

In vitro fertilization outcome in women with diminished ovarian reserve

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Objective

This study aimed to identify factors that affect *in vitro* fertilization (IVF) outcomes in women with diminished ovarian reserve (DOR).

Methods

We reviewed 99 IVF cycles in 52 women with DOR between September 2010 and January 2015. DOR was defined as serum anti-Müllerian hormone level of <1.1 ng/dL or serum follicle-stimulating hormone level of ≥20 mIU/mL. Total 96 cycles in 50 patients were evaluated after excluding fertility preservation cases.

Results

The clinical pregnancy rate was 11.5% per cycle, and the total cancellation rate was 34.4%. Clinical pregnancy rate was significantly associated with the antral follicle count and the cause of the DOR. Age, serum anti-Müllerian hormone and follicle-stimulating hormone levels, antral follicle count, peak estradiol level, and the cause of DOR were significantly associated with cycle cancellation. However, history of previous ovarian surgery remained as a significant factor of clinical pregnancy (model 1: odds ratio [OR] 10.17, 95% confidence interval [CI] 1.46 to 70.84, $P=0.019$; model 2: OR 10.85, 95% CI 1.05 to 111.71, $P=0.045$). In cancellation models, idiopathic or previous chemotherapy group showed borderline significance (model 1: OR 3.76, 95% CI 0.83 to 17.04, $P=0.086$; model 2: OR 3.15, 95% CI 0.84 to 11.84, $P=0.09$).

Conclusion

DOR caused by previous ovarian surgery may show better pregnancy outcome, whereas that caused by chemotherapy could significantly increase the cycle cancellation rate. Furthermore, patients with DOR who previously received gonadotoxic agents may show reduced efficacy and increased risk of IVF cycle cancellation.

Keywords: Diminished ovarian reserve; Fertilization *in vitro*

Introduction

Diminished ovarian reserve (DOR) is often associated with poor ovarian stimulation response, a high cancellation rate, and a significant decline in pregnancy rate during *in vitro* fertilization (IVF) cycle. DOR is characterized by poor fertility outcomes even when assisted reproductive techniques are used and represents a major challenge in reproductive medicine [1]. Poor response to ovarian stimulation usually indicates decreased follicular response, resulting in a reduced number of retrieved oocytes [2]. The European Society of Human Reproduction and Embryology (ESHRE) consensus defines poor

Received: 2016.5.24. Revised: 2016.8.8. Accepted: 2016.8.25.

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ovarian response (POR) to ovarian stimulation as, “when at least two of the following three characteristics are present: (1) advanced maternal age (≥ 40 years) or any of the risk factors for poor ovarian responders, (2) a previous POR (≤ 3 oocytes with a conventional stimulation protocol), and (3) an abnormal ovarian reserve test result (i.e., antral follicle count [AFC] of $< 5-7$ follicles or anti-Müllerian hormone [AMH] level of $< 0.5-1.1$ ng/mL),” as in the Bologna criteria. Two episodes of POR after maximal stimulation are sufficient to define a patient as a poor responder in the absence of advanced maternal age or an abnormal ovarian reserve test result [2].

Although DOR has been one of the main factor results in POR, there has been few studies which had evaluated differences among causes of DOR. A recent retrospective case-control study showed DOR by surgery for endometrioma had better response to controlled ovarian stimulation comparing to idiopathic group [3]. Regardless of the causes, though the resulting DOR is the same, factors that could predict better IVF outcome might exist. Since DOR is a risk factor for POR, it may be important to know a group of patient who will show better IVF outcome to avoid repeated prolonged, tired, high-cost IVF procedures. The aim of this study was to evaluate factors that affect IVF outcomes in women with DOR.

Materials and methods

1. Study population

A retrospective cohort study was conducted by using data on IVF cycles performed in a single IVF center of a tertiary hospital. From September 2010 to January 2015, 99 IVF cycles in 52 patients with DOR were included. Although there has been consensus on the concept of DOR, the definition has been heterogeneously made. We defined DOR based on the Bologna ESHRE consensus of PORs [2], and serum follicle-stimulating hormone (FSH) level over 20 mIU/mL, the level which has been traditionally used as margin at our clinic. DOR was defined as a serum AMH level of < 1.1 ng/dL, which was measured within 6 months to 1 year of the IVF cycle in this study, or a serum FSH level of > 20 mIU/mL, which was measured within 1 to 3 months of the IVF cycle [1]. The exclusion criteria were frozen thawing embryo transfer (ET) cycle, oocyte donation cycle, fertility preservation cycle, IVF cycles in patients whose ovarian reserve test (serum AMH level) was performed at least 1 year prior, and serum FSH levels mea-

sured at least 6 months prior. After excluding the cycles for embryo cryopreservation (3 cycles in 2 patients) for fertility preservation, 96 cycles in 50 patients were examined, finally.

The causes of DOR were aging (age ≥ 35 years, without any surgical history), previous ovarian surgery, idiopathic factor (age < 35 years, neither history of ovarian surgery nor chemotherapy), and chemotherapy history. The IVF outcomes were classified as clinical pregnancy in ET do group, and cancellation in undo group. Clinical pregnancy was defined as an intrauterine gestational sac with an embryo showing normal cardiac activity confirmed on ultrasonography. Patients with cancelled ET were defined as those who had undergone oocyte pickup (OPU) but not ET because of unfertilization or abnormal fertilization and had no retrieved oocytes or had immature oocyte retrieval. Patients with cancelled OPU were defined as those who had cancelled OPU due to the absence of growing follicles in response to stimulation or premature ovulation. The study was approved by the institutional review board of the Severance Hospital, Yonsei University College of Medicine (4-2016-0152).

2. Stimulation protocols and IVF procedure

The ovarian stimulation was performed according to the condition of each patient by using conventional protocols such as gonadotropin releasing hormone (GnRH) agonist long protocol, flexible GnRH antagonist protocol, GnRH agonist microflare, and ultrashort protocol. In certain cycles, soft stimulation or natural IVF cycle was selected. In conventional protocols, recombinant FSH (Gonal-F, Serono, Geneva, Switzerland; Follitrope, LG Lifescience, Seoul, Korea) with or without human menopausal gonadotropin (IVF-M, LG Lifescience) was used with luteal long protocol of a GnRH agonist (Decapeptyl 0.1 mg/day, Ferring; $n=16$) or the GnRH antagonist protocol (Cetrotide 0.25 mg/day, Serono; $n=15$). The GnRH agonist microflare protocol (Decapeptyl 0.05 mg/day, Ferring; $n=17$) or the GnRH agonist ultrashort protocol (Decapeptyl 0.1 mg/day, Ferring; $n=9$) was used with the antagonist (Cetrotide 0.25 mg/day, Serono). The soft stimulation protocol used either 100-mg/day clomiphene citrate (clomiphene, Youngpoong Pharma, Seoul, Korea) or 5 mg/day letrozole (Femara, Novartis, Basel, Switzerland) with 150 IU/day human menopausal gonadotropin (IVF-M, LG Lifescience) and the antagonist (Cetrotide 0.25 mg/day, Serono; $n=29$). The natural IVF cycle was performed by using the antagonist (Cetrotide 0.25 mg/day, Serono), with or without human menopausal gonadotropin

Table 1. Clinical characteristics of the *in vitro* fertilization cycles in women with diminished ovarian reserve

	Non-pregnancy (n=52)	Clinical pregnancy (n=11)	ET cancelled (n=28)	OPU cancelled (n=5)	P-value
Age (yr)	40 (28–46)	35 (31–42) ^{a)}	35 (29–45) ^{a)}	40 (29–42)	0.038 ^{b)}
<35	11 (21.57)	5 (45.5)	12 (44.44)	2 (40.0)	0.092
35–39	14 (26.9)	4 (36.4)	6 (22.22)	0	
40≤	27 (51.9)	2 (18.2)	8 (29.63)	3 (60.0)	
Serum AMH (ng/mL)	0.75 (0–1.26)	0.84 (0.15–1.26)	0.35 (0–1.26)	0.15 (0–0.89)	0.113 ^{b)}
Serum FSH (mIU/mL)	11.6 (5.0–60.8)	11.9 (5.0–39.4)	19.8 (6.0–76.7) ^{a),c)}	18.6 (6.5–76.7)	0.018
Serum E ₂ (pg/mL)	65.27±85.13	42.45±23.51	59.52±71.27	30.0±22.77	0.832
Total AFC (n)	4.61±2.19 ^{c)}	7.09±2.63	3.93±2.91 ^{c)}	3.20±1.30 ^{c)}	0.005
Total Gn dose (IU)	2,421.63±1814.67	3,013.63±1,373.88	1,319.44±1,334.24 ^{a),c)}	180±268.33 ^{a),c)}	0.001
Stimulation days	10.69±3.83	10.81±1.66	11.30±5.80	13.6±4.39	0.563
Peak E ₂ on day of hCG administration (pg/mL)	1,406.9±1051.93	1,870.82±1,581.66	577.35±493.18	442.50±208.60 ^{a)}	0.031
Total oocytes retrieved (n)	3 (1–11)	4 (2–6)	1 (0–5) ^{a),c)}		<0.0001 ^{b)}
No. of MII (n)	2 (0–8)	2 (0–5)	1 (0–2) ^{a),c)}		<0.0001 ^{b)}
No. of 2PN (n)	2 (0–7)	2 (0–5)	0 (0–1) ^{a),c)}		<0.0001 ^{b)}
CES	40.02±26.88	41.82±27.63	0 ^{a),c)}		0.016
TMSC (million)	137.97±154.04	213.57±182.13	114.70±128.59		0.486
COH protocol					0.002
Conventional stimulation	34 (65.4)	10 (46.4)	13 (46.4)	0	
Soft/natural stimulation	18 (34.6)	1 (53.6)	15 (53.6)	5 (100)	
Cause of infertility					0.305
Unexplained	22 (42.3)	5 (45.5)	17 (63)	1 (20)	
EMS	21 (40.4)	5 (45.5)	8 (29.6)	4 (80)	
Male factor	9 (17.3)	1 (9.1)	2 (7.4)	0 (0)	
Cause of diminished ovarian reserve					0.01
Aging	33 (65.4)	3 (27.3)	11 (39.3)	3 (60)	
Previous ovarian surgery	9 (15.4)	5 (45.5)	4 (14.3)	0 (0)	
Idiopathic	14 (22.2)	3 (27.3)	4 (12.1)	1 (20)	
Previous chemotherapy	10 (19.2)	0 (0)	9 (33.3)	1 (20)	
Other	13 (20.6)	0 (0)	10 (30.3)	1 (20)	
Other	0 (0)	0 (0)	4 (14.3)	1 (20)	
Other	0 (0)	0 (0)	5 (15.2)	0 (0)	

Data are presented as median (range), mean±standard deviation, or number (%).

ET, embryo transfer; OPU, oocyte pickup; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; E₂, estradiol; AFC, antral follicle count; Gn, gonadotropin; hCG, human chorionic gonadotropin; MII, metaphase II; PN, pronuclei; CES, cumulative embryo score; TMSC, total motile sperm count; COH, controlled ovarian hyperstimulation; EMS, endometriosis.

^{a)}Comparison with the non-pregnancy group by post hoc analysis; ^{b)}Kruskal-Wallis test was performed, and data are expressed as median (range);

^{c)}Comparison with the clinical pregnancy group by post hoc analysis.

(IVF-M, LG Lifescience; n=10). When one or more leading follicles reached a mean diameter of ≥ 18 mm, 250 μg of recombinant human chorionic gonadotropin (rhCG; Ovidrel, Serono) was given. The oocytes were retrieved around 34 to 36 hours after the rhCG injection. The oocytes were inseminated by using the conventional method (n=47) or via intracytoplasmic sperm injection (n=31), depending on the quality of the gametes. The embryos were transferred 3 days after the retrieval of the oocyte. Luteal phase support was performed by using either a daily dose of 50 mg of progesterone in oil (Progest, Samil, Seoul, Korea) or 800 mg/day micronized progesterone vaginal suppositories (Utrogestan, Brussels, Belgium).

3. Statistical analyses

Data are presented as mean \pm standard deviation for continuous variables, and as numbers and percentages for categorical variables. The baseline characteristics were compared between the non-pregnancy and clinical pregnancy groups, and between the ET and OPU cancelled groups in ET do and undo

cycles, by using one-way analysis of variance for the normally distributed continuous variables, with post hoc analysis using the Bonferroni procedure. A chi-square test was performed for the categorical variables. After the normality tests, the Kruskal-Wallis test was performed for the non-parametrically distributed variables. The univariate and multivariate logistic regression analyses were performed to examine factors that could influence clinical pregnancy and cycle cancellation, respectively. Logistic models were built based on the goodness-of-fit of the model and the multicollinearity of the factors. The factors with a *P*-value of <0.1 in the univariate analysis were included in the logistic model. Data were analyzed by using IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA). A *P*-value of <0.05 was considered statistically significant.

Results

A total 96 IVF cycles in 50 patients were analyzed. Of these

Table 2. Factors that affect clinical pregnancy in women with diminished ovarian reserve

	Univariate		Multivariate (model 1)		Multivariate (model 2)	
	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
Age (yr)	0.87 (0.75–1.01)	0.063				
Serum AMH (ng/mL)	6.83 (0.77–60.86)	0.085			4.91 (0.26–91.8)	0.287
Serum FSH (mIU/mL)	0.98 (0.94–1.03)	0.476				
Total AFC (n)	1.35 (1.07–1.70)	0.013	1.49 (1.03–2.14)	0.034		
Peak E ₂ (pg/mL)	1 (1.0–1.0)	0.308				
Retrieved oocytes, total (n)	1.14 (0.89–1.45)	0.304				
Number of MII (n)	1.16 (0.83–1.63)	0.397				
Number of 2PN (n)	1.46 (0.97–2.20)	0.071	1.18 (0.75–1.86)	0.484	1.52 (0.96–2.39)	0.075
CES	1.00 (0.98–1.03)	0.79				
Cause of infertility						
Unexplained	1					
EMS	1.507 (0.38–6.06)	0.563				
Male factor	0.932 (0.94–9.20)	0.952				
Cause of diminished ovarian reserve						
Aging	1		1		1	
Previous ovarian surgery	9.23 (1.60–53.15)	0.013	10.17 (1.46–70.84)	0.019	10.85 (1.05–11.71)	0.045
Idiopathic+previous chemotherapy	3.6 (0.56–23.21)	0.178	2.60 (0.34–19.67)	0.355	9.06 (0.77–106.66)	0.08

Model 1 was adjusted for the total AFC, number of 2PN, and cause of diminished ovarian reserve. Model 2 was adjusted for the same variables used in model 1, except for AFC, which was substituted with serum AMH level.

OR, odds ratio; CI, confidence interval; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; AFC, antral follicle count; E₂, estradiol; MII, metaphase II; PN, pronuclei; CES, cumulative embryo score; EMS, endometriosis.

cycles, 64 (66.6%) entered ET and 11 (11.5%) had achieved clinical pregnancy after IVF-ET. The mean age of the included cases was 37.5 ± 4.9 years. The mean serum AMH and FSH levels were 0.6 ± 0.4 ng/dL and 20.0 ± 17.7 mIU/mL, respectively. The clinical characteristics of the IVF cycles included are shown in Table 1. Although serum AMH levels did not show significant differences between the groups, AFC showed a significant difference, especially between clinical pregnancy group and the other groups, respectively ($P=0.005$). The controlled ovarian hyperstimulation protocols showed significantly different among groups, however, it may be reflecting the degree of DOR and other characteristics. Although the distribution of the causes of infertility was similar between the groups, the cause of DOR significantly differed ($P=0.01$). In clinical pregnancy group, the proportion of women with previ-

ous ovarian surgery was relatively higher than that in the non-pregnancy group. In the comparison between the ET do and undo group, the cause of DOR significantly differed ($P=0.06$, not shown in Table 1) with higher percentage of women with idiopathic and causes related to previous chemotherapy. None of the women with DOR caused by previous chemotherapy has undergone ET, but all had cycle cancellation.

In a simple comparison, the analyses showed that the total AFC and cause of DOR were significantly related to clinical pregnancy (Table 2). Age, serum AMH level, and number of 2PN showed an association with borderline significance. Logistic model 1 showed significant associations of AFC (odds ratio [OR], 1.49; 95% confidence interval [CI], 1.03 to 2.14; $P=0.034$) and previous ovarian surgery (OR, 10.17; 95% CI, 1.46 to 70.84; $P=0.019$) with clinical pregnancy. In model 2, the adjusted variables included serum AMH level, number of 2PN, and the causes of DOR. Ovarian surgery history remained significantly positively associated with clinical pregnancy (OR, 10.85; 95% CI, 1.05 to 111.71; $P=0.045$).

In terms of cycle cancellation, the univariate analysis revealed significant relationships between age, serum AMH level, serum FSH level, total AFC, peak estradiol (E_2) level on the day hCG was administered, DOR due to previous chemotherapy, and idiopathic cause (Table 3). However, the logistic models with adjusted variables showed associations with borderline significance between the cause of DOR and cycle cancellation due to idiopathic and previous chemotherapy-related causes (Table 4). The logistic models were constructed with adjusted variables, including total AFC, peak E_2 level on the day of hCG administration, controlled ovarian hyperstimulation protocol, the cause of DOR, and serum FSH (model 1) or AMH level (model 2). Model 1 showed positive associations between peak E_2 level on the day of hCG administration (OR, 6.22; 95% CI, 0.81 to 47.63; $P=0.079$) (data not shown in Table 4) and DOR caused by idiopathic and previous chemotherapy-related causes (OR, 3.76; 95% CI, 0.83 to 17.04; $P=0.086$) (Table 4), although not statistically significantly. Model 2 also showed similar results in that peak E_2 level on the day of hCG administration (OR, 5.21; 95% CI, 0.86 to 31.8; $P=0.073$) (data not shown in Table 4) and DOR caused by idiopathic and previous chemotherapy-related causes (OR, 3.15; 95% CI, 0.84 to 11.84; $P=0.09$) (Table 4) were positively but not significantly associated with cycle cancellation.

Table 3. Factors that influence cycle cancellation in women with diminished ovarian reserve

	Univariate	
	OR (95% CI)	P-value
Age (yr)	0.91 (0.83–1.0)	0.042
Serum AMH (ng/mL)	0.28 (0.09–0.87)	0.028
Serum FSH (mIU/mL)	1.05 (1.02–1.08)	0.001
Total AFC (n)	0.81 (0.66–0.99)	0.035
Peak E_2 (pg/mL)	0.99 (0.99–1.0)	0.002
<200	13.0 (2.7–62.72)	0.001
≥200 but <800	4.18 (1.39–12.54)	0.011
≥800	1	
COH protocol		
GnRH agonist long	0 (0–0)	0.998
Antagonist	0.44 (0.09–2.28)	0.330
Ultrashort	0.19 (0.03–1.43)	0.107
Soft stimulation	0.62 (0.15–2.68)	0.524
GnRH agonist microflare	0.28 (0.054–1.43)	0.126
Natural/modified natural	1	
Cause of diminished ovarian reserve		
Aging	1	
Previous ovarian surgery	0.81 (0.23–2.92)	0.751
Idiopathic and previous chemotherapy	3.1 (1.16–7.8)	0.023

OR, odds ratio; CI, confidence interval; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; AFC, antral follicle count; E_2 , estradiol; COH, controlled ovarian hyperstimulation; GnRH, gonadotropin releasing hormone; EMS, endometriosis.

Table 4. Adjusted ORs of the risk factors of cycle cancellation

	Cause of diminished ovarian reserve	Adjusted OR (95% CI)	P-value
Model 1	Aging	1	
	Previous ovarian surgery	1.93 (0.29–12.99)	0.498
	Idiopathic and previous chemotherapy	3.76 (0.83–17.04)	0.086
Model 2	Aging	1	
	Previous ovarian surgery	2.05 (0.34–12.29)	0.433
	Idiopathic and previous chemotherapy	3.15 (0.84–11.84)	0.09

Model 1 of cycle cancellation was adjusted for peak estradiol (<200 pg/dL, ≥200 but <800 pg/dL, and ≥800 pg/dL), serum follicle-stimulating hormone level, total antral follicle count, controlled ovarian hyperstimulation protocol (gonadotropin releasing hormone agonist long, antagonist, ultrashort, soft stimulation, gonadotropin releasing hormone agonist microflare, and natural/modified natural); Model 2 of cycle cancellation was adjusted for the same variables used in model 1, except for serum follicle-stimulating hormone level, which was substituted with serum anti-Müllerian hormone level.

OR, odds ratio; CI, confidence interval.

Discussion

Our study showed a possible significant association between the cause of DOR and IVF outcome, especially in relation to histories of ovarian surgery and chemotherapy. A notable finding is that women with DOR caused by previous ovarian surgery may show higher possibility of clinical pregnancy than those with DOR of other causes. However, among the women with low ovarian reserve, those with DOR caused by chemotherapy could have greater risk of cycle cancellation, not permitting even oocyte retrieval, than those with DOR of other causes. Our study focused on the fact that all cases may have decreased ovarian reserve but that different causes may act differently on the IVF outcome, which may mean that each patient requires individualized counseling and motivation.

Previous studies suggested predictive factors for clinical pregnancy in IVF/intracytoplasmic sperm injection cycles of DOR, such as serum AMH level and AFC on ultrasonography [4,5]. A study reported that patients with serum AMH levels of >0.4 ng/dL showed significantly lower liver birth rates than those with higher AMH levels [6]. They also suggested that every 0.1 ng/dL increase in AMH levels can cause a corresponding increase in clinical pregnancy rate. In contrast to the previous studies, our study showed that serum AMH level was not associated with clinical pregnancy or cycle cancellation in women with low ovarian reserve. In terms of the cause of DOR, few studies have shown a significant association with pregnancy outcome [7,8]. Age and prior chemotherapy have been suggested as related factors. However, evidence is insufficient to prove that idiopathic premature ovarian insufficiency,

repeated ovarian surgery, or other possible factors such as autoimmune diseases can affect IVF outcomes.

Several studies reported a significant decrease in ovarian response to IVF in cancer patients who had undergone chemotherapy [9,10]. In a cohort study, regardless of the type of cancer, response to gonadotropins and the number of oocytes retrieved were significantly decreased in the post-chemotherapy group [10]. Our study shows similar results as the previous study of Chan et al. [10], which showed higher cancellation rates in post-chemotherapy patients than in chemotherapy-naïve patients. However, while the previous study showed low AFC as a factor related to cycle cancellation, our study showed an association with borderline significance between peak E₂ level and chemotherapy-related cycle cancellation. The difference may be caused by the small number of patients included, as only three post-chemotherapy cases were included.

Our study clearly shows a significant relationship between the cause of poor ovarian reserve and IVF outcome. However, its retrospective design and the small number of participants included in the analyses remain major limitations of the study. Heterogeneous character of the participants may provide as bias, so that the interpretation needs to be cautious. Moreover, as the IVF cycles included were intentioned to result in conception, cycles for fertility preservation such as oocyte cryopreservation could yield different results in terms of predictive factors of ovarian response.

In conclusion, the present study shows that women with DOR caused by previous ovarian surgery may benefit from assisted reproductive technologies. Furthermore, counseling patients with DOR who previously received gonadotoxic agents

should be performed with caution, as they may show reduced efficacy and higher risk of IVF cycle cancellation. Fertility preservation may get stressed more, in certain patient groups, who treat with gonadotoxic agents.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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