Reprod Med Biol (2009) 8:145–149
DOI 10.1007/s12522-009-0023-z

ORIGINAL ARTICLE

Predictive factors of successful pregnancy after assisted reproductive technology in women aged 40 years and older

Akihisa Fujimoto · Toshihiro Fujiwara · Hajime Oishi · Tetsuya Hirata · Tetsu Yano · Yuji Taketani

Received: 30 April 2009 / Accepted: 19 June 2009 / Published online: 18 July 2009

Abstract
Purpose This study aimed to investigate the factors that predict successful pregnancy (live birth) in assisted reproductive technology (ART) for infertile women aged 40 and older.
Methods Patients who underwent first ART treatments at the age of 40 and older at our institution were enrolled. Several factors which can be evaluated before the first treatments were retrospectively compared among those patients who did and did not achieve live birth.
Results Nineteen of 119 patients delivered healthy babies. There was no significant difference of live-birth rate among age groups of 40, 41 and 42. No women who underwent the first treatment at age 43 or older achieved live birth. In the successful group, significantly more women held FSH levels under 12 mIU/ml and had regular menstrual cycles (26–32 days) than unsuccessful women of the same age group. In addition, significantly fewer women in the successful group had prior ovarian surgery.
Conclusions Our results show that low FSH levels, regular menstrual cycles and absence of prior ovarian surgery were related to high live-birth rates and they are good prognostic factors in patients between 40 and 42 years of age. On the other hand, none of these parameters were correlated with success in women aged 43 and older.

A. Fujimoto (✉) · H. Oishi · T. Hirata · T. Yano · Y. Taketani
Department of Obstetrics and Gynecology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: fujimoto-tky@umin.ac.jp

T. Fujiwara
Reproduction Center, International University of Health and Welfare, 8-10-16 Akasaka, Minato-ku, Tokyo 107-0052, Japan

Keywords Day 3 FSH level · Female age · IVF outcome · Menstrual cycle length · Prior ovarian surgery

Introduction

Fecundity declines as women get older; this is also the case with women who are undergoing assisted reproductive technology (ART) as a treatment of infertility [1, 2]. Spandorfer and Chung [3] reported that female age predicts over 80% of IVF success. On the other hand, in many developed countries, there has been a trend toward delaying childbirth, and there has been an increase of older infertile patients in recent years. Oocyte donation is one solution. However, in several countries where it is not permitted, such as Japan, many older infertile women have difficulties in treatment.

There are several reports regarding the outcome of ART in older patients. In a large retrospective study in the UK, 1087 cycles were started in 471 women aged 40 years and older, resulting in 57 deliveries (12.1% live birth rate per patient) [4]. In another study including only ICSI patients, 53 women achieved ongoing pregnancy at 12 weeks of gestation in total of 443 patients aged 40 and older, resulting in an ongoing pregnancy rate per patient of 12.0% [5]. In more recent studies, live births in patients at the age of 45 were observed, though the delivery rates were very low (0.7–4.3%) [6–8].

Many of these studies included only the promising patients whose basal FSH levels were relatively low. In several previous studies, clinical pregnancy rates were related to younger age, lower dose of gonadotropins, greater number of mature follicles, endometrial thickness, number of embryos transferred and lower ratio of serum

estradiol to number of oocytes [7, 8]. All of these factors, except age, can be estimated only retrospectively after at least one treatment cycle. There have been no reports regarding prognostic factors which can be evaluated before the first controlled ovarian stimulation.

In this paper we investigated possible prognostic factors of outcome in the women who underwent their first ART cycles at the age of 40 and older.

Patients and methods

Between 2001 and 2006, 1309 IVF/ICSI treatments were performed on 654 patients in IVF Center of the University of Tokyo Hospital. Three hundred and sixty-six of these cycles (26.5%) were carried out in women of age of 40 or older, in which 119 cycles were performed for the first treatment.

A retrospective analysis was performed with these 119 women. The following factors were evaluated before treatment: age at the first visit to our hospital, reproductive history, age at marriage, husband's age, infertility period, length from the first visit to the first ART, day 3 FSH level in a natural cycle, length of the menstrual cycle, presence of uterine fibroid and/or history of previous myomectomy, and presence of ovarian cyst and/or history of previous cystectomy. Cut-off points of day 3 FSH level and length of one menstrual cycle were calculated using an ROC curve.

In patients of GnRH agonist long protocol, nafarelin nasal spray (Nasanyl®; Pfizer Pharmaceuticals, Japan) was started in the mid-luteal phase. On the third day of the following menstruation cycle, ultrasound examination was performed to confirm pituitary suppression, followed by the administration of human menopausal gonadotropin (Nikken hMG®; Kowa Soyaku Co. Ltd., Japan). In patients of GnRH antagonist protocol, hMG was started on the third day of a menstrual cycle, followed by the combination with cetrorelix (Cetrotide®; Shionogi Pharmaceuticals , Japan) 0.25 mg s.c. When the size of the lead follicle reached 18 mm in mean diameter as measured by transvaginal ultrasound, 10000 IU of hCG was administered.

Oocytes were retrieved transvaginally with ultrasound guidance 34 h after hCG injection. They were inseminated or injected with husband's spermatozoa, depending on semen quality. Up to three best-quality embryos were transferred to the uterus 72 h later. The luteal phase was supported with progesterone suppository (200 mg/day) and transdermal estradiol (Estraderm M®; Kissei Pharmaceuticals, Japan). Luteal support was continued up to 7 weeks of gestation, when fetal heartbeat was detected with transvaginal ultrasound. Only the women who delivered live babies as the result of one or more cycles of ART in our hospital by September, 2007 were included in the successful group. Therefore, patients whose pregnancies resulted in spontaneous abortion or who became pregnant in a way other than ART were excluded from the successful group.

Statistical analyses were performed using Statcel® (OMS publishing Inc. Japan). Mann–Whitney *U*-test, chi-square test, Wilcoxon rank-sum test and Fisher's exact probability test were used as appropriate. Significance was defined at a level of $p < 0.05$.

Results

Of 119 women who underwent ART for the first time in our hospital, 19 (16.0%) resulted in live births. The live-birth rate was significantly lower than that of women under 40 at the same period (54.4%). The initial analysis was an evaluation between different starting-age groups (Table 1). The live birth rate at the age of 40 was slightly but not significantly higher than that at the age of 41 or 42. None of the patients who underwent first cycles at 43 years of age or older achieved a live birth ($n = 28$). Thus the live birth rate of a younger group (40–42) was significantly higher than that of an older group (43 and older) ($p < 0.01$).

The contribution of age to the prognosis was so clear that all the following analyses were performed on three groups: patients aged ≤42 who achieved a live birth (group A, $n = 19$), patients aged ≤42 who did not achieve a live birth (group B, $n = 72$) and patients aged ≥43 (group C, $n = 28$).

Between groups A and B, the following factors were significantly different: basal FSH values, length of the menstrual cycle, the length from the first visit to the first ART treatment, presence of ovarian cyst and/or history of previous cystectomy, and history of recurrent abortion.

Table 1 ART outcome according to the starting-age of the patients

Age at first IVF (years)	Number of patients	Live birth	Live birth rate (%)
≤39	463	252	54.4
40	30	7	23.3[a]
41	34	7	20.6[a]
42	27	5	18.5[a]
43	13	0	0[a]
44	7	0	0[a]
45	8	0	0[a]
40–42	91	19	20.9*
43–45	28	0	0*

* $p < 0.01$

[a] ns

Table 2 Characteristics of the three study groups, patients aged ≤42 achieving live birth (group A), patients aged ≤42 who did not achieve live birth (group B) and the patients aged ≥43 (group C)

	Group A Live birth group ($n = 19$)	Group B No live birth group (Age 40–42) ($n = 72$)	Group C No live birth group (Age 43–45) ($n = 28$)	p value (A vs. B)
Age at first visit	40.2 ± 0.9 (39–42)	40.2 ± 1.2 (37–42)	42.8 ± 1.1 (41–45)	(ns)
Age at marriage	32.5 ± 4.6 (26–41)	32.7 ± 4.6 (24–41)	34.7 ± 4.9 (26–41)	(ns)
Duration of infertility (months)	41.3 ± 38.0 (1–144)	45.6 ± 43.6 (1–204)	48.3 ± 54.1 (1–180)	(ns)
Husbands' age	42.5 ± 6.6 (33–63)	40.9 ± 4.1 (28–50)	45.0 ± 5.5 (36–66)	(ns)
Percentage of nulligravida	11 (57.9%)	40 (55.6%)	17 (60.7%)	(ns)
Percentage of nullipara	15 (78.9%)	60 (83.3%)	25 (89.3%)	(ns)
Patients with history of recurrent abortion	0 (0%)	12 (16.7%)	4 (14.3%)	<0.05
Tubal factor	5 (26.3%)	24 (33.3%)	6 (21.4%)	(ns)
Male factor	13 (68.4%)	36 (50.0%)	17 (60.7%)	(ns)
Unexplained infertility	5 (26.3%)	23 (31.9%)	10 (35.7%)	(ns)
FSH ≤12 mIU/ml	14/15 (93.3%)	39/66 (59.1%)	18/25 (72%)	<0.01
Percentage of patients with menstrual cycle length ≥26 days	16/16 (100%)	53/67 (79.1%)	14/23 (60.9%)	<0.05

Ages and duration of infertility are expressed as mean ± SD

Table 3 ART outcome based on the length from the first visit to the first treatment

Length from the first visit to the first ART (months)	Age 40–42 live birth rate (%)	Age 43–45
0–2	38.5 (10/26)*	0/8
3≤	13.8 (9/65)*	0/20
3–5	10.0 (3/30)	0/8
6–11	21.4 (3/14)	0/5
12≤	14.3 (3/21)	0/7

*$p < 0.01$

Basal FSH values were measured in 81 women aged ≤42 (15 in group A and 66 in B). Fourteen of 15 patients in group A had relatively low basal FSH values (≤12 mIU/ml), as did 39 of 66 women in group B. When 12 mIU/ml was selected as the FSH cut-off value, low FSH values were significantly related to high live birth rate (Table 2).

Length of the menstrual cycle was also evaluated. In group B, 14 of 67 patients had length less than 26 days, while none of group A did ($p < 0.05$) (Table 2).

When the length from the first visit to ART was analyzed, shorter periods from the first visit to the first IVF/ICSI treatment (<3 months) were significantly related to higher live birth rate (Table 3). There was no significant difference in live birth rate among subgroups of 3–5, 6–11 and ≥12 months.

None of the patients in group A had ovarian cyst or previous surgery on their ovaries. The history or presence of ovarian cyst was significantly related to lower live birth rate (Table 4).

Twelve of 91 women aged ≤42 had history of recurrent abortion with previous pregnancy. The live birth rate of these subjects was significantly lower than that of the patients with no history of recurrent abortion ($p < 0.05$) (Table 2).

Between the patients in groups A and B, neither age at first visit, age at marriage, duration of infertility, husbands' age, nor the proportion of infertility factors was significantly different (Table 2). In addition, neither the rate of nulligravida nor nullipara was significantly different. History of myomectomy or presence of uterine fibroid was not significantly different, either.

Of 19 patients who achieved a live birth, 13 women did in the first oocyte retrieval cycles, two in the frozen embryo transfer cycles after one failure with fresh embryos, and four in the second oocyte retrieval cycles. No one reached live-birth after the third treatment.

Discussion

Our results demonstrate that there are several prognostic factors of live birth in ART for infertile patients aged 40 and older. The live birth rate of women who started ART at each age between 40 and 42 was not significantly different, while none of the women aged 43 or older delivered. The sharp decline of both pregnancy and live birth rates in patients aged 43 or 44 has also been observed in previous reports [4, 5, 7–9]. In the analysis of the patients aged

Table 4 ART outcome based on the presence of uterine fibroid or ovarian cyst

	Age 40–42 live birth rate (%)	Age 43–45
Uterine fibroid (+)	25.0 (6/24)[a]	0/13
History of myomectomy	10.0 (3/30)[a]	0/0
Uterine fibroid (−)	17.5 (10/57)[a]	0/15
Ovarian cyst (+) or history of cystectomy/adnectomy	0.0 (0/13)*	0/7
Ovarian cyst (−)	24.4 (19/78)*	0/21

* $p < 0.01$

[a] ns

between 40 and 42, ovarian reserve was the main prognostic factor of ART success. Good ovarian reserve is related to low FSH values and absence of ovarian cyst or previous surgeries to the ovaries. Short menstrual cycle length reflects diminished ovarian reserve [10, 11] and poor ART results in such patients were also recently reported [12].

In the groups aged 43 and older, these prognostic factors were not related to live birth. There may be an oocyte aging in this group which can not be assessed in the factors stated here.

History of recurrent abortion before entering ART was inversely correlated to live birth. Our results were different from a previous report [8], which concluded there was no relationship between prior pregnancy and live birth in ART, though they did not see if their patients had history of recurrent spontaneous abortion. Most patients in this study had previous abortions at the age of near 40 or older. In patients aged 40 and older, 87–92% of spontaneous abortion can be attributed to chromosomal abnormality [13, 14]. Some of the patients became pregnant after ART in this study, but none of them delivered. Our result shows that ART procedure can not improve embryo quality in older patients.

In the analysis of the duration from the first visit to the first treatment cycle, more patients with duration less than 3 months achieved a live birth. We suggest the choice of ART to patients aged 40 and over even when the duration of infertility is short and the screening tests showed no problems except their ages, because the chance to conceive for them may be limited. Most of the patients in this group selected ART just after screening of infertility factors and counseling with doctors. After 3 months from the first visit, live birth rate significantly decreased. This result suggests that it is beneficial to decide to undergo ART as early as possible in older infertile women, though the possibility is not totally excluded that some percentage of women who decided to undergo ART within 3 months may achieve pregnancy with treatments other than ART. To determine the efficacy of ART relative to other treatments for older infertile women, a randomized controlled study on a large number of older women is required.

To our knowledge, this is the first report regarding the prognostic factors which can be evaluated before the first ART treatment for older infertile patients. Some of the previous studies included only promising patients with low FSH values [4, 8, 9], and in other reports, oocyte retrieval was canceled in cases of single or two growing follicles [4, 7, 9]. In our study, controlled ovarian stimulation was started in all the patients, only excluding those with no chance of pregnancy due to ovarian failure or other reasons. Oocyte collection was scheduled in the presence of at least one growing follicle. Thus selective bias is considered to be minimized.

In this study, live-birth rate per patient was defined as the indicator of success, while clinical pregnancy rate per treatment cycle was used in many previous reports. There is no doubt that in older infertile patients, pregnancy rates are relatively low and miscarriage rates are high. In our preliminary analysis, miscarriage rates of older patients were significantly higher than those of younger patients. In addition, low ongoing pregnancy rate per cycle leads to repetitive trial of treatment in many cases, which may cause bias in analysis when "per cycle" is set as the main outcome. Therefore, in a study limited to older infertile patients, clinical pregnancy rate per treatment cycle does not seem to be an appropriate index. The information on the delivery rate per patient is more useful for both doctors and patients in counseling of infertility treatment.

In summary, the factors that predict successful pregnancy in ART for infertile women who start the treatment at age 40 and older were as follows: age $\leq$42, basal FSH $\leq$12 mIU/ml, one menstrual cycle length $\geq$26 days, absence of ovarian cyst and no history of recurrent abortion. In women aged 43 and older, the live birth rate is very low irrespective to ovarian reserve. In some countries, unsuccessful older patients may have an option of oocyte donation, whereas in Japan, it is not allowed. Sufficient psychological care together with medical information is necessary in counseling these patients. Thus the results of the present study can be helpful for prognosis of ART in

older infertile women, and can be also helpful for counseling them.

References

1. Devroey P, Godoy H, Smitz J, et al. Female age predicts embryonic implantation after ICSI: a case-controlled study. Hum Reprod. 1996;11:1324–7.
2. van Kooij RJ, Looman CW, Habbema JD, Dorland M, te Velde ER. Age-dependent decrease in embryo implantation rate after in vitro fertilization. Fertil Steril. 1996;66:769–75.
3. Spandorfer SD, Chung PH. An analysis of the effect of age on implantation rates. J Assist Reprod Genet. 2000;17:303–6.
4. Lass A, Croucher C, Duffy S, Dawson K, Margara R, Winston RM. One thousand initiated cycles of in vitro fertilization in women > or = 40 years of age. Fertil Steril. 1998;70:1030–4.
5. Grimbizis G, Vandervorst M, Camus M, Tournaye H, Van Steirteghem A, Devroey P. Intracytoplasmic sperm injection, results in women older than 39, according to age and the number of embryos replaced in selective or non-selective transfers. Hum Reprod. 1998;13:884–9.
6. Spandorfer SD, Bendikson K, Dragisic K, Schattman G, Davis OK, Rosenwaks Z. Outcome of in vitro fertilization in women 45 years and older who use autologous oocytes. Fertil Steril. 2007;87:74–6.
7. Klipstein S, Regan M, Ryley DA, Goldman MB, Alper MM, Reindollar RH. One last chance for pregnancy: a review of 2,705 in vitro fertilization cycles initiated in women age 40 years and above. Fertil Steril. 2005;84:435–45.
8. Tsafrir A, Simon A, Revel A, Reubinoff B, Lewin A, Laufer N. Retrospective analysis of 1217 IVF cycles in women aged 40 years and older. Reprod Biomed Online. 2007;14:348–55.
9. Ron-El R, Raziel A, Strassburger D, Schachter M, Kasterstein E, Friedler S. Outcome of assisted reproductive technology in women over the age of 41. Fertil Steril. 2000;74:471–5.
10. Sherman BM, Korenman SG. Hormonal characteristics of the human menstrual cycle throughout reproductive life. J Clin Invest. 1975;55:699–706.
11. Whelan EA, Sandler DP, McConnaughey DR, Weinberg CR. Menstrual and reproductive characteristics and age at natural menopause. Am J Epidemiol. 1990;131:625–32.
12. Brodin T, Bergh T, Berglund L, Hadziosmanovic N, Holte J. Menstrual cycle length is an age-independent marker of female fertility: results from 6271 treatment cycles of in vitro fertilization. Fertil Steril. 2008;90:1656–61.
13. Guerneri S, Bettio D, Simoni G, Brambati B, Lanzani A, Fraccaro M. Prevalence and distribution of chromosome abnormalities in a sample of first trimester internal abortions. Hum Reprod. 1987;2:735–9.
14. Ljunger E, Cnattingius S, Lundin C, Annerén G. Chromosomal anomalies in first-trimester miscarriages. Acta Obstet Gynecol Scand. 2005;84:1103–7.