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Factors contributing to good oocyte competence and utility rates for *in vitro* fertilization or intracytoplasmic sperm injection in high responders

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To the Editor: The oocyte utility rate (OUR) describes the competence of oocytes to develop into usable embryos that can be transferred or cryopreserved. Except for maternal age, abnormalities due to intra-ovarian and/or extra-ovarian factors may affect the oocyte-granulosa cell interaction, maturation, and zygote development. In this study, we defined OUR as the number of applicable embryos (blastomere and blastocyst) divided by the number of oocytes retrieved from the corresponding stimulation cycle. We compared high and low OUR of cycles with at least 15 oocytes to determine the factors contributing to the huge gap between good and poor OUR to guide promising *in vitro* fertilization (IVF) outcomes.

The study was approved by the Ethics Committee of Peking Union Medical College Hospital (No. S-K1063), and the written consent forms were signed by the involved patients. This study analyzed IVF/intracytoplasmic sperm injection (ICSI) cycles performed at Peking Union Medical College Hospital between January 1, 2013 to December 31, 2019. Cycles harvesting of at least 15 oocytes were chosen and no fresh transfer was performed due to the consideration of ovarian hyperstimulation syndrome (OHSS). Each cycle was assessed using the OUR. After ranking all cases according to the OUR, we considered the highest 10% of cycles as group A and the lowest 10% of cycles as group B.

The ovarian stimulation protocol included the gonadotropin-releasing hormone (GnRH) agonist long protocol, GnRH antagonist protocol, and dual suppression protocol. The recombined follicle-stimulating hormone (rFSH) commencement dosage was determined based on the patient's age, body mass index (BMI), and ovarian reserve test results. Oocyte maturation was triggered by human chorionic gonadotropin (hCG). Oocytes were collected 36 h later. Embryo development was evaluated on day 3 and day 5 or day 6. On day 3, two fresh embryos with top grades were vitrified,[1] whereas the remaining embryos were cultured to blastocysts and then cryopreserved.

Finally, 453 patients were recruited. Group A and B included 43 and 47 patients, respectively. There were no differences in age, BMI, infertility duration, and basal hormone levels between the two groups [Table 1]. A higher proportion of group B have ovulatory disorders or endometriosis; 34% of their cycles were fertilized by ICSI in group B and only 14% in group A.

We noticed that a higher proportion of patients in group B had experienced decreased E_2 over the course of treatment. Furthermore, 44.7% of cycles in group B were suspended with rFSH during the stimulation before the trigger day. There were nearly equal numbers of retrieved oocytes and metaphase II oocytes. However, oocytes from the two groups demonstrated significant development potential. On day 3, 15.8% of embryos had good quality in group A; however, in group B, only 3.7% of embryos had good quality. Group A had more eight-cell blastomeres than group B. Although both groups had similar numbers of embryos for the blastocyst culture, group B had a much smaller formation rate (78.1% *vs*. 7.9%). Group A had an average of 14 embryos for cryopreservation; however, the average was only 2 in group B. Regarding frozen-thawed cycles, group A had a cumulative clinical pregnancy rate of 95.3% and a cumulative live birth rate of 90.7%; however, these two numbers were significantly lower in group B (31.9% and 40.4%, respectively).

Then we applied logistic regression to adjust each factor listed in Table 1 and selected beneficial or detrimental elements to OUR. Previously attempted IVF/ICSI (odds ratio (OR): 0.10, 95% confidence interval (CI): 0.01–0.81), infertility due to endometriosis (OR: 0.16, 95% CI:

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Table 1: Clinical characteristics of the included patients performed IVF/ICSI.

Characteristics	Group A ($n = 43$)	Group B ($n = 47$)	*P* value
Age (yr)	33.09 ± 2.61	32.37 ± 4.17	0.327
BMI (kg/m^2)	21.61 ± 2.31	21.74 ± 2.54	0.811
Infertility duration (yr)	3 (2, 5)	4 (3, 5)	0.155
Primary infertility	72.1 (31/43)	74.5 (35/47)	0.799
Infertility factors			0.033
Tubal	34.9 (15/43)	17.0 (8/47)	
Ovulatory obstacle	23.3 (10/43)	34.0 (16/47)	
Endometriosis	18.6 (8/43)	23.4 (11/47)	
Male	23.3 (10/43)	25.5 (12/47)	
History of any previous IVF/ICSI	14.0 (6/43)	34.0 (16/47)	0.027
Rate of ICSI	20.9 (9/43)	40.4 (19/47)	0.046
Protocols for ovarian stimulation			0.013
GnRH agonist long	20.9 (9/43)	31.9 (15/47)	
GnRH antagonist	23.3 (10/43)	42.6 (20/47)	
Dual suppression	55.8 (24/43)	25.5 (12/47)	
Basal hormone profiles			
FSH (IU/L)	6.03 (4.95, 6.99)	6.00 (5.08, 6.84)	0.843
LH (IU/L)	5.04 (2.72, 6.49)	4.44 (2.92, 5.71)	0.455
E_2 (pg/mL)	38.27 (26.58, 50.37)	43.78 (33.25, 54.54)	0.114
Hormone profiles on hCG day			
FSH (IU/L)	8.73 (6.24, 11.0)	10.57 (7.71, 13.48)	0.401
LH (IU/L)	1.76 (1.35, 2.21)	1.59 (1.21, 2.04)	0.209
E_2 (pg/mL)	6715 (5136, 8222)	6000 (5143, 7436)	0.294
P (ng/mL)	0.92 (0.69, 1.42)	1.1 (0.82, 1.59)	0.119
Gonadotropin consumption (ampul[*])			
rFSH starting dose	3 (2, 4)	3 (2.5, 4)	0.456
Total rFSH	20.5 (12, 27)	20 (15, 28)	0.389
Total HMG	3.5 (2.5, 5)	3 (2.5, 6)	0.990
Total rLH	3 (2, 4)	2 (2, 3)	0.289
Days for ovarian stimulation	11 (10, 11)	10 (9, 11)	0.260
E_2 decline during stimulation	30.2 (13/43)	42.6 (20/47)	0.038
Any suspension of rFSH except on the hCG day	23.3 (10/43)	44.7 (21/47)	0.033
No gonadotropins applied on hCG day	79.1 (34/43)	78.7 (37/47)	0.968
Laboratory results overview			
Oocytes retrieved	18 (16, 20)	20 (18, 22)	0.086
MII oocytes	18 (16, 20)	18 (15, 20)	0.803
Fertility rate	95.2 (689/776)	83.1 (726/874)	<0.001
Cleavage rate	100 (739/739)	96.0 (697/726)	<0.001
Embryo on day 3			
Good-quality embryos	3 (1, 4)	0 (0, 1)	<0.001
Rate of good-quality embryos	15.8 (117/739)	3.7 (26/697)	<0.001
Eight-cell embryos	12 (9, 14)	3 (1, 5)	<0.001
Six-cell embryos	2 (0, 5)	4 (3, 6)	0.019
Blastocyst			
Embryos for blastocyst culture	15 (13, 18)	14 (12, 18)	0.346
Numbers of blastocysts	12 (10, 13)	1 (0, 2)	<0.001
Blastocyst formation rate	78.1 (509/652)	7.9 (52/656)	<0.001
Numbers of 4BB+ embryos	6 (6, 9)	0 (0, 1)	<0.001
4BB+[#] embryo formation rate	46.5 (303/652)	3.4 (22/656)	<0.001
Assisted reproductive outcomes			
Embryos cryopreserved (total)	14 (12, 14)	2 (2, 3)	<0.001
OUR	77.4 (601/776)	11.9 (104/874)	<0.001
CCPR	95.3 (41/43)	40.4 (19/47)	<0.001
CLBR	90.7 (39/43)	31.9 (15/47)	<0.001

Data are presented as % (*n*/N), mean ± standard deviation or median (range). BMI: Body mass index; CCPR: Cumulative clinical pregnancy rate; CLBR: Cumulative live birth rate; IVF: *In vitro* fertilization; ICSI: Intracytoplasmic sperm injection; GnRH: Gonadotropin-releasing hormone; rFSH: Recombined follicle-stimulating hormone; rLH: Recombinant luteinizing hormone; HMG: Human menopausal gonadotropin; hCG: Human chorionic gonadotropin; MII: Metaphase 2; OUR: Oocyte utility rate. [*]Each ampul equals 75 U of gonadotropin. [#]4BB+ embryos refer to blastocysts classified as stage 4–6 and BB, AB, BA, or AA according to the Gardner system.

0.03–0.84), and decreased E_2 during the stimulation process (OR: 0.16, 95% CI: 0.04–0.64) were responsible for poorer OUR. On the contrary, longer ovarian stimulation durations (OR: 3.24, 95% CI: 1.25–8.42) led to better OUR. Compared to GnRH agonist long protocol, GnRH antagonist (OR: 1.39, 95% CI: 1.09–10.04) and dual suppression protocol (OR: 3.74, 95%CI: 1.06–26.86) contributed to promising OUR.

A high OUR is always expected by both physicians and patients. We noticed that previously attempted IVF/ICSI cycles were related to decreases in OUR. This could be attributed to previous improper luteal phase support or stimulation protocol. We also observed that the OUR was threatened when E_2 decreased during the stimulation course. Additionally, this phenomenon was accompanied by the suspension of rFSH in the single factorial analysis. Similarly, a study that compared a reduction in rFSH and coasting concluded that the live birth rate remained the same, independent of the decrease in E_2.[2] In another model, adding the GnRH antagonist induced a decrease in E_2, which is commonly observed in clinical scenarios; the pregnancy rate did not vary according to decreases, plateaus, or increases in E_2, but this study included normal and poor responders.[3] It should be emphasized that although it demonstrated contrary results, our study involved high responders who might have different oogenesis characteristics. Moreover, we allocated subjects to groups according to the OUR, whereas other studies separated patients based on the onset of E_2 decline or withdrawal of rFSH.

The multifactorial analysis indicated that endometriosis was harmful to the OUR. In addition to the compromised number of oocytes, an impairment of oocyte competence has been demonstrated; several studies indicated that fertilization rates were lower with endometriosis than with tubal factor infertility.[4] Morphologically, oocytes from patients with endometriosis exhibit the loss of cortical granules and hardening of the zona pellucida, thus interfering with fertilization.[5] Although it does not have lethal effects on oocytes, physicians should remind patients of its complex threats to OUR.

For high responders, dual suppression and one cycle of oral contraceptives before the long conventional agonist protocol can lead to good OUR. Particularly for high responders with polycystic ovary syndrome, a cycle of contraceptives can induce a decrease in the luteinizing hormone/follicle-stimulating hormone ratio and serum dehydroepiandrosterone sulfate.[6] A non-randomized study also indicated that dual suppression does not disturb endometrial thickness or oocyte quality and number, but that it does dramatically prevent OHSS onset.[7] For endometriosis-associated infertility, pre-treatment with contraceptive pills is both cost-effective and non-inferior compared to long-term pituitary desensitization involved in the ultra-long protocol with a continuous GnRH agonist.[8]

Despite its retrospective nature and limited number, this study can guide future management of low OUR cases, especially for high responders. Patients with a history of IVF/ICSI and endometriosis should be considered at risk for unsatisfactory OUR. During ovarian stimulation, physicians should avoid suspending rFSH before the trigger day and prevent decreased E_2. For high responders, dual suppression and GnRH antagonist can serve as an acceptable protocol, if possible.

Conflicts of interest

None.

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