Recent Progress in In Vitro Fertilization and Intracytoplasmic Sperm Injection Technologies in Japan

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Abstract

The three basic pillars of fertility treatment are the Timing Method, artificial insemination, and in vitro fertilization (IVF). Intracytoplasmic sperm injection (ICSI) is an insemination option in cases where in vitro fertilization fails to result in fertilization. Treatments appropriate to the infertility factors involved are selected and if the selected treatment method fails to result in pregnancy, treatment is stepped-up. In 2005, some 19,112 infants were born in Japan through IVF or ICSI infertility treatments—1.8% of total births. Assisted Reproductive Technology (ART) has already become an indispensable treatment for infertility. However, ART does have limitations, and in approximately 50% of cases pregnancy is not ultimately achieved despite repeated IVF or ICSI treatments. The side-effects of ART include ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy. Countermeasures against these side-effects are implemented, and they are controlled. An issue requiring consideration in the performance of ART is genetic safety, such as the risk of infants being born with chromosomal and morphologic abnormalities and the risk of spermatogenesis-related genetic abnormalities. Care also needs to be taken with respect to epigenetic abnormalities resulting from in vitro manipulation of gametes and embryos.

Key words Assisted reproductive technology (ART), In vitro fertilization (IVF), Intracytoplasmic sperm injection (ICSI)

Introduction

Currently the main pillars of fertility treatment are the Timing Method and Assisted Reproductive Technology (ART). ART usually refers to in vitro fertilization and embryo transfer (IVF-ET, IVF) and microinsemination, but in a broad sense also includes artificial insemination with husband's semen (AIH).

There are several methods of microinsemination available, but currently the method with the highest success rate, intracytoplasmic sperm injection (ICSI), is selected and implemented. Success (pregnancy/births) with IVF was reported by Steptoe and Edwards in 1978,[1] and with ICSI by Palermo et al in 1992.[2] The first successful case of IVF involved fallopian tube factors due to bilateral salpingo-oophorectomy—a case in which pregnancy was impossible with conventional infertility methods. Since then, IVF has been performed when deemed applicable in circumstances such as those listed in Table 1. ICSI is performed in cases where IVF has failed to result in fertilization (Table 1). Accordingly, it is easy to see that ART such as IVF and ICSI plays an important role amongst the various fertility treatments that are currently available. This paper discusses the positioning of ART amongst fertility treatments, as well as its performance record, side-effects, and genetic safety.

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Positioning of ART amongst Fertility Treatments

The three basic pillars of fertility treatment are the Timing Method, artificial insemination, and IVF. ICSI is regarded as an insemination option (method of insemination) when IVF fails to result in fertilization.

There is a diverse range of factors that cause infertility; the basic process of selecting treatments appropriate to each infertility factor is shown in Fig. 1. Fallopian tube, immune, uterine, ovulatory, unexplained, and male factors are all given as causes of infertility, but in many actual cases there are multiple causes, making thinking more complicated.

Treatment methods for female infertility factors begin with the Timing Method, followed by artificial insemination and IVF, in that order. Treatments are selected in accordance with each cause. For example, if the cause is fallopian tube factors, although surgical treatment methods such as salpingoplasty will be considered as far as possible, depending on the damage to the fallopian tubes it is possible that IVF will be chosen as the initial treatment. In cases of ovulatory disor-

Table 1 Application of IVF and ICSI

Application of IVF
1. Fallopian tube infertility
2. Male factor infertility
3. Immune infertility
4. Unexplained infertility
Application of ICSI
1. Oligozospermia; asthenozoospermia
2. Failure to conceive through IVF
3. When testicular sperm extraction (TESE) has been performed

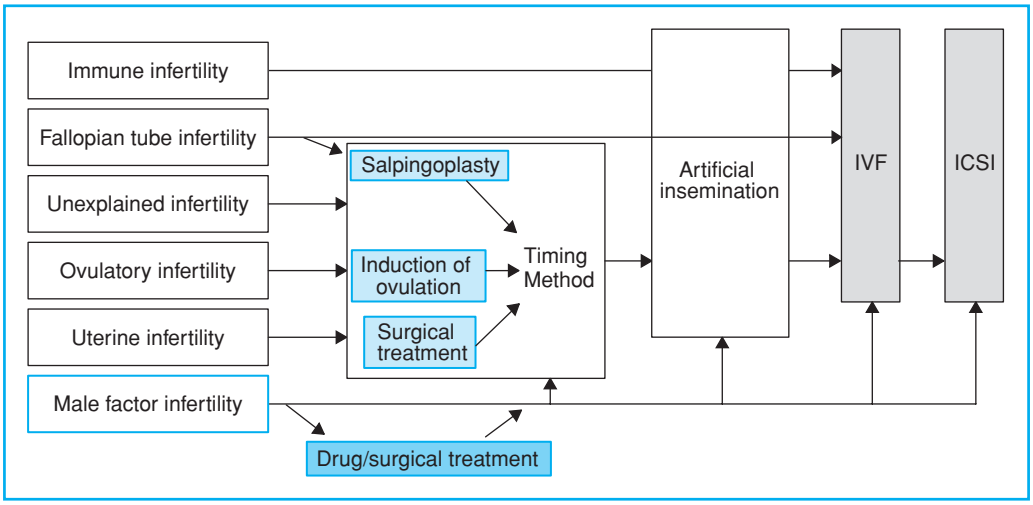

Fig. 1 Fertility treatment process

Table 2 Number of births and cumulative number of births for each treatment method (2005)

	Total number of treatment cycles	Number of births	Cumulative number of births
Treatment using fresh embryos (ova)	42,822	6,706	75,711
Treatment using frozen embryos (ova)*	35,069	6,542	30,194
Treatment using ICSI	47,579	5,864	48,964
Total	125,470	19,112	154,869

* Combined total results for treatment using frozen and thawed embryos and frozen and thawed unfertilized ova.
(Cited from the 2006 Report of the Ethics Committee and the Registry and Survey Sub-committee of the Japan Society of Obstetrics and Gynecology. Journal of the Japan Society of Obstetrics and Gynecology. 2007;59:1717–1739.)

ders, the disorder is treated first using ovulation inducing drugs and the Timing Method applied when the problem has been resolved. However, when such methods do not result in pregnancy, artificial insemination is selected, and if artificial insemination fails to result in pregnancy, IVF becomes a candidate treatment.

Treatments for male infertility factors, depending on the results of sperm density and mobility evaluations, may begin with the Timing Method or artificial insemination or IVF, or directly with ICSI. In the case that the selected treatment method fails to result in pregnancy, treatment is stepped-up. In 2005, some 19,112 births were recorded for infants conceived through IVF or ICSI (including frozen embryo transfer) (Table 2).[3] Since the total number of births in 2005 was 1,067,000, 1.8% of infants, or 1 in every 56 infants born, was conceived through ART. It is a well-known fact that the percentage of total births made up of ART-conceived infants is increasing annually. At healthcare facilities where ART is performed, 38.6% of pregnancies have been conceived through ART (Ministry of Health and Welfare Sciences Research 1999). An infertility center was established 3 years ago in the hospital which the author works for, 33.3% of pregnancies have been conceived through ART. From these figures it can clearly be understood that ART is an important, essential, and irreplaceable fertility treatment method.

Performance Results of ART

In order to perform IVF or ICSI in Japan, the name of the facility and physician performing the procedure are required to be registered with and make reports to the Japan Society of Obstetrics and Gynecology (JSOG), and the JSOG Ethics Committee issues annual reports on the results of ART. Table 3 shows the ART performance results for 2005, the most recent report, which I have adjusted for ease of understanding.[3]

IVF was planned for 42,685 cycles and ova were actually collected in 40,334 cycles. The rate of pregnancy per collected ovum was 22.0% and the production rate for each transfer was 22.9%. ICSI treatment was planned for 44,553 cycles and ova were actually collected in 42,478 cycles; thus the number of ICSI cases exceeds that of IVF cases. The rate of pregnancy per collected ovum was 17.7% and the production rate for each transfer was 19.0%, slightly lower than the IVF rates. Even in ICSI cases where non-ejaculated sperm was used (sperm collected from the epididymis or testes), ova were collected in 2,689 cycles and the rate of pregnancy per collected ovum was 16.9%, with a production rate for each

Table 3 Performance of IVF and ICSI in 2006

	IVF-ET	ICSI	
		Ejaculated sperm	Non-ejaculated sperm
Total number of patients	30,426	28,252	1,911
Treatment cycle	42,685	44,553	2,802
Total number of ova collected	40,334	42,478	2,689
Number of transfers	29,232	28,895	1,900
Pregnancy rate per collected ovum (%)	22.0	17.7	16.9
Pregnancy rate per transfer (%)	30.4	26.0	23.9
Miscarriage rate per pregnancy (%)	21.3	22.2	21.6
Multiple gestation rate per pregnancy (%)	16.0	15.2	15.4
Rate of high-order multiple gestation per multiple pregnancy (%)	6.6	5.6	7.1
Number of births	6,694	5,502	339
Production rate per transfer (%)	22.9	19.0	17.8

(Cited and adjusted from the 2006 Report of the Ethics Committee and the Registry and Survey Sub-committee of the Japan Society of Obstetrics and Gynecology. Journal of the Japan Society of Obstetrics and Gynecology. 2007;59:1717–1739.)

transfer of 17.8%—equivalent to performance results using ejaculated sperm.

The pregnancy rates shown in Table 3 are the rates for 1 treatment cycle. There are cases in which pregnancy is achieved after multiple ART treatment cycles, and looking at the cumulative pregnancy rate for each number of times ART was performed, pregnancy was achieved in 90% of cases when ART was performed 5 times.[4] Moreover, pregnancy was ultimately achieved in 50% of cases treated, with pregnancy extremely difficult in the remaining 50% of cases, even using ART. The United Kingdom's Human Fertilisation and Embryology Authority (2003) has reported that pregnancy was achieved in 31,666 IVF/ICSI treatment cycles out of a total of 156,454 treatment cycles, and 2.4% of these were ectopic pregnancies.

Side-effects and Genetic Safety of ART

The main side-effects of IVF and ICSI are ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy.

OHSS

OHSS is one side-effect of administering ovulation inducing drugs with the aim of collecting multiple ova. Although the pathogenic mechanisms are unclear, peritoneal and pleural effusion may occur as a result of ovarian enlargement and increased vascular permeability, accompanied by abdominal pain, hemoconcentration, and oliguria. OHSS can be easily diagnosed by the presence of enlarged ovaries measuring more than 7 cm in (longest) diameter, lower abdominal pain, and symptom of dehydration. Cases taking a critical course due to thrombosis (multiple organ thrombosis, mesenteric artery thrombosis, cerebral thrombosis, etc.) have been reported. Risk factors for OHSS include patient age of less than 35 years, polycystic ovarian syndrome (PCOS), thin physique, high serum estradiol levels (>4,000 pg/ml), multiple secondary follicles (12–14 mm), a "necklace sign" (multiple small follicles on the ovarian cortex forming a necklace-like ring observed using ultrasound), and implementation of luteal maintenance therapy by administering hCG. Moreover, in the case that pregnancy occurs, OHSS can easily increase in severity due to the effects of endogenous hCG. Occurrence rates are 10–60% for mild cases of OHSS and 1–10% for medium to severe cases requiring additional treatment and hospitalization.

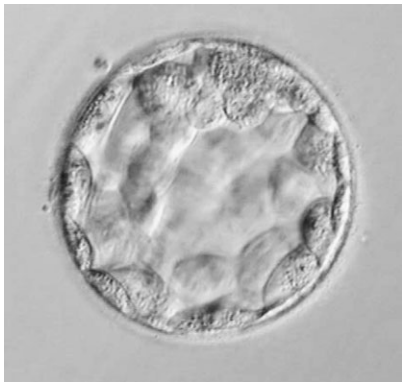

Fig. 2 Embryo at the blastocyst stage

Multiple pregnancy

The occurrence of multiple pregnancies as a result of ART depends on the number of embryos that are transferred. Since the start of IVF in Japan, the JSOG has limited the number of embryos that can be transferred to three or less (1996). Although many facilities today are thought to limit the number of embryos transferred to 2 or less, multiple pregnancies occur in 16% of ART pregnancies, a situation that continues to place a burden on neonatal care, especially NICU care, due to the increased risk of miscarriage and stillbirth. The Japan Society for Reproductive Medicine 2007 Guidelines limit the number of embryos transferred to 2 or less for women aged under 40, for whom the risk of multiple pregnancy is high, and especially women aged under 35, for whom the number of embryos transferred is limited to 1 for first-time patients.

When IVF treatment first began, it was reported that limiting the number of embryos transferred lowered the pregnancy rate. Today, however, with improvements in embryo incubation environments and incubation technologies, the pregnancy rate is not lowered even if only one embryo is transferred if good-quality embryos are selected. The Blastocyst Transfer Method, in which collected ova are cultivated for a longer time and good-quality blastocysts selected for embryo transfer, is a rational procedure in which a single embryo is transferred (Fig. 2).

Genetic safety

As to the question of whether infants born through ART have an increased number of chromosomal abnormalities, there is no evidence of this with IVF, but an increase in the occurrence of sex chromosome abnormalities has been reported for ICSI.[5] An increased occurrence of congenital abnormalities amongst infants born through ART has also been reported (5.4% vs. 3.8%),[6] and the impact of factors such as the mother's age and multiple pregnancy must also be considered.

In cases of oligozospermia and azoospermia, chromosomal abnormalities (Klinefelter Syndrome) and the deletion of spermatogenesis-related genes (DAZ genes, etc.) have been confirmed, and these abnormalities may be passed onto male infants conceived through ICSI.

Safety of epigenetics

Epigenetics involves genome imprinting of specified imprinting genes by influencing gene expression without changing DNA base sequence. This imprinting occurs through the methylation of DNA cytosine as well as methylation and acetylation of the nuclear protein histone.

In animal models, it was recently reported that incubating mouse embryos in a culture solution containing FCS (fetal calf serum) caused imprinting gene abnormalities and delayed embryonic development.[7] In children born though ART as well, the occurrence of disorders related to epigenetic abnormalities [Beckwith-Wiedemann Syndrome (BWS), Angelman Syndrome (AS), retinoblastoma, etc.] has been reported.[8,9] The results of a large-scale survey conducted in the United Kingdom (including 213 BWS cases and 384 AS cases), indicate a relationship between ART and the occurrence of BWS and AS.[10]

Conclusion

In 2005, more than 154,000 infants were born through IVF and ICSI in Japan. IVF and ICSI technologies have reached a generalized level where they are widely known and performed, but still not even the status of genetic risks is clearly known. Furthermore, concerns about the risk of epigenetic abnormalities have also surfaced, but at this point in time it is nearly impossible to analyze the factors involved in the occurrence of epigenetic abnormalities. Many children have been born through ART, and it is extremely important that appropriate approaches be taken and necessary treatments provided in order to also protect such children.

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