Regulating Assisted Reproductive Technologies in Japan

Naoki Takeshita,^{1,2} Kanako Hanaoka,¹ Yukihiro Shibui,¹ Hikoyoshi Jinnai,¹ Yuji Abe,¹ and Harumi Kubo¹

Submitted January 20, 2003; accepted March 17, 2003

INTRODUCTION

Japan's first in vitro fertilization preembryo transfer (IVF-ET) baby was born in 1983 some 5 years behind Louise Brown, the world's first IVF-ET child (1). Subsequent technological advances have been remarkable, and assisted reproductive technology (ART) has now become firmly established in the treatment of infertility. In 1999, 69,019 cycles of IVF-ET had been performed in Japan, with 11,929 babies born as a result; this equates to 1 in 100 live births. The number of facilities performing IVF-ET has increased annually, reaching 423 in 1999 (2). There are few large-scale IVF facilities in Japan handling in excess of 200 cases a year; instead the country is characterized by its numerous small clinics.

To date, however, no legal regulations covering ART have been promulgated in Japan. Since the Japan Society of Obstetrics and Gynecology (JSOG) issued its "Announcements on IVF-ET" in 1983, new statements and revisions have been made in line with the emergence of new technologies. Nevertheless, it is necessary to point out that the development of practical legal regulations has moved slowly in this country. For example, although artificial insemination by donor (AID) was first performed in 1949, for some reason, this date is cited as 1996 in JSOG statements (3). Some couples now travel to countries where IVF is unregulated in order to reap the benefits of ART, including preimplantation genetic diagnosis (PGD),

oocyte donation, and surrogate parenting. As this demonstrates, social and ethical developments are failing to keep pace with the rapid momentum of fertilization treatment technologies. Moreover, this tendency has escalated, particularly within the last few years. This can be partially attributed to the fact that in the early days, there was no way of predicting that ART would advance so far within such a short space of time. In addition, with heightened awareness among the Japanese public, ART has become a major issue within society.

Undeniably, ART has bestowed enormous benefits on humanity, and further technological developments continue to be accomplished. However, if some regulatory measures are not established it is conceivable that this technology, which has advanced of its own accord, will end by bringing misfortune on the human race. Legislative responses to IVF differ around the world. Naturally enough, the legislation reflects the national traits, religious backgrounds, and ethical perspectives of the individual countries. Moreover, when it comes to actually undergoing treatment, the choice of therapy is, to a large extent, determined by the individual. Among developed nations, Japanese legislation on IVF is considered to be particularly rigorous.

The objective of fertility treatment is to achieve pregnancy in the most natural way possible. Improving the pregnancy rate has taken such technological precedence that the incidence of multiple pregnancies has increased, with the resultant emergence of the issue of how to reduce the number of fetuses. This study constitutes a reexamination of Japan's legislative responses to date and takes a look at issues for the future in order that fertilization treatment may return to its origins and safer, more natural pregnancies can be achieved.

¹ The 1st Department of Obstetrics and Gynecology, TOHO University School of Medicine, 6-11-1 Ohmori-nishi Ohta-ku, Tokyo 143-8541, Japan.

² To whom correspondence should be addressed; e-mail: ntakesit@med.toho-u.ac.jp.

MATERIALS AND METHODS

The following is an outline of the legislation relating to fertility treatment together with extracts from the JSOG guidelines, and some additional commentary.

Japan Society of Obstetrics and Gynecology Guidelines (4)

1. Position on "In Vitro Fertilization Pre-Embryo Transfer" (October 1983)

Human in vitro fertilization and preembryo transfer are medical practices that are undertaken as treatment for infertility. In performing these procedures, the ethical, legal, and social foundations of this country must be sufficiently considered and the safety of the method evaluated.

This opinion is believed to constitute the first regulation on assisted reproduction therapy in this country. Since it encompassed major, unprecedented problems, highly detailed explanations were provided with the aim of facilitating a correct understanding of the issues at stake. The following seven items were referenced.

- (i) *This law is intended for those individuals who have no prospect of achieving pregnancy other than via this medical treatment.* The procedures must always be performed after careful consideration and should not, at all costs, be undertaken lightly.
- (ii) *The maneuvers/procedures are to be undertaken on the basis of the latest precautions by physicians who have acquired a high degree of knowledge/technical expertise in the field of reproductive medicine. Moreover, prospective recipients are to be provided with sufficient explanation of the contents of this law and the expected results prior to undergoing treatment. Having understood this explanation, they should then be required to sign a consent form, which must be archived.* Individual patients should be furnished with intelligible explanations on the specific contents of the procedure, the pregnancy rates, miscarriage rates after pregnancy is established, and the incidence of fe-

tal disorders. The contents of the consent forms may be determined by individual facilities, however, the signatures/seals of both parents must be obtained without exception.

- (iii) *Prospective recipients must be married with both parties desiring a child; they should be mentally and physically capable of undergoing pregnancy, childbirth, and child raising, assuming that oocyte retrieval and the maintenance of an implanted fetus are possible.* The contents of this proviso are distinctively Japanese. At this time, IVF was not permitted for common-law marriages. The regulations also stipulated that the woman's own oocytes should be used and that her ovaries must be capable of undergoing implantation and of maintaining a pregnancy.
- (iv) *Fertilized eggs must be handled on the basis of bioethical reasoning and with discretion.* Bioethics encompasses a broad spectrum of ideas. Physicians are required to consider the contents of the Geneva Declaration and to respect human life in performing the procedures.
- (v) *The enforcement of this law prohibits genetic manipulation.* This includes genetic engineering, cloning, and interspecies hybrids/chimera, in consideration of the risk of affecting the gene through biological maneuvers such as virus vector, mechanical maneuvers using micro manipulators, or the use of chemical substances. In recent years, "Laws relating to regulations on human cloning technology" have been promulgated. These laws have not been established in terms of safety, but because the application of human gametes is currently extremely hazardous. This procedure is completely contrary to the aim of in vitro fertilization and is inimical to medical ethics.
- (vi) *Respecting the privacy of married couples undergoing treatment and their success in maintaining a pregnancy.* Society has taken an unnatural interest and curiosity in reproductive medicine, and this can impose a considerable psychological burden of stress on couples undergoing treatment, and moreover, on the unborn

child. These circumstances indicate the importance of protecting IVF recipients and the children to be born of such treatment.

- (vii) *In consideration of the significance of enforcing this law, a forum will be provided for related parties within implementing institutions to air their opinions/requests, in line with necessity.* In vitro fertilization is currently attracting abnormal levels of interest, not only among medical professionals, but also among the public at large. There is a need for timely disclosure of information and for constant efforts to resolve problem issues.

The following is a chronological catalog of JSOG statements.

2. *Position on research relating to the handling of human sperm/oocytes/embryos (1985)*
3. *On the registration reporting system for the clinical implementation of in vitro fertilization pre-embryo transfer (1986)*
4. *Position on the clinical application of pre-conceptual sex selection of X sperm/Y sperm using the Percol gradient (1986)*
5. *Position on the propriety of research using the tissues/organs, etc., of dead fetuses/neonates for research purposes, and the permissible scope of such use (1987)*
6. *Position on antenatal diagnosis of congenital abnormalities and chorionic villus sampling in particular (1988)*
7. *Position on cryopreservation and transplantation of human embryos and oocytes (1988)*
8. *Position on the clinical use of intra cytoplasmic sperm injection (ICSI) (1992)*
9. *Position on the safety of utilizing Percol in pre-conceptual sex selection of X sperm/Y sperm (1994)*
10. *Position on multiple pregnancies (1996)*
11. *Position on artificial insemination by donor (AID) and sperm donation (1997)*
12. *Position on the scope of clinical application of human in vitro fertilization pre-embryo transfer (1998)*
13. *Position on pre-implantation genetic diagnosis (PGD) (1998; partially revised 1999)*

Japan Society of Fertility and Sterility (JSFS) Guidelines (5)

1. *Position on the clinical application of micro-insemination (1990)*
2. *Position on the problems of surrogate mother-break hood (1992)*
3. *On methods of insemination using human round spermatid*
4. *On-intervention in profit-motivated mediatory operators in the field of reproductive medicine (1996)*
5. *On fertilization methods for cultivating human round spermatid (1997)*
6. *On research into the human round spermatid using animal testis (1999)*
7. *On the clinical application of male infertility due to aneuploidy and chromosomal abnormality in spermatozoa (2000)*
8. *On micro-insemination for infertility due to microdeletion in the Y-chromosome (2000)*
9. *The Japan Society of Fertility and Sterility's position on the production of human clones (2001)*
10. *Report on investigations into the application of cloning technology in assisted reproduction therapy (2001)*

As stated above, the Japan Society of Obstetrics and Gynecology and the Japan Society of Fertility and Sterility have played a key role in issuing statements and reports, and in terms of Japanese legislature, the Ministry of Education, Culture, Science and Technology have formulated a law concerning regulations relating to cloning technologies.

RESULTS

Changes in the Frequency of Multiple Pregnancies

The issue of the increased risk to the lives of both the mother and the babies in pregnancies involving four or more fetuses is clearly indicated in JSOG's "Opinion on multiple pregnancies." Accordingly, the number of fertilized eggs to be implanted is limited, in principle, to three or less in consideration of both pregnancy and multiple pregnancy rates. In addition, efforts are currently in progress to reduce, as far as possible, the dosage volumes of gonadotropin (hormone therapy) used in artificial insemination. According to a report by the Perinatal Cycle Committee (6), on the incidence of multiple

pregnancies among women who become pregnant through IVF-ET, 32.4% are twin pregnancies, 80.4% are triplet pregnancies, and 100% are quadruplet or higher-order pregnancies. In addition, the incidence of multiple pregnancies increases in line with the number of embryos transplanted; however, whilst there is no significant increase in the pregnancy rate in transplants involving four or more embryos, the incidence of multiple pregnancy does increase.

The incidence of miscarriage rises with the number of fetuses. It was 1.6% with triplets, 10.0% with quadruplets, and 15.0% with quintuplets. Average intrapartum periods were 37.7 weeks for triplets, 28.7 weeks for quadruplets, and 28.1 weeks for quintuplets.

The Status of Preimplantation Genetic Diagnosis (PGD) in Japan

The JSOG guidelines on the status of PGD in Japan are as follows.

- (a) *PGD is a highly sophisticated medical practice and is performed as part of clinical research.*
- (b) *PGD must be performed by physicians who have acquired a high degree of knowledge and technical expertise in the field of reproductive medicine; these physicians are required to have extensive knowledge of genetic disorders and abundant experience in antenatal diagnosis.*
- (c) *Medical institutions that implement PGD must have previously achieved success in IVF-ET, and are required to have achieved results with antenatal diagnosis.*
- (d) *The application of this law is limited to serious genetic disorders.*
- (e) *In order to perform PGD, it is necessary to apply to this society according to the prescribed methods, and to obtain permission.*
- (f) *Approval to implement PGD is limited to married couples with a strong desire to undergo this procedure and must be mutually consensual.*

The above guidelines have been established, but have not yet reached the stage of clinical application. Moreover, the guidelines are limited to the diagnosis of genetic disorders.

Protocol for Oocyte Stimulation

The emergence of gonadotropin created a powerful method of oocyte stimulation. Gonadotropin has en-

abled the development of multiple ovarian follicles. However, it is not necessarily the case that multiple ovarian follicles will lead to a higher, more favorable pregnancy coefficient, and if ovarian hyperstimulation (OHSS) and multiple pregnancies are also factored into the equation, then the method clearly has its drawbacks. In recent years, ovarian stimulation using clomiphene (the fertility drug) and oocyte retrieval in spontaneous cycles have come to be used (7).

Evaluation of Embryo Quality

It goes without saying that Veeck's classification is currently the most widely referenced document in the grading of embryo quality (8). In addition, the classification of embryo quality according to the morphological appearance and size of the nucleus has also become firmly established (9). In this department, we are also attempting to evaluate embryo quality by focusing on the position and size of pronuclei in combination with Veeck's classification.

Blastocyst Culture

Recently, reproductive techniques that resemble the physiological process, in other words blastocyst transfer, which allows a better harmony between embryonic development and the uterine environment, have become widespread (10). This has made it possible to transplant fewer embryos, and further, provides a greater opportunity to select high quality embryos. The criteria described by Gardner are widely used in the judgement and evaluation of blastocysts (11).

DISCUSSION

Since 1985, IVF-ET has become increasingly successful in Japan. As of 1999, there were 517 institutions performing IVF procedures, half of which also conduct microinsemination. Embryo cryopreservation is being undertaken at 125 facilities and this number is rising every year. The live birth rate has reached approximately 16% per transplantation.

The development of gonadotropin (hMG) in 1975 facilitated the technological success of IVF-ET and led to an exponential increase in the rate of multiple pregnancies involving three or more fetuses. According to a 1996 statement on multiple pregnancies, however, triplet and quadruplet pregnancies had decreased. The effects of the society's statements have been well reflected. There is a sense that fertilization

treatment became widespread because it targeted high pregnancy rates, and that responses to the numerous problems that subsequently emerged have been slow in coming. Multiple pregnancies, meanwhile, are highly risky both in terms of controlling the perinatal period and in neonatal care, and it is not possible to be unreservedly enthusiastic about pregnancies involving three or more fetuses. Various trials are currently being undertaken in an attempt to prevent multiple pregnancies.

The restrictions imposed on multiple pregnancies via the statements of the society represent one such attempt, and as mentioned above, this measure has been effective. Researchers are also contriving to find ways of transplanting fewer embryos without further reducing the pregnancy rate. In other words, a means of sorting out the most competent embryos. Research into the evaluation of embryo quality is focusing on a variety of indices. These include the use of PGD in the screening of fertilized eggs. However, PGD raises a number of issues both ethically and in terms of the precision of the technology involved. Under normal circumstances, the use of PGD is limited to screening for genetic disorders; however, it is anticipated that this technique will be applied to the evaluation of embryo quality in the future. In Japan, PGD is still being conducted at the research level and is being targeted at genetic disorders, however, much is expected of future developments. According to a report by Munne *et al.*, aneuploid screening reduces embryo loss after implantation (12).

The sequential media system developed by Gardner has made it possible to cultivate embryos to the blastocyst stage. This has, in turn, made it possible to synchronize the return of the embryo with the physiological window of implantation of the uterine endometrium. According to the Cochrane Review of blastocyst stage embryo transfer, there are no significant differences in the pregnancy rate, the live birth rate, or the incidence of multiple pregnancies with this technique as compared to the conventional Day 2/3 transfer, however, it is anticipated that improving the culture medium will allow for greater certainty in transferring only "good" embryos that have reached the blastocyst stage.

Evaluating cytoplasm is considered to be an important part of embryo quality evaluation, however, at this point in time, there does not seem to be an effective method of achieving this. The ultimate goal of fertilization treatment is to achieve pregnancy as

naturally and safely as possible. It is considered that advances will continue to be made in the technology. Nevertheless, the treatment is both undertaken by and in humans. In consequence, this treatment is perpetually surrounded by the value systems and ethical perspectives of individuals. Individuals come together and form a society, and the laws governing ART differ from country to country. Despite repeated investigation, surrogate parenting remains illegal in this country. However, the practice is undertaken in the United States, and there are, in fact, a number of Japanese who head stateside. Legislation in this country has been established on the basis of the social and religious background of its citizens. Accordingly, these regulations should be respected and adhered to. Finally, timely studies should be duplicated and improvements made, and it is necessary to formulate regulations that respond to the demands of the times.

REFERENCES

1. Steptoe PC, Edwards RG: Reimplantation of a human embryo with subsequent tubal pregnancy. *Lancet* 1976;1:880–882
2. Guideline of Japan Society of Obstetrics and Gynecology—The number of institution which have performed or registered IVF-ET—2000
3. Statement of Japan Society of Obstetrics and Gynecology, 1983
4. Statement of Japan Society of Obstetrics and Gynecology. *Acta Obstet Gynaecol Jpn* 1999;51:15–43
5. Guideline of Japan Society Fertility and Sterility
6. Aono T, Yanaihara T: The situation of super multiple pregnancy and future problem of sterile treatment. *The Study for Attitude of Sterile Treatment*, The Ministry of Welfare, Tokyo, 1998, pp. 132–138
7. Kaijima H, Teramoto S, Kato O: Protocol of oocyte retrieval using clomiphene citrate stimulation. *Clin Obstet Gynecol* 2000;54:1372–1375
8. Veeck LL: *Atlas of the Human Oocyte and Early Conceptus*, Vol.2. Baltimore, Williams & Wilkins, 1991
9. Tesarik J, Greco E: The probability of abnormal preimplantation development can be predicted by a single static observation pronuclear stage morphology. *Hum Reprod* 1999;14:1318–1323
10. Gardner DK, Lane M, Calderon I, Leeton J: Environment of the preimplantation human embryo in vivo: Metabolite analysis of oviduct and uterine fluids and metabolism of cumulus cell. *Ferti Steril* 1996;65(2):349–353
11. Gardner DK, Lane M, Stevens J, Schlenker T, Schoolcraft WB: Blastocyst score affects implantation and pregnancy outcome: Towards a single blastocyst transfer. *Fertil Steril* 2000;73(6):1155–1158
12. Gianaroli L, Magli MC, Munne S: Will preimplantation genetic diagnosis assist patient with a poor prognosis to achieve pregnancy? *Hum Reprod* 1997;12:1762–1767