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ASSISTED REPRODUCTION TECHNOLOGIES

Efficacy, safety, and trends in assisted reproductive technology in Japan-analysis of four-year data from the national registry system

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Abstract
Purpose This study aimed to evaluate the efficacy, safety, and trends in assisted reproductive technology (ART) in Japan.
Methods Data pertaining to treatment cycles, pregnancy rate, live birth rate, age distribution, single embryo transfer rate, and multiple pregnancy rate were analyzed for patients registered in the national ART registry system of Japan from 2007 to 2010.
Results The total number of treatment cycles was 161,164, 190,613, 213,800, and 242,161 in 2007, 2008, 2009, and 2010, respectively. The number of ART treatments administered to patients aged ≥40 years was 31.2 %, 32.1 %, 33.4 %, and 35.7 %, respectively, showing an increasing trend from 2007 to 2010. In each of these years, the total pregnancy rate per embryo transfer was 24.4 %, 21.9 %, 22.3 %, and 21.9 % for fresh cycles, respectively, and 32.0 %, 32.1 %, 32.5 %, and 33.7 % for frozen cycles, respectively. The single embryo transfer rate was 49.9 %, 63.6 %, 70.6 %, and 73.0 %, respectively, showing an increasing trend, while the multiple pregnancy rate was 11.5 %, 6.8 %, 5.3 %, and 4.8 %, respectively, showing a decreasing trend.
Conclusions From 2007 to 2010 in Japan, the number of ART treatment cycles, number of elderly patients treated, and the single embryo transfer rate increased, while the multiple pregnancy rate decreased. However, the overall pregnancy rate remained stable during the study period.

Keywords Assisted reproductive technology · Single embryo transfer · Multiple pregnancy · Japan Society of Obstetrics and Gynecology

Capsule Trends of ART in JAPAN.

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Introduction

Human in-vitro fertilization and embryo transfer (IVF-ET) was first successful in the United Kingdom in 1978 [1], and it was successfully performed for the first time in 1983 at Tohoku University in Japan [2]. Since then, the prevalence of facilities offering assisted reproductive technology (ART) treatment has remarkably increased in Japan, with a considerable increase in the number of treatment cycles administered. These large-scale data pertaining to ART treatment are considered to be significant for determining the efficacy, safety, and trends in ART in Japan. In fact, in the United States of America (USA), ART data are collected and analyzed to indicate the progress of treatment at the national level [3–6].

In Japan, the national registry of ART was introduced in 2007. The data of all patients who underwent ART treatment were processed through the online registration system by Japan Society of Obstetrics and Gynecology (JSOG). Data collection from all clinics and hospitals providing ART treatment was made mandatory, and the first summaries were released worldwide in 2008 [7]. Since then, the online registration system has been utilized and the data until 2010 has been accumulated over 99 % facilities of registered centers in Japan. Recently, a report concerning the association of ART treatment on the birth weight of neonates was published on the basis of these data [8].

In this study, data on the following parameters were collected from the Japan ART registry and analyzed to observe the trends in ART treatment from 2007 to 2010 and clarify the current status of ART treatment in Japan: number of facilities offering ART treatment; number of treatment cycles; age distribution at treatment; and rates of single embryo transfer (SET), pregnancy, abortion, multiple births, and live births.

Materials & methods

All data analyzed in the present study was provided by the JSOG. This study was approved by the registration and research subcommittee of the JSOG ethics committee, and the data were provided in accordance with the determined guidelines.

Patients and registry system

All facilities conducting ART treatment are required to register with the JSOG online registration system, which consists of a web-based registry. A summary of the registered data is annually disclosed on the JSOG website home page. All data were extracted from the JSOG database from 2007 to 2010. Patient age, residence (prefecture, institution), any government subsidies for ART treatment, cause of infertility, treatment protocols, post-procedural complications, and obstetric outcomes were recorded.

For scrutinizing the accuracy of the data, the staff of JSOG and local government audit registered institutions once a year and evaluate the status of registration. In addition, registering the data of individual ART treatment is linked to the governmental grant for the patient. If a facility does not provide the data, the patient could not be received the grant.

Outcome measurements

The number of ART institutions, number of treatment cycles, age distribution, treatment outcomes, SET rates, and multiple pregnancy rates were investigated during the study period. Pregnancies were confirmed by ultrasound detection of a gestational sac.

Results

Table 1 shows the number of ART facilities, number of treatment cycles, pregnancy rate, delivery rate, miscarriage rate, multiple pregnancy rate, and the number of live births during the four years.

There is no law regarding egg donation in Japan. Therefore, autologous eggs are officially used in the registered cycles.

ART facilities

The number of registered facilities was 606, 609, 625, and 591 in 2007, 2008, 2009, and 2010, respectively. In 2010, 250 facilities (42.6 %) had performed <100 cycles, 226 (38.5 %) had performed 101–500 cycles, 59 (10.1 %) had performed 501–1,000 cycles, and 52 (8.9 %) had performed >1,000 cycles.

Number of treatment cycles

The total number of treatment cycles was 161,164, 190,613, 213,800, and 242,161 in 2007, 2008, 2009, and 2010, respectively; there was an annual increase of approximately 30,000 cycles. Consequently, the number of treatment cycles in 2010 was 1.5 times that in 2007.

The number of fresh IVF and intracytoplasmic sperm injection (ICSI) cycles gradually increased over the study period, whereas that of frozen IVF cycles drastically increased from 2008. The number of frozen cycles approximately doubled in 2010 compared with that in 2007.

Insemination and ICSI in fresh cycles

Insemination cycles gradually increases in each of the years. And also, the proportion of ICSI cycles gradually increased each year (53.4 %–57.2 %).

SET rate

The rate of fresh and frozen SET cycles increased from 2008. In 2010, the overall SET rate was 73.0 %, the fresh SET rate was 70.0 %, and the frozen SET rate was 75.4 %.

Pregnancy rate

The pregnancy rate per embryo transfer (ET) in each of the four years was 26.4 %, 23.8 %, 24.3 %, and 23.7 % for IVF cycles; 22.9 %, 20.4 %, 20.8 %, and 20.7 % for ICSI cycles;

Table 1 Characteristics of ART in Japan from 2007 to 2010

	2007	2008	2009	2010
Number of ART clinics	606	609	625	591
Submitted data	603(99.5 %)	603(99.0 %)	622(99.5 %)	587(99.3 %)
Number of ART cycles				
Fresh	115,686	130,498	139,873	158,391
Frozen	45,478	60,115	73,927	83,770
Total	161,164	190,613	213,800	242,161
Fertilization procedure in fresh cycle				
IVF-ET	52,477	57,719	61,366	65,239
ICSI	61,813	71,350	76,790	90,677
Others[a]	1,396	1,429	1,717	2,475
Total	115,686	130,498	139,873	158,391
Number of retrieval				
	112,459	127,081	136,094	153,788
Number of embryo transfer				
Fresh	62,260	63,549	63,726	65,077
Frozen	43,589	57,846	71,367	81,300
Total	105,849	121,395	135,093	146,377
Number of SET and SET rate				
Fresh	28,968(46.5 %)	38,048 (59.9 %)	42,913(67.3 %)	45,522(70.0 %)
Frozen	23,845(54.7 %)	39,155(67.7 %)	52,464(73.5 %)	61,308(75.4 %)
Total	52,813(49.9 %)	77,203(63.6 %)	95,377(70.6 %)	106,830(73.0 %)
Number of pregnancy				
Fresh	15,200	13,914	14,221	14,255
Frozen	13,965	18,597	23,216	27,382
Pregnancy rate (Per ET)				
Fresh (IVF-ET)	26.4 %	23.8 %	24.3 %	23.7 %
Fresh (ICSI)	22.9 %	20.4 %	20.8 %	20.7 %
Fresh total	24.4 %	21.9 %	22.3 %	21.9 %
FER	32.0 %	32.1 %	32.5 %	33.7 %
Pregnancy rate in fresh cycle (Per retrieval)				
IVF-ET	14.4 %	12.2 %	11.5 %	10.4 %
ICSI	12.9 %	10.0 %	9.7 %	8.7 %
Number of miscarriage				
Fresh	3,611	3,372	3,508	3,575
Frozen	3,501	4,605	5,876	6,998
Miscarriage Rate (per pregnancy)				
Fresh (IVF-ET)	23.2 %	23.1 %	23.6 %	23.9 %
Fresh (ICSI)	24.2 %	25.2 %	25.6 %	26.0 %
FER	25.1 %	24.8 %	25.3 %	25.6 %
Number of live-birth				
Fresh	9,206	8,665	9,743	9,471
Frozen	8,414	11,757	15,920	18,211
Live birth Rate (per ET)				
Fresh (IVF-ET)	16.2 %	15.0 %	16.9 %	16.1 %
Fresh (ICSI)	13.7 %	12.6 %	14.1 %	13.5 %
FER	19.3 %	20.3 %	22.3 %	22.4 %
Number of infant resulting from ART				
Fresh	10,338	9,279	10,226	9,934
Frozen	9,257	12,425	16,454	19,011
Total	19,595	21,704	26,680	28,945

Table 1 (continued)

	2007	2008	2009	2010
All live birth in JAPAN	1,089,818	1,091,156	1,070,035	1,071,304
ART infant rate per national birth	1.8 %	2.0 %	2.5 %	2.7 %
Number and rate of multiple pregnancy (per intrauterine pregnancy)				
twin	3,078(11.0 %)	2,099(6.7 %)	1,880(5.2 %)	1,906(4.7 %)
triplet or more	143(0.5 %)	40(0.1 %)	37(0.1 %)	40(0.1 %)
total	3,221(11.5 %)	2,139(6.8 %)	1,917(5.3 %)	1,946(4.8 %)
Unknown outcome of pregnancy	3,828(13.1 %)	3,491(10.7 %)	1,751(4.7 %)	2,644(6.4 %)

ART assisted reproductive technology, *IVF* in vitro fertilization, *ICSI* intracytoplasmic sperm injection, *FER* frozen embryo replacement
Others[a] include gamate intrafallopian transfer and zygote intrafallopian transfer

and 32.0 %, 32.1 %, 32.5 %, and 33.7 % for frozen embryo replacement (FER) cycles, respectively.

The pregnancy rate per retrieval in each of the four years was 14.4 %, 12.2 %, 11.5 %, and 10.4 % for IVF cycles and 12.9 %, 10.0 %, 9.7 %, and 8.7 % for ICSI cycles, respectively, showing a decreasing trend over the years. However, the pregnancy rate per ET remained more or less constant during the study period.

Miscarriage rate

The miscarriage rate per pregnancy achieved through IVF-ET, ICSI, and FER fluctuated between 23 % and 26 % each year. The miscarriage rate for patients aged below 35 years remained almost constant at 20 % each year, whereas it gradually increased each year for patients aged above 35 years. At the age of 42, the miscarriage rate was approximately 50 % each year.

Live birth rate per ET

The live birth rate per ET in each of the four years was 16.2 %, 15.0 %, 16.9 %, and 16.1 % for fresh IVF-ET cycles; 13.7 %, 12.6 %, 14.1 %, and 13.5 % for fresh ICSI cycles; and 19.3 %, 20.3 %, 22.3 %, and 22.4 % for FER cycles, respectively, remaining more or less constant for fresh IVF-ET and ICSI cycles and showing a slight increasing trend for FER cycles.

Number of live births through ART

The number of live births through ART increased each year: 19,595, 21,704, 26,680, and 28,945, respectively. The proportion of live births through ART was 2.7 % of all live births in Japan in 2010 [9].

Multiple pregnancy rate

The multiple pregnancy rate for twins and triplets decreased from 2008. Overall, it decreased from 11.5 % to 4.8 %.

Unknown outcome of pregnancy

Some cases could not be tracked their pregnancy outcomes after confirming gestational sac in each year. These rates were 13.1 %, 10.7 %, 4.7 %, and 6.4 % respectively.

Age distribution each year

Figure 1 shows that the number of ART treatments increased each year. For patients aged above 40 years in particular, the rate was 31 %, 32 %, 33 %, and 36 % in 2007, 2008, 2009, and 2010, respectively.

Pregnancy rate by age each year

Figure 2 shows that the pregnancy rate per treatment cycle was almost constant at approximately 25 % for patients aged below 33 years; it gradually decreased from 34 years of age. At the age of 41, the pregnancy rate was approximately 10 %. Moreover, this rate was similar each year when patients were stratified by age.

SET rate and pregnancy rate for fresh and frozen cycles each year

Figure 3 shows that although the SET rate increased after 2008, the pregnancy rate remained almost constant.

Outcome by age group

Table 2 presents the pregnancy rate, live birth rate, miscarriage rate, SET rate, and multiple pregnancy rate on the basis of age groups in 2010.

The pregnancy rate in each of the four groups (under 35, 35–39, 40–42, and over 42 years) was 25.9 %, 20.0 %, 10.9 %, and 3.4 %, respectively, and the live birth rate was 18.8 %, 13.4 %, 5.7 %, and 1.2 %, respectively, in each group. These rates were lower in the group with older females. On the other hand, the miscarriage rate was 18.8 %, 24.6 %, 40.0 %,

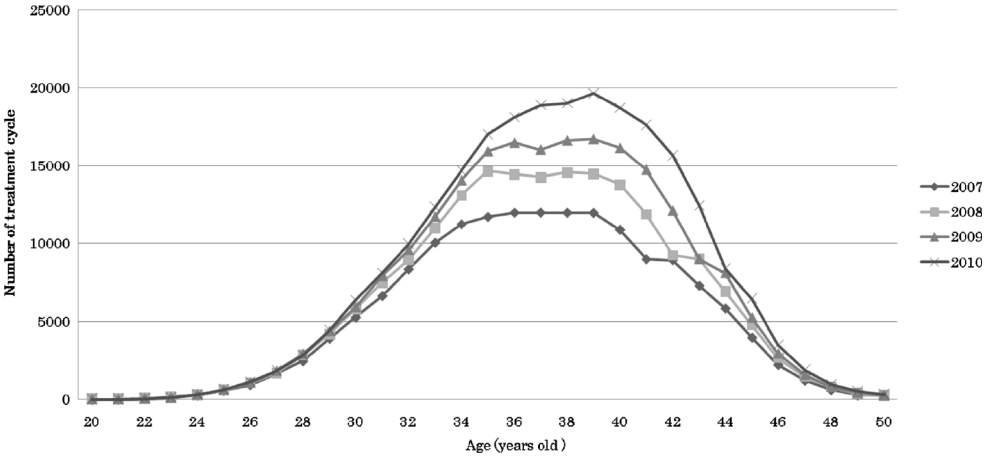

Fig. 1 Age distribution for ART treatment each year (2007–2010) in Japan. Note: Age distribution for ART treatment from 2007 to 2010

and 57.9 %, respectively, in each group, being higher in the group with older females. Further, the SET rate was 79.9 %, 72.0 %, 67.0 % and 67.7 %, respectively, and the multiple pregnancy rate was 5.0 %, 5.0 %, 4.2 %, and 3.2 %, respectively. SET and multiple pregnancy rate were slightly decreased in the group with older females.

Discussion

The present study reviewed four-year data obtained from the national registry system of the JSOG to note the trends in ART treatment in Japan over this period. In Japan, all ART facilities are registered with the JSOG since 2007, and it has been mandatory to report cycle-based clinical data.

ART data have been submitted from more than 99 % of all registered facilities each year, and the present data are believed to accurately reflect the current status of ART in Japan.

ART facilities and treatment cycles

In Japan, facilities which treat using ART need to resister with JSOG. The number of registered facilities is 606, 609, 625, and 591, respectively, in each year. However, the number of clinics that actually provide ART varied slightly over the four years with an average of 550 each year (not shown in Table 1). The number of ART facilities in Japan is reportedly much greater than that in other countries [6, 11, 15].

The number of total treatment cycles increased to 242,161 in 2010, which is approximately 1.5 times that in 2007. During the same period in Europe, the number of treatment cycles increased each year [10, 11], while it remained stable in the USA [3–6]. In Australia and New Zealand, it decreased in 2010, despite an increasing tendency up to 2009 [12–15].

However, the number of treatment cycles per million females of reproductive age (15–45 years) is not larger than that in other European countries. In 2008, this number was 7,831 in Japan [16], 13,069 in Belgium, 12,712 in Denmark, and 10,790 in Iceland [11].

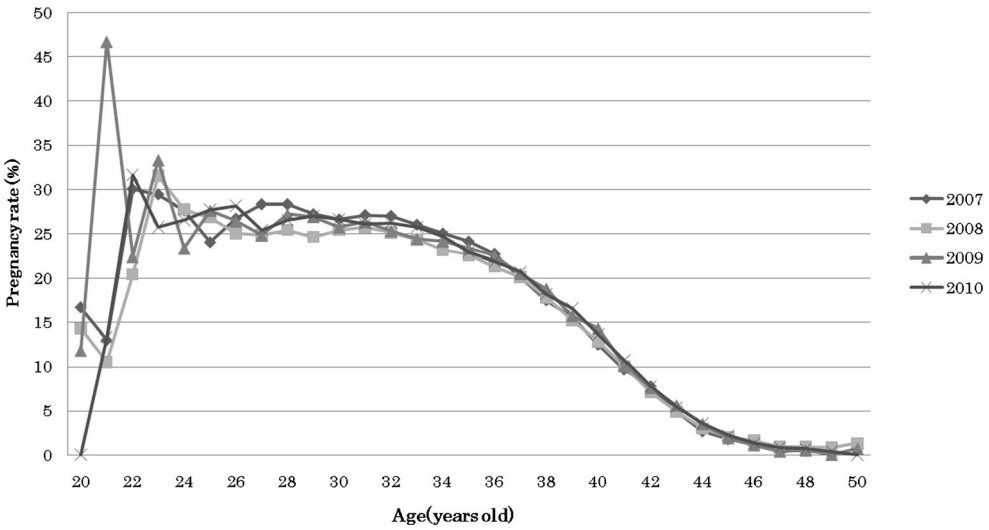

Fig. 2 Pregnancy rate by age each year (2007–2010) in Japan. Note: Pregnancy rate by age from 2007 to 2010

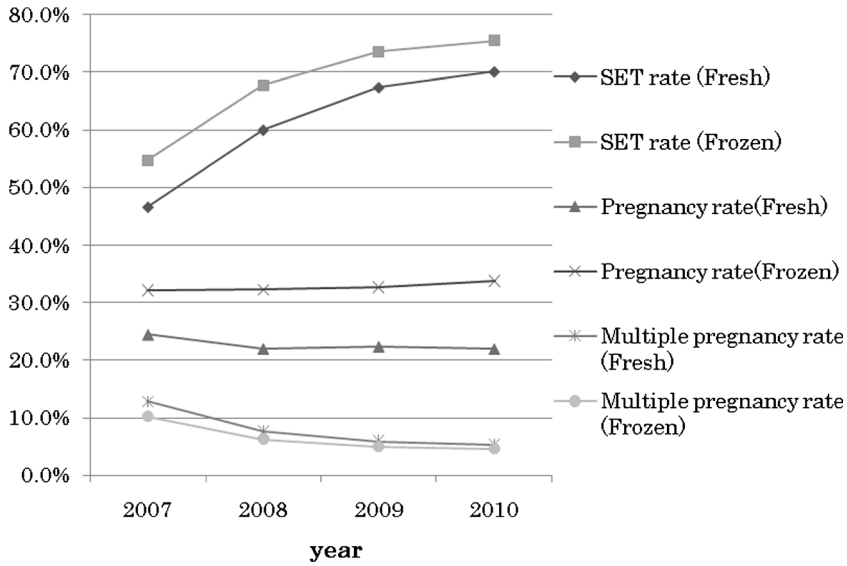

Fig. 3 SET rate, pregnancy rate with fresh and frozen cycles, and the total multiple pregnancy rate each year (2007–2010) in Japan. Note: The pregnancy rate is calculated per ET

During the review period, the total number of ART treatment cycles in Japan was more than that in the USA and European countries. This may be because of the number of ART facilities and the increased rate of older females undergoing ART in Japan compared with that in other countries.

Pregnancy rate

The pregnancy rate per ET cycle remained almost constant over the four years: approximately 24 % for fresh IVF-ET cycles, 20 % for fresh ICSI cycles, and 32 % for FER cycles. However, the pregnancy rate per retrieval decreased each year for fresh cycles. In 2010, it was 10.4 % for IVF cycles and 8.7 % for ICSI cycles. These rates are low when compared with those reported from the USA and other European countries [6, 11]. This difference can be attributed to several reasons. First, the rate of cryopreservation of all embryos is increasing, which was 27 % in 2010. As a result, the rate of embryo transfer per retrieval showed an annual decrease (55.4 %, 50.0 %, 46.8 %, and 42.3 % in 2007, 2008, 2009, and 2010, respectively) for fresh cycles. Second, the number of older patients, particularly those aged above 40 years, who underwent ART, increased. Third, in Japan, autologous eggs are officially used in the registered cycles as above-mentioned in Result section. This resulted in an annual increase in the proportion of treatment cycles administered to patients aged ≥40 years (36 % in 2010). This percentage is higher than that reported from the USA [3–6] and Europe [10, 11]. Fourth, ART treatment in Japan is less expensive compared with the international standard [17]; therefore, patients find it financially feasible to undergo repeated cycles.

The rate of pregnancy in frozen cycles is higher in each age than that in the fresh cycles.

Although selective embryo transfer was conducted in frozen and fresh cycles, the pregnancy rates were different between these cycles. For one possibility, it might be the different condition of endometrium.

SET rate and multiple pregnancy rate

SET has contributed to the decrease in multiple pregnancy rates. Furthermore, there is no evidence of a significant difference in the cumulative live birth rate between single embryo transfer in two cycles and double embryos transfer in one cycle [18].

Many reports state that SET is a safe and effective form of treatment for these reasons [18–22]. The Japanese law does not require the use of SET; therefore, until 2007, the multiple

Table 2 Outcome by age group in 2010

Age	Pregnancy, n (%)	Live birth, n (%)	Miscarraige, n (%)	SET,n (%)	Multiple pregnancy, n (%)
≦34	16,288(25.9)	11,853(18.8)	3,065(18.8)	35,031(79.9)	785(5.0)
35–39	18,507(20.0)	12,452(13.4)	4,560(24.6)	43,638(72.0)	889(5.0)
40–42	5,655(10.9)	2,959(5.7)	2,261(40.0)	19,117(67.0)	236(4.2)
≧43	1,187(3.4)	418(1.2)	687(57.9)	9,044(67.7)	36(3.2)

Pregnancy rate, delivery rate, miscarriage rate, SET rate, and multiple pregnancy rate in each age group in 2010

pregnancy rate achieved through ART increased (11.5 % in Table 1), resulting in a disruption of perinatal medicine. The SET rate increased from 46.5 % to 70.0 % for fresh cycles and from 54.7 % to 75.4 % for frozen cycles over the study period. In 2008, the JSOG recommended the use of SET and transfer of two embryos under special conditions. Since this recommendation, the SET rate drastically increased. In association with the increasing SET rate, the multiple pregnancy rate decreased from 11.5 % to 4.8 %. The SET rate in Finland and Sweden is over 60 % and the multiple birth rate is less than 10 % [11]. On the other hand, the SET rate in the USA and European countries is approximately 10 %–20 % and the multiple pregnancy rate is approximately 20 %–30 % [3–6, 10, 11].

Although the SET rate dramatically increased over the four years, the pregnancy rate per ET remained considerably stable. Therefore, the implementation of SET may contribute to the safety and efficacy of ART treatment.

Conclusions

During the period from 2007 to 2010 in Japan, the number of ART treatment cycles, number of older patients, and SET rate increased while the multiple pregnancy rate decreased. The results suggest that SET may be necessary to decrease perinatal risk

The present results clearly showed the increasing ART treatment cycles in older women. In Japan, it continued trend toward delaying marriage along with women's participation in society. This has been a contributory factor of aging in birth and declining birth rate. Indeed, the number of birth in Japan was less than half compared with 60 years ago. At present, declining birth rate is a serious issue in Japanese society. Women's age could be clearly a factor for lower fecundity and live birth rate as shown in Table 2. Therefore, it is urgent to prepare the environments for raising children during the most fertile period in women.

Further reviews of the national registry system data are required to monitor and improve ART treatment in Japan.

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Conflict of interest The authors declare that they have no conflict of interest.

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