a sizeable proportion of ART singletons origin from twin gestations, where spontaneous

Table 3. The number of children with cerebral palsy, neurological sequelae and neurodevelopmental diseases in the survivor cohort according to time of vanish of co-twin

			Vanish time			Spearman correlation* (r)	P value
		Singletons	Early	Intermediate	Late		
No. of live-born children		5237	424	187	31		
No. of children with (per 1000):	Cerebral palsy	22 (4.2)	3 (7.1)	2 (10.7)	0	–0.008	0.85
	Neurological sequelae	95 (18.1)	4 (9.4)	5 (26.7)	2 (64.5)	–0.09	0.022
	Neurodevelopmental diseases	216 (41.0)	14 (33.0	5 (80.2)	3 (96.8)	–0.109	0.006

Early vanish = spontaneous reduction <8th gestational week, intermediate vanish = >8th and <22nd gestational week; late vanish = recorded as stillbirth of co-twin >22nd gestational week (Pinborg et al, 2005). *Spearman correlation coefficient (r) for ordinal data between the early, intermediate and late vanish of co-twin group

reductions occurred. This correlates with a study on 6377 IVF infants showing that elevated risk ratios of five perinatal outcomes of IVF singletons diminished (although remained elevated) when restricted to infants with only one live fetus in early pregnancy (Schieve et al, 2004).

In 2001 52% of IVF/ICSI treatments in Europe implemented dual embryo transfer, 36% multiple and only 12% single embryo transfers (Nyboe Andersen et al, 2005). Although rates of elective single embryo transfer are rising all over Europe, in particular in Finland and the other Nordic countries, there is still a way to go before the goal of a markedly reduced twin birth rate is reached. The findings on vanishing twins are a further argument for diminishing the IVF twin birth rates. **BJHM**

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KEY POINTS

- The true rate of vanishing twins in spontaneous singletons is unknown.
- Between 10 and 15% of assisted reproductive technology singletons are born after a twin gestation in early pregnancy.
- In-vitro fertilization (IVF) singletons from vanishing pregnancies have lower birth weight and gestational age than singletons from single gestations.
- There is a tendency that long-term outcome is also affected in IVF singletons from vanishing twin pregnancies.