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The oocyte-to-baby rate of day 2, day 3 versus day 5 embryo transfer: a retrospective study

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Summary

Objectives: To investigate whether the time of embryo transfer (ET) affect the oocyte-to-baby rate. *Materials and Methods:* The database was retrospectively analyzed including total number of oocytes collected and corresponding oocyte-to-live baby born (LBB) rate. Then the relationship between different time of embryo transfer and oocyte-to-baby rate was compared. In a year period all patients undergoing infertility treatment were included in the study. The outcome parameters were total number of oocytes collected and corresponding oocyte-to-LBB. *Results:* For patients under the age of 35 years, there was no increase in oocyte-to-LBB regardless of the time of ET. For patients older than 35 years, the oocyte use rate increased significantly when embryo was transferred on day 2. Oocyte-to-baby rates were also analyzed after grouping patients on the number of oocytes retrieved per cycle. For patients < 35 years, the oocyte-to-LBB rate increased significantly on day 3 if < ten oocytes were obtained. whereas for patients > 35 years, the oocyte-to-baby rate was best on day 2 when about 15 oocytes were retrieved. *Conclusions:* This retrospective analysis demonstrated the relationship between the time of ET and ooctye-to-baby rate that is indicative of a more biologically efficient reproductive system.

Key words: Oocyte; In vitro fertilization; Time of embryo transfer; Live birth rates.

Introduction

For a long time, it was believed that the retrieval of multiple oocytes in in vitro fertilization (IVF) cycle was beneficial to the success because more embryos can be produced for transfer. However, despite collection of multiple oocytes and availability of many embryos, recent data demonstrate that the success rates of IVF treatment are still low, and that the majority of oocytes/embryos do not produce live births. It was reported recently that < 5% of the retrieved oocytes and about 15% of the transferred embryos gave rise to babies [1, 2].

A couple of papers have debated the most appropriate metrics to measure efficiency in assisted reproduction technology (ART) cycles. Live birth per retrieval cycle and live birth per embryo transfer (ET) are the standard metrics used. The denominator of these metrics can also be per cycle initiated [3] or per IVF treatment as a whole [4] that includes also the success of the derived frozen embryo transfer cycles [5]. However, these metrics do not assess the biological competence of the oocytes. A new metric, "oocyte-to-baby rate" was recently proposed to assess the efficiency of ART procedures. The metric takes into account all the oocytes collected and all the embryos obtained and used in each retrieval cycle [1, 6, 7]. Using this new metric, Patrizio and Sakkas found that only approximately 5% of the retrieved oocytes could produce a baby in young non-donor IVF patients, and that the oocyte-to-baby rate declined progressively to 1% for women 40 years or older. Surprisingly, the oocyte-to-baby rate in donor oocyte cycles was also low [1, 8].

Recently, some protocols have used better oocyte utilization rate, such as with minimal or mild ovarian stimulation protocols. However, there are no data in the literature evaluating the effect of time of ET on live-birth rates. This retrospective study was conducted to understand whether the time of ET would affect the biological efficiency of oocytes generated in IVF.

Materials and Methods

This study analyzed 1,360 cycles performed at the Shanghai First Maternity and Infant Hospital between 2008 and 2009. Oocyte donor cycles were excluded. Patients were divided into three groups according to the time of ET (group 1, ET on day 2; group 2, ET on day 3; group 3, ET on day 5). Two types of analyses were conducted. First, the authors analyzed the effect of timing of ETs on overall oocyte-to-baby rate in different age groups. Second, the relationships between oocyte-to-baby rate with the time of ET and the oocyte yield within each age group were studied.

The protocol of ovarian stimulation consisted predominantly of downregulation with leuprolide acetate at a dose of 1.25 mg starting in the midluteal phase of the preceding menstrual cycle followed by use of recombinant human follicle-stimulating hormone (FSH). When two leading follicles had a mean diameter of 18 mm, recombinant human chorionic gonadotropin (hCG) was administered, and oocyte retrieval was carried out 36 hours

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Table 1. — *Oocyte-to-baby rate in patients without frozen embryos.*

	Day 2					Day 3					Day 5					*p* value
		Number of			LBB per		Number of			LBB per		Number of			LBB per	
Age group	oocytes	ET	FHB	LBB	Oocyte (%)	oocytes	ET	FHB	LBB	Oocyte (%)	oocytes	ET	FHB	LBB	Oocyte (%)	
< 35	585	123	19	16	2.6	261	60	13	10	3.8[a]	1,080	198	54	46	4.3	0.293
35-37	189	69	7	6	3.2	68	17	2	2	2.9	237	47	6	5	2.1	0.781
> 38-40	282	119	6	5	1.8	80	36	1	0	0	121	26	3	2	1.7	0.278

ET: total number of embryos transferred; FHB: total number of fetal heartbeats; LBB: total number of live babies born

Table 2. — *Oocyte-to-baby rate in patients with frozen embryos.*

	Day 2					Day 3					Day 5					*p* value
		Number of			LBB per		Number of			LBB per		Number of			LBB per	
Age group	oocytes	ET	FHB	LBB	Oocyte (%)	oocytes	ET	FHB	LBB	Oocyte (%)	oocytes	ET	FHB	LBB	Oocyte (%)	
< 35	5,099	793	242	207	4.05	2,969	320	120	116	3.9	5,567	774	217	172	3.1	0.018
35-37	344	109	22	21	6.1	349	79	19	12	3.4[a]	962	147	37	29	3.0	0.033
> 38	399	121	15	10	2.5	359	74	10	6	1.7	124	19	4	1	0.8	0.4

ET: total number of embryos transferred; FHB: total number of fetal heartbeats; LBB: total number of live babies born
[a] Final LBB per oocyte is not statistically significantly different between day 2 and day 3 group, $p = 0.736$.

later. Progesterone supplementation (60 mg in oil) by intramuscular injection was started on the day of oocyte retrieval in all cases.

Fresh ETs were carried on day 2, day 3 or day 5 after oocytes retrieval using Wallace soft catheters under ultrasound guidance. Excess good quality embryos were cryopreserved on the day of ETs. Frozen ETs were performed in both hormone replacement cycles and natural cycles. The former involved 17β-estradiol with doses that increased progressively from two to six mg per day. The latter were performed on day 3 to day 4 after surge of serum LH. Luteal support consisted of daily take of 17β-estradiol (two to six mg) and intramuscular injection of progesterone (60 mg) for hormone replacement cycles or daily intramuscular injection of progesterone (60 mg) natural cycles).

A pregnancy test was performed 14 days after ET. If the test was positive, progesterone supplementation was continued for ten more weeks. The authors defined clinical pregnancies as those with visualization of fetal heartbeat on ultrasound at day 42 of gestation. The treatment outcome was presented as clinical pregnancies per oocyte retrieved and per ET. A spontaneous abortion was referred to pregnancy loss that occurred after visualization of the fetal heartbeat. The live birth event and the number of infants born were also assessed.

Statistical analysis comparing live births per oocyte in relation to the time of ET was performed using chi-square analysis using SPSS 15.0 software.

Results

Oocyte-to-baby rate

There were a total of 19,075 oocytes in the 1,360 oocyte retrieval cycles analyzed (Group 1: 4,860 oocytes, 535 cycles; Group 2: 2,768 oocytes, 212 cycles; Group 3: 8,091 oocytes, 613 cycles). The total number of usable embryos, i.e. good quality embryos suitable for fresh ET and cryopreservation, were 9,339 (50% of the total oocytes collected), of which 3,131 (33.5%) were used for fresh ET and 6,208 (66.5%) were cryopreserved.

Oocyte-to-baby rate and age of patients

The outcomes of the oocytes used (oocyte-to-baby rate) relative to the day of ET are presented in Tables 1-3. In patients with no spare embryos suitable for cryopreservation, and the live babies born (LBB) rate per oocyte collected did not differ significantly among the three ET groups for patients under the age of 35 years (Table 1). For patients older than 35 years, the ooctye usage rate was higher in the day 2 group than the other groups, while there was no statistical difference (Table 1).

In patients with frozen embryos available, for patients younger than 35 years, oocyte-to-baby rate was similar in groups with ET performed on day 2 and day 3 (4.05% *vs.* 3.9%; $p = 0.736$) (Table 2). The rate was significantly lower in the day 5 ET group when compared to the other two group ($p = 0.0018$). For patients aged 35 to 37 years, the oocyte-to-LBB rate was significantly higher in group 1 than in the other two groups (6.1% *vs.* 3.4% *vs.* 3.0%, $p = 0.033$). In the patients older than 37 groups, the oocyte-to-baby rate was not significantly different among these three ET groups ($p = 0.4$).

Outcomes of live baby rate and number of oocytes retrieved

In patient younger than 35 years, the oocyte-to-LBB rate was significantly higher in the day 3 group and lower in the day 5 group when the number of oocyte retrieved was less than ten. In patients between age 35-37 years and with less than 15 oocytes retrieved, the oocyte-to-baby rate in the day 2 group was higher than the other two groups, while there was no statistical difference (6.0% *vs.*1.0% *vs.* 2.9%, $p = 0.066$). It was found that the oocyte wastage was greater when more oocytes were retrieved in terms of live birth regardless of the time of ET in those two age subgroup. The time of ET had no effect on the oocyte-to-baby rate for patients older than 38 years (Table 3).

Table 3. — *Oocyte-to-bay rate in all patients according to the number of oocytes collected.*

		Number of ooctyes			Number of ET			LBB			LBB per oocyte (%)			*p* value
Age group	oocyte	Day 2	Day 3	Day 5	Day 2	Day 3	Day 5	Day 2	Day 3	Day 5	Day 2	Day 3	Day 5	
< 35	1-5	217	52	203	98	24	40	11	6	6	5.1	11.5	3.0	0.063
	6-10	1,190	445	839	290	107	170	60	40	49	5.0	9.0	5.8	0.011
	11-15	1,955	615	2,435	300	88	394	76	23	86	3.9	3.7	3.5	0.823
	16-20	1,325	924	2,251	174	76	260	45	23	51	3.4	2.5	2.3	0.119
	>20	997	1,194	919	54	85	108	15	24	26	1.5	2.0	2.8	0.125
35-37	1-5	122	19	123	61	9	11	5	1	2	4.1	5.2	1.6	0.431
	6-10	164	65	293	61	26	54	10	4	14	6.1	6.2	4.8	0.798
	11-15	135	114	368	29	31	67	8	1	11	6.0	1.0	2.9	0.066
	16-20	91	89	258	19	17	39	3	3	3	3.3	3.4	1.2	0.295
	>20	21	130	157	8	13	23	1	5	4	4.8	3.8	2.5	0.764
> 38	1-5	190	73	20	99	20	5	5	0	1	2.6	0	5	0.14
	6-10	262	99	77	82	20	14	5	0	1	1.9	0	1.3	0.198
	11-15	183	79	57	57	30	10	4	2	1	2.2	2.5	1.8	0.954
	16-20	0	118	66	0	9	9	0	2	0	0	1.7	0	0.747
	>20	46	130	25	2	31	7	1	2	0	2.2	1.5	0	0.644

ET: total number of embryos transferred; LBB: total number of live babies born.

Discussion

In this study, the authors evaluated the effect of time of ET on the oocyte-to-baby rate. The result showed that the majority of oocytes retrieved and the majority of ETs fail to produce live births, which is in agreement with previous study [1]. However, the oocyte-to-baby rate in young patient (< 35 years) was significantly higher in the day 3 group than the other groups, while in those between 35-37, years, the day 2 group was significantly higher than the other groups. These data indicates that despite the retrieval of an equivalent number of oocytes, it may better the oocyte-to-baby rate by changing the time of ET according to patients' age and number of oocytes retrieved. The following hypotheses may explain the relationship between time of ET and oocyte-to-baby rate.

First, in a natural cycle, only one antral follicle becomes dominant while the remainder of developing follicles undergo atresia. In contrast, during ovarian stimulation for ART these follicles are rescued, whose cytoplasm and nuclear is intrinsically abnormal [9, 10]. In vitro culture systems can affect the oocyte's development competence, especially for those oocytes from older patients. The present study found that reducing culture time in vitro in patients older than 35 years have higher oocyte-to-baby rate, which demonstrate that reducing culture time in vitro may have beneficial role in compensating for these effects. While for these younger than 35 years, extending the culture time in vitro shows the converse results, which indicated that the more reproductive competent oocytes may have the ability to endure the in vitro culture circumstance and these less competent oocytes undergo developmental retardation due to those in vitro effects. From this point, it is culture time in vitro that affects the live birth rate whether the cohorts are older or not.

Secondly, the present study showed that the oocyte-to-baby rate is low in all groups. During blastocyst culture, few embryos develop into blastocyst while most embryos undergo the fate of developmental retardation, which may be due to the impact of suboptimal laboratory conditions on both oocytes and embryos. These may have substantial effect on older patients. The present data show that a significantly low LBB rate on day 5 and majority of oocytes retrieved are wasted.

Identification of the best ET time can have many important clinical applications. Current oocyte quality parameters do not necessarily correlate with competence, in spite of more and more refined ways to assess oocyte's biological potential, however, none of these is perfect to select the best oocytes to inseminate. The present data show that ET time affect oocyte-to-baby rate. If these data are confirmed by others, it may be a better and simple choice in clinic to change ET time according to age and acquired oocytes, which may better oocyte wastage.

The long-held assumption that more oocytes are better is definitely contradicted by the studies of Patrizio *et al.* [1, 8]. The present data showed that the retrieval of 15 or fewer oocytes was associated with the highest oocyte-to-baby rate, which indicates that referring to oocyte-to-baby live rate, more oocytes may have a disadvantage. It is the time to better control ovarian stimulation protocol to acquire appropriate oocytes. Changing control ovarian stimulation protocols and ET time may have better oocyte-to-baby rate.

In summary, the authors retrospectively identified that whether transfer is performed on day 2, day 3 or day 5 does make a difference on the oocyte-to-baby rate. Moreover, these findings indicate that embryos can be safely scheduled according to patient's age and oocytes acquired.

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