Human Reproduction, Vol.33, No.5 pp. 924–929, 2018
Advanced Access publication on March 9, 2018 doi:10.1093/humrep/dey044

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Live birth rates in the first complete IVF cycle among 20 687 women using a freeze-all strategy

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Submitted on October 7, 2017; resubmitted on December 14, 2017; accepted on February 9, 2018

STUDY QUESTION: What is the chance of having a child following one complete IVF cycle for patients using a freeze-all strategy?

SUMMARY ANSWER: The chance of having a child after the first complete IVF cycle was 50.74% with the freeze-all strategy.

WHAT IS KNOWN ALREADY: Several studies have reported on live birth rates (LBRs) based on only the fresh embryo transfer cycle or fresh and frozen–thawed embryo transfer cycles. However, the LBR using a freeze-all strategy in IVF is unknown.

STUDY DESIGN SIZE AND DURATION: This retrospective cohort study included 20 687 women who started their first IVF cycles using a freeze-all strategy during the period from 1 January 2007, through 31 March 2016, in China.

PARTICIPANTS /MATERIALS, SETTING, METHODS: Data on 20 687 women undergoing their first complete cycles using a freeze-all strategy from 2007 to 2016 were analyzed to estimate LBRs. The LBR in a complete cycle was defined as the chance of a live birth from an ovarian stimulation cycle including all subsequent frozen embryo transfers from this stimulation. The relationship between LBR and number of oocyte was explored.

MAIN RESULTS AND THE ROLE OF CHANCE: The LBR for the first complete cycle was 50.74% for patients using a freeze-all strategy. By age group, the LBR declined from 63.81% for women under 31 years old to 4.71% for women over 40 years old after the first complete cycle. The LBRs improved as the number of oocytes retrieved increased up to 25 in the freeze-all strategy.

LIMITATION AND REASONS FOR CAUTION: This was a retrospective study without a control group. Data on BMI and smoking status were not collected in this database.

WIDER IMPLICATIONS OF THE FINDINGS: Our results showed that 50.74% of patients could achieve a live birth after the first complete cycle via a freeze-all strategy. In addition, the LBRs were positively correlated with the number of oocytes retrieved via the freeze-all strategy. These findings are critical for patients and clinicians in making an informed decision to embark on IVF treatment.

STUDY FUNDING/COMPETING INTEREST(S): This work was supported by grants from the National Natural Science Foundation of China (NSFC) (31770989 to Y.W.) and the Shanghai Ninth People's Hospital Foundation of China (JYLJ030 to Y.W.). None of the authors have any conflicts of interest to declare.

Key words: live birth rate / IVF / live birth / freeze-all strategy / frozen–thawed embryo transfer

Introduction

Since the first child conceived by IVF was born in 1978, considerable breakthroughs have been made in IVF. With the rapid development of cryopreservation techniques, frozen embryo transfer (FET) has become an alternative to fresh embryo transfer (ET) in IVF treatment. FET helps to increase the cumulative pregnancy rate per ovarian stimulation cycle while decreasing the risk of ovarian hyperstimulation syndrome (OHSS) and the need for additional ovarian stimulation and oocyte retrievals (Barnhart, 2014).

In recent years, a freeze-all strategy has been suggested as a way to further improve IVF outcomes (Roque *et al.*, 2013; Chen *et al.*, 2016). In the freeze-all strategy, all embryos are cryopreserved, and the frozen–thawed embryos are transferred in subsequent cycles into a more 'physiologic environment' (Roque *et al.*, 2015). By adopting this strategy, the potential deleterious effects of controlled ovarian stimulation (COS) on the endometrium could be avoided, and better results would be obtained (Barnhart, 2014; Shapiro *et al.*, 2011a, b). Previous studies have shown a significant increase in pregnancy rates and live birth rates (LBRs) and a marked decrease in the risk of OHSS and perinatal and maternal morbidity with a freeze-all strategy (Barnhart, 2014; Chen *et al.*, 2016; Devroey *et al.*, 2011; Evans *et al.*, 2014; Roque *et al.*, 2013). The results from a randomized clinical trial involving 1508 women with polycystic ovary syndrome (PCOS) indicated that patients had a higher frequency of live birth (49.3 vs 42.0%) and a lower frequency of OHSS (1.3 vs 7.1%) after the first FET compared with ET (Chen *et al.*, 2016). A meta-analysis including 633 women aged 27–33 years old showed a more than 30% increase in clinical and ongoing pregnancy rates when employing the freeze-all strategy compared with fresh embryo transfer (Roque *et al.*, 2013). However, among the three included studies in that meta-analysis, two studies were performed in patients with high ovarian response. As all previous studies evaluating this strategy were conducted in highly selected patient populations, IVF outcomes in the general infertility population are unknown (Roque *et al.*, 2017). To investigate the LBR in the general infertility population employing the freeze-all strategy, we analyzed data from a cohort of 20 687 women undergoing IVF treatment.

A high number of oocytes retrieved is important in IVF treatment, which improves the chances of pregnancy and live birth. Previous studies on the relationship between the number of oocytes retrieved and IVF outcomes have shown conflicting results (Baker *et al.*, 2015; Briggs *et al.*, 2015; Hamoda *et al.*, 2010; Ji *et al.*, 2013; Sunkara *et al.*, 2011). Furthermore, the majority of previous studies have focused on the clinical or ongoing pregnancy rate or have analyzed the LBR following fresh cycles. The association between the number of oocytes retrieved and the LBR in the freeze-all strategy has not been reported. Therefore, another objective of this study was to evaluate the LBR per ovarian stimulation cycle as a function of the number of oocytes retrieved via the freeze-all strategy. In addition, considering that maternal age is an important factor affecting both the number of oocytes retrieved and the LBR, we explored the relationship between oocyte number and LBRs across different age groups.

Materials and Methods

Ethical approval

The study protocol was approved by the Ethics Committee (Institutional Review Board) of the Shanghai Ninth People's Hospital.

Study population

The data in this study were obtained from an IVF database that included all records for IVF treatments and outcomes in patients who undertook IVF treatment in the Shanghai Ninth People's Hospital affiliated to JiaoTong University School of Medicine (a large hospital-based tertiary care reproductive center in Shanghai, China) since 2007. In this study, the clinical outcomes of IVF are presented via a patient-anchored approach with all embryo transfer cycles attached to the patient undergoing IVF treatment.

Women who underwent their first IVF cycles using a freeze-all strategy during the period from 1 January 2007, through 31 March 2016, were included. All the cycles for these women were extracted from the database. We excluded women who underwent treatment for the express purpose of storage of eggs or embryos, women who received treatment with donor semen, and women with cycle cancellation or no oocytes retrieved. Patients who did not become pregnant but still had frozen embryos remaining were also excluded from our study. Women who had a live birth were censored from further analysis. One complete cycle was defined as all the frozen–thawed embryo transfer attempts resulting from one round of ovarian stimulation in the study.

Outcomes

A live birth was defined as a birth exhibiting any sign of life irrespective of the weeks of gestation according to the World Health Organization. Just as in other studies, we also modified the definition to capture as many viable births as possible (Luke *et al.*, 2012; Nelson *et al.*, 2011; Smith *et al.*, 2015). In this study, we defined a live birth as an infant born alive after 24 weeks of gestation who survived more than 28 days. Deliveries of twins or higher-order multiple pregnancies were counted as one live birth in this study. The LBR for a complete cycle was the chance of a live birth from an ovarian stimulation cycle including all subsequent FETs from that stimulation cycle.

Statistical analysis

Data were obtained for the women's age (grouped as <31, 31–34, 35–37, 38–40 or >40 years old), infertility type (primary or secondary), cause of infertility (tubal disease, ovulatory disorder, endometriosis or male factor), type of cycle (IVF, ICSI or IVF+ICSI), number of oocytes retrieved (grouped as 1–5, 6–10, 11–15, 16–20, 21–25 or >25 oocytes), number of embryos created, and live births.

The characteristics of the patient cohort were described using the mean with the SD or the median with the interquartile range for continuous variables and number of cases with percentages for categorical variables. The LBRs across age groups and categories of number of oocytes retrieved in the first complete cycle were calculated, and the trends were tested. Multivariate logistic regression analysis was performed to identify independent correlates between each potential confounding factor, especially the number of oocytes retrieved and the LBR. The results were reported as adjusted odds ratios (aORs) with 95% CIs. Two-tailed P values <0.05 were considered significant. All statistical analyses were performed using the statistical package Stata, version 12 (StataCorp. Stata Statistical Software: Release 12. College Station, TX, USA).

Results

Characteristics of the study population

After exclusions, the eligible cohort included 20 687 women. Among them, 10 497 patients (50.74%) had a live birth after the first complete cycle in the freeze-all strategy. The characteristics of the patients in the first complete cycle are presented in Table I. Approximately 43.31% of the women were under 31 years of age, 30.71% were aged 31–34, 12.75% were aged 35–37, 7.07% were aged 38–40 and 6.16% were older than 40 years of age. More than half the women suffered from primary infertility, and the main cause of infertility was tubal factor (67.97%). IVF was performed in 66.38% of the first complete cycles, ICSI in 27.38% of cycles and both IVF and ICSI in 6.24% of cycles. The

median number of oocytes retrieved in the first complete cycle was 7 (interquartile range: 3–13) and the median number of embryos created in the first complete cycle was 5 (interquartile range: 2–9). The total number of frozen–thawed embryo transfer cycles in the first complete IVF cycle was 22 622.

Table I Characteristics of 20 687 women in the first complete cycle.

Characteristic	N (%)
Number of women	20 687
Women's age (year), mean (SD)	31.83 (0.03)
<31	8960 (43.31)
31–34	6352 (30.71)
35–37	2638 (12.75)
38–40	1463 (7.07)
>40	1274 (6.16)
Infertility type	
Primary infertility	10 601 (51.24)
Secondary infertility	10 086 (48.76)
Causes of infertility*	
Tubal	14 324 (67.97)
Ovulatory	2554 (12.12)
Endometriosis	2060 (9.78)
Male cause	6701 (31.80)
Type of cycle	
IVF	13 732 (66.38)
ICSI	5665 (27.38)
IVF+ICSI	1290 (6.24)
Number of oocytes retrieved, median (first quartile, third quartile)	7 (3, 13)
Number of embryos created, median (first quartile, third quartile)	5 (2, 9)
Number of frozen–thawed embryo transfer cycles	22 622

*The causes of infertility are not mutually exclusive.

LBR in the first complete cycle

The overall LBR in the first complete cycle among 20 687 women using the freeze-all strategy was 50.74% (95% CI: 50.06–51.43%). The LBR significantly decreased with increasing age (Fig. 1, test for trend: $P < 0.001$). In women who were younger than 31 years old who used the freeze-all strategy, the LBR for the first complete cycle was 63.81% (95% CI: 62.80–64.80%). This rate decreased to 4.71% (95% CI: 3.61–6.02%) for women over 40 years old. Table II presents the LBR according to the oocyte number. The LBR was 20.60% (95% CI: 19.73–21.49%) for women with 1–5 oocytes retrieved, and it increased to 90.09% (95% CI: 87.88–92.02%) for women with more than 25 oocytes retrieved (test for trend: $P < 0.001$). Figure 2 visually displays the association between LBR, female age and oocyte number. The LBR rose with the increased number of oocytes up to and beyond 25 oocytes. For a given number of oocytes, the LBR decreased with increasing age.

Logistic regression analysis for the LBR

Table III shows the estimated aORs and 95% CIs between LBR and independent variables. The results revealed a negative relationship between LBR and female age. After adjusting for other factors, the aOR for LBR consistently decreased from 0.80 (95% CI: 0.75–0.87) in women aged between 31 and 34 years old (women under 31 years old as reference) to 0.08 (95% CI: 0.06–0.10) in women older than 40 years of age. The LBR was positively related to the number of oocytes. Compared with women with 1–5 oocytes, the probability of having a live birth was more than four times higher for women with 6–10 oocytes (95% CI: 4.08–4.78), and it increased to more than 24 times higher for those women with more than 25 oocytes (95% CI: 19.04–30.39). In addition, women with secondary infertility were more likely to have a live birth than women with primary infertility (aOR = 1.18, 95% CI: 1.10–1.26). Women who had ICSI performed were less likely to have a live birth than women who underwent IVF alone (aOR = 0.87, 95% CI: 0.80–0.94).

Discussion

This analysis of data on birth outcomes after a freeze-all strategy involving 20 687 women over ten years showed that the average LBR

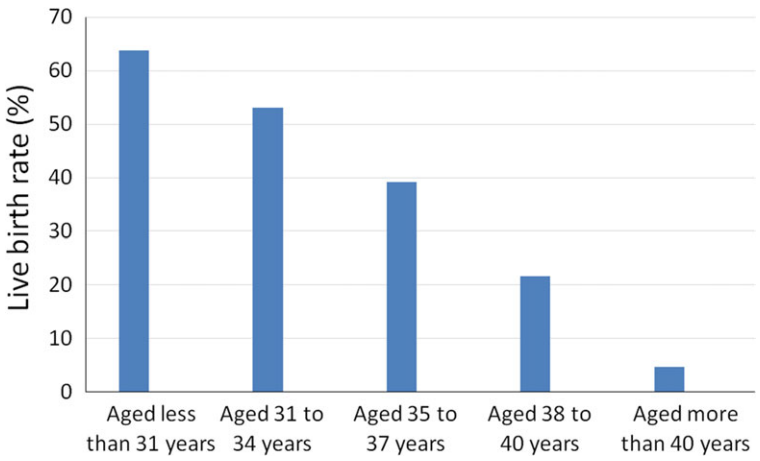

Figure 1 Live birth rates (LBRs) after the first complete cycle among 20 687 women.

Table II Live birth rate after the first complete cycle, stratified by the number of oocytes retrieved.

Oocytes retrieved	Number of women	Number of live births	Live birth rate % (95% CI)
Total	20 687	10 497	50.74 (50.06, 51.43)
1–5	8239	1697	20.60 (19.73, 21.49)
6–10	5055	2950	58.36 (56.98, 59.72)
11–15	3507	2568	73.22 (71.73, 74.68)
16–20	2017	1631	80.86 (79.08, 82.56)
21–25	1021	887	86.88 (84.65, 88.89)
>25	848	764	90.09 (87.88, 92.02)

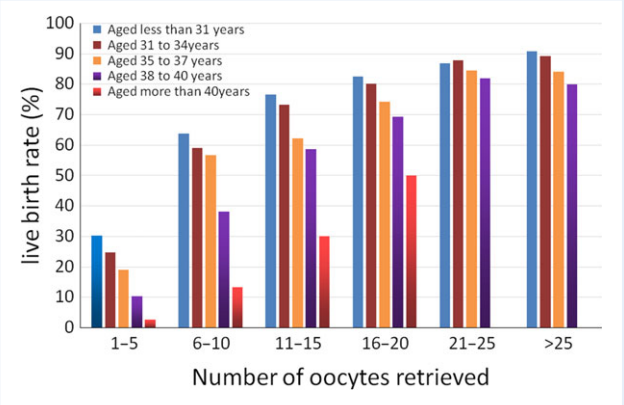

Figure 2 LBRs after the first complete cycle, stratified by age and the number of oocytes retrieved.

Table III Odds ratio for a live birth among 20 687 women.

	aOR	95% CI	*P*
Age (years)			
<31	1		
31–34	0.80	0.75–0.87	<0.001
35–37	0.59	0.54–0.66	<0.001
38–40	0.32	0.27–0.37	<0.001
>40	0.08	0.06–0.10	<0.001
Infertility type			
Primary infertility	1		
Secondary infertility	1.18	1.10–1.26	<0.001
Type of cycle			
IVF	1		
ICSI	0.87	0.80–0.94	<0.01
IVF+ICSI	1.08	0.97–1.21	>0.05
Number of oocytes retrieved			
1–5	1		
6–10	4.42	4.08–4.78	<0.001
11–15	7.97	7.25–8.76	<0.001
16–20	11.89	10.48–13.49	<0.001
21–25	18.33	15.12–22.21	<0.001
>25	24.05	19.04–30.39	<0.001

Analysis by logistic regression. aOR, adjusted odds ratio; CI, confidence interval.

for the first complete cycle was 50.74%. By age group, the LBR after the first complete cycle declined from 63.81% for women under 31 years old to 4.71% for women over 40 years old. The LBR increased as the number of oocytes retrieved increased, even up to and beyond 25 oocytes. To our knowledge, this is the first study to estimate the LBR per patient after a freeze-all strategy in a large population-based cohort of infertility patients.

In recent years, there has been an accelerating trend toward the adoption of the freeze-all strategy. One main reason for the widespread application of this strategy is to essentially eliminate the possibility of OHSS. Another reason is the significantly increased pregnancy rates and LBRs with the adoption of a freeze-all strategy, which has been reported in previous research. The better IVF outcomes with this strategy are partly attributed to avoiding exposure to the supraphysiological hormonal levels following COS, which can have a detrimental effect on embryos and placentation, and to the synchrony between the endometrium and embryos that can result from delayed transfer of frozen–thawed embryos. A few studies focusing on the freeze-all strategy have been conducted in recent years (Chen *et al.*, 2016; Shapiro *et al.*, 2011a, b). However, they have been limited to small sample sizes or highly selected patients with poor generalizability, and they have only reported the clinical pregnancy rate and LBR per embryo transfer cycle. In the present study, we estimated the LBR per complete cycle in a large general population to explore the applicability of the freeze-all strategy in all IVF patients. Our results indicated that the average chance of a live birth after the first complete cycle was 50.74% in the freeze-all strategy, which is higher than the LBR with the conventional IVF strategy (including a single fresh and zero or more frozen–thawed embryo transfers) reported in previous research. A prospective study including 156 947 UK women undergoing IVF treatment between 2003 and 2010 revealed that the LBR for the first complete cycle was 29.5% for the conventional IVF strategy (Smith *et al.*, 2015). A retrospective cohort study conducted among 12 869 women who started their first IVF cycle between 2009 and 2011 in Belgium found that the LBR for the first complete cycle was 29.6% for patients using the conventional IVF strategy (Neubourg *et al.*, 2016). On one hand, our results provide evidence for the clinical application of the

freeze-all strategy to the whole infertility population. On the other hand, in addition to their protocols, many other factors including age, cause of infertility and smoking history were different between our study and previous studies, which may also contribute to the different results. So, large multicenter randomized controlled trials are needed to evaluate the freeze-all strategy.

Many studies have been performed to investigate the relationship between LBR and the number of oocytes retrieved, but they have yielded inconsistent results. Some researchers have reported that there exists an optimal number of oocytes to achieve the maximum LBR while maintaining an acceptable risk of OHSS. A large-scale study involving 400 135 IVF cycles performed between April 1991 and June 2008 in the UK reported a non-linear relationship between the number of oocytes retrieved and LBR (Sunkara *et al.*, 2011). The best LBRs were obtained when the number of oocytes was 15, and LBRs steadily declined beyond 20 oocytes. Another study conducted among 3131 infertile women who started their first IVF cycle during January 2009 to December 2010 showed that LBRs increased up to eight oocytes and then plateaued (Cai *et al.*, 2013). A retrospective cohort study involving 256 381 IVF cycles found the LBRs rose with an increasing number of oocytes up to 15, above which the rates plateaued (Steward *et al.*, 2014). However, the above three studies reported the LBRs based on fresh embryo transfer cycles. Other researchers estimated the LBR based on complete cycles including fresh and frozen–thawed embryo transfers, and they proposed that the higher the number of oocytes, the higher the chances of a live birth. They speculated that the decrease in the LBR per fresh embryo transfer after a certain number of oocytes can be obviated by an increase in the LBR as a result of pregnancies from frozen–thawed embryo transfers. Baker *et al.* (2015) reported LBRs increased as a function of oocyte number up to more than 26 oocytes in a retrospective cohort of 231 815 IVF cycles. Ji and Drakopoulos found that the LBRs in the first IVF cycle increase with the number of oocytes up to and beyond 15, and the number of oocytes is an important independent predictor of live birth per complete cycle (Drakopoulos *et al.*, 2016; Ji *et al.*, 2013). As these studies reported the LBR based on a conventional IVF strategy (including a single fresh and zero or more frozen–thawed embryo transfers), the relationship between the LBR and number of oocytes in the freeze-all strategy was still unknown. Our study found the LBR after the first complete cycle rose with an increasing number of oocytes up to and beyond 25 oocytes in the freeze-all strategy. We believe that the benefit of using the freeze-all strategy derives from decreasing the incidence of late-onset OHSS and avoiding impairment of the endometrium. These results also added information on the association between oocyte number and LBR.

There were some limitations to this study. First, because data on BMI and smoking status were not collected in this database, we could not analyze the effects of these variables on LBRs. Second, considering that this is a retrospective study without a control group, randomized controlled trials are needed in the future.

Conclusion

According to the results of this study, 50.74% of patients using the freeze-all strategy achieved a live birth after the first complete cycle. In addition, the LBR was positively correlated with the number of oocytes retrieved via the freeze-all strategy. These findings are critical for patients and clinicians in making an informed decision to embark on IVF treatment.

Acknowledgements

We gratefully acknowledge all the staff of the department of assisted reproduction in Shanghai Ninth People's Hospital for their support and cooperation.

Authors' roles

Y.P.K. and Y.W. supervised the entire study, including the procedures, conception, design and completion. Q.J.C., X.F.L., Q.F.L. and L.W. were responsible for the collection of data. Q.Q.Z. contributed the data analysis and drafted the article. Y.W. participated in the interpretation of the study data and in revisions to the article.

Funding

Grants from the National Natural Science Foundation of China (NSFC) (31770989 to Y.W.) and the Shanghai Ninth People's Hospital Foundation of China (JYLJ030 to Y.W.).

Conflict of interest

None of the authors have any conflicts of interest to declare.

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