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Original Article

Cumulative live birth rate of advanced-age women more than 40 with or without poor ovarian response

Huiqun Yin, Hong Jiang*, Ruibing He, Cunli Wang, Jie Zhu, Zhenyi Cao

Reproductive Medicine Center, 105th Hospital of the People's Liberation Army (PLA), 230031 Hefei, China

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ABSTRACT

Objective: The aim of this study was to investigate cumulative live birth rate (CLBR) per oocyte retrieval cycle and per patient in women over 40 years old undergoing IVF/ICSI treatments, stratified for age, ovarian response and oocyte retrieval cycle number.

Materials and methods: 244 patients with poor ovarian response (POR) and 372 patients with normal ovarian response (NOR) were retrospectively investigated.

Results: Of the patients aged 40 to 43 years, CLBR per oocyte retrieval cycle and per patient (4.3%; 8.8%) in POR group were both lower than those in NOR group (15.8%; 24.8%) ($P < 0.01$). No significant differences in live birth rate (LBR) per oocyte retrieval cycle or CLBR per patient were observed in the group of POR patients irrespective of oocyte retrieval cycles they underwent. Similarly, CLBR per patient in NOR group did not increase significantly with the oocyte retrieval cycle number. However, LBR per oocyte retrieval cycle in the first cycle (Cycle 1, 20.3%) was significantly higher than that in the second cycle (Cycle 2, 9.2%) and the third cycle (Cycle 3, 4.4%) ($P < 0.01$). And 94.8% (73/77) of live births were achieved during the first two cycles. Of the patients aged 44 to 45 years and over 45 years old, there were no significant differences in CLBR per oocyte retrieval cycle or per patient between POR and NOR groups.

Conclusion: Relatively higher cumulative live birth rate was only found in the patients aged 40 to 43 years without poor ovarian response. These findings may provide some information that further subclassification of advance-age women according to ovarian response may help both clinicians and patients to balance decision-making about their infertility treatment.

Introduction

Women over 40 years old undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) now represent the most rapidly growing population in the world [1], especially in China with the "one child" policy abandoned. It was widely acknowledged that the decline of fertility in advanced-age women was associated with a decline of implantation rate and pregnancy rate, and an increase of miscarriage rate [2], which might be due to declines in oocyte quality and quantity [3,4]. However, age is not the only influencing factor for IVF outcomes. Ovarian reserve, which refers to the quantity and quality of residual ovarian follicles and oocytes, also plays an important role in female fertility. Ovarian reserve may diminish with the aging, representing elevated basal follicle-stimulating hormone (FSH) and/or abnormally low anti-Müllerian hormone (AMH), low antral follicle count (AFC). Diminished ovarian reserve is associated with poor ovarian response (POR), which usually indicates a depression of ovarian response to gonadotropin stimulation, resulting in reduction of retrieved oocytes [5]. Currently, preimplantation genetic screening (PGS) confirmed that there was an inverse relationship between advanced maternal age and embryo euploidy [6]. Implantation and live birth rates per transfer cycle could be improved for women of advanced age after PGS [7–9]. However, PGS for patients with POR was limited by the high incidence of cycles that intend but cancel PGS or cycles that do not reach transfer [10,11]. Therefore, accurate IVF outcome statistics for women over 40 years old according to ovarian response and oocyte retrieval cycle number also appear to be important for reproductive specialists to provide what they consider best and cost-effective treatment in aged patients.

However, little was known about the differences of cumulative live birth rate (CLBR) in repeated cycles in patients with advanced age between POR and normal ovarian response (NOR). Therefore,

* Corresponding author. Reproductive Medicine Center, 105th Hospital of the People's Liberation Army (PLA), 424 West Changjiang Road, 230031 Hefei, China. Fax: +86 551 65123513.
E-mail address: jiangh105@sina.com (H. Jiang).

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the aim of the study was to compare CLBR per oocyte retrieval cycle or patient between the advanced-age patients with POR and NOR underwent IVF/ICSI treatment, in order to provide some information for consultation of IVF treatment to advanced-age patients.

Materials and methods

Patients

616 women over 40 years old (40–50 years) received IVF/ICSI treatments from January of 2014 to December of 2016 in our reproductive center were enrolled in this retrospective study. The inclusion criteria were: (1) all women underwent oocyte retrieval operation; (2) all frozen embryos were thawed for transfer. The exclusion criteria were the presence of any of the following conditions: (1) infertility due to a uterine factor (e.g., endometrial synechiae); (2) cancer; (3) systemic disease (e.g., diabetes mellitus, thyroid disease, autoimmune disease); (4) preimplantation genetic testing (PGT); and (5) polycystic ovarian syndrome (PCOS).

Patients were divided into two groups: POR (n = 244) and NOR (n = 372) groups. And each group was further divided into 40–43 y, 44–45 y and over 45 y subgroups. Patients fulfilled at least two of the three following features according to the Bologna criteria were defined as poor responders (POR group) [12]: (i) advanced maternal age (≥40 years) or any other risk factors for POR (genetic abnormalities for POR, previous ovarian surgery, ovarian endometrioma, previous chemotherapy); (ii) a previous POR (≤3 oocytes retrieved with a conventional stimulation protocol); and (iii) an abnormal ovarian reserve test (i.e. AFC <5–7 follicles or AMH <1.1 ng/ml). Patients without PCOS and POR were defined as normal ovarian responders (NOR group). All patients provided written informed consent for the procedures. The study was approved by the Reproductive Medical Ethics Committee of 105th hospital of PLA (Chinese People's Liberation Army).

Ovarian stimulation protocols

Ovarian stimulation protocols adopted in this study included: gonadotrophin-releasing hormone agonist (GnRH-a) long protocol, GnRH-a ultra-long protocol, GnRH-a short protocol, microdose flare-up protocol, GnRH antagonist protocol, pituitary down-regulation with medroxyprogesterone acetate (MPA) protocol and luteal-phase ovarian stimulation protocol [13–16]. During ovarian stimulation, the patients with POR received high dose of gonadotrophin for initiation and prolonged stimulating period, while no adjuvants such as dehydroepiandrosterone, growth hormone, testosterone or melatonin were used. Ovulation was triggered with human chorionic gonadotropin (hCG) when at least 1–2 follicles reached 18 mm in diameter, followed by oocyte retrieval approximately 36 h after hCG administration.

IVF laboratory procedures

Oocytes were fertilized by conventional IVF or ICSI according to the results of semen analysis. The fertilized oocytes were cultured individually in G1-plus or G1/G2-plus sequential media. On day 3, normal fertilized embryo with ≥5 blastomeres and fragmentation <50% was defined as available embryo, and the one with ≥6 blastomeres and fragmentation <20% was defined as good-quality embryo. Blastocysts were evaluated on the basis of the expansion of the blastocoel and the number and cohesiveness of the inner cell mass (ICM) and trophectoderm (TE) cells, according to Gardner's criteria [17]. Blastocysts superior to grade 3CC (grade 3–6, subgrade AA, AB, BA, BB, BC, CB) on day 5 or on day 6 were defined as available blastocysts.

Embryos were vitrified/warmed using a commercial vitrification freezing/warming kit (Kitazato, Japan) and according to the manufacturer's instructions. Briefly, embryos were placed into equilibration solution for 5–10 min (cleavage embryo for around 8 min, shrunk blastocyst for 5 min) at room temperature. Thereafter, the embryos were transferred into the vitrification solution for approximately 40 s, and loaded onto the tip of Cryotop with a very small volume, plunged into liquid nitrogen immediately. Before freezing, the blastocysts would be artificially shrunk for dehydration of the blastocoel by the laser method. For the warming procedure, the Cryotop containing the cleavage embryos/blastocysts was transferred into thawing solution with 1.0 M sucrose (pre-warmed at 37 °C) for 1 min. Thereafter, the embryos were transferred sequentially into dilution solutions with 0.5M sucrose for 3 min and washed twice with washing solution for 5 min at room temperature. Post-warming embryos survival was defined as >50% of the cells remaining intact. Embryos were cultured for 1 to 2 h, and then were transferred into the uterine cavity.

Embryo transfer

For fresh cycle, cleavage embryos on day 3, or blastocysts on day 5, were transferred to the uterus under abdominal ultrasound guidance. Usually, if more than five good-quality embryos, or only one non-good quality but available embryo was achieved on day 3, extended culture to day 5 or day 6 would be performed. Available blastocysts were selected for transfer or vitrificated. If patients with serum progesterone levels on the day of hCG administration >2.0 ng/ml, endometrial cavity fluid, risk of ovarian hyperstimulation syndrome (OHSS) or MPA protocol, fresh embryos transfer would be cancelled.

For frozen embryo transfer cycle, endometrial preparation was carried out in hormone replacement cycles, which comprised approximately 95% of the cycles, or in natural cycles.

Outcome measures

Live birth was defined as the delivery of at least one live-born infant after ≥28 weeks' gestation. CLBR was presented as live birth episodes per patient per oocyte retrieval to account for the first live birth [18]. Both fresh and frozen-thawed embryo transfers were included to calculate cumulative live birth (CLB). In view of "one child" policy, only one live birth episode is possible for one woman during the study. CLBR per patient was calculated by all live birth episodes as numerator, all patients who had undergone oocyte retrieval as denominator. CLBR per oocyte retrieval cycle was calculated by all live birth episodes as numerator, all oocyte retrieval cycles as denominator.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) for continuous variables following normal distribution, and the numbers (percentage) for categorical variables. Student's t-tests were performed for continuous variables. For non-continuous variables, statistical comparisons were performed using the Chi-squared test or Fisher's exact test. Statistical analysis was performed using GraphPad Prism 6. The two-tailed value of $P < 0.05$ was considered statistically significant.

Results

Out of 244 patients with POR who underwent 551 oocyte retrieval cycles, the total live births were 15. The total CLBR per patient and per oocyte retrieval cycle in the POR group (6.1% and

2.7%) were significantly lower than those in the NOR group (21.8% and 13.6%) ($P < 0.01$), which have 372 patients underwent 596 oocyte retrieval cycles.

The CLBR per oocyte retrieval cycle and per patient between POR and NOR groups stratified by age were shown in Table 1. In subgroup of 40–43 y, CLBRs per oocyte retrieval cycle and per patient in POR group (4.3% and 8.8%) were significantly lower than those in NOR group (15.8% and 24.8%) ($P < 0.01$). In subgroups of 44–45 y and over 45 y, there were no significant differences in CLBR per oocyte retrieval cycle or per patient between POR and NOR group.

In addition, two cases of intermediate abortions caused by premature rupture of fetal membrane in the NOR group and one case of fetal death caused by umbilical cord around neck in the POR group occurred during pregnancy. Birth defects were identified in two babies among 96 live births. One was diagnosed as congenital colonic stricture in POR group, the other was diagnosed cerebral palsy in NOR group.

In view of the differences of CLBR between POR and NOR were only observed in the subgroup of 40–43 y, the cycle characteristics of these patients and cumulative live births according to oocyte retrieval cycles number were analyzed further in the below. Out of 436 patients in the subgroups of 40–43 y, 125 patients with POR underwent 256 oocyte retrieval cycles, the other 311 ones with NOR underwent 487 cycles. Cycle characteristics, ovarian stimulation protocols and IVF laboratory outcomes of the patients between POR and NOR were summarized in Table 2. The mean basal FSH level in POR group was significantly higher compared with NOR group. Conversely, the mean bilateral AFC, number of oocytes retrieved and MII, available embryos on day 3 in POR group were less than those in NOR group. Accordingly, the proportion of cycles without available embryo in POR group was significantly higher than that in NOR group. The good-quality embryo rate on day 3 was comparable between the two groups. In addition, there were four cycles of no oocyte-cumulus-complexes obtained after oocyte retrieval in POR group.

When the impact of IVF cycles number was investigated, the relationship between live births and oocyte retrieval cycles was shown in Table 3. No significant differences in LBR per oocyte retrieval cycle or CLBR per patient were observed among POR patients irrespective of oocyte retrieval cycles they underwent. Similarly, CLBR per patient in NOR group did not increase significantly with the oocyte retrieval cycle number. However, LBR per oocyte retrieval cycle in the first cycle (Cycle 1, 20.3%) was significantly higher than that in the second cycle (Cycle 2, 9.2%) and the third cycle (Cycle 3, 4.4%) ($P < 0.01$). And 94.8% (73/77) of live births were achieved during the first two cycles.

Table 1
Comparison of CLBR per oocyte retrieval cycle and per patient between POR and NOR groups stratified by age.

	POR	NOR	P-value
40–43 y			
Patients (n)	125	311	
Oocyte retrieval cycles (n)	256	487	
CLB (n)	11	77	
CLBR/cycle (%)	4.3% (11/256)	15.8% (77/487)	<0.01
CLBR/patient (%)	8.8% (11/125)	24.8% (77/311)	<0.01
44–45 y			
Patients (n)	75	53	
Oocyte retrieval cycles (n)	169	93	
CLB (n)	3	4	
CLBR/cycle (%)	1.8% (3/169)	4.3% (4/93)	NS
CLBR/patient (%)	4.0% (3/75)	7.5% (4/53)	NS
Over 45 y			
Patients (n)	44	8	
Oocyte retrieval cycles (n)	126	16	
CLB (n)	1	0	
CLBR/cycle (%)	0.8% (1/126)	0	–
CLBR/patient (%)	2.3% (1/44)	0	–

Note: CLB, cumulative live birth; CLBR/cycle, cumulative live birth rate/oocyte retrieval cycle.

Discussion

How to help advanced-age patients have a live birth within short time has been a tough and urgent challenge for reproductive specialists due to the elder age, the fewer live births. Although so many works have been done to improve pregnancy outcomes of aged patients for years, there is little progress achieved until now. Besides female age, ovarian reserve also plays an important role to have a baby, due to inter-individual variability during ovarian aging process. Therefore, if IVF outcomes of aged patients are presented according to their ovarian characteristics, it would be helpful to set up criteria for IVF admission to couples with acceptable chances for pregnancy, guide individual therapeutics and predict pregnancy outcomes preferably. In the present study, we found that an extremely lower CLBR per oocyte retrieval cycle (2.7%) and per patient (6.1%) were observed in the patients aged 40 to 50 years old with POR. Relatively, the aged patients with NOR had an acceptable CLBR per oocyte retrieval cycle (13.6%) and per patient (21.8%). IF the CLBRs were further stratified by age, the differences were only observed in the subgroup of 40–43 y.

It has been widely accepted that age is a crucial factor influencing pregnancy outcomes of IVF, and success rates of assisted reproduction decline with increasing age. However, the relationship between female age and reproductive capacity is very complex [19]. When assessing IVF outcomes in aged patients, an important point needs to be emphasized that the older a patient, the more likely will her cycle be cancelled before embryo transfer, either because her ovaries do not respond to stimulation or no available embryos are obtained. In the present study, there were 21.5% and 4.7% of cycles without available embryo for patients aged 40 to 43 years with POR and NOR before embryo transfer, and the risk of having no available embryo in aged patients with POR was significantly higher than those with NOR. It should be clearly explained as part of a thorough informed consent to such patients before IVF procedure. Comprehensibly, AFC, AMH, number of oocytes retrieved and available embryos in patients with POR were lower than those with NOR. However, the rate of good-quality embryo on day 3 was comparable in two groups, suggesting that ovarian reserve might not always accurately represent oocyte quality for aged patients. A study from Busnelli et al. [20] also failed to detect any association between live birth and biomarkers of ovarian reserve (serum FSH, serum AMH and AFC). Therefore, the marker of ovarian reserve, such as AFC and AMH, are better at predicting the number of oocytes rather than oocyte quality [21].

Usually, after a cycle fails, patients want to know what their chances are of having a live birth if they continue treatment. The present study showed that LBR per oocyte retrieval cycle and CLBR per patient in the POR patients were very low, and which showed no significant difference whatever the stimulated cycles they underwent. As far as the NOR patients aged 40 to 43 years were concerned, the majority of live births (94.8%) were achieved within the first two oocyte retrieval cycles, and the LBR per cycle in Cycle 1 was significantly higher than that in Cycle 2 and Cycle 3, suggesting that the chance of having a live birth for these patients will be extremely low after two consecutive cycles. Furthermore, CLBR per oocyte retrieval cycle and per patient were extremely low for the patients over 44 years old irrespective of patients with NOR or POR. These findings may provide some information for both clinicians and patients over 40 years old to balance decision-

Table 2
Comparison of clinical and cycle characteristics of patients between POR and NOR in the subgroup of 40–43 y.

Characteristics	POR	NOR	P-value
Oocyte retrieval cycles (n)	256	487	
Age (years)	41.5 ± 1.2	41.4 ± 1.3	NS
BMI (kg/m^2)	23.4 ± 3.4	23.5 ± 3.5	NS
Duration of infertility (years)	6.2 ± 6.4	6.0 ± 5.6	NS
Primary infertility (%)	12.5% (32/256)	14.0% (68/487)	NS
Basal serum FSH (mIU/ml)	12.1 ± 5.0	8.0 ± 2.9	<0.01
Bilateral AFC (n)	2.7 ± 1.3	9.5 ± 2.5	<0.01
AMH (ng/ml)	0.5 ± 0.3	3.6 ± 2.0	<0.01
Ovarian stimulation protocols			
GnRH-a long protocol	6	167	
GnRH-a short protocol	49	50	
GnRH-a ultra-long protocol	3	48	
Microdose flare-up protocol	55	18	
GnRH antagonist protocol	104	180	
Luteal-phase ovarian stimulation protocol	10	10	
Pituitary down-regulation with MPA protocol	29	14	
ICSI cycles proportion (%)	30.5% (78/256)	28.3% (138/487)	NS
Oocyte retrieval (n)	3.1 ± 1.8	9.0 ± 5.4	<0.01
MII (n)	2.6 ± 1.6	7.3 ± 4.6	<0.01
Available embryo (n)	1.4 ± 1.3	4.0 ± 2.9	<0.01
Good-quality embryo rate (%)	59.9% (357/596)	58.2% (1808/3104)	NS
Proportion of cycles without available embryo (%)	21.5% (55/256)	4.7% (23/487)	<0.01

Note: BMI, body mass index; FSH, follicle-stimulating hormone; AFC, antral follicle count; AMH, anti-Müllerian hormone; GnRH-a, gonadotrophin-releasing hormone agonist; MPA, medroxyprogesterone acetate; NS, not statistically significant.

Table 3
Comparison of LBR per oocyte retrieval cycle and CLBR per patient stratified by women undergoing different cycle between POR and NOR groups in the subgroup of 40–43 y.

Consecutive cycles		Cycle 1	Cycle 2	Cycle 3	≥ Cycle 4	P-value
POR	Total cycles (n)	125	70	38	23	
	Live births (n)	6	3	1	1	
	LBR/cycle (%)	4.8	4.3	2.6	4.3	NS
	CLB (n)	6	9	10	11	
	CLBR/patient (%)	4.8	7.2	8.0	8.8	NS
NOR	Total cycles (n)	311	109	45	22	
	Live births (n)	63	10	2	2	
	LBR/cycle (%)	20.3[a,b]	9.2	4.4	9.1	<0.01
	CLB (n)	63	73	75	77	
	CLBR/patient (%)	20.3	23.5	24.1	24.8	NS

Note: Cycle, oocyte retrieval cycle; Cycle 1/2/3/4, the first/second/third/fourth oocyte retrieval cycle; LBR/cycle, live birth rate/oocyte retrieval cycle; CLB, cumulative live birth; CLBR/cycle, cumulative live birth rate/oocyte retrieval cycle.
[a] Significant difference was found compared with Cycle 2.
[b] Significant difference was found compared with Cycle 3.

making about their infertility treatment. In 2012, the Ethics Committee of the American Society for Reproductive Medicine (ASRM) had recommended that clinicians could refuse or stop providing fertility treatment for those whose prognosis is very poor or futile based on professional and ethical judgments ("futility" being defined as treatment that has a <1% chance of achieving a live birth; "very poor prognosis" being defined as treatment for which the odds of achieving a live birth range from 1% to 5% per cycle) [22]. On the other hand, decisions about treating or refusing always should be patient-centered and flexible. Clinicians may treat such patients upon patients' request, if the clinician has assessed the physiologic and psychological risks, costs of treatment, and fully informed the patients of the low chance of success.

Gleicher et al. [23] reported that POR patients with age 41 to 42 years appeared to equalize live birth rates irrespective of nonselective single, two-embryo, three or more embryos transferred, suggesting that starting at that age even transferring three embryos are no longer enough to create high live-birth chances. Furthermore, it was reported that single embryo transfer in women over 40 years old appeared to lower the chance of a pregnancy. Pregnancy rate increased as more embryos were transferred, but there was no difference in pregnancy or twin pregnancies rates for aged patients when two or three embryos were transferred [24,25]. In this study, two or three available embryos were usually transferred whatever in fresh embryo transfer or frozen-thawed embryo transfer cycles. The results demonstrated that there were no significant differences in pregnancy and live birth rates per cleavage-embryo transfer cycle in the patients aged 40 to 43 years between POR and NOR (data not shown). It suggested no difference in pregnancy and live birth rates of patients between POR and NOR under the similar age and number of embryos transferred.

As already known, a homogeneous population of patients with POR based on Bologna criteria at low LBR per cycle varying from 2.6% to 18.3% [13,21,26–29], irrespective of treatment protocol used [27,29]. Relative lower CLBR per oocyte retrieval cycle in patients with POR were observed in the present study. One possible explanation is the different age composition in patients enrolled. Another explanation might be that the number of oocytes retrieved was different, which was an independent variable related to live birth rate [27,30].

Nevertheless, this is a retrospective, single-center, and observational cohort study, instead of a prospective randomized clinical trial. Due to the retrospective study design, several of the baseline and stimulation characteristics significantly differed between patients with or without POR.

In conclusion, advanced-age patients with POR need to accept lower oocyte yield and pregnancy outcomes. Relatively higher cumulative live birth rate was only found in the patients aged 40 to 43 years with normal ovarian response. These findings may provide some information that further sub-classification according to ovarian reserve or response may help both clinicians and patients to balance decision-making about their infertility treatment.

Conflicts of interest

There is no conflict of interest.

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