

Cumulative Live Birth Rates of Women ≥ 38 Years With Poor, Normal and High Ovarian Response

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Abstract

Background

Previous studies have reported that live birth rate (LBR) decreased with aging, however, no study has evaluated the cumulative LBR (CLBR) in accordance with the ovarian response in advanced maternal age (AMA) patients. This study aims to investigate the relationship between the ovarian response and the CLBR in AMA patients.

Methods

913 women ≥ 38 years underwent in vitro fertilization (IVF) and fresh embryo transfer (ET) between January 2014 and June 2019 were enrolled in this retrospective study. All subjects were categorized into three groups, poor ovarian response (POR) group: 1–3 oocytes retrieved ($n = 127$), normal ovarian response (NOR) group: 4–15 oocytes retrieved, and high ovarian response (HOR) group: more than 15 oocytes retrieved. The primary outcome was the CLBR in one oocyte retrieval cycle after transfer of all fresh and frozen embryos. Logistic regression models were used to derive the odds ratio (OR) to identify the relationship of CLBR with different ovarian response, adjusting for age and body mass index.

Results

Compared with women in POR group, the women in other groups (NOR and HOR groups) achieved higher CLBR [adjusted OR (aOR) = 2.12, 95% confidence interval (CI), 1.16–4.38 for NOR group; aOR = 2.93, 95% CI, 1.44–5.97 for HOR]. The LBR of the fresh ET and the neonate characteristics showed no significant difference among the three groups.

Conclusion

Ovarian response is significantly associated with CLBR in women with advanced age.

Background

With the increased competition in today's society, and the calling to pursue personal value, an increasing number of women decide to postpone their motherhood. However, the decreased number of antral follicle counts (AFC) and alterations in DNA integrity with aging place women at a disadvantage for achieving pregnancy, and there are increased risk factors for pregnancy related complications for both mother and baby [1, 2]. Therefore, the demand for assisted reproduction technologies (ART) has substantially increased for the advanced maternal age (AMA) patients.

The live birth rate (LBR) decreased with aging. According to the European Society of Human Reproduction and Embryology (ESHRE), the delivery rate for women aged 40 years or older underwent in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) was 8.5% in 2015, while which was 23.7% for the women younger than 35 years old [3]. However, most studies only investigated the outcome of the first embryo transfer (ET) cycle, and did not evaluate the cumulative LBR (CLBR) following transfer of all fresh and frozen embryos obtained in one oocyte retrieval cycle, which is known as the most meaningful index to evaluate the success of IVF/ICSI, especially for AMA patients [4]. There were some studies involved in the association of the number of oocytes retrieved and ovarian response with the LBR and CLBR, and found CLBR increased significantly with the number of oocytes retrieved, but only the women with young age were included in their study [5, 6]. Recently, Devesa et al. [7] evaluated the CLBR following a single stimulation cycle for the women aged 38 years or older, and found that the CLBR was higher with increased number of oocytes retrieved, but they treated the number of oocytes retrieved as a continuous variable and categorized patients into four groups based on their age range as 38–39; 40–41; 42–43; ≥ 44 , instead of classifying the women according to their ovarian response categories.

In order to fill in the gaps in the literature, we aim to investigate the association between the ovarian response based on the number of oocytes retrieved and the CLBR of AMA patients in one oocyte retrieval cycle, and hypothesize that the CLBR of the AMA patients would be highest for higher ovarian responders, and lowest for poor ovarian responders.

Methods

Study population

This is a retrospective study of 913 women who underwent fresh ET first and/or subsequent frozen-thawed cycles following one IVF/ICSI cycle. The study was carried out in the Reproductive Centre of the 901th Hospital of the Joint Logistics Support Force of the People's Liberation Army (PLA) between January 2014 and June 2019. Women ≥ 38 years at the time of treatment and transferred all the viable embryos available and/or achieved a live birth were included. Cycles with oocyte donation, embryo biopsy, or high risk of ovarian hyperstimulation syndrome (OHSS) were excluded. The study was approved by the Reproductive Medicine Ethics Committee of the 901th Hospital of the Joint Logistics Support Force of the PLA. All the patients provided written informed consent. Patients were divided into three groups based on ovarian response: poor ovarian response (POR) with 1-3 oocytes retrieved; normal ovarian response (NOR) with 4-15 oocytes retrieved; and high ovarian response (HOR) with more than 15 oocytes retrieved. Demographic information including patients' age, infertility duration and type, body mass index (BMI), the basic serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol (E_2), prolactin, and the number of AFC were extracted from medical records.

Ovarian stimulation and embryo transfer

All the patients received a controlled ovarian stimulation beginning from day 2 or day 3 of menses with a starting dose of 150-300 IU recombinant FSH (r-FSH, Merck Serono, Italy) and/or urinary gonadotrophins (HMG, Lizhu, China) based on the patient's age, hormone profile, AFC, and BMI. The dose of gonadotrophin was adjusted according to the ovarian response through monitoring a serial of ultrasonography and serum levels of FSH, LH, E₂, and progesterone. 250 µg recombinant human chorionic gonadotropin was used to trigger ovulation (rHCG, Merck Serono, Germany) when one or two leading follicles reached 18 mm or more in diameter.

All the oocytes ≥ 12 in diameter were retrieved transvaginally 36 hours later. Conventional IVF or ICSI was performed 2-4 hours after oocyte retrieval according to the sperm quality. Embryo quality was graded according to Cummins et al. [8].

Fresh ET was performed under ultrasound guidance three or five days after oocyte retrieval. For luteal phase support, intramuscular injection progesterone at a dose of 40 mg per day was started the day of the oocyte retrieval and maintained until a negative β -hCG or 10 weeks of gestation. Supernumerary available embryos were cryopreserved on day 3, day 5 or day 6 post oocyte retrieval following vitrification standard protocols. For FET cycles, hormone replacement treatment was carried out for endometrial preparation. The protocol has been described in detail elsewhere [9]. The frozen embryos were thawed with commercial warming kit (Kitazato Biopharma Co., Shizuoka, Japan) and cultured for 2 hours before transferred into the uterine cavity.

Definition of outcomes

The primary outcome in this study was CLBR, calculated as the proportion of cycles that achieved at least one cumulative live birth per oocyte retrieval (the delivery of at least one live-born infant in the fresh ET or in the subsequent frozen-thawed cycles until all frozen embryos were used). Live birth was defined as birth of at least one newborn that exhibits any sign of life. Cumulative pregnancy rate (CPR) was calculated as the proportion of cycles that achieved at least one clinical pregnancy per oocyte retrieval. Clinical pregnancy was defined as the presence of a gestational sac on ultrasound 30-35 days after ET. Miscarriage was defined as the loss of clinical pregnancy less than 24 weeks' gestation. The premature infant was defined as preterm birth less than 37 weeks' gestation. Multiple pregnancy was defined as at least two detectable gestational sacs or heartbeats on ultrasound. Low birth weight was defined as birth weight less than 2,500g at birth, and the birth weight 4,000g or heavier was defined as macrosomia.

Statistical Analysis

Mean with standard deviation (SD) [or median with interquartile range (IQR)] was reported for continuous variables, and proportions with numbers for categorical variables. Comparisons among POR, NOR, and HOR groups were compared using the one-way ANOVA test for continuous variables and chi-square test for categorical variables.

Univariate and multivariable logistic regression analyses were used to derive the odds ratio (OR) to identify the relationship of CLBRs and CPRs with different ovarian response. In the adjusted model, the results of fresh ET were adjusted for age, BMI, endometrial thickness, the number of embryos transferred, and the number of good embryos transferred. Furthermore, the cumulative results were adjusted for age and BMI.

All analyses were performed with STATA 16.0 (StataCorp, College Station, Texas, USA), a two-tailed P value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

As shown in Table 1, a total of 913 participants who underwent the first fresh ET without missing on confounders were included in the analyses. No significant differences in infertility duration and type, basal LH, E₂, and prolactin were found among POR, NOR, and HOR groups. However, the participants in the HOR group were younger, as well as a lower level of serum FSH and AFC when compared with other groups. Furthermore, the BMI was lower in the NOR group compared with those in the POR group.

Table 1
Characteristics of the infertile women, n = 913

	POR group (n = 127)	NOR group (n = 683)	HOR group (n = 103)	p value
Age (year), mean (SD)	42.1 (2.9)	40.6 (2.3) *	39.6 (1.9) *,#	< 0.001
Infertility duration (year), mean (SD)	5.0 (4.8)	5.6 (4.6)	5.2 (4.3)	0.382
Infertility type, % (n)				
Primary infertility	11.8 (15)	12.9 (88)	12.6 (13)	0.946
Secondary infertility	88.2 (112)	87.1 (595)	87.4 (90)	
BMI (kg/m ²), mean (SD)	24.8 (3.8)	23.8 (3.0) *	24.3 (3.0)	0.001
Basal FSH (IU/L), mean (SD)	12.4 (6.9)	9.5 (4.3) *	7.5 (2.1) *,#	< 0.001
Basal LH (IU/L), mean (SD)	5.0 (2.9)	4.9 (3.0)	5.0 (2.4)	0.923
Basal oestrogen (pg/mL), median (IQR)	48.0 (52.0)	44.5 (42.0)	46.4 (46)	0.384
Basal prolactin (ng/mL), median (IQR)	10.7 (7.4)	11.0 (7.0)	12.1 (8.4)	0.321
AFC (n), mean (SD)	5.2 (3.2)	9.7 (6.0) *	16.1 (7.0) *,#	< 0.001
POR, poor ovarian response; NOR, normal ovarian response; HOR, high ovarian response; ET, embryo transfer; BMI, body mass index; FSH, follicle stimulating hormone; LH, luteinizing hormone; AFC, antral follicle count; SD, standard deviation; IQR, interquartile range.				
*, P < 0.05 compared with poor ovarian response group; #, P < 0.05 compared with normal ovarian response group.				

The Outcomes Of Controlled Ovarian Stimulation

As shown in Table 2, the participants in the POR group had less days of ovarian stimulation and the dosage of gonadotropin administrated, and thinner endometrium compared with other two groups. The numbers of oocytes retrieved, available embryos, good quality embryos increased progressively with the ovarian response, and the average numbers of available embryo in the POR, NOR and HOR groups were 1.9, 4.7 and 9.2, respectively. Furthermore, the cryopreservation rate was also highest in the HOR group (46.6%) and lowest in the POR group (0.8%).

Table 2
The outcomes of controlled ovarian hyperstimulation

	POR group	NOR group	HOR group	p value
Days of ovarian stimulation (day), mean (SD)	7.8 (3.1)	9.8 (2.4) *	10.6 (2.4) *,#	< 0.001
Total gonadotropin dose (IU), mean (SD)	1963.2 (884.5)	2364.1 (766.3) *	2344.3 (693.9) *	< 0.001
Endometrial thickness (mm), mean (SD)	9.7 (2.5)	10.9 (2.6) *	11.4 (2.6) *	< 0.001
Oocytes retrieved (n), mean (SD)	2.4 (0.7)	8.6 (3.4) *	19.1 (2.9) *,#	< 0.001
Available embryos (n), mean (SD)	1.9 (0.7)	4.7 (2.3) *	9.2 (3.8) *,#	< 0.001
Good quality embryos (n), mean (SD)	1.5 (0.8)	3.3 (2.1) *	6.2 (3.8) *,#	< 0.001
Cryopreservation rate, % (n)	0.8 (1)	25.8 (176) *	46.6 (48) *,#	< 0.001
POR, poor ovarian response; NOR, normal ovarian response; HOR, high ovarian response; SD, standard deviation.				
*, P < 0.05 compared with poor ovarian response; #, P < 0.05 compared with normal ovarian response.				

The outcomes of fresh embryo transfer and cumulative embryo transfer

Table 3 presents the outcomes of fresh embryo transfer and cumulative embryo transfer in the POR, NOR, and HOR groups. For fresh ET, a lower number of embryos and good quality embryos as well as less proportion of blastocyst were transferred in the POR group compared with the other groups, and the rates of clinical pregnancy and live birth in the HOR group were comparable to the NOR group, but significantly higher than those in the POR group. The miscarriage rate showed no significant difference among the three groups (39.1% vs. 34.6% vs. 35.7%). For cumulative ET, the participants in the HOR group had a significantly higher rate of clinical pregnancy and live birth than the NOR and LOR groups.

Table 3
The outcomes fresh ET and cumulative ET following one oocyte retrieval cycle

	POR group	NOR group	HOR group	p value
First ET				
Embryos transferred (n), mean (SD)	1.9 (0.7)	2.6 (0.6) *	2.5 (0.5) *	< 0.001
Good quality embryo transferred (n), mean (SD)	0.7 (0.8)	1.8 (1.1) *	2.1 (0.9) *,#	< 0.001
Blastocyst ET cycle, % (n)	0.8 (1)	1.5 (51) *	25.2 (26) *,#	< 0.001
Clinical pregnancy, % (n)	18.1 (23)	31.8 (217) *	40.8 (42) *	0.001
Miscarriage rate, % (n)	39.1 (9)	34.6 (75)	35.7 (15)	0.906
Live birth rate, % (n)	11.0 (14)	20.6 (141) *	26.2 (27) *	0.011
Cumulative ET				
Clinical pregnancy, % (n)	18.1 (23)	37.2 (254) *	50.5 (52) *,#	< 0.001
Live birth rate, % (n)	11.0 (14)	24.9 (170) *	36.9 (38) *,#	< 0.001
ET, Embryo transfer; POR, poor ovarian response; NOR, normal ovarian response; HOR, high ovarian response.				
*, P < 0.05 compared with poor ovarian response; #, P < 0.05 compared with normal ovarian response.				

Table 4 shows the OR for clinical pregnancy and live birth among POR, NOR, and HOR groups. For the fresh ET, the rates of clinical pregnancy and live birth in the POR, NOR and LOR groups were all comparable after adjusting for age, BMI, endometrial thickness, the number of embryos transferred, and the number of good embryos transferred. For cumulative ET, after adjusted for age and BMI, the adjusted OR (aOR) for clinical pregnancy were 2.20 [95% confidence interval (CI), 1.34 to 3.61] in the NOR group and 3.01 (95% CI, 1.63 to 5.62) in the HOR group, and the aOR for live birth were 2.12 [95% confidence interval (CI), 1.16 to 3.86] in the NOR group and 2.93 (95% CI, 1.44 to 5.97) in the HOR group compared with the POR group.

Table 4

Odds ratio for reproductive outcome among poor, normal and high ovarian response groups

	Fresh ET, OR (95% CI)		Cumulative ET, OR (95% CI)	
	Unadjusted	Adjusted [⊠]	Unadjusted	Adjusted [‡]
Clinical pregnancy				
Poor response	Reference	Reference	Reference	Reference
Normal response	2.11 (1.30 to 3.40)	0.95 (0.55 to 1.66)	2.68 (1.66 to 4.32)	2.20 (1.34 to 3.61)
High response	3.11 (1.71 to 5.67)	0.92 (0.46 to 1.87)	4.61 (2.54 to 8.35)	3.02 (1.63 to 5.62)
Live birth rate				
Poor response	Reference	Reference	Reference	Reference
Normal response	2.10 (1.17 to 3.77)	0.89 (0.46 to 1.75)	2.67 (1.49 to 4.79)	2.12 (1.16 to 3.86)
High response	2.87 (1.41 to 5.82)	0.79 (0.34 to 1.81)	4.72 (2.38 to 9.36)	2.93 (1.44 to 5.97)
ET, embryo transfer; OR, odds ratio; CI, confidence interval.				
[⊠] , adjusted for age, body mass index, endometrial thickness, the number of embryos transferred, and the number good embryo transferred.				
[‡] , adjusted for age and body mass index.				

Neonate Characteristics

As shown in Table 5, after cumulative ET, there were 14, 191, and 41 neonates born in POR, NOR, and HOR groups, respectively. The mean birth weight was 3304.6 g in the POR group, 3155.9 in the NOR group, and 3259.8 g in the HOR group ($P = 0.524$). There are no significant differences in the rates of the premature infant, cesarean, multiple pregnancy, low birth weight, and macrosomia among the three groups.

Table 5
Neonatal characteristics born from cumulative embryo transfer

	POR group (n = 14)	NOR group (n = 170)	HOR group (n = 38)	p value
No. of neonate (n)	14	191	41	
Birth weight (g), mean (SD)	3304.6 (759.6)	3155.0 (712.9)	3259.8 (533.3)	0.524
Premature infant rate, % (n)	14.3 (2)	20.0 (34)	18.4 (7)	0.862
Cesarean rate, % (n)	71.4 (10)	77.7 (132)	76.3 (29)	0.270
Multiple pregnancy rate, % (n)	0	12.4 (21)	7.9 (3)	0.294
Low birth weight rate, % (n)	7.1 (1)	15.2 (29)	4.9 (2)	0.164
Macrosomia rate, % (n)	7.1 (1)	14.1 (27)	7.3 (3)	0.401
POR, poor ovarian response; NOR, normal ovarian response; HOR, high ovarian response.				

Discussion

IVF is an essential technique in infertility treatment, especially for AMA patients. Many previous studies have suggested that an increase in the number of oocytes retrieved and the generation of surplus cryopreserved embryos can increase CLBR [10, 7]. Our results showed that the LBR of the women ≥ 38 years following fresh ET were similar among poor, normal, and high ovarian responders, while a higher CLBR would be achieved for normal and high ovarian responders compared with poor ovarian responders. Furthermore, no significant differences were found in neonate characteristics born from different ovarian responders.

It is known that the quality and quantity of embryos, decreased with aging, are the most critical predictors to evaluate the success of IVF/ICSI [1, 11]. A large study from UK with 400,135 patients demonstrated that the LBR rose with an increasing number of oocytes up to 15, plateaued between 15–20 oocytes, and steadily declined beyond 20 oocytes [12]. However, another recent retrospective multicenter analysis with 14,469 patients concluded that CLBR does not reach a plateau and continuously increase with the number of oocytes retrieved, and evident in all age categories [13]. Furthermore, the age-related CLBR would benefit from increased available embryos [14]. Devesa et al. [7] focused on AMA patients and categorized them into four age-groups and found that the CLBR in women over 43 years old could not be improved irrespective of the number of oocytes retrieved. In this study, the patients' age ranged from 38 to 50 years old, for the women aged more than 43 years, 33.1% (42) of them were in the POR group, 11.8% (n = 44) of them were in the NOR group, and only 1.9% (2) of them were in the HOR group. Even though, a significant increase of CLBR was found with the ovarian responsibility after adjusting for age, indicating that the number of oocytes retrieved might be the most important predictor of the success of IVF/ICSI for AMA patients. Moreover, the cryopreservation rates in POR, NOR and HOR groups were 0.8%, 25.8%, and

46.6%, respectively, increased progressively with the ovarian responsibility. More supernumerary embryos in high ovarian responders may be the reason for the AMA patients achieving higher CLBR.

In contrast to previous study, this study targeted women aged 38 years or older, and found that there was no significant difference in LBR after fresh ET among the POR, NOR, and HOR groups after adjusting for potential confounders. Possibly because of the age-related poor embryo quality and increased embryo aneuploidy rate [15, 16]. It was reported that the embryos aneuploid rate in the women aged less than 35 years was about 50% and increased to over 80% for the women older than 44 years. The euploid rate and number of embryos per cycle were counterbalanced across all maternal ages [17, 18]. Therefore, some researchers suggest selecting euploid embryos from available embryos through preimplantation genetic testing (PGT) to increase LBR in AMA patients [19]. However, the likelihood of having at least one euploid embryo decreased significantly with the female age, and increased significantly with every additional embryo available, obtaining one euploid embryo may need at least 6–16 Day 3 embryos for women older than 40 years old [20]. Therefore, it is hard for aged women to get enough available embryos for PGT and find euploid embryos to transfer. In this study, the mean [standard deviation (SD)] available embryos were only 1.9 (0.7) for poor ovarian responders, 4.7 (2.3) for normal ovarian responders, and 9.2 (3.8) for high ovarian responders. Thus, PGT may only benefit for high ovarian responders who have enough available embryos.

It has been demonstrated that excessive ovarian response is closely related to the risk of OHSS and the detrimental effect on endometrial receptivity [21], and more than 15 oocytes retrieved would significantly increase OHSS risk without improving LBR [22]. Thus, main explains why the LBR does not increase with the increased oocytes retrieved after fresh ET. It should be emphasized that all patients who had a high risk of OHSS after ovarian stimulation were performed “freeze-all” strategy and excluded for this analysis, which may underestimate the relationship between the CLBR and the number of oocytes retrieved. Furthermore, since the late onset OHSS are usually associated with pregnancy, more attention was given to the pregnant patients, especially to the higher ovarian responder, and no moderate and severe OHSS was found among the three groups.

In contrast to previous study, the strength of this study is the use of CLBR following one oocyte retrieval cycle to evaluate the success of IVF/ICSI for AMA patients based on ovarian response category. There are also limitations that need to be mentioned. Firstly, the retrospective study design with the inherent problems relating to selection bias, resulted in the difference of several baseline characteristics, which is associated with patients’ ovarian response. Thus, univariate and multivariable logistic regression analyses were used to minimize the influence of these variables. Secondly, the different stimulation protocols might have acted as confounders to the results. However, they might have affected all groups in a similar way.

Conclusions

In conclusion, ovarian response is significantly associated with CLBR of the women with advanced age. Randomized controlled trials focused on AMA patients need to be done to confirm our findings.

List Of Abbreviations

LBR, live birth rate; CLBR, cumulative live birth rate; AMA, advanced maternal age; IVF, in vitro fertilization; ET, embryo transfer; POR, poor ovarian response; NOR, normal ovarian response; HOR, high ovarian response; OR, odds ratio; AFC, antral follicle counts; ART, assisted reproduction technologies; ICSI, intracytoplasmic sperm injection; OHSS, ovarian hyperstimulation syndrome; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E₂, oestradiol; rHCG, recombinant human chorionic gonadotropin; CPR, cumulative pregnancy rate; SD, standard deviation; IQR, interquartile range; CI, confidence interval; PGT, preimplantation genetic testing.

Declarations

Ethics approval and consent to participate

The study was approved by the Reproductive Medicine Ethics Committee of the 901th Hospital of the Joint Logistics Support Force of the People's Liberation Army. All the patients provided written informed consent.

Consent for publication

Not Applicable.

Availability of data and materials

Data supporting the findings of this study are available within the article. Additional data are available from the corresponding author, upon reasonable request.

Competing interests

The authors declare that they have no competing interest.

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Authors' contributions

CL and HJ contributed to the design and implementation of the study. YL, XW, FN, and YL collected the data. CL conducted the statistical analyses and wrote the first version of the study. All authors approved the final version. All authors read and approved the final manuscript.

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