

SPECIAL ARTICLE

Trends in the Use of Intracytoplasmic Sperm Injection in the United States

Tarun Jain, M.D., and Ruchi S. Gupta, M.D., M.P.H.

ABSTRACT

BACKGROUND

Intracytoplasmic sperm injection (ICSI) was initially developed as part of in vitro fertilization (IVF) to treat male-factor infertility. However, despite the added cost, uncertain efficacy, and potential risks of ICSI, its use has been extended to include some patients without documented male-factor infertility.

METHODS

We analyzed national data on assisted reproductive technology reported to the Centers for Disease Control and Prevention, to determine temporal trends in the use of ICSI and IVF in the United States, and we examined differences in the use of ICSI between states with and those without mandated insurance coverage.

RESULTS

From 1995 to 2004, the number of fertility clinics and fresh-embryo cycles and the rates of IVF-related pregnancies and live births increased. The percentage of IVF cycles with the use of ICSI also increased dramatically (from 11.0% to 57.5%), while the percentage of diagnoses of infertility attributed to male-factor conditions remained stable. The ratio of ICSI procedures to diagnoses of male-factor infertility steadily increased each year, suggesting an increasing use of ICSI for conditions other than male-factor infertility. From 1999 to 2004, there was an increasing use of ICSI relative to the percentage of patients with male-factor infertility in states with and those without mandated insurance coverage. For any given year, however, states with insurance coverage had a higher ratio of ICSI use to diagnoses of male-factor infertility than did states without insurance coverage ($P < 0.001$).

CONCLUSIONS

Since 1995, the use of ICSI in the United States has increased dramatically, while the proportion of patients receiving treatment for male-factor infertility has remained stable. State-mandated health insurance coverage for IVF services is associated with greater use of ICSI for infertility that is not attributed to male-factor conditions.

From the Department of Obstetrics and Gynecology, University of Illinois at Chicago College of Medicine (T.J.); the Institute for Healthcare Studies, Feinberg School of Medicine, Northwestern University (R.S.G.); and the Children's Memorial Research Center, Children's Memorial Hospital (R.S.G.) — all in Chicago. Address reprint requests to Dr. Jain at the Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, University of Illinois at Chicago, 820 S. Wood St., Rm. 285, Chicago, IL 60612, or at tjain@uic.edu.

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THE INTRODUCTION OF IN VITRO FERTILIZATION (IVF) in 1978¹ led to advances in treatment for infertility.² However, effective treatment for male-factor infertility (determined on the basis of abnormal semen measurements) was not available until 1992, when intracytoplasmic sperm injection (ICSI) was introduced as part of the IVF process in selected cases.³

In 1994, the American Society for Reproductive Medicine published guidelines regarding the use of ICSI as a safe and effective technique for the management of male-factor infertility.⁴ However, with the increasing availability and use of assisted reproductive technology, it is unclear to what extent fertility centers in the United States have followed these guidelines or have expanded the use of ICSI for indications other than male-factor infertility.

Furthermore, it has been shown that in states with mandated insurance coverage for IVF, the use of such services is nearly three times that in states with no mandated coverage (probably because more people are able to access an otherwise costly treatment).⁵ It is not known whether the use of ICSI for infertility that is not attributed to male-factor conditions likewise varies with insurance coverage.

We conducted a study to analyze the temporal trends in the use of ICSI in the United States and to examine differences in the use of ICSI between states with and those without mandated insurance coverage.

METHODS

COLLECTION OF DATA

In accordance with the Fertility Clinic Success Rate and Certification Act of 1992, the Centers for Disease Control and Prevention (CDC) compiles and publishes annual data on the use of assisted reproductive technology and success rates at fertility clinics throughout the United States.⁶ Each year, the Society for Assisted Reproductive Technology, which is an affiliate of the American Society for Reproductive Medicine, collects data from the individual clinics and shares them with the CDC. To date, the CDC has published annual clinic-specific data for the 10-year period from 1995 to 2004.

Pertinent data from the Assisted Reproductive Technology Success Rates Reports from 1995 to 2004 were downloaded from the CDC Web site for analysis.⁷ Data for each year were entered into a

database (Microsoft Access 2000) for analysis. Only IVF cycles involving fresh embryos from non-donor eggs were analyzed, since these made up the majority of cycles and the CDC reported sufficient information for this analysis to be conducted. Reports from most years provided clinic-specific summary data expressed in percentages for several variables of interest: cycles resulting in pregnancy, cycles resulting in live births, cycles with ICSI, patients with a diagnosis of male-factor infertility, and patients with a mixed diagnosis (both male-factor and female-factor infertility). Reports from 1995 to 1998 did not include the last variable. In order to calculate total percentages, we converted the clinic-specific percentages to raw numbers, added them, and then reconverted the data into percentages (as previously reported).⁵

The clinic-specific CDC data from 1995 to 1998 included all age groups. The available data from 1999 to 2004 excluded women 43 years of age and older. This exclusion, however, resulted in the exclusion of less than 5% of the overall number of fresh IVF cycles for any given year. Thus, the results and analysis from 1999 to 2004 are limited to women younger than 43 years of age.

To assess the use of ICSI relative to the number of patients with a diagnosis of male-factor infertility, a new variable, the ratio of ICSI use to diagnoses of male-factor infertility, was created. We first calculated the number of cycles involving the use of ICSI and then divided by the total number of patients with a diagnosis of male-factor infertility (including male-factor infertility alone and a mixed diagnosis of both male-factor and female-factor infertility). Since the data from 1995 to 1998 did not include patients with a mixed diagnosis, we calculated the ratio of ICSI use to male-factor infertility only for the years 1999 to 2004.

The states with a comprehensive mandate for insurance companies to cover the diagnosis and treatment of infertility (including IVF and ICSI) were Illinois, Massachusetts, and Rhode Island (as previously reported).⁵ Mandates were enacted in these three states in 1991, 1987, and 1989, respectively. There was adequate time for these three states to adjust to the mandate before 1995, the first year of analysis in our study. Since New Jersey and Connecticut enacted their comprehensive mandates in 2002 and 2005, respectively, data from these two states were included in the “no mandate” category.

STATISTICAL ANALYSIS

The chi-square test was used to analyze all trends, and Pearson's chi-square test was used to analyze differences in proportions between categories. Linear regression was used to assess the relationship between the size of the fertility clinic and the use of ICSI. All reported P values are two-tailed. Analyses were performed with the use of STATA statistical software (version 8.0).

RESULTS

Table 1 shows the trends in the use of assisted reproductive technology in the United States from 1995 to 2004. Despite the federal requirement for annual reporting of success rates, each year approximately 5 to 11% of the fertility clinics either did not submit their data to the Society for Assisted Reproductive Technology and the CDC or did not provide verification by the medical director of the clinic that the tabulated success rates were correct. The number of fertility clinics and the number of fresh-embryo cycles in the United States increased from 1995 to 2004, as did pregnancy and live-birth rates. From 2000 to 2004, however, the proportion of oocyte retrievals that resulted in live births was consistently lower for procedures with ICSI than for procedures without ICSI.

As shown in Figure 1A, the percentage of IVF cycles with ICSI in the United States increased by a factor of approximately five, from 11.0% in 1995 to 57.5% in 2004; since 2001, the majority of cycles involved ICSI. In contrast, diagnoses of male-factor infertility remained steady over the time period analyzed (1999 to 2004), with a resulting increase over time in the ratio of ICSI use to diagnoses of male-factor infertility. These findings suggest an increasing use of ICSI for infertility that is not attributed to male-factor conditions (Fig. 2).

Table 2 and Figure 1B show the trends in the use of ICSI in relation to state-mandated insurance coverage. From 1995 to 2004, both the number of fresh-embryo cycles and the percentage of cycles involving ICSI increased in states with and states without mandated insurance coverage. In these two groups of states, however, the percentage of total fresh-embryo cycles did not significantly vary during this time period. From 1999 to 2004, male-factor infertility accounted for a greater proportion of IVF cycles involving ICSI in states without mandated insurance coverage than in states with man-

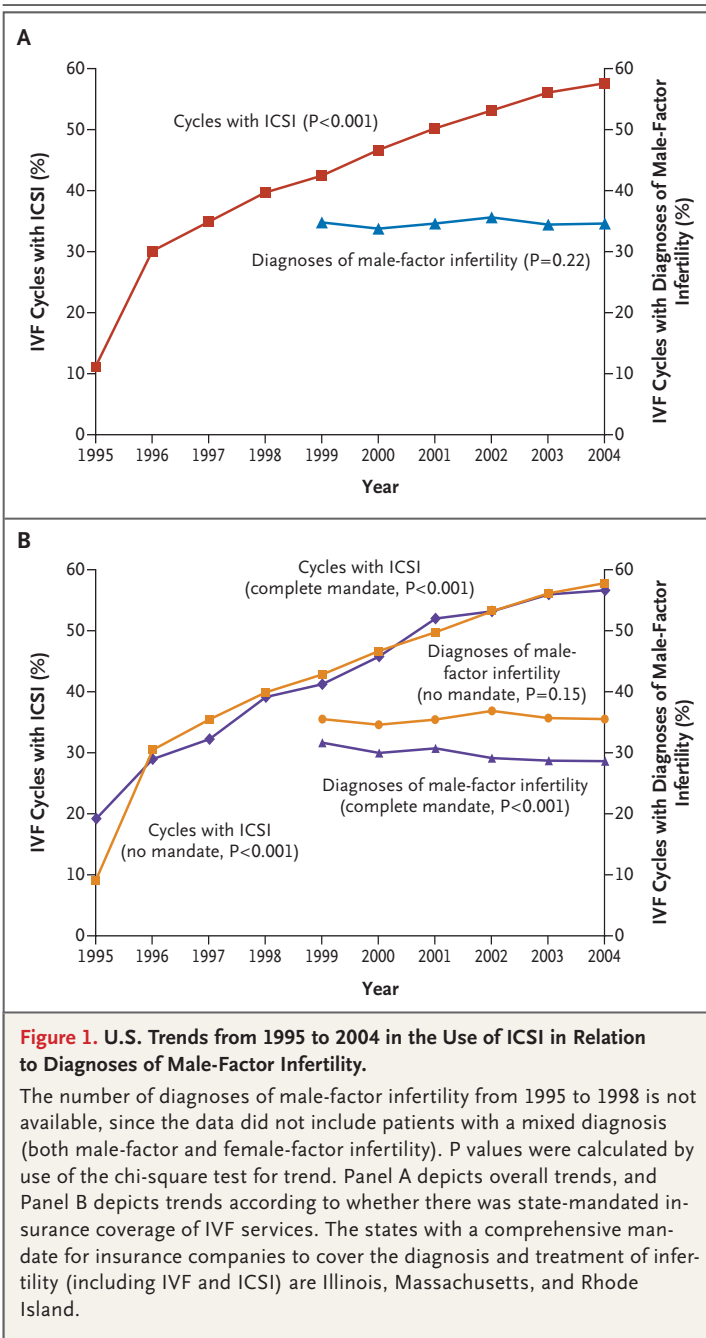
Table 1. Trends in the Use and Outcomes of Assisted Reproductive Technology in the United States from 1995 to 2004.*

Variable	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	P Value†‡
Assisted reproductive technology clinics — no.	300	315	354	390	399	408	421	428	437	461	
Clinics reporting verified outcome data — no. (%)	281 (93.7)	300 (95.2)	335 (94.6)	360 (92.3)	370 (92.7)	383 (93.9)	384 (91.2)	391 (91.4)	399 (91.3)	411 (89.2)	
Fresh-embryo cycles initiated — no.	45,906	49,584	55,002	61,650	63,123	71,556	77,102	81,888	86,753	89,533	
Pregnancies — % of initiated cycles	24.4	27.3	29.5	30.5	30.6	30.7	32.8	34.3	34.4	33.7	<0.001
Live births — % of initiated cycles	19.6	22.6	24.0	24.9	25.2	25.4	27.0	28.3	28.3	27.7	<0.001
Live births — % of oocyte retrievals	22.8	26.2	27.8	28.9	29.2	29.6	31.4	32.6	32.4	31.6	<0.001
Non-ICSI	NA	NA	NA	NA	NA	31.0	32.6	34.0	33.4	32.9	<0.001
ICSI‡‡	NA	NA	NA	NA	NA	28.6	30.6	31.9	31.9	30.9	<0.001

* Data from 1995 to 1998 are for women of all ages, and data from 1999 to 2004 are for women younger than 43 years of age. Retrieval refers to the procedure of obtaining oocytes after controlled ovarian stimulation. NA denotes not available.

† P values for data from 1995 to 2004 were calculated by means of tests for trend. Data on non-ICSI and ICSI live births from 1995 to 1999 were not available, so the analysis of the test for trend for these two variables is restricted to 2000 to 2004.

‡ P<0.001 for all comparisons of non-ICSI with ICSI live births per oocyte retrieval in the same year.



dated insurance coverage (Fig. 1B). This observation is consistent with the much greater use of IVF overall in states with mandated coverage,⁵ such that more patients in these states are likely to undergo IVF for other indications that might be treated with other, less expensive approaches in states without mandated coverage. Furthermore, for any given year from 1999 to 2004, states without mandated insurance coverage had a signifi-

cantly lower ratio of ICSI use to diagnoses of male-factor infertility than states with such coverage (Fig. 2).

In order to assess whether clinic volume might be confounding our findings regarding insurance coverage and ICSI use, we also evaluated whether there was a relationship between fertility-clinic volume and ICSI use. We used the number of fresh IVF cycles initiated in each clinic as a marker of clinic volume. The absence of a significant relationship between the number of cycles initiated in 2004 and the rates of ICSI use ($r = -0.011$, $P = 0.83$) suggests that insurance-related differences in ICSI use were not explained by differences in clinic volume.

DISCUSSION

Our study shows that use of ICSI in the United States increased between 1995 and 2004, while the proportion of patients with male-factor infertility receiving treatment remained steady. These results indicate that the use of ICSI for infertility that is not attributed to male-factor conditions is steadily increasing. Furthermore, there was more use of ICSI for infertility not attributed to male-factor conditions in states with mandated health insurance coverage for IVF services than in states without mandated insurance coverage.

Considering the remarkable success of ICSI in the treatment of male-factor infertility, many fertility centers have extended the indications for ICSI when semen measurements are normal to include cases of unexplained infertility,^{8,9} fertilization failure in a previous IVF cycle,¹⁰ and few or poor-quality oocytes available for insemination.^{11,12} Some centers have even advocated for the routine use of ICSI in all IVF cycles.^{13,14} Proponents of such indications for ICSI suggest that its routine use generates more accurate information about oocyte quality and maturity, bypasses any potential barriers to fertilization, and optimizes fertilization outcomes.^{12,14}

The progressive increase in the use of ICSI for infertility that is not attributed to male-factor conditions is surprising, however, given the limited data that provide support for this approach. Some studies have shown that ICSI is successful in cases of fertilization failure in a previous IVF cycle (perhaps because of an occult male factor),^{15,16} but such cases are relatively uncommon.¹⁷ Several studies, however, have shown that clinical outcomes are

not improved with ICSI for infertility that is not attributed to male-factor conditions.¹⁸⁻²³ The largest of these studies, a multicenter, randomized trial comparing clinical outcomes after ICSI or traditional IVF in couples with infertility that was not attributed to male-factor conditions, showed lower rates of implantation and pregnancy in the ICSI group.²¹ We also found that live-birth rates (the proportion of oocyte retrievals resulting in live births) were lower among patients who underwent ICSI than among patients who underwent conventional IVF. However, we do not have access to patient- or cycle-specific data, and thus we cannot rule out the possibility that these differences in outcomes were due to other differences between patients who underwent ICSI and patients who underwent conventional IVF.

An additional concern with the broader, routine use of ICSI is the possibility of associated risks. Studies have shown increased risks of new aberrations in sex and autosomal chromosomes,^{24,25} major congenital anomalies,^{26,27} and imprinting disorders^{28,29} in children conceived with the use of ICSI. However, it is unclear whether the increased risks associated with the use of ICSI are attributable to the procedure or to underlying abnormalities in persons with male-factor infertility. If the reported adverse pregnancy outcomes associated with ICSI are in fact attributable to this procedure, the increasing numbers of these procedures means that even small absolute risks could result in substantial numbers of adverse outcomes, with associated costs for patients and society.

Moreover, ICSI is an expensive procedure from the perspective of patients and third-party payers,^{30,31} and it requires considerably more medical resources and laboratory time than conventional IVF.^{21,32} These concerns have led others to conclude that ICSI should not be routinely performed when semen measurements are normal.^{21,22,32-36}

Our study showed that mandated insurance coverage was associated with increased use of ICSI for patients with infertility that was not associated with male-factor conditions. Given our observational study design, this finding does not establish a cause-and-effect relationship; furthermore, it may not reflect the practice of individual fertility clinics. However, financial considerations may have influenced physicians' practices and patterns of use.³⁷⁻³⁹ According to the American Society for Reproductive Medicine, the average charge to patients for a single IVF cycle in the United States is

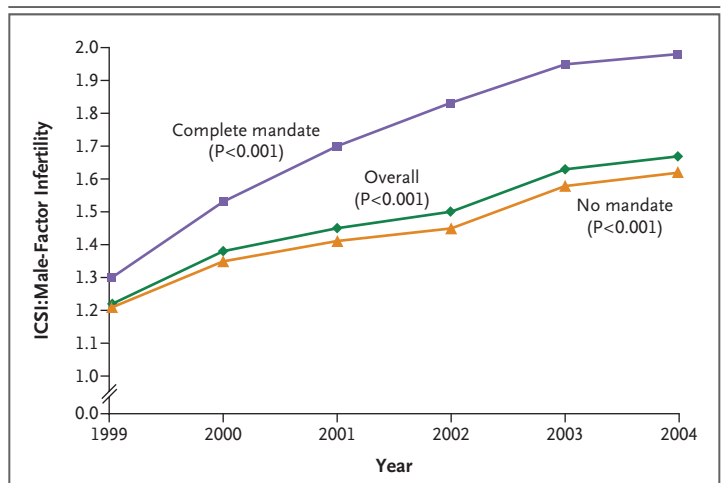


Figure 2. U.S. Trends from 1999 to 2004 in the Ratio of ICSI Use to Diagnoses of Male-Factor Infertility.

P values were calculated by use of the chi-square test for trend. $P < 0.001$ for all comparisons of the ICSI:male-factor ratio during the same year in states with and those without mandated insurance coverage. The states with a comprehensive mandate for insurance companies to cover the diagnosis and treatment of infertility (including IVF and ICSI) are Illinois, Massachusetts, and Rhode Island.

\$12,400 (which is usually paid in full by patients before the start of an IVF cycle).⁴⁰ The use of ICSI can add approximately \$1,500 to this charge. Insurance companies typically reimburse fertility centers at a capitated amount that is negotiated in advance of the procedure and is usually from 30 to 50% of the amount charged to individual patients; adding ICSI to the treatment plan increases reimbursement from insurance companies, generally by another 10 to 15%. Many patients in states without mandated insurance coverage may be unwilling or unable to afford the added cost of ICSI, especially if the infertility is not attributed to male-factor conditions or if multiple IVF attempts are needed.

We do not have access to patient-specific or cycle-specific information. Thus, we cannot rule out the possibility that in states with mandated insurance coverage, as compared with other states, there were more patients with a potential indication for ICSI other than male-factor infertility, including a low oocyte yield and previous standard IVF cycles that failed. We also cannot rule out the possibility that the diagnosis of male-factor infertility was underreported. However, we are unaware of any data suggesting that such discrepancies exist between states with and states without mandated insurance coverage.

Table 2. Trends in the Use of Assisted Reproductive Technology in the United States from 1995 to 2004, According to State-Mandated Insurance Coverage.*

Variable	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	P Value†
States with complete mandate‡											
Fresh-embryo cycles initiated — no.	8,497	10,019	10,334	10,802	11,704	12,883	13,148	13,269	14,523	15,338	
Total fresh-embryo cycles — % initiated in all states	18.5	20.2	18.8	17.5	18.5	18.0	17.1	16.2	16.7	17.1	
Cycles with ICSI — %	19.2	28.9	32.2	39.1	41.2	45.7	52.0	53.1	55.9	56.6	<0.001
Overall male-factor diagnosis — %§	NA	NA	NA	NA	31.6	29.9	30.7	29.1	28.7	28.6	<0.001
Male factor diagnosis only — %					17.5	15.7	16.4	15.9	16.1	16.7	
States with no mandate											
Fresh-embryo cycles initiated — no.	37,409	39,565	44,668	50,848	51,419	58,673	63,954	68,619	72,220	74,195	
Cycles with ICSI — %	9.0	30.3	35.3	39.8	42.7	46.5	49.6	53.2	56.0	57.7	<0.001
Overall male-factor diagnosis — %§	NA	NA	NA	NA	35.4	34.5	35.3	36.8	35.6	35.4	0.15
Male factor diagnosis only — %					17.2	17.1	17.2	18.1	17.4	17.1	
P value for cycles with ICSI¶	<0.001	0.006	<0.001	0.23	0.003	0.08	<0.001	0.85	0.83	0.004	
P value for male-factor diagnosis					<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	

* Data from 1995 to 1998 are for women of all ages, and data from 1999 to 2004 are for women younger than 43 years of age. NA denotes not available.

† P values, calculated by the chi-square test for trend, were for data from 1995 to 2004, except that P values for patients with a diagnosis of male-factor infertility were for data from 1999 to 2004, since complete data on male-factor diagnoses from 1995 to 1998 were not available.

‡ The states with a comprehensive mandate for insurance companies to cover the diagnosis and treatment of infertility (including IVF and ICSI) are Illinois, Massachusetts, and Rhode Island. Data for total fresh-embryo cycles are percentages of all fresh-embryo cycles initiated in all states (with and without a mandate).

§ Overall male-factor diagnosis includes both male-factor diagnosis only and mixed diagnosis (male-factor and female-factor infertility).

¶ The P value is for the comparison of the percentage of IVF cycles with ICSI between states with and those without mandated insurance coverage.

|| The P value is for the comparison of the overall percentage of male-factor diagnoses between states with and those without mandated insurance coverage. Complete data on male-factor diagnoses from 1995 to 1998 were not available.

In summary, the use of ICSI in the United States has been steadily increasing over a 10-year period, and ICSI has been performed in the majority of IVF cycles since 2001, even though the percentage of diagnoses of infertility attributed to male-factor conditions has remained stable. Furthermore, state-mandated health insurance coverage for IVF services is associated with increased

use of ICSI for infertility that is not attributed to male-factor conditions. Strategies appear to be warranted to curtail the use of ICSI without evidence-based support.

No potential conflict of interest relevant to this article was reported.

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