Comparative study of assisted reproductive outcomes between young patients with occult premature ovarian insufficiency and advanced-age patients

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Abstract

Objective: The purpose of this study was to compare the pregnancy outcomes among young patients with occult premature ovarian insufficiency (OPOI), advanced-age patients with diminished ovarian reserve (DOR), and advanced-age patients with normal ovarian reserve.

Methods: We retrospectively reviewed 324 women who underwent their first cycles of *in vitro* fertilization/intracytoplasmic sperm injection. The women were divided into the following groups: young women with OPOI, advanced-age women with DOR, and advanced-age women with normal ovarian reserve. The outcomes were compared among the different groups:

Results: The rates of live birth and embryo implantation in the young OPOI group were significantly higher than in the advanced-age DOR group, but comparable to those in the advanced-age normal ovarian reserve group. Moreover, the abortion rate was significantly lower in young OPOI patients compared with advanced-age patients with or without DOR.

Conclusion: Higher embryo implantation and live birth rates and a lower abortion rate can be achieved in young patients with OPOI compared with older patients. The better outcomes in advanced-age patients with normal ovarian reserve compared with DOR may be related to egg quantity rather than quality.

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Introduction

Occult ovarian failure was first described in 1988[1] as the triad of infertility, regular menses, and elevated (sometimes normal) plasma levels of follicle-stimulating hormone (FSH). Anti-Müllerian hormone (AMH) and antral follicle count (AFC) are considered to be more reliable and accurate predictors of ovarian reserve and ovarian response than baseline FSH levels;[2] however, there is currently no clear standard for diagnosing occult premature ovarian insufficiency (OPOI). In 2009, Streuli et al.[3] described OPOI as partial ovarian insufficiency in women under the age of 40, including infertility, slightly raised FSH levels, low AMH levels, and/or resistance to ovarian stimulation in women with either regular or irregular cycles.[3] In 2010, Oktay et al.[4] also defined primary occult ovarian insufficiency as infertility and a low ovarian response to *in vitro* fertilization treatments. In 2017,[5] Guzel et al.[6] defined OPOI (also known as incipient ovarian failure or diminished ovarian reserve) as a serum AMH level ≤1.1 ng/mL (as a hormone marker of diminished ovarian reserve (DOR)) according to one of the Bologna criteria, while Humaidan et al.[7] proposed a new poor ovarian response classification and standard in 2016, and updated the poor ovarian reserve prestimulation parameters to AFC <5 or AMH <1.2 ng/mL, and advanced age as 35 years.

Pregnancy is uncommon in patients with premature ovarian insufficiency (POI) and egg donation is often the only solution.

Letur et al.[8] found that, of 518 patients treated for POI including OPOI, only 17 patients (mean age 31.5 years) conceived (pregnancy rate 3.3%) (with or without hormone replacement therapy). Another study[9,10] found a low number and quality of remaining oocytes, ovarian hyporesponse, high ovulation cancellation rate, decreased clinical pregnancy and live birth rates, and a high miscarriage rate in patients with POI after treatment with assisted reproductive technology (ART). Özelçi et al.[11] found that the numbers of mature oocytes and total oocytes retrieved from younger women with DOR (<35 years) were lower, but their clinical pregnancy rates were slightly higher than those of older women with DOR (*in vitro* fertilization (IVF)-embryo transfer cycle). In addition, Cohen et al.[12] showed that, among 59 IVF/intracytoplasmic sperm injection (ICSI) cycles (40% IVF/60% ICSI), the pregnancy rate of young women with DOR (age ≤38 years, AMH ≤1.1 ng/mL or antral follicular count ≤7) was 17% (10/59), the live birth rate was 8.5% (5/59), and the miscarriage rate was 50%. Chang et al.[13] also found that the clinical pregnancy rate of young women with DOR (age <37 years, normal menstrual cycle, basal serum FSH (bFSH) >10 IU/L, AMH <1.1 ng/mL, AFC <6) was significantly higher than in older women with DOR, and lower than in young women with normal ovarian reserve.

The demand for ART has increased substantially among women of advanced

reproductive age. The common standard definitions for advanced reproductive age are 40 years[6] and 35 years.[7] The 2010 annual report of the American Centers for Disease Control ART reported live birth rates following IVF-fresh embryo transfer cycles in women aged 35 to 37 years of 31.9%, 38 to 40 years 22.1%, 41 to 42 years 12.4%, 43 to 44 years 5%, and >44 years only 1%.[14] Devesa et al.[15] also found that cumulative live birth rates decreased significantly with increasing age among women ≥38 years, with the most prominent and clinically relevant decline observed at 42 to 43 years, and clear evidence of a lack of success in women aged ≥44 years (25.9% at 38–39 years, 16.4% at 40–41 years, 7% at 42–43 years and 1.2% from 44 years onwards). A higher number of retrieved oocytes was associated with higher cumulative live birth rates up to 41 years of age, but there was no clear benefit from 44 years onwards. The decline in the live birth rate might be caused by low egg quality in older women, an increased oxidative stress response, oocyte damage caused by reactive oxygen species, mutation and deletion of mitochondrial DNA, or decreased telomerase activity.[16–18]

The purpose of this study was to compare the pregnancy outcomes among young patients with OPOI, advanced-age patients with DOR, and advanced-age patients with normal ovarian reserve, to provide guidance for clinical practice.

Materials and Methods

Study population

Patients who underwent their first cycles of IVF/ICSI treatment at the Reproductive Medical Center of the First Affiliated Hospital of Zhejiang University School of Medicine between April 2013 and December 2018 were included in this study. This study was approved by the Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (reference number: 2018-1080) and verbal consent was obtained from all patients. The patients were classified into young OPOI (Group A), advanced-age DOR (Group B1), and advanced-age with normal ovarian reserve groups (Group B2). The cutoff values for advanced age and poor ovarian reserve were determined in accordance with the new POSEIDON criteria[7] for poor ovarian response. Young OPOI patients (Group A) met the following criteria: 1) age >20 but ≤34 years; 2) infertility; 3) regular menstruation; and 4) AFC <5.[1,3–5,7] The criteria for advanced-age patients with DOR (Group B1) were age ≥35 years with poor ovarian reserve prestimulation parameters (AFC <5), and the criteria for advanced-age patients with normal ovarian reserve (Group B2) were age ≥35 years with normal ovarian reserve (AFC ≥5) and regular menstruation. The exclusion criteria were as follows: 1) ovarian cyst, polycystic ovary syndrome, endometriosis; 2) surgery for ovarian malignant tumor (excluding benign gonadal tumors and ectopic pregnancy) or endocrine disorders; 3) history of radiotherapy and chemotherapy; 4) chromosomal abnormalities (not including chromosome polymorphisms); 5) autoimmune diseases, 6) hereditary diseases; 7) smoking and alcoholism; 8) abnormal uterus or uterine malformation; 9) more than two spontaneous abortions; and 10) IVF contraindication.

Cycle monitoring and IVF/ICSI

Young OPOI patients and advanced-age DOR patients were treated with the mild ovulation protocol (oral clomiphene or letrozole on the second or third day of the menstrual cycle for 5 days, followed by gonadotropin human menopausal gonadotropin or FSH administration until human

chorionic gonadotropin (hCG) injection) if the AFC was ≤3 on the second day of the menstrual cycle, as shown by ultrasonography, or with the short protocol (starting on day 2 or 3 of the menstrual cycle with a gonadotropin-releasing hormone agonist (GnRHa) and human menopausal gonadotropin or FSH until hCG injection) if the AFC was >3. Advanced-age patients with normal ovarian reserve were treated with the long-term luteal phase protocol (standard luteal phase ovarian stimulation protocol with pituitary suppression with a GnRHa). The initial dose for each patient was determined according to age, body mass index (BMI), and AFC. The criteria for hCG administration (5000–10,000 IU, Livzon Pharmaceutical Group Inc., China) were the presence of three or more follicles ≥16 to 18 mm in diameter, and a consistent rise in serum estradiol concentration. Oocyte aspiration was performed using vaginal ultrasound at 34 to 36 hours after hCG injection. ICSI was performed using standard procedures.

According to the international morphological grading system,[19] embryos were divided into four grades. Grade I: blastomeres even in appearance with transparent and even cytoplasm, and no debris; grade II: blastomeres even in appearance with <20% cytoplasmic debris; grade III: blastomeres not irregular and 20% to 50% cytoplasmic debris; and grade IV: blastomeres not irregular but >50% cytoplasmic debris. Grade I–II embryos were regarded as high-quality and grade I–III embryos could be used for transplantation. One or two embryos were transplanted 3 days after egg collection and the remaining embryos were processed for blastocyst culture and cryopreservation.

Study endpoints

Biochemical pregnancy was defined as early abortion within 5 weeks of pregnancy, with an hCG blood level >25 mIU/mL or positive urine pregnancy test, but no gestational sac on ultrasound examination. Clinical pregnancy was defined as the presence of a fetal sac and fetal heart beat on ultrasound at 4 weeks after transplantation. High-quality embryo rate was defined as grade I/II 2 pronucleus embryos/2 pronucleus eggs cleaved ×100%, implantation rate as embryos implanted/embryos transplanted ×100%, clinical pregnancy rate as number of clinical pregnancy/number of transplantation ×100%, and live birth rate as number of live birth/number of transplantation ×100%

Statistical analyses

Statistical comparisons were made using SPSS Statistics for Windows, Version 19.0 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± standard deviation (SD). Quantitative data with a normal distribution were expressed as mean ± SD and compared with t-tests. Numerical data were reported as rate (%). Differences among χ^2 tests. Multivariate logistic regression was performed to determine the risk factors correlated with the live birth rate. Variables including maternal age, paternal age, duration of infertility, AFC, number of pregnancies, oviductal factors, male semen factors, BMI, bFSH, and FSH/LH were included in the logistic regression model. A P-value < 0.05 was considered to be statistically significant.

Results

Comparison of general clinical data among the three groups

A total of 324 women (maximum age 46 years) were included in this study: 117 in Group A, 171 in Group B1, and 36 in Group B2. There were significant differences in maternal and paternal ages, AFC,

bFSH, FSH/luteinizing hormone (LH), duration and type of infertility, and history of attachment or Fallopian tube resection among the three groups (all $P < 0.05$). However, there were no significant differences in BMI, type of fertilization, and oviductal factors (without Fallopian tube resection) among the three groups (Table 1).

Comparison of IVF/ICSI outcomes among the three groups

The numbers of eggs acquired and embryos transferred were significantly higher in Group B2 compared with Group A and Group B1 ($P < 0.05$). All fertilized eggs cleaved in Group A, while one fertilized egg in Group B1 and two in Group B2 did not cleave. The rate of normal fertilization among the three groups was comparable. However, the rates of high-quality embryos, embryo transfer cancellation, and no-egg-obtained cycles differed significantly among the three groups ($P < 0.05$). The embryo transfer cancellation rates were significantly higher in Groups A and B1 compared with Group B2, and the blastocyst formation rate was significantly higher in Group A than in Groups B1 and B2 (all $P < 0.05$) (Table 2).

Comparison of clinical outcomes among the three groups

Eighty-eight patients in Group A, 120 patients in Group B1, and 35 patients in Group B2 underwent embryo transfer. The clinical pregnancy rate, biochemical pregnancy rate, ectopic pregnancy rate, and fetal malformation rate were similar in all three groups. However, the live birth rate and embryo implantation rate in Group A were 35.2% and 30.7%, which were significantly higher than in Group B1 ($P < 0.05$) but comparable to Group B2. The twin rate was significantly higher in

Group B2 compared with the other two groups ($P < 0.05$), but was comparable between Groups A and B1 (Table 3).

Relationships between infertility-related factors and IVF/ICSI outcomes in young patients with OPOI and advanced-age patients

We conducted logistic regression analysis to assess if infertility-related factors were cofounding factors that might affect the live birth rates in young patients with OPOI and advanced-age patients. Prior to ART, we comprehensively examined each patient's immunity, blood coagulation, and endocrine function factors, as well as infertility-related factors such as maternal age, paternal age, duration of infertility, AFC, number of pregnancies, oviductal factors, male semen factors, BMI, bFSH, and FSH/LH in all the included patients. After adjusting for potential confounders, only AFC independently affected the IVF-embryo transfer live birth rates in these patients (odds ratio, 95% confidence interval, 1.157 (1.053–1.272), $P = 0.002$) (Table 4).

Discussion

Young OPOI patients have normal menstruation, and are usually only diagnosed with decreased ovarian function after an infertility examination. Guzel et al.[5] used AMH and AFC to assess ovarian function and found that 4.4% of 963 young females (≤30 years) with regular menstruation had OPOI, while Shestakova et al.[20] diagnosed OPOI in 23 patients with unexplained oligomenorrhea and/or infertility. Izhar et al.[21] also found that the predictive value of AFC was similar to that of AMH for OPOI. In the current study, patients in the young OPOI group were unaware of their decreased ovarian function prior to the study. AMH tests were not carried out at our reproduction center at that time, and

Table 1. Clinical characteristics of the three groups.

	Group A (n = 117)	Group B1 (n = 171)	Group B2 (n = 36)	P
Maternal age (years)	30.18 ± 2.78^a	39.47 ± 2.65^b	39.89 ± 2.06^b	<0.001
BMI (kg/m^2)	21.67 ± 3.30	23.01 ± 3.25	23.24 ± 2.87	0.375
AFC	3.08 ± 0.94^a	2.88 ± 1.01^b	11.08 ± 4.14^b	<0.001
bFSH (IU/L)	12.2 ± 7.68^a	10.45 ± 4.99^b	7.39 ± 1.84^c	0.009
bE2 (pg/mL)	47.25 ± 28.59	56.73 ± 32.38	44.96 ± 18.30	0.183
bLH (IU/L)	4.92 ± 5.86	4.53 ± 1.95	4.66 ± 1.95	0.708
FSH/LH	3.30 ± 2.16^a	2.56 ± 1.22^b	1.88 ± 0.96^c	<0.001
E2 (hCG day)	1400.29 ± 1575.24^a	1313.19 ± 1310.18^a	3480.00 ± 1964.86^b	0.004
Duration of infertility (years)	3.29 ± 2.15^a	5.01 ± 4.51^b	5.53 ± 3.69^b	<.001
Paternal age	31.68 ± 3.26^a	40.88 ± 5.64^b	41.94 ± 5.33^b	<0.001
Number of pregnancies	87 ± 1.34	2.08 ± 1.56	1.89 ± 1.32	0.175
Type of fertilization				
IVF	89 (76.0)	125 (73.1)	33 (91.6)	0.145
ICSI	28 (24.0)	46 (26.9)	3 (8.4)	0.131
Cause of infertility (%)				
Primary infertility	$69 (58.9)^a$	$25 (14.6)^b$	$8 (22.2)^b$	<0.001
Secondary infertility	$48 (41.1)^{aa}$	$146 (85.4)^b$	$28 (77.8)^b$	<0.001
History of attachment or Fallopian tube resection	$7 (5.9)^a$	$33 (19.3)^b$	$3 (8.3)^{ab}$	0.003
Oviductal factor (without Fallopian tube resection)	35 (29.9)	63 (36.8)	15 (39.5)	0.318
With male factor	$38 (32.5)^a$	$49 (28.6)^a$	$3 (8.3)^b$	0.017

Values presented as mean $\pm$ SD or n (%). Different lower case letter (a, b, c) indicates significant difference. BMI, body mass index; AFC, antral follicle count; bFSH, basal serum follicle-stimulating hormone; bE2, basal serum estradiol; bLH, basal serum luteinizing hormone; hCG, human chorionic gonadotropin.

Table 2. Outcomes after *in vitro* fertilization/intracytoplasmic sperm injection in the three groups.

	Group A (n = 117)	Group B1 (n = 171)	Group B2 (n = 36)	P
Number of eggs obtained	2.65 ± 2.42^a	2.66 ± 2.30^a	8.53 ± 4.34^b	<0.001
Number of embryos transferred	1.09 ± 0.82^a	1.12 ± 0.95^a	1.78 ± 0.79^b	0.014
Rate of normal fertilization (%)	67.7 (210/310)	66.1 (301/455)	72.3 (222/307)	0.192
Rate of high-quality embryos (%)	$52.3 (110/210)^a$	$50.3 (151/300)^a$	$35.9 (79/220)^b$	0.001
Rate of embryo transfer cancellation (%)	$24.7 (29/117)^a$	$29.8 (51/171)^a$	$2.7 (1/36)^b$	0.010
Rate of no-egg-obtained cycles (%)	$10.2 (12/117)^{ab}$	$14.6 (25/171)^a$	0^b	0.038
Blastocyst formation rate (%)	$70.5 (12/17)^a$	$33.3 (6/18)^b$	$43.8 (25/57)^b$	0.068

Values presented as mean $\pm$ SD or % (n).
Different lower case letter (a, b) indicates significant difference. Letter 'ab' means that there is no statistical difference with the letter a or b.

AMH level was therefore replaced by AFC <5 in the current study.[7]

In this study, young OPOI patients had a lower AFC and higher bFSH level than advanced-age women with DOR. This may suggest that occult DOR should be actively detected in young patients. The duration of infertility, paternal age, type

Table 3. Comparison of clinical outcomes among the three groups.

	Group A (n = 88)	Group B1 (n = 120)	Group B2 (n = 35)	P
Clinical pregnancy rate (%)	38.6 (34/88)	28.4 (34/120)	40 (14/35)	0.210
Biochemical pregnancy rate (%)	1.1 (1/88)	0.8 (1/120)	5.7 (2/35)	0.122
Embryo implantation rate (%)	30.7 (39/127)[a]	18.8 (36/191)[b]	30.3 (20/66)[a]	0.029
Spontaneous abortion rate (%)	1.1 (1/88)[a]	10 (12/120)[b]	8.6 (3/35)[b]	0.034
Live birth rate (%)	35.2 (31/88)[a]	20.8 (20/120)[b]	31.4 (11/35)[ab]	0.007
Twin rate (%)	5.7 (5/88)[a]	1.6 (2/120)[a]	17.1 (6/35)[b]	0.002
Ectopic pregnancy rate (%)	2/88	1/120	0	0.503
Fetal malformation rate (%)	0	1/120	0	0.598

Values presented as % (n).
Different lower case letter (a, b) indicates significant difference. Letter 'ab' means that there is no statistical difference with the letter a or b.

Table 4. Logistic regression analysis of factors related to infertility and live birth.

	OR (95% CI)	P value
Paternal age (years)	0.943 (0.872–1.019)	0.136
Maternal age (years)	0.970 (0.884–1.065)	0.524
AFC	1.157 (1.053–1.272)	0.002
Duration of infertility (years)	0.931 (0.848–1.022)	0.134
Number of pregnancies	1.069 (0.859–1.331)	0.548
Oviductal factor (without Fallopian tube resection)	1.038 (0.541–1.990)	0.911
History of attachment or Fallopian tube resection	0.659 (0.258–1.680)	0.382
With male semen factor	0.815 (0.402–1.652)	0.570
BMI	0.913 (0.827–1.009)	0.076
bFSH (IU/L)	0.930 (0.864–1.002)	0.055
FSH/LH	1.121 (0.942–1.333)	0.197

OR, odds ratio; CI, confidence interval; AFC, antral follicle count; BMI, body mass index; bFSH, basal serum follicle-stimulating hormone; LH, luteinizing hormone.

of infertility, oviductal factors (with or without attachment or Fallopian tube resection), and male semen factors differed among the three groups. However, the subsequent multivariate regression analysis showed that these were not independent factors affecting the IVF/ICSI live birth outcomes. The American Society for Reproductive Medicine and the British Andrology Society[22,23] both recommended that semen donation should be restricted to men aged <40 years; however, the number of studies on paternal age is limited and the results have been discrepant. Mariappen et al.[24] found that neither male age nor semen parameters influenced clinical pregnancy or live birth outcomes from IVF. This result was consistent with our findings. The attachment or Fallopian tube resection rate was higher in advanced-age women with DOR than in the other groups, which might suggest that the decrease in ovarian reserve in advanced-age women might be related to ovariectomy or salpingectomy, while young OPOI patients might have more idiopathic declines in ovarian reserve.

Ovarian reserve and female age are closely related to the number and quality of

follicles in the ovary and reflect the woman's reproductive potential and infertility. Most DOR patients have an ovarian hypo-response to ovulation treatment, resulting in fewer eggs acquired and undesirable reproductive outcomes. However, the occult status in some patients, as in OPOI, and consequent lack of early detection, may lead to POI, making it much harder for the woman to have a child of her own. However, in young patients with DOR, a smaller number of eggs does not necessarily mean that the quality of the eggs is reduced, and once the eggs are acquired, the possibilities of high-quality embryos and clinical pregnancy are higher. In contrast, older women with DOR may have lower clinical pregnancy and live birth rates and a higher miscarriage rate.[13] Older women with normal ovarian reserve may have a pregnancy advantage due to a larger number of follicles, but this advantage will disappear at much older ages.[15]

The lower ovarian reserve in the young OPOI and advanced-age DOR groups resulted in fewer eggs obtained and a reduced embryo transfer rate, and higher rates of embryo transfer cancellation and no-egg-obtained cycles compared with the advanced-age normal ovarian reserve group. However, the rates of high-quality embryos and blastocyst formation in the young OPOI group were significantly higher than in the advanced-age normal ovarian reserve group. These results were consistent with recent studies[15,25] suggesting that, even though young OPOI patients might have a hypo-ovarian response, their embryonic potential should not be ignored. Although patients in Group B2 had normal ovarian reserve, the rate of high-quality embryos was no higher than that in Group B1, and although the blastocyst formation rate was higher in Group B2 than Group B1, the difference was not significant. These results may be related to the different promotion programs used in the advanced-age groups; advanced-age patients with normal ovarian reserve in this study underwent the luteal phase long program to obtain more eggs. However, another study[26] showed a negative effect of FSH dose on embryo quality and blastocyst formation rate, suggesting that this might not be applicable for older women, given that a higher FSH dose is needed for oocyte retrieval in these patients.

Having a healthy baby is the ultimate goal of infertile patients, and the live birth rate is therefore a critical factor in the assessment of ART outcomes, given that a clinical pregnancy does not necessarily lead to a live birth. Keefe et al.[27] reported that older women had a higher rate of miscarriage than younger women because eggs collected from older women underwent more mitoses before meiosis, and oxidative injury thus resulted in shorter telomeres, disordered meiosis, and chromosome aneuploidy. Our study supported this finding. In this study, although the pregnancy rates in the three groups were similar, the embryo implantation and live birth rates were significantly higher in the young OPOI group compared with the advanced-age DOR group, and the abortion rate was significantly lower than in both advanced-age groups. Although the live birth rate in the advanced-age normal ovarian reserve group was lower (31.4%) than in young OPOI patients and higher than in advanced-age DOR patients, the differences were not significant. Moreover, the miscarriage rates were similar in both advanced-age groups. The pregnancy advantage shown by advanced-age women with normal ovarian reserve may thus reflect the higher numbers of eggs and embryos, while egg quality was similar to that in advanced-age DOR patients.

Conclusions

The decreased ovarian reserve in young women with OPOI and older women with

DOR implies a lower ovarian response, leading to fewer eggs and embryos. However, young OPOI patients can achieve higher embryo implantation and live birth rates, and had a significantly lower abortion rate than advanced-age patients (with or without DOR). Although older women with normal ovarian reserve had higher embryo implantation and live birth rates than those with DOR, the difference in live birth rates was not significant, possibly reflecting differences in egg quantity rather than quality. Young patients with OPOI may be easily overlooked in the early stage, due to their occult status, and may thus progress to POI. More attention should therefore be paid to the early screening of ovarian function in infertile women, including women of childbearing age, and the indications for IVF/ICSI should be widened for these women.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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