

The natural history of multiple pregnancies after assisted reproduction: is spontaneous fetal demise a clinically significant phenomenon?

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Objective: To determine the rate of spontaneous fetal demise after heartbeats are demonstrated in multiple pregnancies conceived after IVF-ET.

Design: Retrospective case series.

Setting: University-based IVF-ET program.

Patients: Eighty-one patients in whom initial transvaginal ultrasound (US) study, performed at 5 to 6 weeks of gestation, identified more than one gestational sac. Total number of sacs was 191.

Intervention: Patients were followed by serial US examinations.

Main Outcome Measure: Outcome of pregnancies.

Results: Twenty-four empty gestational sacs were identified in 21 patients, of whom 15 delivered, 2 miscarried, and 4 are currently ongoing beyond first trimester. Of the 167 initially viable embryos, 9 (5%) underwent spontaneous fetal demise. In 5 of these 9 pregnancies, initial US identified significant interfetal size variation.

Conclusions: The rate of spontaneous fetal demise for a specific embryo in multiple gestation, after fetal heartbeats have been identified in early pregnancy, is 5%. This rate is similar to that seen in spontaneous conceptions. The chance of future fetal demise increases if first trimester interfetal size variation is significant. *Fertil Steril* 1993;60:127-30

Key Words: Spontaneous fetal demise, multiple pregnancies, in vitro fertilization

High-resolution transvaginal sonography allows early recognition of multiple pregnancies. The rate at which multiple gestational sacs are observed on ultrasonography in early pregnancy is, however, higher than the actual number of infants delivered. Although spontaneous fetal demise ("vanishing twin") undoubtedly occurs, the actual rate of this phenomenon is controversial. In 1982, Landy et al. (1) summarized data from nine studies and calculated the frequency of vanishing twin to be 53% to 78%. These data lacked, however, pathological

confirmation, and the authors suggested that low-quality ultrasound (US) images (at that time) may explain these surprisingly high figures. Lower rates of spontaneous fetal demise have been reported recently, especially after fetal heartbeats have been demonstrated on ultrasonography. Dickey et al. (2) found that when two heartbeats were detected, the probability of delivering twins was 84% to 90%, depending on maternal age (the chance for twin delivery was found to be higher for patients < 30 years of age).

These findings may have relevance to the debate regarding the best timing of selective fetal reduction, a procedure that has been introduced in recent years in an attempt to reduce the complications associated with high-order multiple gestations. Other unresolved questions are the number of fetuses for

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which the procedure should be considered, and the number of fetuses that should be left intact. An earlier transvaginal procedure is easier and probably safer to perform (3–5), yet it has been criticized on the basis of the potentially high rate of spontaneous fetal loss associated with the vanishing twin phenomenon. To address these issues, we decided to determine the rate of spontaneous fetal demise in our IVF-ET program in cases in which initial sonography identified more than one gestational sac.

MATERIALS AND METHODS

Records of patients who conceived in our IVF-ET program were reviewed, and 81 pregnancies in which initial sonographic evaluation, performed 3 to 4 weeks after ET, demonstrated more than one gestational sac were identified. Serial sonographic studies were performed weekly until the end of the first trimester to monitor the growing pregnancy, particularly, identification of fetal heartbeats (approximately 6 weeks' gestation) and measurement of fetal crown-rump length. Thereafter, sonographic follow-up studies were performed every 2 to 4 weeks. During the first trimester, the Elscint ESI-1000 US imaging system (Elscint Inc., Haifa, Israel) with a 6.5-MHZ vaginal probe was used.

Patients' ages ranged from 20 to 40 years (mean, 31.4 years). Fifty-five patients with two gestational sacs, 23 with three gestational sacs, and 3 with four gestational sacs were included in this study. In the study group, selective fetal reduction was not performed, allowing us to evaluate the natural history of multiple gestations diagnosed in early pregnancy. However, during the last 4 years, if more than two fetuses were identified on ultrasonography, the option of induced fetal reduction was offered to patients. These procedures were performed transvaginally, as previously described (3), in 20 patients who have already delivered. These patients were excluded from our present study.

Because of gestational age variability and the reproducibility of crown-rump length measurement (1.2 mm [12]), we calculated the ratio of the difference in crown-rump length between the largest and smallest embryo and the crown-rump length of the smallest embryo. For each sonographic study performed, this ratio was used as a numeric expression of interfetal size variation.

RESULTS

The initial sonographic evaluation identified a total of 191 gestational sacs. Their outcome is summarized in Table 1.

Empty Sacs

Twenty-four empty gestational sacs were observed (13% of the total number of gestational sacs) in 21 pregnancies. In 9 pregnancies, one empty sac was observed in association with one viable fetus; in 11 cases there was a total of 3 gestational sacs (9 with 1 empty sac, and 2 with 2 empty sacs); and in one case there were 4 gestational sacs, 2 of which were empty. Of these pregnancies, 19 ended in delivery (>27 weeks), and 2 were miscarried.

Living Embryos

Of the 167 embryos with demonstrated heartbeats, 9 have disappeared during follow-up, for a total of 5.4% (95% confidence limit of 2.5% to 10.0%) spontaneous fetal demise rate (Table 1). Twelve (7.2%) other fetuses were lost as spontaneous abortions (SABs): 2 losses in early pregnancy (8 and 10 weeks) and 10 late abortions (13, 18, 21, and 22 weeks).

Table 2 summarizes the outcome of pregnancies with multiple viable embryos without empty sacs. In 46 patients two living embryos were seen initially. Forty-one delivered twins after 27 weeks, and 3 had spontaneous late abortions (weeks 13, 18, and 22). In 2 patients one fetus had vanished; both had a term singleton delivery. Twelve patients had triplet pregnancies, and 9 of them delivered triplets after 27 weeks. Three patients experienced spontaneous demise of one fetus and delivered twins after 27 weeks. In 2 patients four living embryos were documented in early pregnancy. One had a miscarriage at 21 weeks, and the other had a twin delivery at 37 weeks after one fetus vanished in the first trimester, and one died in utero at 29 weeks.

Vanishing Embryos

In 5 of the 9 vanishing fetuses, initial US evaluation identified significant interfetal size variation. These cases are summarized in Table 3. A ratio of interfetal size variation of 0.6 was found in only two patients in whom spontaneous fetal demise did not occur ($P < 0.01$ by Fisher's exact test). In the remaining four cases, one fetus died at 8 weeks, one at 18 weeks, one at 29 weeks, and in one case we could not ascertain the exact timing of fetal disappearance; however, it was past 10 weeks' gestation.

DISCUSSION

Our data suggest that the chance of a patient with multiple fetuses to deliver a number of infants

Table 1 Distribution and Outcome of All Gestational Sacs Identified Initially

No. of sacs per patient	Total sacs	Empty sacs	SAB	Spontaneous reduction	Delivery >27 wk
2	110	9	7	3	91
3	69	13	1	4	51
4	12	2	4	2	4
Total	191 (100)*	24 (12)	12 (7)	9 (5)	146 (76)

* Values in parentheses are percents.

identical to the number of gestational sacs identified in early pregnancy is 83% (50 of 60 pregnancies, Table 2). However, when a specific embryo is followed after documentation of heart activity, the risk of its spontaneous demise is only 5%, substantially lower than previously reported. The finding of an empty gestational sac in association with multiple gestation does not confer an increased risk of pregnancy loss. We observed a 10% miscarriage rate in these cases (2 of 21 patients).

Reports originating only a decade ago suggest that the rate of embryonic disappearance is as high as 53.3% to 71% (1, 6, 7). Because these data were obtained using transabdominal ultrasonography, one may assume that the lack of high-quality imaging may have led to errors in diagnosis, mainly overdiagnosis of gestational sacs. More recent data, based on high-resolution, high-frequency transvaginal transducers, suggest that the rate of fetal demise (after heartbeats have been identified) is significantly lower than previously reported. Jarjour and Kletzky (8) found in singleton pregnancies that 93% of living fetuses with crown-rump length compatible with gestational age, progressed to term. Surveying 40 patients who had two gestational sacs, Kelly et al. (9) found that spontaneous fetal demise occurred in one third of pregnancies. However, only six fetuses (7.5%) had arrest of development after

fetal heart activity had been detected by US, a rate very similar to that seen in singleton pregnancies (8) and in our study. Dickey et al. (2) reported the outcome of 277 multiple pregnancies and found that when two beating hearts were detected, the probability of delivering twins was 90% for women < 30 years and 84% for maternal age > 30. The probabilities for triplets with three documented heartbeats was 90% and 44%, respectively.

Can we predict spontaneous fetal demise? Biochemically, vanishing twin conceptions are characterized by a slower rise of hCG than that observed in normally progressing twin pregnancies (9). Sonographically, it seems that when conception time is well established, persistent size-dates discrepancy early in pregnancy may indicate a poor prognosis. In well-dated pregnancies, a fetal crown-rump length significantly smaller than expected appears to be associated with increased risk of aneuploidy (10), a factor commonly associated with pregnancy loss. In the study by Jarjour and Kletzky (8), transvaginal US demonstrated heartbeats in 16 pregnancies in which the fetal pole was smaller for gestational age by 1 to 2 weeks. This growth retardation persisted in six cases, all ending in SABs. In the other 10 pregnancies, crown-rump length measurements caught up and became compatible with gestational age. All these pregnancies progressed to term. In our series, the disappearance of 5 of 9 fetuses could have been predicted on the grounds of significant interfetal crown-rump length variability (Table 3). Similarly, Stern and Coulam (11) reported that 79% of embryos with heart activity at 6 weeks' gestation, who were small for age, underwent SAB, compared with only 8% of embryos who were of normal size for gestational age. Interestingly, these results that were obtained for singleton spontaneous conceptions are similar to our data obtained for IVF-ET patients, suggesting that fetal survival is not influenced by the way pregnancy was achieved (spontaneously or by assisted reproduction). It should be noted, however,

Table 2 Outcome of Pregnancies With Multiple Viable Embryos

Group	No. of subjects	Outcome per pregnancies		
		No. of newborn = no. of embryo	No. of newborn < no. of embryo	Abortion
Twins	46	41	3	2
Triplets	12	9	3	—
Quadruplets	2	—	1	1
Total	60 (100)*	50 (83)	7 (12)	3 (5)

* Values in parentheses are percents.

Table 3 Spontaneous Embryo Demise in Cases With Significant Interfetal Size Variation

Case	No. of gestational sacs	Gestational age	Crown-rump length	Outcome
		<i>wk</i>	<i>cm</i>	
1	2	7 4/7	0.96; 0.48	3,105 g
2	2	10	3.5; 1.0	2,950 g
3	3	9	2.18; 1.9; 0.5	2,960 g; 2,530 g
4	3	8 3/7	1.4; 1.48; 0.9	2,030 g; 3,100 g
5	3	6 3/7	0.5; 0.2; empty	SAB

that some interfetal size variability in multiple gestation may be a normal finding. Isada et al. (12) studied patients having triplets and higher multiples and found considerable interfetal size variability during the first trimester (3 to 6 mm). Follow-up to term was not possible in that study because selective fetal reduction was performed.

The clinical significance of our findings is mainly related to the information that should be given to patients with multiple pregnancies early in first trimester when the number and viability of the fetuses can be ascertained sonographically (6 to 7 weeks' gestation). This information is especially significant when selective fetal reduction is considered. The main criticism against an early procedure has been the earlier time in gestation when this procedure is performed, not allowing for natural selection to take place. It has been suggested that the result of early selective termination may be the loss of additional embryos from natural causes, thus losing the entire pregnancy. In our experience, as well as in others (5), however, the risk of unintentionally losing additional embryos after early selective termination is small. Of the first 20 cases in which early (7 to 8 weeks) elective transvaginal reduction was performed, none of the 41 remaining fetuses vanished spontaneously after the procedure (4). Similar results have been reported by Vauthier-Brouzes and Lefebvre (5), using the same procedure in 22 patients. Moreover, serial sonographic evaluations and hCG levels may have some value in tracing those relatively few pregnancies in which spontaneous fetal demise is more likely, implying that selective fetal reduction should be deferred in those cases or that the smaller embryo is the one that should be reduced. One must, however, bear in mind that spontaneous fetal demise may occur even if crown-rump length is compatible with gestational age and hCG slope is normal. On the other hand, selective termination by the end of the first trimester is associated with a higher rate of pregnancy loss (4).

In summary, the risk of losing a specific fetus in multiple gestation after fetal heartbeats were identified is small (5%). This information may be useful to all patients with multiple pregnancy and, in particular, for those considering selective fetal reduction.

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