FERTILITY AND STERILITY®
VOL. 82, NO. 6, DECEMBER 2004

Published by Elsevier Inc.
Printed on acid-free paper in U.S.A.

Spontaneous embryonic loss after in vitro fertilization with and without intracytoplasmic sperm injection

Giovanni B. La Sala, M.D.,[a] *Giuseppe Nucera, M.D.,*[a] *Andrea Gallinelli, M.D.,*[a] *Alessia Nicoli, B.Sc.,*[a] *Maria Teresa Villani, M.D.,*[a] *and Isaac Blickstein, M.D.*[b]

Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; Kaplan Medical Center, Rehovot; and the Hadassah-Hebrew University School of Medicine, Jerusalem, Israel

Objective: To determine whether pregnancies after IVF, with and without intracytoplasmic sperm injection (ICSI), have different early spontaneous loss rates.

Design: Retrospective analysis of IVF/ICSI dataset.

Setting: The Center of Reproductive Medicine, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy.

Patient(s): Women undergoing IVF with or without ICSI.

Intervention(s): First-trimester sonography at 6–7 weeks to count the number of embryos with positive heartbeat. The number of embryos lost was calculated from a second-trimester sonogram.

Main Outcome Measure(s): Embryonic loss rates related to the initial number of embryos, maternal age <35 or ≥35 years, and IVF procedure.

Result(s): In vitro fertilization and ICSI had similar embryonic loss rates (odds ratio [OR] 1.2, 95% confidence interval [CI] 0.9–1.7, and OR 1.3, 95% CI 0.9–1.8 for women aged <35 years and ≥35 years, respectively). Younger women had fewer losses after IVF (OR 0.7, 95% CI 0.5-0.9). Multiples had lower loss rates compared with singleton pregnancies.

Conclusion(s): In vitro fertilization and ICSI have similar spontaneous embryonic loss rates. Factors other than the initial number of embryos, maternal age, and IVF technique, such as embryo quality or uterine environment, might be involved in the outcome of multiple pregnancies in assisted reproductive technology procedures. (Fertil Steril® 2004;82:1536–9. ©2004 by American Society for Reproductive Medicine.)

Key Words: IVF, ICSI, multiple pregnancy, embryonic loss, maternal age

Received January 12, 2004; revised and accepted April 16, 2004.

Reprints will not be available. Address correspondence to: Isaac Blickstein, M.D., Kaplan Medical Center, Department of Obstetrics and Gynecology, Rehovot 76100, Israel (FAX: 972-8-9411944; E-mail: blick@netvision.net.il).

[a] Department of Obstetrics and Gynecology, Arcispedale Santa Maria Nuova.

[b] Department of Obstetrics and Gynecology, Kaplan Medical Center, and the Hadassah-Hebrew University School of Medicine.

0015-0282/04/$30.00
doi:10.1016/j.fertnstert.2004.04.062

Recent data from the Centers for Disease Control and Prevention, the Society for Reproductive Medicine, and the Society for Assisted Reproductive Technology imply that, in the year 2000, more than half of the assisted reproductive technology (ART) procedures with fresh, non-donor eggs or embryos were done with standard IVF techniques, whereas in nearly 46% of ART procedures, eggs were fertilized through intracytoplasmic sperm injection (ICSI) (1). Intracytoplasmic sperm injection has undoubtedly revolutionized the treatment of male infertility and is currently used by most ART centers as the primary treatment for male infertility (2).

There has been controversy regarding whether the risks associated with ICSI are procedure-related or are owing to the use of defective sperm (2). There has been concern about increased risks of chromosome aneuploidy and congenital malformations, as well as the influence of ICSI on embryonic development and zygotic splitting (2).

In vitro fertilization, with or without ICSI, poses a major risk for multiple births and represents an increasingly important public health problem in the United States (3) and in many countries worldwide (4). The risk for multiple births after ART is primarily related to the patient's age and to the number of transferred embryos, two factors that are also associated with spontaneous embryonic and fetal loss (5). Recently, Tummers et al. (6) studied ART pregnancies and found overall loss rates of

TABLE 1

Effect of IVF and ICSI on spontaneous embryonic loss by starting number of embryos.

Pregnancies (n)		Number of fetuses on second-trimester scan				
		0	1	2	3	4
Four embryos on first-trimester scan						
IVF	17	2 (11.8)	0	2 (11.8)	3 (17.6)	10 (58.8)
ICSI	17	2 (11.8)	1 (5.9)	3 (17.6)	3 (17.6)	8 (47.1)
Total	34	4 (11.8)	1 (2.9)	5 (14.7)	6 (17.7)	18 (52.9)
Three embryos on first-trimester scan						
IVF	50	4 (8.0)	11 (22.0)	16 (32.0)	19 (38.0)	
ICSI	36	3 (8.3)	6 (16.7)	11 (30.6)	16 (44.4)	
Total	86	7 (8.1)	17 (19.8)	27 (31.4)	35 (40.7)	
Two embryos on first-trimester scan						
IVF	143	21 (14.7)	36 (25.2)	86 (60.1)		
ICSI	118	9 (7.6)	26 (22.0)	83 (70.4)		
Total	261	30 (11.5)	62 (23.7)	169 (64.8)		
One embryo on first-trimester scan						
IVF	333	91 (27.3)	242 (72.7)			
ICSI	248	59 (23.8)	189 (76.2)			
Total	581	150 (25.8)	431 (74.2)			

Note: Data are presented as n (%).

La Sala. Spontaneous embryonic loss in IVF vs. ICSI. Fertil Steril 2004.

21.7% and 17.1% for singletons and twins, respectively. After positive heart activity had been recorded, embryonic/fetal death occurred in 12.2% of singleton and in 7.3% of twin pregnancies (6). However, studies on spontaneous embryonic and fetal loss related to the initial number of embryos and maternal age did not exclude the potential effect of ICSI. In the absence of such data, we focused on spontaneous losses in multiple pregnancies to compare IVF and ICSI pregnancies as related to maternal age and number of transferred embryos.

MATERIALS AND METHODS

During the study period January 1, 1992 to December 31, 2002, there were 1076 clinical pregnancies after ART in our nonprivate clinic at Arcispedale Santa Maria Nuova, at Reggio Emilia, Italy. This ART service has some unique features related to constraints prohibiting disposal and freezing of surplus embryos. Moreover, only day 2–3 embryos are transferred without assisted hatching. Sixty-nine patients were excluded because of loss to follow-up (n = 27) and incomplete or spurious entries (n = 87). The patients included in the study population (n = 962) comprised mainly (>95%) women of Italian origin, who were nearly all nulliparous, with a mean (± SD) age of 34.2 ± 4.0 years. All patients underwent IVF either with (n = 419) or without (n = 543) ICSI. The database includes detailed information related to the ART procedures and to obstetric variables. The data were prospectively collected and regularly updated.

After biochemical diagnosis of pregnancy, all pregnant patients underwent first-trimester transvaginal sonography at 4–5 weeks after ovum pick-up to count the number of embryos with positive heartbeat. Gestational age was established by subtracting 14 days from the embryo transfer date. The number of embryos lost was calculated from a second-trimester sonogram.

In the first part of the study, we evaluated the frequency of first-trimester embryonic losses after conventional IVF and ICSI, by comparing the number of fetuses in the first and second trimester in each gestation. Because this analysis focused on first-trimester losses (the so-called "vanishing twin syndrome"), we included patients (n = 29) who subsequently underwent second-trimester multifetal pregnancy reduction (not performed at our hospital).

Next, we compared the frequency of lost embryos by maternal age (<35 or ≥35 years) between conventional IVF and ICSI pregnancies. Finally, we counted the frequencies of pregnancies in which the entire set seen on first-trimester ultrasound was lost in IVF and ICSI gestations, as well as the respective frequencies of pregnancies in which the entire set survived into the second trimester.

The data were retrospectively collected and evaluated with a commercial software program (Excel; Microsoft Corporation, Redmond, Washington). We used additional software (True Epistat; Math Archives, Round Rock, TX) to compare frequencies by Fisher exact tests. We derived odds ratio (OR) and Cornfield's 95% confidence intervals (CI). The ethics committee of the hospital approved the study.

TABLE 2

Frequencies of lost embryos by the starting number of embryos and maternal age in IVF and ICSI pregnancies.

Starting no. of embryos	IVF		ICSI	
	Total no. of embryos	Lost embryos	Total no. of embryos	Lost embryos
<35 y				
4	52	10 (19.2)	44	13 (29.5)
3	84	28 (33.3)	57	14 (24.6)
2[a]	172	37 (21.5)	134	19 (14.2)
1	160	40 (25)	150	34 (22.6)
Total[b]	468	115 (24.6)	385	80 (20.8)
≥35 y				
4	16	6 (37.5)	24	7 (29.2)
3	66	22 (33.3)	51	18 (32.3)
2[a]	114	41 (36.0)	102	25 (24.5)
1	173	51 (29.5)	98	25 (25.5)
Total[b]	369	120 (39.3)	275	75 (27.3)

Note: Data are presented as n (%).

[a] Odds ratio 0.5; 95% confidence interval 0.3–0.8.

[b] Odds ratio 0.7; 95% confidence interval 0.5–0.9.

La Sala. Spontaneous embryonic loss in IVF vs. ICSI. Fertil Steril 2004.

RESULTS

Women undergoing IVF were significantly older compared with those undergoing ICSI (34.6 ± 3.9 years vs. 33.7 ± 4.0 years, respectively, $P<.001$). In addition, more embryos were transferred during IVF cycles compared with ICSI (5.3 ± 3.1 vs. 4.7 ± 2.3, respectively, $P<.001$).

Table 1 shows the spontaneous embryonic loss of embryos developing after conventional IVF or ICSI. The comparison between IVF and ICSI showed no effect of the mode of conception on the number of fetuses surviving to the second trimester. Overall, the early loss rates of quadruplets, triplets, twins, and singletons after IVF were 28.1%, 33.3%, 27.2%, and 27.3%, respectively. The respective figures for ICSI were 29.4%, 29.6%, 18.6%, and 23.8%.

For the analysis shown in Table 2, we counted the frequency of embryonic losses by the number of embryos seen on the first-trimester scan, in women aged <35 and ≥35 years. In the first comparison, between IVF and ICSI pregnancies, there was no significant difference in the frequency of embryonic loss (OR 1.2, 95% CI 0.9–1.7 for women aged <35 years, and OR 1.3, 95% CI 0.9–1.8 for women aged ≥35 years). The similarity between loss rates after IVF and ICSI was consistently seen when comparisons were made for each starting number of embryos, suggesting that spontaneous embryonic loss rates are similar in both modes of ART, irrespective of the initial number of embryos. However, when we compared the effect of maternal age within the methods of ART, there were significantly more losses among older women who underwent conventional IVF, which stems from the significantly higher loss rates among twin pregnancies. This effect was not seen among women who conceived with ICSI.

When we separately counted pregnancies in which all embryos were lost (Table 3), there was no significant difference between IVF and ICSI pregnancies (OR 1.1, 95% CI 0.7–1.9 for women aged <35 years, and OR 1.4, 95% CI 0.8–2.4 for women aged ≥35 years). Table 3 also shows that the same was true for pregnancies in which the entire set survived (OR 0.7, 95% CI 0.5–1.1 for women aged <35 years, and OR 0.9, 95% CI 0.6–1.3 for women aged ≥35 years). However, when the effect of maternal age was evaluated within the modes of conception, the data again indicated significantly more losses among older women who underwent conventional IVF, which stems from the significantly higher loss rates among twin pregnancies (Table 3). This effect was not seen among women who conceived with ICSI.

DISCUSSION

The Reggio Emilia ART data set represents a series of clinical pregnancies occurring in a homogeneous population of Italian nulliparas. In this analysis, we examined the natural fate of live embryos visualized by first-trimester transvaginal sonography, as related to the mode of ART conception, number of embryos, and the woman's age.

The present study leads to several observations. First, we found that spontaneous embryonic loss is uninfluenced by mode of conception, irrespective of whether the pregnancies started as viable quadruplets, triplets, twins, or singletons.

Second, we can corroborate the report by Dickey et al. (5) of a positive relationship between maternal age and spontaneous reduction rates, but only in the IVF pregnancies and not in the ICSI population. It is possible that this distinction

TABLE 3

Frequencies of loss and survival of the entire set.

Starting no. of embryos	Total loss/pregnancies		Total survival/pregnancies	
	IVF	ICSI	IVF	ICSI
<35 y				
4	1/13 (7.7)	1/11 (9.1)	8/13 (61.5)	5/11 (45.4)
3	2/28 (7.1)	1/19 (5.3)	11/28 (39.3)	10/19 (52.6)
2	8/86 (9.3)[a]	3/67 (4.5)	57/86 (66.3)	51/67 (59.3)
1	40/160 (25.0)	34/150 (22.7)	120/160 (75.0)	116/150 (77.3)
Total	51/287 (17.8)[b]	39/247 (15.8)	196/287 (68.3)	182/247 (73.7)
≥35 y				
4	1/4 (25.0)	1/6 (16.7)	2/4 (50.0)	3/6 (50.0)
3	2/22 (9.1)	2/17 (11.8)	8/22 (36.4)	6/17 (35.3)
2	13/57 (22.8)[a]	6/51 (11.8)	29/57 (50.9)	32/51 (62.7)
1	51/173 (29.5)	25/98 (25.5)	122/173 (70.5)	73/98 (74.5)
Total	67/256 (26.2)[b]	34/172 (19.8)	161/256 (62.9)	114/172 (66.3)

Data are presented as n (%).

[a] Odds ratio 0.3, 95% confidence interval 0.1–0.9.

[b] Odds ratio 0.6, 95% confidence interval 0.4–0.9.

La Sala. Spontaneous embryonic loss in IVF vs. ICSI. Fertil Steril 2004.

is not a chance event, because Orvieto et al. (7), who compared 100 cases after ICSI with 100 cases after conventional IVF, found that ICSI pregnancies were characterized by a lower clinical abortion rate than IVF pregnancies, probably because of the mean younger age of women in the ICSI group.

An intriguing finding of a recent comparative study indicates that complete pregnancy loss occurred in 5.1% of the IVF/ICSI twin pregnancies, compared with 21.1% in singletons (6). The investigators concluded that the embryologic potential for successful development is not the same for twins and singletons and that twin pregnancies after IVF/ICSI have a better survival potential than singletons. Our data fully support this observation, and, in addition, we could show that this was also the case in triplet and quadruplet gestations (Table 3). One possible explanation for this phenomenon is that our loss rate for singletons was excessive, but this explanation might be discarded because our rate was similar to other published series from Europe (6, 8) and the United States (9). Another explanation could point to the mode of conception, but the general observation was true for both ICSI and IVF pregnancies. Finally, our data could show that the age distribution in our series was also not the reason for this observation, because the general observation was true for women aged both <35 and ≥35 years (Table 3).

A potential explanation comes from the unique circumstances of the ART protocols in Reggio Emilia, whereby all available embryos were transferred in each cycle. It could be speculated that higher implantation rates per transfer (i.e., development of more than one live embryo) might represent a better capacity of the uterus for early embryonic development and/or better embryonic quality. Conversely, implantation of one embryo only despite transfer of many embryos might represent poor uterine capacity and/or poor embryonic quality, and hence a higher miscarriage rate. Table 3 also shows that intact survival of the entire set of multiples is lower than that of singletons but without significant plurality-dependent difference.

In summary, our observations suggest that there is no difference between loss and/or survival rates of multiple gestations after conventional IVF or ICSI. Other factors, such as embryo quality or uterine environment, might be involved in the outcome of ART multiple pregnancies.

References

1. Centers for Disease Control and Prevention. 2000 assisted reproductive technology success rates. National summary and fertility clinic reports. Available: http://www.cdc.gov/reproductivehealth/ART00/index.htm. Accessed January 1, 2004.
2. Khorram O, Patrizio P, Wang C, Swerdloff R. Reproductive technologies for male infertility. J Clin Endocrinol Metab 2001;86:2373–9.
3. Wright VC, Schieve LA, Reynolds MA, Jeng G. Assisted reproductive technology surveillance, United States, 2000. MMWR Surveill Summ 2003;52:1–16.
4. Blickstein I. The worldwide impact of iatrogenic pregnancy. Int J Gynaecol Obstet 2003;82:307–17.
5. Dickey RP, Taylor SN, Lu PY, Sartor BM, Storment JM, Rye PH, et al. Spontaneous reduction of multiple pregnancy: incidence and effect on outcome. Am J Obstet Gynecol 2002;186:77–83.
6. Tummers P, De Sutter P, Dhont M. Risk of spontaneous abortion in singleton and twin pregnancies after IVF/ICSI. Hum Reprod 2003;18:1720–3.
7. Orvieto R, Ben-Rafael Z, Ashkenazi J, Yoeli R, Messing B, Perri T, et al. Outcome of pregnancies derived from assisted reproductive technologies: IVF versus ICSI. J Assist Reprod Genet 2000;17:385–7.
8. Wisanto A, Bonduelle M, Camus M, Tournaye H, Magnus M, Liebaers I, et al. Obstetric outcome of 904 pregnancies after intracytoplasmic sperm injection. Hum Reprod 1996;11(Suppl 4):121–9.
9. Coulam CB, Opsahl MS, Sherins RJ, Thorsell LP, Dorfmann A, Krysa L, et al. Comparisons of pregnancy loss patterns after intracytoplasmic sperm injection and other assisted reproductive technologies. Fertil Steril 1996;65:1157–62.