

This issue marks the beginning of a new section of the *Journal*, the "Bioethics and Law Forum." As its first editor, I am pleased to see the level of interest in ethical and legal issues related to issues in infertility and can predict that there will be no shortage of interesting and provocative questions addressed in the "Forum" in the upcoming months. The articles appearing this month are the result of a debate that took place between Drs. Peter Schlegel and Dolores Lamb at the 23rd Annual Meeting of the American Society of Andrology, held March 26–29, 1998, in Long Beach, California, the topic of which was the safety of intracytoplasmic sperm injection (ICSI). These articles raise a number of points to consider as the technology progresses. Future articles in the "Forum" will feature an analysis of paying for

Viagra and an examination of the ethical issues in separating sperm as an aid to gender selection.

The "Forum" is also intended to be a section of the *Journal* through which readers have a chance to share their views on controversial subjects. I encourage you to send letters in response to "Forum" articles or regarding other ethical and legal issues that you find interesting in your own practice or research as well as suggestions for topics that deserve attention in future issues. I look forward to hearing from you.

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Debate: Is ICSI a Genetic Time Bomb? No: ICSI Is Safe and Effective

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Intracytoplasmic sperm injection (ICSI) has revolutionized the treatment of male-factor infertility. ICSI provides treatment options for men with the most severe forms of male infertility, including men who require sperm retrieval from the reproductive tract. In this debate, I will argue that ICSI is clearly effective in comparison with standard treatments, and I will review the overall results of ICSI treatment. I will also demonstrate the safety of ICSI; this assessment will be based on miscarriage rates following application of ICSI as well as on the lack of demonstrated birth defects following ICSI treatment.

In order for ICSI to be performed, *in vitro* fertilization (IVF) must occur. Steps of *in vitro* fertilization typically include luteal suppression of pituitary control of the ovaries followed by ovarian hyperstimulation using human follicle-stimulating hormone (FSH) or FSH-like agents. Transvaginal retrieval of oocytes can then be performed when optimal oocyte development is recognized. ICSI involves placement of a single spermatozoon into the cytoplasm of each oocyte as part of IVF. During this process, the oocyte is mechanically stimulated to undergo

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activation. The fertilization of oocytes is documented by the observation of the presence of two pronuclei, usually 18 to 24 hours after the ICSI procedure is performed. Fertilized oocytes may be incubated *in vitro*, and these embryos are transferred to the uterus 48 to 72 hours after the ICSI procedure. (Schlegel and Girardi, 1997).

ICSI is applied in cases where a low fertilization rate is expected. Specifically, ICSI is recommended when failed fertilization has occurred in a previous IVF cycle, when very few sperm are present in the ejaculate, when sperm motility is very limited, when sperm morphology is severely abnormal, or when sperm must be retrieved from the reproductive tract of azoospermic men. In these cases, ICSI is applied to improve the fertilization rate to a level similar to one that would be achieved if spermatozoa were normal.

At The New York Hospital–Cornell Medical Center, a series of 1,509 ICSI cycles performed between September 1993 and June 1996 were compared to a simultaneous series of 1,836 IVF cycles performed at the same institution. The 1,509 evaluated ICSI cycles involved 1,330 cycles with ejaculated sperm and 179 cycles with surgically retrieved sperm. Clinical pregnancies (as detected by a fetal heartbeat on transvaginal ultrasound at 7 weeks of gestation or later) were noted for 45.9% of ICSI cycles and for only 38.7% of IVF cycles. The difference in clinical pregnancies was statistically significant ($P = 0.001$; Table 1).

Of the 692 clinical pregnancies, 4 were ectopic and 69 were terminated as a result of either miscarriage or therapeutic abortion. There were 619 ongoing pregnancies. Therefore, the delivery and ongoing pregnancy rate per oocyte retrieval was 41%.

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Table 1. ICSI results at the New York Hospital—Cornell Medical Center (September 1993–June 1996)*

	ICSI	IVF
Number of cycles with oocyte retrieval	1,509	1,836
Fertilization rate	71.7%	68%
Fertilizations per oocyte injected or inseminated	9,544/13,331	11,900/17,505
Transfer of embryos per cycle	94.4% (1,432)	92.2% (1,693)
Average number of embryos transferred	3.3	3.4
Clinical pregnancies (number)	45.9% (692)†	38.7% (710)

ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization.

* Results provided courtesy of G. Palermo et al, 1996.

† $P = 0.001$ vs. IVF clinical pregnancy rate.

Pregnancy outcome is dependent on maternal age. For women less than 30, 54% of retrievals resulted in ongoing pregnancies at Cornell. A similar result in ICSI cycles involved women aged 31 to 33 years. Older women had a worse prognosis. For women aged 37 to 40, pregnancy rates of 31–35% were observed, whereas pregnancy rates per retrieval range from 11–18% for women 41 years of age and higher (Rosenwaks, personal communication; Palermo, personal communication).

The ability of ICSI to treat cases in which IVF is unlikely to achieve fertilization has been previously reported. Schlegel et al (1995) reported on results of IVF with and without micromanipulation in a series of sequential cycles performed at one center using sperm retrieved from the epididymis via microsurgical epididymal sperm aspiration (MESA). In this study, a pregnancy rate of 27% was achieved using IVF and the more primitive forms of micromanipulation (i.e., partial zona dissection or subzonal insertion). After application of ICSI, a clinical pregnancy rate of 52% was achieved. Using data from two institutions, Silber et al (1994) reported an increase in pregnancy rates from 9%, using IVF, to 48%, using ICSI, in cycles where ICSI was applied to sperm retrieved through MESA.

The importance of ICSI in the treatment of male-factor infertility is also well documented. A review of data published by the Society for Assisted Reproductive Technologies of the American Society for Reproductive Medicine (SART) as well as recently published data from other U.S. centers clearly show the superiority of IVF/ICSI over IVF alone in the treatment of infertility. In 1992, the IVF success rate for male-factor infertility for deliveries per oocyte retrieval was only 15.3%, whereas in 1993 it was 16.8% and in 1994 it was 20.2%. With the introduction of ICSI, centers that have published ICSI results from the United States have documented a 27.7% ongoing pregnancy or delivery rate per retrieval. In most cases, these cycles involved far more severe cases of male-factor infertility than that which has been included in the SART

Table 2. Malformations in children born after intracytoplasmic sperm injection (ICSI)

Author	No. of major malformations/no. of children born	
	n	%
Bonduelle et al (1995b)	23/877	2.6
Govaerts et al (1995)	3/76	3.9
ICSI Task Force (Tarlitzis, 1996)	18/763	2.3

results in the past. Therefore, despite having a more difficult population to treat, better results have been obtained with IVF and ICSI than were previously achieved with IVF alone (Schlegel, 1997).

Two major studies have investigated the risk of congenital malformations in those children born following ICSI. The U.S. study by Palermo et al (1996) found that major and minor malformations were present in 6.7% of all children after IVF and in 2.6% of children after ICSI. This major study of 578 neonates was a strong indication of the safety of the ICSI procedure.

The study published by Bonduelle et al (1996), in which the researchers reported on 877 children born after ICSI who were followed for up to 2 years, is a more extensive study. The preclinical and clinical miscarriage rates were very similar to those that have been reported using IVF alone or using IVF with ICSI; these rates are also similar to those reported in naturally occurring pregnancies. These findings are compared in Table 2. This analysis suggests that ICSI does not increase the risk of early pregnancy loss. Bonduelle et al also reported on malformations in children born after ICSI, and they compared their results to those reported in several previously published studies. They found a major malformation rate per child born after ICSI of 2.6%. This rate is very similar to that of a smaller series reported by Govaerts et al (1995) and the ICSI task force Tarlitzis (1996) (see Table 2). The malformation rates reported in assisted reproduction surveys are presented in Table 3. Overall, major malformation rates of between 2.2 and 3.6% were reported. These values are very similar to those that have been reported for ICSI. Frequency of malformations at birth in the general population has been reported to be 2.1 to 7.1% for major malformations and 7.3 to 40.7% for minor malformations (Table 4). A wide range of variation in the malformation rates reported by different surveys is the consequence of using different criteria for considering a condition to be a "malformation." For example, a minor hemangioma that will often resolve spontaneously might be considered a minor malformation in some series but not in others. Minor conditions of this type may be present in up to one-half of all children born.

One type of abnormality that does appear to be in-

Table 3. Malformation rates in assisted reproduction surveys*

Study	Study period	No. of malformations/total no. of children	Malformations (%)
United Kingdom			
Beral and Doyle (1990)†	1978–1987	35/1,581‡	2.2
Rizk et al (1991) (single center)	1978–1987	24/961‡	2.5
Australia and New Zealand			
Lancaster et al (1995)	1992–1993	247/9,807§	2.5
France			
Rufat et al (1994)	1987–1989	40/1,669	2.9
Bachelot et al (1995)	1986–1993	337/13,380¶	2.5
Israel			
Friedler et al (1992) (national survey)	1982–1989	32/1,475	2.2
USA			
Medical Research International et al (1995)	1993	164/6,870#	2.3
Schattman et al (1995)		11/303**	3.6
World Collaborative Report	1991	165/8,036	2.1

* Adapted from Bonduelle et al, 1996.

† MRC Working Party on Children Conceived by IVF.

‡ Malformation rate during the first week of life, including seven chromosomal anomalies and excluding pyloric stenosis, heart murmur, undescended testes, hydrocele, positional talipes, congenital dislocation of the hip, malformations of skin and integument, anomalies of the abdominal wall, and unspecified anomalies of the ears and nose.

§ Malformation rate in infants and fetuses of at least 20 weeks' gestation, excluding 31 abortions for fetal abnormality at gestational age of ≥ 16 weeks.

|| Malformation rate including three therapeutic abortions and six malformations diagnosed after the first week of life during follow-up.

¶ Malformation rate including children born alive, therapeutic abortions, and stillbirths, including 23 chromosomal anomalies.

Birth defects per neonate after in vitro fertilization treatment.

** Major anomalies within the first year of life, assessed by questionnaire (68% response), 2.6% minor anomalies.

creased in children after the application of ICSI is the rate of sex-chromosome abnormalities. Sex-chromosome abnormalities generally do not cause major malformations. Children born following natural conception have a 0.19 to 0.23% incidence of sex-chromosome abnormalities (Hook and Hamerton, 1977; Nielsen and Wohlert, 1991; Jacobs et al, 1992). After ICSI, Bonduelle et al (1996) have noted a 0.8% frequency of sex-chromosome abnormalities. There were eight abnormalities detected in the evaluation of 997 karyotypes. Four abnormalities involved 47,XXY (Klinefelter's), one involved 47,XYY, two involved 47,XXX, and one involved mosaic 46,XX/47,XXX karyotype (Bonduelle et al, 1996). Since these sex chromosome abnormalities typically occurred in couples in which the woman was under 35 years of age and in which very severe male-factor infertility was present,

it is likely that the sex-chromosome abnormality was derived from a mosaic abnormality of the germ cells in the father rather than from the ICSI procedure itself. Certainly, sex-chromosome abnormalities are more common in men with severe male-factor infertility (Rucker et al, 1998).

Some have suggested that the source of genetic material for a child is relatively unimportant. Certainly, children who are adopted are raised by their adoptive parents and have value equal to that of other children. Similarly, children born after donor insemination have significant value. However, the desire of couples to have their own "genetic" children is clearly demonstrated by studies that have looked at the choice of ICSI as an infertility treatment. Schover et al (1996) reported that 93% of couples who seek infertility treatment choose ICSI as a means of having their own genetic children. Of the couples who choose donor insemination, 75% cite financial issues as the primary indicator in their choice of treatment. The importance of having their own genetic children is clearly critical to patients. For example, it would be ludicrous to propose that children who are born at a hospital on a given day be given to random parents; parents want to have their own genetic children.

In summary, it is clearly demonstrated by these data

Table 4. Malformation rates at birth in the general population*

Author	Major (%)	Minor (%)	Sample size
Leppig et al (1987)	3.8	40.7	4,305
Marden et al (1964)	2.1	14.7	4,412
Mehes (1983)	2.2	17.2	4,589
Myriantopoulos and Chung (1974)	7.1	7.3	53,257

* Adapted from Bonduelle et al, 1996.

that ICSI is an effective treatment for severe male-factor infertility. At selected centers, pregnancy rates of up to 41% (per attempt) can be achieved. Major and minor malformation rates are not affected by the application of ICSI nor is the rate of early pregnancy loss. Any change in the rate of chromosomal abnormalities is likely related to pre-existing conditions in the fathers who provide sperm for ICSI rather than to the ICSI procedure itself, but ICSI allows these men to procreate when they otherwise could not.

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Rebuttal to Schlegel Argument

Dr. Schlegel has argued that good animal (rodent) models do not exist to study the safety of ICSI because of species-specific variations in fertilization. This is certainly true, and at this point in time, it is reasonable to agree that based upon fertilization data from hundreds of IVF laboratories that are using tens of thousands of eggs, the ICSI procedure (i.e., the microinjection of sperm into eggs) is relatively safe when performed by highly trained personnel. The major unresolved question concerns the use of ICSI to bypass all natural biological barriers to defective sperm.