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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Required number of blastocysts transferred, and oocytes retrieved to optimize live and cumulative live birth rates in the first complete cycle of IVF for autologous and donated oocytes

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Abstract

Purpose To investigate live birth rate (LBR) and cumulative live birth rate (CLBR) to achieve the first newborn per blastocyst transferred and oocyte retrieved in the first complete IVF cycle of autologous and donated oocytes and identify the possible success factors**.**

Methods This was a retrospective cohort study of a private IVF center. There were 1867 cycles, 1241 of which were fresh transfers and 626, their subsequent thawing transfers.

Results We found significant variables by binary logistic regression. For LBR, female infertility and the day of blastocyst transferred were relevant; however, for CLBR, the numbers of blastocysts available for future transfers, oocyte age, and maternal age were more critical. Oocyte age is a negative factor that begins to affect CLBR gradually beyond 36 years; from that age, there are significant worse results in polycystic ovary syndrome and poor responder patients.

Conclusion The LBR and CLBR were optimized for oocyte recipients when eight oocytes were retrieved (63.6%; 87.9%); at most, fourteen oocytes should be assigned to avoid freezing surplus blastocysts. Thirteen autologous oocytes (69.2%; 92.3%) were ideal for optimization. CLBR optimized after three blastocysts in donor oocytes (81.8%) and four for autologous oocyte patients (80.9%). Our outcomes are valuable for doctors and infertile couples, and they give us information on what we can expect from a first complete IVF cycle.

Keywords Cumulative live birth rate · Live birth rate · Blastocyst transferred · First IVF complete cycle · Oocyte retrieved

What does this study add to the clinical work?

For recipients and autologous oocytes, eight oocytes or three blastocysts and thirteen oocytes or four blastocysts, respectively, optimized LBR and CLBR in the first complete IVF cycle.

Introduction

In most countries, it has been estimated that more than 50% of couples seek medical attention for their infertility problems. Advanced maternal age (AMA) is one of the most common causes of infertility; AMA has led to an increase in the average age of the first pregnancy and a reduction in the cumulative live birth rates (CLBR) [1]. Live birth rate (LBR) and CLBR are defined as the possibility of achieving a live

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newborn after using fresh embryos and all frozen embryos resulting from an in vitro fertilization (IVF) stimulation cycle of the same oocyte collection [2]. Although there has been a decrease in the number of embryos transferred, several studies indicate an improvement in the success rate of IVF accumulated in recent decades [3] due to consistent clinical results between fresh and frozen–thawing embryo transfers (FET) that have been reported with high survival rates of blastocysts with the vitrification method [4].

An important counseling aspect in assisted reproductive technology (ART) is identifying failure risk and the limit of treatments [2]. Each couple should consider either renouncing or changing their gametes according to their chances of success, beliefs, and values regarding the cost–benefit that will be obtained. Thus, when couples start their first cycle, they often want to know their chance of having a newborn with their fresh or frozen surplus embryos. Although there have been several studies that have examined live birth and cumulative live birth rates in different scenarios [5] and other articles that studied the impact of various factors on live birth rates, this research examined them considering all aspects simultaneously and at all ages; because to our knowledge, more information is necessary to be focused their effects on LBR and CLBR in the first complete IVF cycle, especially for the number of blastocysts transferred and oocytes retrieved.

Materials and methods

A retrospective cohort study of a private ART center was investigated, where we analyzed 1867 cycles, of which 1241 were first IVF fresh transfer, and 626 were their subsequent FET, of autologous (AO) and donated oocytes (DO), from January 1, 2009 to January 30, 2023. Both fresh and FET were included. The study was designed by the ARL and approved by the Institutional Review Board of ANU, number 201911; the data were anonymous, following all rules regarding protecting personal information.

For the predictive ability, it was essential to include both low- and high-prognosis couples when considering the social realities of the population studied. All patients had primary infertility (no newborn before).

Inclusion criteria were established

Patients between 30 and 45 years old, diagnosed with polycystic ovary syndrome (PCOS) and poor ovarian responder (POOR), tubal obstruction, grade I of endometriosis, and all patients who received fresh oocyte donation.

Exclusion criteria established

The presence of any additional female pathology, use of any extraction of sperm technique from patient, body mass index BMI ≥ 30, severe endometriosis, hydrosalpinx, patients with some indicator of ovarian hyperstimulation syndrome (OHSS), and couples who have a morphological sperm selection technique (IMSI) or chemical sperm selection technique (PICSI) before intracytoplasmic sperm injection (ICSI) or who performed preimplantation genetics test for aneuploidies (PGTA) or the used of frozen sperm or oocytes.

All patients of their AO received GnRH antagonist protocol in conventional IVF stimulation. Oocyte donors were healthy women aged 18–30, selected by international consensus. For all oocyte recipients' transfers and FET, the endometrial preparation was with exogenous administration of estrogen and progesterone. At the time of embryo transfer, the mean endometrial thickness was 8.7 ± 1.9 mm, and the mean estradiol concentration was 332.3 ± 361.6 pg/ml. Clinical pregnancies were confirmed when a gestational sac with a fetal heartbeat was detected by ultrasound at seven weeks of pregnancy. Live birth (LB) was defined as the delivery of any live-born infant (at least 24 weeks or more of gestation) in the fresh or the subsequent FET cycles. Only the first delivery was considered in the analysis. Embryos were cultured under 5% oxygen and the same culture medium (Vitrolife). Those blastocysts reaching an inner diameter of over 160 m on day 5 or 6 were transferred or vitrified. In our clinic, all transfers and vitrification [4] are made in the blastocyst stage with *viable potential blastocysts* in their different combinations of internal cell mass and trophectoderm, according to the Gardner classification [6]. Regardless of the semen sample, we included patients only with a diagnosis of terato-, astheno-, or asthenoteratozoospermia, according to the criteria of the World Health Organization, with fresh seminal samples, a density gradient centrifugation procedure, recovery of at least 2 million progressive motile sperm for ICSI and/or IVF, and DFI per sperm chromatin dispersion tests (SCD) [7]. Reproductive success was measured per blastocyst transfer, per number of blastocysts transferred, and per number of oocytes retrieved needed to achieve a live birth.

Statistical analysis

The selecting variables were based on their statistical frequency and scientific relevance. The nominal and ordinal candidate predictor variables were subjected to bivariable analysis by chi-square test to evaluate statistical

relationships between each candidate predictor and the outcomes, LB and CLBR. For the binary logistic regression analysis (BLRA), the determinants involved were identified and selected for their frequency relevance, according to the knowledge by literature and the information provided by the data [8]. Maternal and oocyte age were grouped into three age groups: ≤ 35, 36 to 39, and ≥ 40 years old [9]; in this study, maternal age is the age of the woman who received the transfer, and oocyte age is the age of the oocyte at the time of retrieval; for DFI were grouped in ≤ 15, 16 to 29, and ≥ 30% [7]. Prognostic power was evaluated with internal validation using data from the same study cases; the study population was randomly divided into two groups: 70% of the validation set and 30% of the training set and bootstrapping test. We used the standard method of entry for exploratory analysis and backward stepwise; we also verified the results with $p = 0.157$, a detention rule equivalent to using the AIC criterion [10].

We calculated the area under the curve (AUC) of the receiver operating characteristics (ROC) in training and test groups to evaluate the factors' discriminating capacity. The Hosmer–Lemeshow test evaluated regression calibration. The uncertainties uncovered by the instrument were evaluated by pseudo-coefficients r^2, Nagelkerke, and Cox–Snell [10]; the p value considered statistically significant was 0.05. Beta coefficients were used to calculate the predicted probability of live birth rate for each observation in the validation data set. The Kaplan–Meier estimator was used to evaluate the CLBR per blastocyst transferred through Log-rank, Breslow, and Tarone–Ware tests according to each categorical group. Microsoft Excel software was used for some analyses and graph generation. Statistical analysis was performed using the Statistical Package for the Social Sciences 26 SPSS and MedCalc 20 Software.

Results

In Table 1, we show the general baseline characteristics of the population. All the clinical characteristics of the factors are shown in Table 2; the probability of having a child for DO and AO in LBR was 68.06% and 50.95%; for CLBR, it was 84.58% and 79.66%, respectively. In oocyte age, women ≥ 40 had the lowest LBR (40.15%) and CLBR (67.04%). By analyzing the number of oocytes retrieved by groups of oocytes, the highest rates were when recovered between 11 and 15 oocytes, LBR (56.6% or 70.7%), and CLBR (86.26% or 87.50%). For DFI, ≥ 30% had the lowest rates among all factors studied, including LBR (30.05%) and CLBR (55.95%). For female infertility, the lowest rates were for the POOR patients, LBR (42.33%) and CLBR (71.16%), followed by PCOS and endometriosis grade I, respectively.

Table 1 General baseline characteristics of the population

Women age, autologous oocytes	37.9 ± 3.2	
Male age	39.61 ± 6.1	
Women age, donor oocytes	25.43 ± 2.7	
Women age, recipient oocytes	40.23 ± 3.0	
Number of oocytes retrieved	12.9 ± 3.5	15,969
Number of fresh blastocysts transferred	1.71 ± 0.29	2081
Number of FET blastocysts transferred	1.60 ± 0.40	999
Number of available blastocysts	3.5 ± 1.5	6104
Fertilization rate	81.80%	(13,063/15969)
Top-embryos rate on day 3	64.79%	(8464/13063)
Top-blastocyst rate on day 5 or 6	39.38%	(5145/13063)
Blastocysts formation rate	46.72%	(6104/13063)
Frozen blastocyst rate	30.79%	(4023/13063)
Pregnancy rate (PR)	64.30%	(798/1241)
Cumulative pregnancy rate (CPR)	93.15%	(1156/1867)
Miscarriage rate	12.54%	(145/1156)
Single fetus rate	86.05%	(870/1011)
Twins fetus rate	13.94%	(141/1011)

For the day of blastocyst transfer, day 5 or 6, there were significant differences in favor of day five. There was no significant difference between the numbers of blastocysts transferred for FET, but yes, for fresh transfers. Our overall rate of one blastocyst transfer was 32%. Regarding the number of blastocysts available in AO, LBR plateaued and optimized after two blastocysts (80%) and CLBR for four blastocysts (87.60%). Per oocyte age, we found that in patients between 36 and 39 and ≥ 40 years, the average number of those who did not have a newborn was 8.8% and 20.1% for POOR and 7.1% and 7.3% for PCOS.

For the BLRA, we analyzed these variables: number of blastocysts transferred, day of transferred, oocyte age, maternal age, DFI, number of oocytes retrieved, female infertility, sperm diagnostic, number of available blastocysts, and oocytes' origin AO or DO. The variables selected as significant predictors of LBR and CLBR are presented in Table 3. We found five essential factors in each rate. The r^2, Nagelkerke, and Hosmer–Lemeshow calibration were satisfactory for training and validation sets. Concerning reference groups, BLRA showed common factors that were associated with LBR and CLBR, like oocyte age, DFI, and the number of available blastocysts. Additionally, only female infertility and the day of transfer were important for LBR, and maternal age and the number of blastocysts transferred were more critical for CLBR. Table 3. The area under the AUC of the ROC curves were 0.784 and 0.826, indicating how much the analysis could discriminate between LBR and non-LBR couples. Figure 1, comprising data, shows that the discriminatory capacity of this predictive analysis could be considered adequate for these factors [11].

Table 2 Clinical characteristics of the study population, according to live birth rate and cumulative live birth rate after blastocysts transfers in the first complete IVF cycle

Variables	Groups	*n*	LBR in fresh	*p*-value	CLBR; fresh, and 3 thawing transfers	*p*-value
Total number of transfer			1241		1867	
General LBR/CLBR			710 (57.21)		1011 (81.46)	
Maternal age	≤ 35 years	172	95 (55.2)	0.002	157 (91.27)	< 0.001*
	36 to 39 years	510	322 (63.13)		435 (85.29)	
	≥ 40 years	559	293 (52.41)		419 (74.95)	
Oocyte age	≤ 35 years	575	362 (62.95)	< 0.001*	492 (85.56)	< 0.001*
	36 to 39 years	402	242 (60.19)		342 (85.07)	
	≥ 40 years	264	106 (40.15)		177 (67.04)	
Sperm DNA fragmentation index	≤ 15%	408	312 (76.47)	< 0.001*	389 (95.34)	< 0.001*
	16 to 29%	497	297 (59.75)		434 (87.32)	
	≥ 30%	336	101 (30.05)		188 (55.95)	
Origin of oocytes	Donated	454	309 (68.06)	< 0.001*	384 (84.58)	0.032
	Autologous	787	401 (50.95)		627 (79.66)	
Female infertility	Oocyte recipient	454	309 (68.06)	< 0.001*	384 (84.58)	< 0.001*
	Tubal obstruction	158	109 (68.98)		143 (90.50)	
	PCOS	302	153 (50.66)		250 (82.78)	
	POOR	274	116 (42.33)		195 (71.16)	
	Endometriosis grade I	53	23 (43.39)		39 (73.58)	
Day of blastocysts transferred	Day 5	844	460/522 (65.40)	< 0.001*	623/914 (68.16)	< 0.001*
	Day 6	369	249/158 (42.81)		376/852 (44.13)	
	Combined	0			68	
Number of blastocysts transferred per transfer	0	33	28	< 0.001*	33	0.805
	1	588	220/345(63.76)		322/588 (54.76)	
	2	1246	490/868 (56.45)		689/1246 (55.29)	
Number of autologous oocytes retrieved	1 to 5	113	47 (41.59)	< 0.001*	84 (74.33)	0.022
	6 to 10	255	120 (47.10)		184 (72.20)	
	11 to 15	182	103 (56.66)		157 (86.26)	
	16 to 20	109	58 (53.20)		91 (83.48)	
	21 to 25	56	28 (50)		48 (85.71)	
	≥ 26	72	45 (62.5)		63 (87.5)	
Number of donor oocytes retrieved	6 to 10	166	112 (67.5)	0.136	136 (81.90)	0.201
	11 to 15	184	130 (70.7)		161 (87.50)	
	16 to 20	104	67 (64.4)		87 (83.70)	
Number of autologous blastocysts available per cycle	1	11	7 (63)	< 0.001*	7 (63.63)	< 0.001*
	2	180	144 (80)		146 (79.78)	
	3	83	45 (54.22)		65 (78.31)	
	4	158	49 (31.01)		198 (87.60)	
	5	112	49 (43.75)		168 (81.55)	
	6	84	39 (46.43)		177 (83.09)	
	7	66	26 (39.39)		137 (82.03)	
	8	38	23 (60.53)		51 (89.47)	
	≥ 9	30	19 (63.33)		62 (88.57)	
Number of donor blastocysts available per cycle	3	68	49 (72.06)	0.191	56 (82.35)	0.009
	4	94	65 (69.15)		77 (81.91)	
	5	129	84 (65.12)		111 (86.05)	
	6	101	70 (69.31)		89 (88.12)	
	7	19	14 (73.68)		16 (84.21)	
	8	39	27 (69.23)		34 (87.18)	

Values are expressed as mean ± SD or % (n)

Values in parentheses are percentages

LBR live birth rate, *CLBR* cumulative live birth rate

X^2 = Chi-square test

*$p < 0.05$

Success rates were evaluated per blastocyst transferred to create Kaplan–Meier curves Fig. 2. Except for maternal age (long-rank test: X^2 5.5, < 0.0613), there are significant differences between oocyte origin, female infertility, DFI, and oocyte age in all subgroups, 95%CI (2.804–3.031) $p < 0.001$ for all Log-rank, Breslow, and Tarone–Ware tests comparisons. These curves show CLBR depending on the total blastocysts used until the first newborn. This allowed us to calculate the blastocysts for each variable; we show all graphs and descriptive results only for oocyte origin. It demonstrates blastocysts per blastocyst that CLBR increased in DO after three blastocysts at 81.8% (95% CI 80.8–82.8), after four at 88.7% (95% CI 87.7–86.7), representing an increase of 6.9% per every additional blastocyst; in AO, after four blastocysts at 80.9% (95% CI 79.9–81.9), after five at 86.4% (95% CI 85.4–87.4), representing an increase of 5.5% per every additional blastocyst.

The LBR and CLBR were optimized for oocyte recipients when eight oocytes (63.6% CI 62.6–64.6; 87.9% CI 86.9–88.9) were obtained, for fourteen oocytes (79.4% CI 78.4–80.4; 97.10% CI 96.1–98.1) it was higher rate. Thirteen autologous oocytes (69.2% CI 68.2–70.2; 92.3% CI 91.3–93.3) were ideal for optimization. Figure 3.

Discussion

For almost a decade, one of the most suitable and accepted indicators by the scientific community to report the results of ART has been LBR and CLBR for one or several complete cycles of IVF. It has been agreed that the CLBR is more meaningful to patients and clinicians than cycle-based success rates [2] [12–15]. Hence, to evaluate CLBR for several cycles in time, cohorts of studies with data from the late nineties and early 2000s included variability because of the time of the cohort. i.e., different stimulations protocols, some patients with blastocyst transfers, others with embryo transfer on day two and day three, and frozen embryos with slow freezing technique and vitrification [12, 13, 15–17]; some reported CLBR based on the total number of embryos transferred or the number of oocytes retrieved in several consecutive cycles.

Regarding the number of oocytes retrieved to reach the live birth, in the context of traditional ovarian stimulation, there are two positions, one of which the more significant number of eggs has a higher CLBR [16, 17], and the other, which does not necessarily have a more substantial number is better for outcomes [18]. Some authors found an improvement in CLBR with increasing oocyte yield; Polyzos et al. [16] suggest that CLBRs continuously grow with the number of oocytes retrieved in suitable prognosis patient's ≤ 40 years old. Others report that LBR per cycle does not rise significantly after a certain number of oocytes are retrieved (i.e., between 10 and 12) [18]. Some studies even reported an apparent decline in the LBR with a high oocyte retrieved [19, 20]. Two systematic reviews suggested that retrieving 12–18 oocytes is associated with maximal fresh LBR; they found a positive association between the number of oocytes and the CLBR. However, this association varies according to patients' age [21] [22] and there is no consensus on the optimum number of oocytes that could balance an optimal CLBR without the risk of ovarian hyperstimulation syndrome OHSS [20] [23].

It is risky to generalize that a great number of oocytes retrieved are better when there is no consideration of oocyte age and female infertility; these factors affect the quality of the oocytes and blastocysts. The concept of oocyte competence is associated with the ability of oocytes to perform reproductive functions [24]. The quality has been defined based on the morphology of the oocyte and often on oocyte age. Using different oocyte competencies, AO and DO, could be more beneficial for evaluating the effect of these on the CLBR. We found that after nineteen oocytes, CLBR had no increase at all. Cycles performed with DO are also consistently associated with higher LBR and CLBR than those achieved with their AO within different age categories [24].

We found the lowest CLBR for the oldest patients when they used AO, 67.04%, similar to other authors, in the first cycle, 64.6% [25] and 69.8% [26]. Our results show that in the group of ≥ 40 years, there were most miscarriages, not only for oocyte recipients but also for POOR and DFI ≥ 30 patients. The impact of female infertility and DFI on the variability of oocyte repair is minor in a young oocyte; in women with AMA over 40 years, samples with a high DFI show the impact on clinical outcomes, embryo development, poor quality, reduced fertilization rate, blastocyst rate, lower implantation and pregnancy rates, and increased miscarriage rates [27]. Our population used the SDC technique for DFI analysis; logistically and economically, no other routine methods were performed for patients. However, a good correlation exists between DFI rates reported with different techniques [7].

Our study did not include patients with PGTA so that chromosomal abnormalities could explain the differences in clinical outcomes between age groups. When maternal age and oocyte age were combined, for oocyte recipients, the highest CLBR was in patients with maternal aged 35–39 years, and the lowest CLBR was in patients ≥ 40 years; even if we use DO, AMA affected the CLBR, this can be one of the explanations of miscarriages and live birth rates reduced, due to impaired cellular senescence and defective endometrial receptivity in these women [28].

Concerning female infertility, some authors consider that even though PCOS patients typically produce more oocytes, these are often of poor quality and show a low

Table 3 Binary logistic regression analysis for the predictive factors of live birth rate and cumulative live birth rate in the first complete IVF cycle

Live birth rate (LBR)	OR	Lower CI 95%	Upper CI 95%	*p*-value	B	Cummulative live birth rate (CLBR)	OR	Lower CI 95%	Upper CI 95%	*p*-value	B
Oocyte age ≤ 35	R group			< 0.001		Oocyte age ≤ 35	R group			0.094	
Oocyte age 36 to 39	1.545	0.936	2.551	0.089	0.435	Oocyte age 36 to 39	2.648	1.083	6.471	0.033	0.974
Oocyte age ≥ 40	0.625	0.351	1.112	0.010	−0.470	Oocyte age ≥ 40	1.050	0.539	2.045	0.086	0.049
DFI ≤ 15	R group			< 0.001		DFI ≤ 15	R group			< 0.001	
DFI 16 to 29%	0.458	0.331	0.633	< 0.001	−0.782	DFI 16 to 29%	0.364	0.196	0.676	< 0.001	−1.011
DFI ≥ 30%	0.137	0.095	0.199	< 0.001	−1.985	DFI ≥ 30%	0.084	0.046	0.155	< 0.001	−2.471
Female infertility oocyte recipients	R group			< 0.001		Num of blastocysts transferred. one	R group			< 0.001	
Tubal obstruction	0.554	0.325	0.944	0.030	−0.591	2 blastocysts	0.992	0.509	1.935	0.981	−0.008
PCOS	0.287	0.171	0.481	< 0.001	−1.248	3 blastocysts	0.568	0.297	1.085	0.086	−0.566
POOR	0.165	0.084	0.325	< 0.001	−1.799	4 blastocysts	0.148	0.069	0.318	0.000	−1.910
Endometrioisis	0.256	0.115	0.570	< 0.001	−1.361	5 blastocysts	0.174	0.066	0.459	0.000	−1.748
						6 blastocysts	0.070	0.022	0.223	0.000	−2.658
One available blastocyst	R group			< 0.001		2 to 3 available blastocysts	R group			< 0.001	
≥ 8 blastocysts	0.192	0.042	0.885	0.034	−1.649	≥ 8 blastocysts	4.377	1.410	13.584	0.011	1.476
6 to 7 blastocyst	0.151	0.034	0.671	0.013	−1.888	6 to 7 blastocyst	3.479	1.517	7.977	0.003	1.247
4 to 5 blastocyst	0.171	0.039	0.738	0.018	−1.768	4 to 5 blastocyst	4.184	2.085	8.397	0.000	1.431
2 to 3 blastocyst	0.954	0.219	4.147	0.949	−0.048						
Day 5 of blastocyst transferred	R group			< 0.001		Maternal age ≤ 35	R group			0.005	
Day 6	0.434	0.302	0.624	< 0.001	−0.834	Maternal age 36 to 39	0.324	0.117	0.899	0.030	−1.126
						Maternal age ≥ 40	0.246	0.106	0.572	0.001	−1.402

CI confidence interval, *R Group* reference group, *OR* odds ratio adjusted

(LBR) r^2 Nagelkerke 0. 321. Cox–Snell 0.238; HL 0. 549; Model, X^2 329.71; $p < 0.001$; % global 73.4%

(CLBR) r^2 Nagelkerke 0.325; Cox–Snell 0.197; HL 0.257; Model, X^2 207.27; $p < 0.001$; % global 82.3%

$p < 0.05$

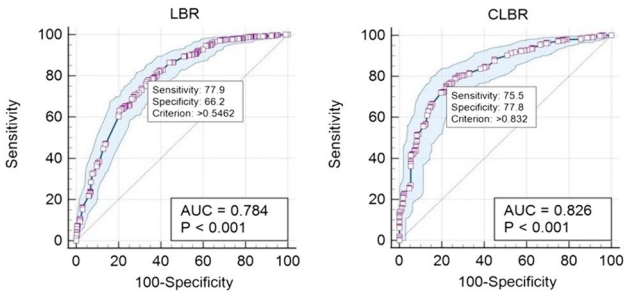

Fig. 1 ROC Curves for LBR and CLBR predictive factors in the first complete IVF cycle. The straight line is the diagonal reference or line of non-discrimination. *AUC* area under the curve

rate of fertilization and blastulation [29]; in their studies, they reported it more appropriate to evaluate the CLBR by the number of embryos to be transferred and not by the number of oocytes, [12]. In PCOS patients, high CLBR can be obtained when the number of oocytes retrieved was 15 or more [29]; however, the rate of embryos available and embryo quality was lower when over 18 oocytes were retrieved and even worse if women's age increased [29]. Oocyte age is a negative factor that begins to affect CLBR gradually beyond 36 years; related to female infertility from that age, we found significantly worse results for POOR and PCOS patients [29, 30]

In a recent study [23], they reported that nine oocytes, or four embryos, can optimize LBR, and there was no increase in the CLBR with more than 12–15 oocytes or nine embryos in the perspective of regular responders with minimal stimulation; at the same time, this research found that thirteen oocytes optimize the LBR and CLBR for AO (traditional stimulation protocol). For DO, eight oocytes optimize the LBR and CLBR; at most, fourteen should be assigned in the first cycle to avoid excess freezing of surplus blastocysts in oocyte recipients.

Given the quick changes in the last 10 years, not only in the management of ovarian stimulations [23] but also in incubation technology, time-lapse, low concentration of oxygen, blastocyst culture for transfer, and vitrification [4] of surplus blastocysts, it has achieved high pregnancy and live birth rates, revolutionizing the deferred handling of transfers, the use of embryo and oocyte banking, single embryo transfer, SET, and the PGTA [31].

Nowadays, we have more blastocysts viable per cycle than 20 years ago, and we believe that in this vitrification era, with blastocyst transfer, we could consider each blastocyst as a single opportunity for achieving a live birth; in the last two decades, the expectations of LBR and CLBR have been changed for the first complete IVF cycle. For example, another study [31] analyzed a period of 10 years (2007 to 2017); during this time, the chance of having a live-born baby increased from 27 to 36.3% per complete IVF cycle,

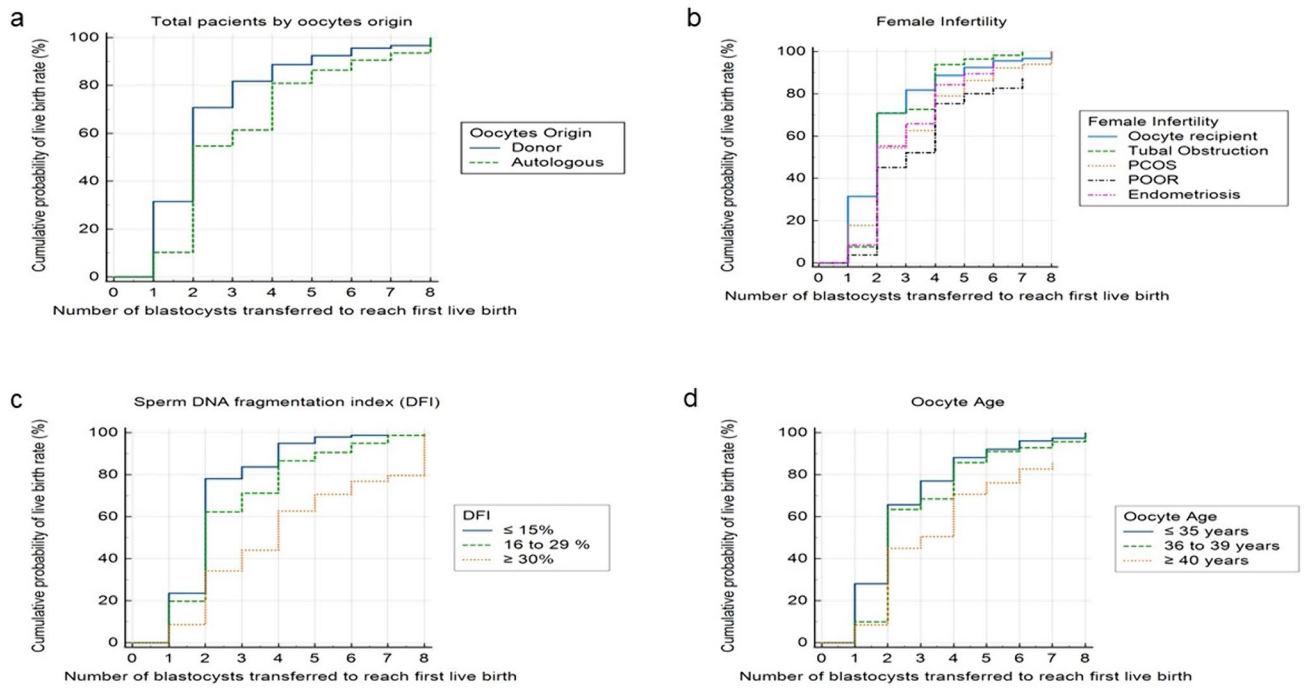

Fig. 2 Kaplan–Meier Curves for CLBR per number of blastocysts transferred to reach first live birth. Oocyte origin, (log-rank test: X^2 64.71) (**a**), female infertility, (log-rank test: X^2 91.37) (**b**), DFI, (log-rank test: X^2 103.98) (**c**), and Oocyte age, (log-rank test: $X.^2$ 68.29) (**d**). All $p < 0.001$

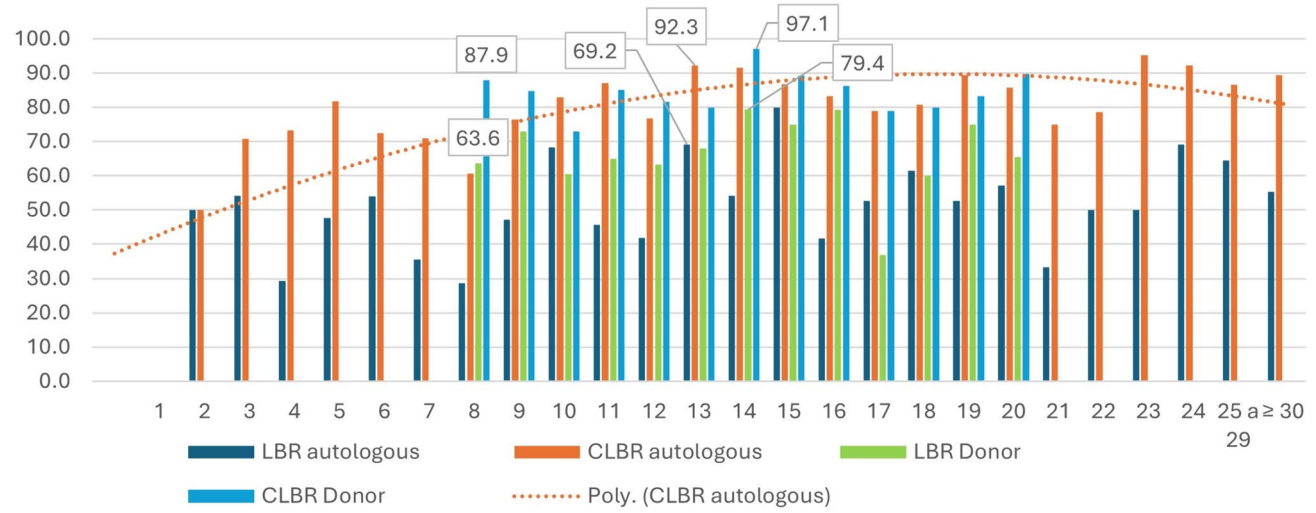

Fig. 3 Live birth rates (LBR fresh, $n=710$) and cumulative live birth rates (CLBR $n=1011$), according to the number of oocytes retrieved. The dotted lines show polynomial trend line

and with low multiple birth rates, because of these technology changes.

Other studies show blastocyst stage transfer was associated with higher CLBR 56.48%, more than cleavage stage [14]. In our research, for AO and DO, LBR was 50.95% and 68.06%, and CLBR was 79.66% and 84.58%, respectively. A Danish fertility clinic [5] found a CLBR of 64.0% after multiple ovarian stimulations, and they considered only using blastocyst transfer, too. Even in single embryo transfers, blastocyst vitrification is essential in improving CLBR. It allows for a lower number of oocytes retrieved needed to achieve an LB and a shortened time to get it [31]; for instance, with the freeze-all strategy, the chance of having a child after the first complete IVF cycle was 50.74% [32].

Another study found that five blastocysts will maximize LBR in SET fresh transfer by ≤ 36 years old patients [33]; there are other positions regarding the CBLR and blastocyst; a Cochrane review found higher LBR after blastocyst more than cleavage stage transfer in fresh cycles, but they reported that the situation remains unclear for CLBR [34].

Blastocyst transfer literature displays discordant results regarding the transfer day for fresh and FET cycles. A recent meta-analysis [35] recommends that ART practitioners should preferably transfer D5 rather than D6 blastocysts in both fresh and FET cycles. Although transferring a D6 vitrified-warmed blastocyst remains a reasonable option, prioritizing a D5 embryo would reduce the time to a successful pregnancy [36]. In our study, all blastocysts vitrified on D5 or D6 were warmed on D5 progesterone and transferred after 2 or 3 h; we found differences in favor of blastocysts transferred on D5 for LBR and CLBR. According to numbers three to four, blastocysts optimized CLBR for DO and AO, respectively. As in previous studies [12] [25], with Kaplan–Meier, we could determine at which point of the curve the couple is and then, in agreement with them, decide to continue or move toward ovum donation, remaining childless, or make another cycle.

The strengths of our study include the robust size of the cohort and the wide range of demographic variables assessed of all the couples with inclusion criteria (14 years had been included), followed by all subsequent blastocyst FET of the same cohort until they got their first newborn.

The discriminatory capacity can be considered adequate with a value of AUC for LBR and CLBR. Optimization of stimulation protocols and the effectiveness of the blastocyst vitrification technique can explain the high CLBR in this study. The main area for improvement is the retrospective design, where unmeasured confounders might play a role. Large prospective controlled trials are needed to validate the current findings. Secondly, it would be helpful in subsequent studies to include the anti-Müllerian hormone test; not all patients had this test because it had been routinely implemented in the clinic since 2012; these hormone values could influence the evaluation of ovarian reserve, which could change the overall percentage prediction. Third, other variables like the trophectoderm and ICM could provide further information in future analysis.

The data reported here are initial explorations to propose a post-treatment model that could predict the chances of success before starting the second cycle in couples whose first complete cycle was unsuccessful. When predicting the second cycle, all factors mentioned in this study and the outcome from the first complete cycle would be critical to consider before starting over [8] [37].

We found common and different predictor factors between LBR and CLBR. For LBR, female infertility and the day of

blastocyst transfer were relevant; however, for CLBR, the number of blastocysts available for future transfers, oocyte age, and maternal age was more critical. Our outcomes are valuable both for doctors and infertile couples who will carry out their first IVF/ICSI cycle with AO or DO; they not only give us information on what we can expect from the complete cycle regarding LBR and CLBR but also help us to decide whether to continue with another cycle after not having a newborn in the first one.

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Declarations

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