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Research Article

Strongly Recommend Evaluation of Clinical Outcomes of IVF/ICSI with Cumulative Pregnancy Rate

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Abstract

Objective: In order to reduce the multiple pregnancy rates, we strongly recommend the use of cumulative pregnancy rate after one oocytes retrieval cycle and all the available embryos transferred to assess the clinical outcomes of IVF/ICSI.

Methods: We estimated cumulative pregnancy rate per oocyte retrieval among patients undergoing IVF/ICSI in 2011 at our center. Couples were followed until either discontinuation (no embryo to transfer) or pregnancy with visualization of gestational sac on ultrasound. Analyses were stratified according to maternal age.

Results: A total of 1907 oocyte retrievals yielded 19833 oocytes. Mean age (± SD) was 30.0 (± 4.1) years, mean number of transfer per oocyte pickup was 1.4 mean number of embryo transferred was 1.8. The cumulative pregnancy rate per oocyte retrieval was 68.7%, the multiple pregnancy rates were 24.5% and the miscarriage rate was 13.1%. While the same number of embryos transferred, no statistically significant difference was detected between fresh and the FET cycles with respect to pregnancy rate, implantation rate, multiple pregnancy rate and miscarriage rate. Among patients who were older than 35 years of age, the cumulative pregnancy rate was significant decreased (P<0.05) and the miscarriage rate was significant increased (<0.05).

Conclusion: During ART cycles, maternal age remain a factor that influence the cumulative pregnancy rate per oocyte retrieval, reducing the number of embryos transferred does not influence the success, while the multiple pregnancy rate was significant lower, this strategy yields a lower pregnancy in a fresh IVF cycle, but the difference is almost completely overcome by an additional frozen embryo transfer cycle.

Keywords: Cumulative live birth rate; IVF/ICSI; Number of embryo transferred; Single embryo transfer; Multiple pregnancy

Introduction

Since the first successful "test-tube baby" born in 1978, there are about 4 million people born by *in-vitro* fertilization (IVF) techniques globally. With the development of assistant reproductive techniques (ART), people start to put more consideration on the negative effects of IVF complications in both mother and the baby, while pursuing the pregnancy rate increasing. The most representative high-risk factors of ART should be the multiple pregnancy and ovary hyper-stimulation syndrome (OHSS). To decrease these complications, the concepts of single embryo transfer or reducing the number of embryo transferred are accepted gradually. Since 2004, the parameters, such as single and full-term pregnancy, live birth, healthy baby and comfortable pregnancy, have been used as the evaluation criteria of successful IVF in many developed country. However, most of the current studies still used the treatment cycle or transfer cycle as per to evaluate the pregnancy rate [1-4], this kind of measures not only misleading the physician take the pregnancy rate as the only one goal, but also bearing statistical limitations, because that does not show the difference of pregnancy rate in different patients with same stimulation protocol during various embryo transfer strategies. For each couple who will undertake IVF/ICSI treatment, it is more important to know the cumulative pregnancy rate per stimulation cycle than the pregnancy rate per single cycle. This paper is the retrospective analysis of cumulative pregnancy rate per oocyte-retrieval cycle in the Reproduction Center of the First Affiliated Hospital of Nanjing Medical University from Jan to Dec 2011.

Subjects and Methods

Subjects

From Jan 2011 to Dec 2011, of the patients who undertook their first IVF/ICSI cycle in the Reproduction Center of the First Affiliated Hospital of Nanjing Medical University, there were 1907 patients completed their treatment cycles up to date Dec 31, 2013. The definition of cycle completed is there is no embryo left for transfer or clinical pregnancy gained. The ages of patients were between 20 to 43 years old, and all received GnRH-a long or short protocol.

Methods

Protocol of ovarian stimulation

Fresh cycle: The routine IVF - ET ovarian hyper-stimulation regimen of our reproduction center was used, and the controlled ovarian hyper-stimulation protocol used was the GnRH-a long protocol or short protocol, and HCG 5000 to 10000 IU was intra-muscular injected when there were 3 to 4 leading follicles up to 16 mm in diameter; ultrasound guided oocytes retrieval was done 34 to 36 hours later for IVF/ICSI procedure and embryos transferred on the third day after fertilization.

Frozen-thaw embryo transfer: The frozen cleavage stage embryos or blastomere from the previous fresh cycle were used, and the natural cycle or hormone replacement cycle with endometrial preparation was chosen depending on the ovulation status of the patients. For the natural cycle, the patient should have regular menses, normal ovulation and the ultrasound monitoring of ovulation was started since the 11th day of menstruation. For the replacement cycle, the patient took estradiol valerate (Progynova, Schering, Germany) since the third day of menstruation, and the initial dosage of Progynova was selected from 2 to 4 mg / day depending on the previous endometrial status of the patients, the dosage was increased basing on the endometrial proliferation. When the thickness of endometrium was ≥ 8 mm by ultrasound monitoring, luteal support was given to make the endometrium developed into secretion phase. The cleavage stage

embryos were transferred on day 4 of luteal support, and day 6 if blastomere transferred. The medicines used continued. The luteal support was routinely used after the procedures. Blood β-HCG was tested on day 14 after embryo transfer, and clinical pregnancy confirmed by day 45 ultrasound showed gestation sac.

Statistical considerations

The relevant patient data were obtained from the CCRM database of the Reproduction Center of Nanjing University, including age, etiology of infertility, basal antral follicle count (AFC), number of oocytes retrieved, fertilization rate, clinical pregnancy profiles, and relevant statistical analyses were conducted. The SPSS19.0 software was used for statistical analysis. The data were expressed with mean (x) ± SD, the t-test was used for comparisons of means, and chi-square test was used for comparison of rates. The significant level was $P<0.05$.

Results

Of the patients who undertook their first cycle from Jan 2011 to Dec 2011, there were 1907 patients completed their treatment cycles up to date Dec 31, 2013, which including 752 fresh cycles of pregnancy, 417 cycles of none transferable embryo achieved by fresh cycle or pregnancy failure with none frozen embryos left after ET, 558 cycles of none transfer or pregnancy failure by fresh cycle but pregnancy gained by frozen transfer, and 180 cycles of pregnancy failure by fresh cycle and none frozen embryos left. The cumulative pregnancy rate per oocytes retrieval cycle was 68.7%, the twins rate was 24.5%, and the abortion rate was 13.1%. The mean number of ET procedure times was 1.4 per oocytes retrieval cycle and the mean number of embryo transferred per cycle was 1.8 (Table 1).

Number of patients with oocytes retrieval (cycles completed)	**1907**
Number of patients pregnant in fresh cycle	752
Number of patients none transferrable embryos achieved or none frozen embryo left after pregnancy failure	417
Number of patients pregnant underwent FET	558
Number of patients with pregnancy failure by FET and none frozen embryo left	180
Maternal Age, year	30.0 ± 4.1
Duration of infertility, year	4.5 ± 3.0
Basal FSH (U/L)	7.6 ± 3.7
Number of antral follicle	13.3 ± 5.4
Number of oocytes retrieved	10.4 ± 5.9
Cumulative pregnancy rate (per oocyte retrieval cycle)	68.7% (1310/1907)
Twins pregnancy rate	24.5% (322/1310)
Abortion rate	13.1% (171/1310)
Mean number of cycles of ET per oocyte retrieved	1.4
Mean number of embryos transferred per ET cycle	1.8

Table 1: The clinical outcomes of cycles with oocytes retrieval.

The relationship between age and cumulative pregnancy rate: The patients were divided into 5 groups basing on their ages, i.e. 20-25y, 26-30y, 31-35y, 36-40y and >40y.

The cumulative pregnancy rate was found decreased in trend with the increasing of age, and when the patient was older than 35, the cumulative pregnancy rate decreased significantly ($P<0.05$). When the patients was >40, the cumulative pregnancy rate was only 15.4%, while the abortion rate was as high as 50.0% (Table 2).

Age (year)	**20-25**	**26-30**	**31-35**	**36-40**	**>40**
Number of cycles with oocytes retrieval	265	831	611	187	13
Total number of cycles	380	1196	884	264	18
Number of cycles with pregnancy gained	185	601	411	111	2
Number of abortion cycles	24	65	57	25	1
Number of twins cycles	51	142	105	23	0
Number of ET embryos	695	2177	1591	442	25
Mean number of ET procedure times	1.4	1.4	1.4	1.4	1.4
Mean number of ET embryos	1.83	1.82	1.80	1.67	1.39
Cumulative pregnancy rate	69.8%	72.3%	67.3%	59.4%*	15.4%*
Twins pregnancy rate	27.6%	23.6%	25.5%	20.7%	0%
Abortion rate	13.0%	10.8%	13.9%	22.5%*	50%*

Table 2: The relationship between age and cumulative pregnancy rate
*Comparing with patients who age ≤ 35y, $P<0.05$.

Comparisons of number of transfer and pregnancy outcomes: Since 2009, we changed embryo transfer strategy in our reproduction center, to reduce the number of embryos transferred and the cycles with 3 embryos transferred were decreased a lot.

Basing on the 2011 whole year data, the cycles with 3 embryos transferred only accounted for 0.16% (6/3861), the cycles with 2 embryos transferred accounted for 78.8% (3043/3861), and 1 embryo transfer accounted for 21.0% (812/3861).

When the number of embryos transferred was the same, the pregnancy rate, implantation rate, twins pregnancy rate and abortion rate were not significantly different between fresh cycles and frozen cycles ($P>0.05$).

When comparing the pregnancy rate between 2 vs. 1 embryo(s) transfer, it was significantly higher for the former both in fresh and frozen cycles ($P<0.05$), and the twins pregnancy rate was also significantly increased ($P<0.05$) (Table 3).

Discussion

There are various methods used for pregnancy rate of IVF/ICSI calculation. Currently common used measures for IVF successful rate evaluation in China and in the world is the pregnancy rate of single

stimulation cycle or embryo transfer cycle, though obvious limitation did exist due to it is a horizontal indicator. While during the IVF treatment, many patients need multiple cycles for successful pregnancy. The use of cumulative pregnancy rate may evaluate the IVF treatment outcome in a longitudinal way, and make the individualized analysis possible. In the reports on cumulative pregnancy rate, some studies cumulated all the cycles with oocytes retrieval and embryo transfer [5-7] or calculated with the methods of statistics [8], and other studies exclude the frozen cycles when calculating cumulative pregnancy rate [9-12].

	1 embryo transferred		2 embryos transferred		3 embryos transferred	
	Fresh cycle	FET cycle	Fresh cycle	FET cycle	Fresh cycle	FET cycle
Total number of cycles	254	558	1525	1518	2	4
Pregnancy rate	27.6%	31.2%	44.7%*	43.5%*	0	50.0%
Implantation rate	27.6%	31.2%	28.4%	27.2%	0	33.3%
Abortion rate	12.9%	17.2%	14.2%	15.0%	0	0
Twins pregnancy rate	0	0	29.0%*	26.6%*	0	50.0%

Table 3: Comparisons of pregnancy outcomes among different number of embryos transferred *Comparing with 1 embryo transferred, P<0.05.

However, these methods of calculation on cumulative pregnancy rate may cause deviation, and we use the oocytes retrieval cycle to analyze the cumulative pregnancy rate after one oocytes retrieval cycle and all the available embryos transferred.

By summarizing the 1907 oocytes retrieval cycles, we found that the cumulative pregnancy rate per oocytes retrieval cycle was still up to 68.7% with twins pregnancy rate at 24.5%, even reduced the number of embryos transferred (mean number of embryos transferred was 1.8). By analyzing the sub-group patients of different age, we found that the age is an important factor influencing the cumulative pregnancy rate. The cumulative pregnancy rate decreased with the increasing of age, while the abortion rate increased. When the age of patients above 35y, their cumulative pregnancy rate was significantly lower than younger patients (P<0.05), and abortion rate significantly increased (P<0.05). It was postulated that this might due to the regressive ovary function, decreased oocytes quality, lower quality of embryos, which caused clinical pregnancy rate decreasing and natural abortion rate increasing.

Our study showed that there are relationship between multiple pregnancy and number of embryos transferred, the clinical pregnancy rate and multiple pregnancy rate of IVF-ET were increased with the increasing of the number of embryos transferred, which was consistent with literature reports [13-15]. The various complications of multiple pregnancies severely deteriorate the health of mother and baby, such as abortion, preeclampsia, intra-uterus fetus asphyxia, premature delivery etc. [16]. Study reported that the perinatal mortality in twins' pregnancy was at least 4 times increased and 6 times increased comparing with that in single pregnancy [17]. The risk of premature delivery was increased 7 to 40 times and the risk of low-born-weight and the risk of were increased 10 to 75 times in multiple pregnancies, and the risk of fetal anomaly in twins' pregnancy was increased 50% [18]. Meanwhile, this study also demonstrated the relevance between IVF and low-born-weight [19]. Therefore, multiple pregnancies are one of the challenges in the ART area, and it must be solved. With the gradual development and mature of the ART techniques, the goals and concepts of IVF-ET treatment are changed, i.e. multiple pregnancy should be avoided and minimized with the high pregnancy rate maintained.

The good frozen cycle pregnancy rate is the safeguard for number of embryos transfer reduction. When the number of embryos transferred was the same these were no significant difference between fresh and frozen cycles. Therefore, when the number of embryos transferred reduced during fresh cycle, it will mean more frozen embryos available for further transfer. This is not only good for a reasonable pregnancy rate in fresh cycle, but also is helpful for a considerable high cumulative pregnancy rate, and effectively reduce the multiple pregnancy rate. This increase the chance of embryo growth on a natural endometrial environment, avoid the implantation of embryo on the super-stimulated secretion endometrium. So, from the point of view of fetus health care, it is beneficial for both mother and baby.

Studies showed that the principle of embryo transfer should be ideally balanced between pregnancy rate and multiple pregnancy rates by considering maternal age, quality of embryos and availability of high-quality embryos left for further transfer. By optimizing the cultivation condition, selection of high-quality embryos and control of number of embryo transferred per cycle, the optimal cumulative pregnancy rate will be achieved and multiple pregnancy and unnecessary fetus lost will be also avoided [20]. In this study, the cumulative pregnancy rate was relatively high, though twins pregnancy rate was also rather high, which suggested that there is still a large space for us to reduce the number of embryo transferred, and optimization of embryo transfer strategy is a must.

Above all, the cumulative pregnancy rate per oocytes retrieval cycle is one of the important measures to evaluate the efficacy of IVF treatment. When the number of embryo transferred reduced, the cumulative pregnancy rate did not changed though the pregnancy rate of fresh cycle did decreased, and the multiple pregnancy rates was significantly decreased, which is beneficial for perinatal complications reduction in both mother and baby.

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