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Egg Quality and Pregnancy Outcome in Young Infertile Women with Diminished Ovarian Reserve

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Background: This study investigated the quality and quantity of eggs and embryos as well as the clinical pregnancy outcome in young infertile women with diminished ovarian reserve (DOR) after *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI).

Material/Methods: We retrospectively reviewed records of 4285 infertile women and divided them into 3 groups according to age and ovarian reserve: young women with normal ovarian reserve (n=1695), young women with DOR (n=1121), and older women with DOR (n=1469).

Results: In young women with DOR, the proportion of high-quality embryos was significantly higher than in older women with DOR and lower than in young women with normal ovarian reserve ($P<0.01$). The proportions of ovulation cancellation, ovulation without egg acquisition, and ovulation without available embryos in young women with DOR were significantly higher than in young women with normal ovarian reserve. The rates of biochemical pregnancy, clinical pregnancy, and embryo implantation in young women with DOR were significantly higher than in older women with DOR, and lower than in young women with normal ovarian reserve. The miscarriage rate was 19.17% in young women with DOR, significantly lower than in older women with DOR (33.90%), and higher than in young women with normal ovarian reserve.

Conclusions: Young women with DOR have ovarian hypo-response and low numbers of acquired eggs and embryos, but the possibilities of high-quality embryo and good clinical pregnancy are higher once eggs are acquired. The indications to IVF/ICSI can be widened and active treatments should be administered for these women.

MeSH Keywords: Fertilization *in Vitro* • Sperm Injections, Intracytoplasmic • Young Adult

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Background

Diminished ovarian reserve (DOR) refers to the reduced number and quality of remaining oocytes in the ovary [1]. The incidence of DOR ranges from 6% to 64% in infertile women of different ages [2]. Not only reduced number and quality of remaining oocytes are observed in these patients, but also ovarian hyporesponse, high ovulation cancellation rate, increased use of ovulation stimulants, reduced number of acquired eggs, decreased clinical pregnancy and live birth, and high miscarriage rate can be present in these women after treatment with assisted reproductive technology (ART) [3,4]. Repeat failures after ovulation, ovulation cancellation, unavailability of embryos, and failure of implantation significantly increase the physiological and psychological burdens in DOR patients, especially the young women with DOR.

Generally, ovarian reserve is evaluated according to age, baseline follicle-stimulating hormone (FSH) level, baseline antral follicle count (AFC), and baseline anti-Mullerian hormone (AMH) level [5]. Age is an important factor affecting the quality of eggs and the ovarian reserve [6]. Little is known about differences in the quality of eggs, pregnancy outcome, and clinical outcome between young women with DOR and older women with DOR. In this study, we retrospectively reviewed women of different ages and with different ovarian reserves and investigated the ovarian response and pregnancy outcome of DOR women receiving treatment with ART. Our results may provide evidence for the management of DOR in young patients.

Material and Methods

Subjects

We retrospectively reviewed medical records of infertile women who received *in vitro* fertilization/intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET) in the Reproductive Medicine Research Center of the Affiliated Sixth Hospital of Sun Yat-sen University between January 2017 and December 2017. These women were divided into 3 groups according to age and ovarian reserve [7]: (1) young women with normal ovarian reserve: women were younger than 37 years, the menstrual cycle was normal; the baseline hormones were in normal ranges (bFSH <10 IU/L, bE2 <50 pg/ml), AMH was ≥1.1 ng/ml, AFC was ≥6; (2) young women with DOR: women were younger than 37 years, the menstrual cycle was normal, bFSH was ≥10 IU/L, AMH was <1.1 ng/ml, AFC was <6; and (3) older women with DOR: women were no younger than 37 years, the menstrual cycle was normal, bFSH was ≥10 IU/L, AMH was <1.1 ng/ml, and AFC was <6. Exclusion criteria were: 1) Polycystic ovary syndrome (PCOS) patients; 2) patients with endometriosis at stage II or higher stage or adenomyosis; 3) patients had other endocrine diseases such as hyperprolactinemia and thyroid diseases; 4) patients had immune diseases; 5) patients had a history of repeated implantation failure; and 6) patients had diseases (such as intrauterine adhesion and endometrial polyp) that affected embryo implantation. A total of 4285 women were retrospectively reviewed, including 1695 young women with normal ovarian reserve, 1121 young women with DOR, and 1469 older women with DOR. The age, body mass index (BMI), duration and type of infertility, baseline FSH, and AMH are shown in Table 1.

Protocol for controlled ovarian hyperstimulation (COH)

The protocol for COH was determined individually according to age, BMI, baseline sexual hormones, AMH, and AFC. For women with normal ovarian reserve, a long protocol was used, and ovarian hyperstimulation syndrome was prevented with appropriate antagonists for those with BMI <18 and AFC ≥15. For women with DOR, the mild ovulation protocol was used if AFC was ≤3 at the second day of menstrual cycle as shown by ultrasonography or protocol with antagonists was used if AFC was >3. The initial dose was determined individually according to age, BMI, and AMH. A long down-regulation protocol was administered in the midluteal phase (MLP) of the prior menstrual cycle before ovulation; 14 days later, ultrasonography was done and sexual hormone levels were determined; Gonadotropins (Gn, rFSH; Serrano, Switzerland) were intramuscularly injected after down-regulation succeeded. For the protocol with antagonists, Gn was intramuscularly injected starting on the second day of the menstrual cycle, and the dose of Gn was adjusted according to the follicle size as determined by transvaginal ultrasonography and the sexual hormone levels. GnRH-ant (Serrano, Switzerland) was administered until the date of HCG. For the mild ovulation protocol, Clomiphene/Letrozole was orally administered starting on the second day of menstrual cycle for 4–5 days, and Gn was injected according to the follicular development thereafter; if necessary, GnRH-ant (Serrano, Switzerland) was used for the prevention of early ovulation until the date of HCG. When 2–3 follicles were 16–18 mm in diameter, hHCG at 4000–10000 U was intramuscularly injected, and transvaginal ultrasonography was performed 34–38 h later for ultrasound-guided egg collection. Eggs larger than 10 mm were collected for further routine IVF or ICSI.

Embryo culture, observation, and transplantation

IVF/ICSI was used according to the semen condition of the male. The fertilization was observed at 16–20 h after egg collection, and embryo cleavage was observed 72 h later. According to the international morphological grading system [5], the embryos were divided into 4 grades. In grade I, blastomeres were even in appearance, their cytoplasm was transparent and even, and

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Table 1. General characteristics of women in three groups.

	Young women with normal ovarian reserve (n=1695)	Young women with DOR (n=1121)	Old women with DOR (n=1469)	*P*
Age (yr)	31.20±6.24	32.59±4.73	41.02±3.61	0.73
BMI (kg/m^2)	22.17±1.56	21.90±2.11	22.33±1.92	0.16
Duration of infertility (yr)	3.84±1.56	4.22±2.41	4.86±2.16	0.43
AFC (n)	12.72±3.50	4.82±1.31	4.61±1.22	<0.001
bFSH (U/L)	8.12±2.24	11.54±1.22	11.82±1.61	<0.001
AMH (ng/ml)	3.59±1.22	0.64±0.26	0.55±0.39	<0.001
Cause of infertility (n/%)				
Oviductal factor	797 (47.02)	516 (46.03)	733 (49.90)	0.22
Endometriosis	227 (13.39)	139 (12.40)	168 (11.44)	0.26
Ovulation disorder	176 (10.38)	119 (10.62)	139 (9.46)	0.44
Male factor	104 (6.14)	83 (7.40)	101 (6.88)	0.51
Male & female factor	219 (12.92)	145 (12.93)	194 (13.21)	0.39
Unknown factor	172 (10.15)	119 (10.62)	136 (9.26)	0.60

there was no debris. In grade II, blastomeres were even in appearance and the proportion of cytoplasmic debris was <20%. In grade III, blastomeres were not irregular and the proportion of cytoplasmic debris was 20–50%. In grade IV, blastomeres were not irregular and the proportion of cytoplasmic debris was >50%. Grade I–II embryos were regarded as high-quality, and grade I–III embryos could be used for transplantation. Two embryos were transplanted at 3 days after egg collection and the remaining embryos were processed for blastocyst culture and cryopreservation.

Luteal phase support protocol and pregnancy outcome

In the luteal phase support protocol, progesterone at 40 mg/d was intramuscularly injected once daily and a progesterone soft capsule (Utrogestan) at 200 mg/d was placed in the vagina. The pregnancy outcome was evaluated during follow-up. Biochemical pregnancy was defined as blood β-HCG of ≥25 U/L at 12 days after transplantation, and clinical pregnancy was defined as the presence of fetal sac and fetal heart under ultrasound at 4 weeks after transplantation. Implantation rate was defined as the ratio of fetal sac number to transplanted embryo number under ultrasound.

Observations and data collection

The number of acquired eggs, number of normal fertilized eggs, number of high-quality embryos, number of ovulation cancellations, number of ovulations without egg acquisition, number of ovulations without available embryos, biochemical pregnancy rate, clinical pregnancy rate, miscarriage rate, and ectopic pregnancy rate were determined. 2PN fertilization rate=2PN fertilized eggs/acquired eggs ×100%; high-quality embryo rate=grade I/II 2PN embryos/2PN eggs cleaved ×100%; implantation rate=embryos implanted/embryos transplanted ×100%; clinical pregnancy rate=number of clinical pregnancy/number of transplantation ×100%.

Statistical analysis

Statistical analysis was done with SPSS version 13.0. Quantitative data with normal distribution are expressed as mean ± standard deviation ($\bar{\chi}$±S) and compared with *t* test, while data with abnormal distribution are presented as medians (P25, P75) and were compared with the Kruskal-Wallis test. Qualitative data are expressed as rates and were compared using the chi-square test. A value of P<0.05 was considered statistically significant.

Results

General characteristics of women in different groups

There were 4285 women included in this study: 1695 young women with normal ovarian reserve, 1121 young women with

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Table 2. Outcomes after IVF/ICSI in three groups.

	Young women with normal ovarian reserve (n=1695)		Young women with DOR (n=1121)		Old women with DOR (n=1469)		*P*
Number of eggs acquired	11.82±3.14		3.41±1.33		3.16±1.42		<0.001
Type of fertilization							
IVF	1223	(72.15%)	793	(70.74%)	1024	(69.71%)	0.44
ICSI	472	(27.84%)	328	(29.26%)	449	(30.57%)	0.57
Rate of normal fertilization	78.86%	(15800/20035)	68.81%	(2630/3822)	40.10%	(1861/4642)	0.01
Rate of cleavage	98.98%	(15639/15800)	93.92%	(2470/2630)	82.32%	(1532/1861)	<0.001
Rate of high quality embryos	56.0%	(8848/15800)	40.99%	(1078/2630)	29.93%	(557/1861)	<0.001
Rate of ovulation cancellation	3.13%	(53/1695)	9.72%	(109/1121)	10.07%	(148/1469)	<0.001
Rate of ovulation without egg acquisition	0.71%	(12/1695)	7.40%	(83/1121)	10.48%	(154/1469)	<0.001
Rate of ovulation without available embryos	6.02%	(105/1695)	22.21%	(249/1121)	29.88%	(439/1469)	<0.001

DOR, and 1469 older women with DOR. There were no marked differences in the age, BMI, and duration and type of infertility among the 3 groups. The AFC was 4.82±1.31 in young women with DOR, which was comparable to that in older women with DOR, but significantly lower than that in young women with normal ovarian reserve. The baseline FSH in women with DOR was significantly higher than that in women with normal ovarian reserve (p<0.01), but AMH in women with DOR was markedly lower than that in young women with normal ovarian reserve (p<0.01) (Table 1).

Outcomes after IVF/ICSI in 3 groups

The number of eggs acquired in women with DOR was significantly smaller than that in women with normal ovarian reserve (3.41±1.33 and 3.16±1.42 *vs.* 11.82±3.14; p<0.01). There was no marked difference in the type of fertilization. The rate of normal fertilization was 68.81% in young women with DOR, which was significantly higher than in older women with DOR, but still markedly lower than in young women with normal ovarian reserve (p=0.01). The cleavage rate in young women with DOR was comparable to that in young women with normal ovarian reserve, but higher than in older women with DOR. The rate of high-quality embryos in young women with DOR was 40.99%, which was significantly lower than in young women with normal ovarian reserve (56.02%; p<0.01), but markedly higher than in older women with DOR (29.93%; p<0.01). The rate of ovulation cancellation, rate of ovulation without egg acquisition, and rate of ovulation without available embryos in young women with DOR were similar to those in older women with DOR, but markedly higher than in young women with normal ovarian reserve (p<0.01) (Table 2).

Clinical outcomes in 3 groups

In the 305 young women with DOR, transplantation of fresh embryos was performed, biochemical pregnancy was found in 143 women (46.89%), clinical pregnancy was observed in 120 women (39.34%), and the rate of embryo implantation was 25.19%, which were significantly higher than those in older women with DOR (29.39% biochemical pregnancy, 21.15% clinical pregnancy, and 18.47% embryo implantation) (p <0.01), but markedly lower than in young women with normal ovarian reserve (60.41% biochemical pregnancy, 55.67% clinical pregnancy, and 46.94% embryo implantation) (p <0.01). In young women with DOR, the miscarriage rate was 19.17%, which was significantly lower than in older women with DOR (33.90%; p<0.01), but markedly higher than in young women with normal ovarian reserve (8.93%; p<0.01). There was no significant difference in the ectopic pregnancy rate among the 3 groups (p=0.72) (Table 3).

Discussion

The ovarian reserve refers to the number and quality of follicles in the ovary and reflects the potential of follicles to develop into high-quality oocytes, as well as indicating the women's reproductive potential. DOR refers to a reduced number and quality of follicles in the ovary and the potential of follicles to develop into high-quality oocytes is compromised, causing infertility. In ovulation treatment, DOR patients usually have ovarian hyporesponse and a small number of eggs acquired, and they often develop premature ovarian failure (POF). Especially, young women with DOR have poor reproductive condition and strong pregnancy expectation, which significantly increases their physiological and psychological burden. Clinicians should pay more attention to the prognosis of DOR patients after treatment.

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Table 3. Clinical outcomes of women in three groups.

	Young women with normal ovarian reserve (n=1695)	Young women with DOR (n=1121)	Old women with DOR (n=1469)	*P*
Number of transplantation	821	305	279	<0.001
Rate of biochemical pregnancy	60.41% (496/821)	46.89% (143/305)	29.39% (82/279)	<0.001
Rate of clinical pregnancy	55.67% (457/821)	39.34% (120/305)	21.15% (59/279)	<0.001
Rate of embryo implantation	46.94% (536/1142)	25.19% (102/405)	18.47% (70/379)	<0.001
Early miscarriage rate	8.93% (41/457)	19.17% (23/120)	33.90% (20/59)	<0.001
Ectopic pregnancy rate	1.53% (7/457)	2.50% (3/120)	1.69% (1/59)	0.72

In this study with large sample size, women with and without DOR were investigated. Results showed DOR predicted the compromised response to Gn-induced ovulation, and the rate of MII eggs, rate of normal fertilization, and rate of high-quality embryos and clinical pregnancy in young women with DOR were superior to those in older women with DOR, but still poorer than in young women with normal ovarian reserve.

Currently, age, baseline FSH (bFSH), AMH, and inhibin-B are widely used to clinically predict the ovarian reserve [8]. Although a variety of studies have shown that the ovarian reserve reduces linearly in women older than 37 years [9], the size of the follicular pool, rate of follicle atresia, genetics, environment, and history of ovarian surgery can affect the ovarian reserve. Thus, in clinical practice, the ovary reproductive age is inconsistent with the actual age of the woman, and in a majority of women, DOR is a major cause of infertility [10]. Although bFSH is often employed for the evaluation of ovarian reserve, it varies significantly in different menstrual cycles; an increase in FSH alone only indicates a low rate of egg acquisition and cannot predict the pregnancy rate [11]. AMH is a glycoprotein secreted by the granular cells in the preantral follicles and antral follicles and can reflect the reserve of the original follicular pool [12]. Thus, AMH is widely used in the prediction of clinical pregnancy outcome and the ovarian response to Gn after ART. Low AMH level usually predicts a poor ovarian response [13], but the kits used for the AMH detections vary among hospitals and thus the reported thresholds vary among studies. Inhibin-B fluctuates significantly in the menstrual cycle and thus is not recommended for the assessment of ovarian reserve [14]. Currently, there is no consensus on the concept of DOR. In the present study, bFSH ≥10 IU/L, AMH <1.1 ng/ml and AFC <6 were used to define DOR. Our results showed there were no marked differences in the bFSH, AMH, and number of eggs acquired between young women with DOR and older women with DOR, but the AMH and number of eggs acquired in young women with DOR were significantly lower than in young women with normal ovarian reserve, which contributed to the reduced numbers of total embryos and high-quality embryos, rate of ovulation cancellation, rate of failed egg acquisition, and rate of ovulation without available embryos. These indicate that DOR predicts a poor ovarian response.

Egg quality is clinically assessed according to the egg morphological score, fertilization condition, and number of high-quality embryos, together with pregnancy rate, rate of embryo implantation, and miscarriage rate. Our results showed higher rates of normal fertilization, cleavage, high-quality embryos, embryo implantation, and pregnancy in young women with DOR, but the miscarriage rate was lower than in older women with DOR. These results indicate that young women with DOR have reduced ovarian response to Gn, which contributed to the reduced numbers of egg acquired and total embryos but had little influence on the quality of eggs and embryos. Once the eggs are acquired, the possibility of these eggs to form transplantable embryos and high-quality embryos in young women with DOR was higher than in older women with DOR, predicting a good clinical outcome. This was consistent with result reported by Lauren et al. in a recent study [15]. As compared to young women with normal ovarian reserve, the rates of high-quality embryos, pregnancy, and embryo implantation were lower and the miscarriage rate was higher in young women with DOR, although there were no marked differences in the rates of normal fertilization and cleavage. Thum et al. investigated the chromosomal karyotype before transplantation by embryo genetic assay, showing the incidence of karyotype abnormality in DOR women younger than 35 years did not increase, and thus they speculated that DOR could not cause chromosomal karyotype abnormality in embryos [16]. We postulate that this might be related to the causes of DOR, which include X chromosomal abnormality, history of ovarian surgery (such as salpingectomy and oophorocystectomy), pelvic infection, environmental pollution, unhealthy lifestyle, and work pressure, which can cause damage to the ovary and atresia follicle ahead of time and egg degeneration [17,18], and are also harmful for the embryo implantation, thus affecting the clinical pregnancy outcome.

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It has been reported that reproductive potential and number of quality eggs decreases with age [19], which was also confirmed in the present study: the rates of normal fertilization, cleavage, high-quality embryos, pregnancy, and embryo implantation in older women with DOR were significantly lower and the miscarriage rate was significantly higher as compared to young women with and without DOR. This indicates that the majority of follicles degenerate with age due to apoptosis, causing atresia follicle; therefore, the number of remaining follicles is reduced and cannot meet the requirement for transplantation. Keefe et al. reported that the eggs collected from older women experienced more mitoses before meiosis as compared to those from young women, and thus oxidative injury caused telomere shortening, disordered meiosis, and increased the number of oocytes with chromosome aneuploidy, leading to increased rates of infertility and miscarriage [20].

Conclusions

DOR indicates the compromised ovarian reserve, ovarian hyporesponse, and reduced numbers of eggs acquired and embryos. For young women with DOR, the possibility of acquiring transplantable embryos and high-quality embryos is high and the clinical pregnancy outcome is good once eggs are acquired. However, young women with DOR are at risk for premature ovarian failure. Thus, the indications to IVF/ICSI should be widened for these women, and active treatments need to be administered before premature ovarian failure. We recommend widening the indications to IVF/ICSI and active treatments to help fertilization.

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