Journal of Infertility and Reproductive Biology

J Infertil Reprod Biol, 2021, Volume 9, Issue 2, Pages: 70-78. https://doi.org/10.47277/JIRB/9(2)/70

Does Preovulatory Follicle Number Affect Probability for Achievement of at Least One Top Quality Embryo from Poor Responder Women Undergoing Assisted Reproduction Treatment?

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Received: 10/04/2021 Accepted: 14/06/2021 Published: 20/06/2021

Abstract

Choosing the ideal treatment protocol based on the prediction of normal, poor, or excessive response might guide clinicians to achieve these treatment goals. Patient-oriented strategies regarding the number of oocytes intended to induce a top-quality embryo (TQE) are needed. We aimed to evaluate the prognostic cycle characteristics for achieving at least one top-quality embryo during ovulation induction among poor responder patients. The medical records of 426 patients with low oocyte yield following controlled ovarian hyperstimulation (COH) treatment for in vitro fertilization-embryo transfer (IVF–ET) procedures between 2008 and 2013 were evaluated. One hundred and thirty-two patients exhibiting poor ovarian response based on the 2011 ESHRE diagnostic criteria were included after exclusion of couples with male factor infertility, endometriosis, chromosomal abnormalities, and any other condition reducing fertility. When the cycle characteristics of women aged ≥35 years were analyzed selectively, a significantly positive correlation has been found between the numbers of >14 mm follicles and generation of top-quality embryos following IVF-ET unlike women <35 years old. Despite the clinical and live birth rates among the two age groups were comparable, the number of >14 mm follicles needed to achieve at least one TQE during COH among ≥35 years old group was determined as 3.5 with a sensitivity of 73% and specificity of 67% (p:0.004). Minimal stimulation protocols might be a reasonable choice for poor responder women younger than 35 years due to a favorable prognosis when compared to older counterparts.

Keywords: Fertility, Ovarian follicle, Oocyte retrieval, In vitro fertilization, Embryonic development

Introduction

During controlled ovarian stimulation (COS) for in vitro fertilization and embryo transfer (IVF–ET) procedures, the application of the best treatment tailored to a woman's unique reproductive characteristics is the mainstay of individualized controlled ovarian stimulation (ICOS). Maximizing the chances of pregnancy by the achievement of a certain number of oocytes with fertilization potential and eliminating the iatrogenic and avoidable risks resulting from ovarian hyperstimulation must be balanced during ICOS. Individualization of treatments in IVF–ET should be based on a prediction of the individual ovarian response (1). Choosing the ideal treatment protocol based on the prediction of a normal, poor, or excessive response might guide clinicians in achieving these treatment goals (2). Determination of the number of oocytes necessary to obtain at least one euploid embryo for transfer in individual patients considering their ovarian reserve might increase the success of treatment cycles and decrease the burden of COS (3-5). The association between the numbers of oocytes and live births in 400,135 IVF treatment cycles has been evaluated previously and demonstrated that live birth rates plateaued when harvested oocyte numbers exceeded ~15 (6). La Marca and Sunkara's systematic review concluded that it was possible to use the predictive value of antral follicle count (AFC) and anti-Müllerian hormone (AMH) levels as the best surrogate markers for ovarian reserve, and for predicting the whole spectrum of ovarian responses with reliable accuracy. They recommended categorizing the expected ovarian response to stimulation by tailoring individualized therapeutic strategies for each patient (7).

Ovulation induction for IVF–ET usually results in a poor ovarian response in terms of dominant follicles among poor responder infertile women. Increasing gonadotropin dose, using adjuvant treatment choices, such as the use of androgens, growth hormone, and luteal phase estradiol supplementation have been evaluated extensively, but a unique and effective treatment protocol has not yet been invented to augment the number of induced dominant follicles needed to produce healthy oocytes (8). Current investigations have revealed that the more follicles generated during ovulation induction for IVF-ET, the more chance for good quality embryos regardless of woman age. Determining the exact number of stimulated follicles needed to achieve 'good quality and euploid embryos' following IVF–ET cycles for individual patients might enable clinicians to use more

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patient-friendly COH protocols. This strategy might enable infertile patients to cope with the burden of ovulation induction and avoid having unnecessarily induced follicles during COH.

In this retrospective study, we aimed to evaluate the prognostic cycle characteristics in terms of the number of >14 mm follicles for achieving at least one top-quality embryo (TQE) following COS among poor responder patients.

Methods

This retrospective study was conducted in a tertiary health center after obtaining permission for the research from the hospital's institutional review board. The medical records of 426 patients with low oocyte yield following COH treatment for an IVF–ET procedure between 2008- 2013 in the IVF Unit of the institution performing around 50 IVF-ET cycles per month and covering the interior Anatolian region of Turkey as catchment area were evaluated. Patients exhibiting a poor ovarian response (POR) based on the 2011 Bologna diagnostic criteria established by ESHRE were included in the study after exclusion of couples with male factors, endometriosis, chromosomal abnormalities, any other chronic medical conditions like endocrinological abnormalities, and congenital uterine anomalies which could influence fertility potential of the women. According to Bologna criteria, poor response during IVF-ET treatment procedures has been defined as follows: the presence of at least two of the following three features: (1) advanced maternal age or any other risk factor for POR; (2) a previous POR (≤3 oocytes with a conventional stimulation protocol) and (3) an abnormal ovarian reserve test (ORT) or in the absence of advanced maternal age or abnormal ORT, two episodes of POR after maximal stimulation have been sufficient to define a patient as a poor responder. The COH and IVF–ET outcomes of the remaining 132 patients were evaluated. Two consecutive IVF-ET cycle outcomes of 7 (5%) out of 132 patients have been included in the study. IVF treatment cycles of the remaining 125 (95%) patients have been included in the study only once. The primary outcome measure of the study was determining the number of preovulatory (>14 mm) follicle numbers for the achievement of one TQE. Secondary outcome measures of the study were determining the clinical and live birth rates among poor responder women younger and older than 35 years old. All investigations were approved by the local ethics committee of the hospital and informed consent was obtained from all patients for the use of their records.

Ovulation induction procedures have been conducted by utilization of oral contraceptive (OC) microdose flare-up, long GnRH agonist, or GnRH Antagonist protocol. Microdose flare-up stimulation protocol has been conducted as follows: OC (Desolett; Organon, Oss, The Netherlands) was started on day 1 of the previous cycle for 21 days and 40 micrograms of leuprolide acetate (Lucrin; Abbott, Cedex, France) subcutaneously (sc.) has been started as twice daily 3 days after cessation of OC, followed by 225 IU/day im. human menopausal gonadotropin (hMG) (Menogon; Ferring, Istanbul, Turkey) and 225 IU/day sc. recombinant Follicular Stimulating Hormone (FSH) (Gonal-F; Merck Serono, Istanbul, Turkey) utilization for ovarian stimulation on the third day of initiation of leuprolide acetate. Long GnRH agonist protocol has been conducted as follows: 1,5 mg leuprolide acetate has been started subcutaneously on 21. day of the previous menstrual cycle until the third day of menstruation. On the third day of menstruation, leuprolide acetate dose has been decreased to 1 mg and 225 IU/day hMG and 225 IU/day recombinant FSH have been concomitantly started. For both OC microdose flare-up and long GnRH agonist protocols, leuprolide acetate and gonadotropins have been administered until ovulation triggering.

GnRH Antagonist stimulation protocol has been conducted as follows: 225 IU/day hMG and 225 IU/day recombinant FSH have been started on day 3 and 0.25 mg cetrorelix (Merck Serono; İstanbul, Turkey) has been administered daily when two or more follicles reached 13-14 mm in diameter until ovulation triggering. The doses of hMG and recombinant FSH have been adjusted according to the ovarian response during ovarian stimulation. The first visit for transvaginal ultrasonographic folliculometry procedure has been performed on the fifth day of ovarian stimulation and every other day until ovulation triggering. Folliculometry procedures have been performed by the same ultrasonography operator on the day of hCG ovulation triggering by measuring the mean of the width and length of each follicle larger than 10 millimeters. Recombinant human chorionic gonadotropin (hCG) (250 micrograms sc., Ovitrelle, Merck Serono, Istanbul, Turkey) or urinary hCG (10.000 IU im., Pregnyl, Schering Plough, İstanbul, Turkey) was administered when at least two leading follicles reached a mean diameter of 18 mm. Oocyte retrieval has been conducted by using transvaginal ultrasonography guidance after 36 hours following hCG injection. Intracytoplasmic sperm injection (ICSI) procedure has been performed for all oocytes harvested and metaphase II oocytes were reviewed after 16 hours following ICSI. Fertilization of the oocytes harvested from poor responder IVF-ET patients has been liberally performed by using ICSI procedures in our IVF-ET unit as a policy. One to 3 best quality embryos have been transferred under ultrasonographic guidance on day 3 for all patients. Following the embryo transfer (ET), all patients received vaginal progesterone (Crinone 8% gel, Serono) supplementation twice a day for luteal phase support until menstruation or for 8 weeks after ET procedure in case of a clinical pregnancy establishment. Clinical pregnancy was defined as the presence of a gestational sac with accompanying fetal heartbeat on ultrasonography at least 4 weeks after ET.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS Statistics software (v. 22.0, IBM Corp., Armonk, NY, USA). Normal distribution of data was evaluated by using the Kolmogorov–Smirnov test. Normally distributed continuous variables were presented as the mean ± standard deviation and were compared by using independent-sample Student's t-tests. Data without a normal distribution were tested by using the Mann–Whitney U test. Receiver operating characteristic (ROC) curve analyses were used to evaluate the relationship between the numbers of >14-mm follicles induced during COH and TQE achievement among poor-responder women aged <35 and ≥35 years old respectively. Comparisons of categoric variables were done using Fisher's exact test, or the chi-squares test, and p values <0.05 were considered statistically significant. Correlation analysis results were presented by using Spearman's rank correlation coefficient r and as 95% confidence intervals (CIs) for comparison of unique cycle characteristics and TQE achievement.

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Results

Based on evaluation of the medical records of 426 patients with low oocyte yield following COH treatment for an IVF–ET procedure, 132 poor responder women (30%) were selected for further statistical analysis regarding the inclusion and exclusion criteria of the study. The IVF–ET cycle outcomes of the study patients are presented in Tables 1-4.

When the cycle characteristics of all poor responder women were analyzed separately, the ROC curve analysis revealed a significant positive relationship between the number of >14 mm follicles and TQE numbers achieved following COH (n= 132; area under curve= 0.69, p= 0.001; 95% CI= 0.58–0.80). Based on the same ROC curve analysis, the number of >14 mm follicles needed to achieve at least one TQE during COH among poor responder women regardless of age stratification was determined as 4.5 with a sensitivity of 67%, specificity of 65%, the positive predictive value of 33.9% and negative predictive value of 88.2%. When the cycle characteristics of women aged ≥35 years were analyzed separately, the ROC curve analysis revealed a significant positive relationship between the number of >14 mm follicles and TQE numbers achieved following COH (Figure 1; n= 97; area under curve= 0.71, p= 0.004; 95% CI= 0.58–0.84).

Based on the same ROC curve analysis, the number of >14 mm follicles needed to achieve at least one TQE during COH among ≥35 years old group was determined as 3.5 with a sensitivity of 73%, specificity of 67%, the positive predictive value of 29.2% and negative predictive value of 89.8%. When women aged <35 years were analyzed separately, the ROC curve analysis did not reveal such a statistically significant relationship (Figure 2; n= 35; area under curve = 0.67; p=0.13).

Naturally, a significant relationship between the number of oocytes harvested by oocyte pick-up procedure and the production of top-quality embryos among poor-responder women regardless of woman age has been observed (Figure 3; n=132; area under curve= 0.75; p<0.001).

When the total gonadotrophin dose was evaluated for the achievement of at least one TQE, no statistically significant relationship could be determined regardless of the age group (n=132; area under the curve: 0.50; p= 0.96). The 'empty follicle syndrome' and fertilization failure rates were similar among young and old women when age ≥35 years was assigned as a poor prognostic factor for oocyte quality. The numbers of days of COH, basal follicle-stimulating hormone (FSH) levels, and total basal AFCs were not correlated with the production of at least one TQE (r= 0.08, p= 0.34; r= 0.11, p= 0.17; and r= 0.15, p= 0.08, respectively). Conversely, the serum estradiol level on the day of stimulating ovulation with human chorionic gonadotrophin (hCG) was positively correlated with the achievement of at least one TQE (r= 0.36; p= 0.03). When IVF-ET cycle outcomes of patients have been compared according to the clinical pregnancy achievement status, cyle outcomes are comparable except M2 oocyte number and good quality number (Table 3).

When IVF-ET cycle outcomes of patients <35 and ≥35 years old have been compared, cycle outcomes are comparable except woman age, body mass index, the total number of antral follicle count, and transferred embryo number (Table 4).

Table 1. Clinical characteristics of the study group (N=132)

Parameter	N	Minimum	Maximum	Mean	Std. Deviation
Age	132	25	48	36,89	4,609
Body Mass Index (BMI)	132	15	37	26,34	4,015
IVF-ET treatment number	132	1	6	1,36	0,691
Day 3 E2 (pg/mL)	132	10,1	175,0	52,513	28,3364
E2 level on stimulation day 4	132	11,0	865,0	154,147	148,2921
E2 level on hCG day (pg/mL)	121	17	3158	1131,96	688,562
P level on hCG day (ng/mL)	120	0,2	4,2	0,871	0,6706
Day 3 FSH (IU/L)	132	3,6	19,0	9,893	3,0104
Day 3 LH (IU/L)	132	1,1	12,1	5,624	2,4478
Right ovary antral follicle count	132	0	4	2,33	1,000
Left ovary antral follicle count	132	0	4	2,38	1,038
Stimulation days	132	4	22	9,80	2,191
Total gonadotropins used (IU)	132	1575	9800	4135,30	1487,201
Endometrial thickness on hCGday (mm)	132	1	17	9,20	2,358
> 14 mm follicle number	132	0	12	3,89	2,672
Oocytes retrieved	132	0	11	3,33	2,674
M2 oocyte number	132	0	10	2,43	2,279
2PN number	132	0	10	1,41	1,676
Embryo number	132	0	10	1,34	1,662
Transferred embryo number	83	1	3	1,49	0,632

Abbreviations= BMI: Body Mass Index, E2: Estradiol, P: Progesterone, FSH: Follicle Stimulating Hormone, LH: Luteinising Hormone, hCG: human chorionic gonadotropin

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Table 2. The comparison of poor responder patients' cycle parameters according to the number of preovulatory follicles > 14 mm based on cut-off number of 4.5 (N:132)

Parameter	> 14 mm follicles <4.5 (N=76) Mean±SD	> 14 mm follicles >4.5 (N=56) Mean±SD	P value
Age (years)	37.0±4.6	36.6±4.5	0.77**
Body mass index (BMI) (kg/m^2)	24.2±3.9	26.4±4.1	0.98**
Cycle number (n)	1.3±0.5	1.3±0.8	0.69**
Day 3 FSH level (mIU/mL)	9.82±2.91	9.98±3.16	0.76*
Day 3 LH level (mIU/mL)	5.47±2.53	5.82±2.33	0.18**
Day 3 E2 level (pg/mL)	54.84±33.19	49.35±19.80	0.27*
Total antral follicle count (n)	4.58±1.77	4.88±1.72	0.39**
Stimulation days (n)	9.82±2.61	9.79±1.44	0.64**
Total gonadotropins used (IU)	4267±1615	3955±1286	0.54**
Cancellation rate (n,%)	28/76 (36.8%)	1/56 (1.8%)	<0.001
E2 level on hCG day (pg/mL)	762±514	1560±614	<0.001**
P level on hCG day (ng/mL)	0.83±0.74	0.91±0.57	0.08**
Endo thickness on hCG day (mm)	8.6±2.3	10.0±2.1	0.002**
Oocytes retrieved (n)	1.61±1.42	5.66±2.15	<0.001**
M2 oocyte number (n)	1.11±1.25	4.23±2.12	<0.001**
2PN number (n)	0.62±0.84	2.48±1.91	<0.001**
Embryo number (n)	0.59±0.83	2.36±1.94	<0.001**
Good quality embryo number (n)	0.42±0.49	0.80±0.40	0.006**
Top quality embryo number (n)	0.12±0.32	0.34±0.47	0.002**
Fertilization rate (%)	54.5±34.9	57.8±31.2	0.61*
Transferred embryo number (n)	1.25±0.50	1.65±0.65	0.003**

*P values were calculated by using Independent Samples t test, ** P values were calculated by using Mann Whitney U test.

Table 3. The comparison of poor responder patients according to the cycle outcomes based on clinical pregnancy achievement status (N:132)

Parameter	Clinical Pregnancy (+) (N=10) Mean±SD	Clinical Pregnancy (-) (N=122) Mean±SD	P value
Age (years)	36.2±4.1	36.9±4.6	0.54**
Body mass index (BMI) (kg/m^2)	24.6±3.3	26.4±4.0	0.17**
Cycle number (n)	1.3±0.4	1.3±0.7	0.97**
Day 3 FSH level (mIU/mL)	9.76±3.57	9.90±2.97	0.88*
Day 3 LH level (mIU/mL)	6.30±2.98	5.56±2.40	0.52**
Day 3 E2 level (pg/mL)	61.12±28.98	51.80±28.28	0.32*
Total antral follicle count (n)	5.50±2.01	4.64±1.72	0.24**
Stimulation days (n)	9.40±0.96	9.80±2.26	0.52**
Total gonadotropins used (IU)	3702±1136	4170±1510	0.51**
Mean follicle number (n)	4.40±2.63	3.84±2.68	0.47**
Cancellation rate (n,%)	-	29/122 (23.7%)	-
E2 level on hCG day (pg/mL)	1428±768	1105±678	0.17**
P level on hCG day (ng/mL)	0.77±0.35	0.88±0.69	0.92**
Endo thickness on hCG day (mm)	10.05±1.57	9.13±2.40	0.23**
Oocytes retrieved (n)	4.30±2.49	3.25±2.68	0.16**
M2 oocyte number (n)	3.80±2.20	2.32±2.25	0.03**
2PN number (n)	1.80±0.78	1.38±1.72	0.06**
Embryo number (n)	1.60±0.84	1.32±1.71	0.10**
Good quality embryo number (n)	1.00±0.00	0.55±0.50	0.006**
Top quality embryo number (n)	0.40±0.51	0.20±0.39	0.13**
Fertilization rate (%)	59.5±26.8	56.0±34.0	0.76*
Transferred embryo number (n)	1.40±0.51	1.51±0.64	0.73**

*P values were calculated by using Independent Samples t test, ** P values were calculated by using Mann Whitney U test.

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Table 4. The comparison of poor responder patients according to the cycle characteristics and cycle outcomes based on chronological age categories (N:132)

Parameter	<35 years old (N=35) mean±SD	≥35 years old (N=97) mean±SD	P value
Age (years	30.9±2.9	39.0±2.9	<0.001**
Body mass index (BMI) (kg/m^2)	24.7±2.7	26.9±4.2	0.003**
Cycle number (n)	1.4±0.6	1.3±0.7	0.10**
Day 3 FSH level (mIU/mL)	9.94±3.23	9.87±2.94	0.89*
Day 3 LH level (mIU/mL)	5.29±1.77	5.74±2.64	0.72**
Day 3 E2 level (pg/mL)	56.69±35.60	51.00±25.25	0.31*
Total antral follicle count (n)	5.39±1.50	4.49±1.79	0.008**
Stimulation days (n)	10.20±2.76	9.66±1.94	0.51**
Total gonadotropins used (IU)	4192±1565	4114±1465	0.76**
Mean follicle number (n)	4.14±2.98	3.79±2.56	0.73**
Cancellation rate (n,%)	6/35 (17.1%)	23/97 (23.7%)	0.42***
E2 level on hCG day (pg/mL)	1077±535	1151±737	0.72**
P level on hCG day (ng/mL)	0.79±0.39	0.90±0.74	0.81**
Endo thickness on hCG day (mm)	9.89±2.04	8.95±2.42	0.02**
Oocytes retrieved (n)	3.40±2.89	3.30±2.60	0.99**
M2 oocyte number (n)	2.31±2.38	2.47±2.25	0.58**
2PN number (n)	1.20±1.81	1.48±1.62	0.27**
Embryo number (n)	1.17±1.80	1.40±1.61	0.38**
Top quality embryo number (n)	0.26±0.44	0.20±0.39	0.44**
Fertilization rate (%)	50.6±35.0	58.6±32.5	0.28*
Transferred embryo number (n)	1.09±0.42	1.64±0.63	<0.001**
Clinical pregnancy rate (n,%)	2/35 (5.7%)	8/97 (8.2%)	0.47****
Livebirth rate (n,%)	2/35 (5.7%)	5/97 (5.2%)	0.59****

*P values were calculated by using Independent Samples t test, ** P values are calculated by using Mann Whitney U test, *** Pearson Chi Square test, **** Fisher's Exact test.

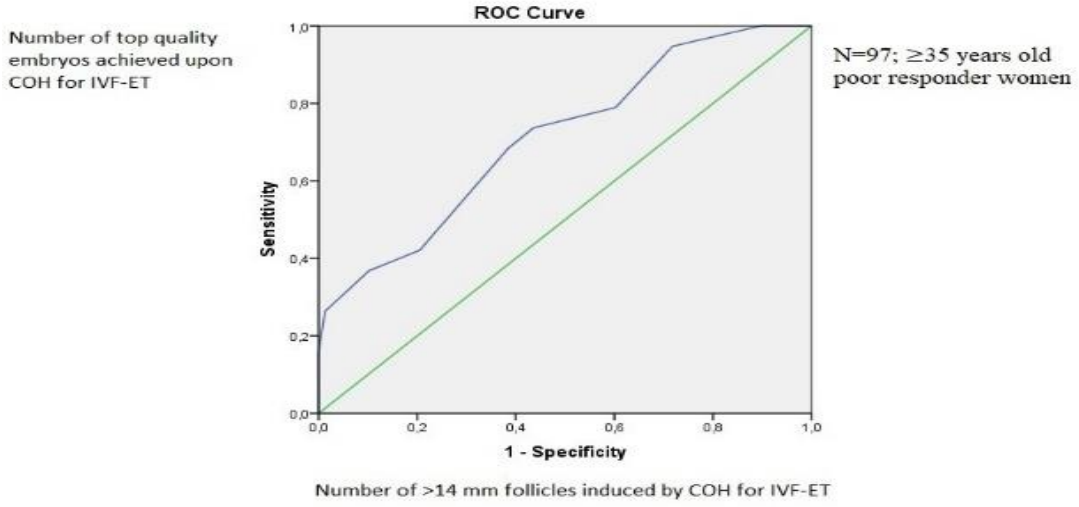

Figure 1. The receiver operating characteristic (ROC) curve analysis revealing a positive significant relationship between the number of >14 mm follicles induced during ovarian stimulation and top quality embryo achievement among ≥35 years old poor responder women (N=97; Area under curve: 0.71; p=0.004; %95 CI=0.58-0.84).

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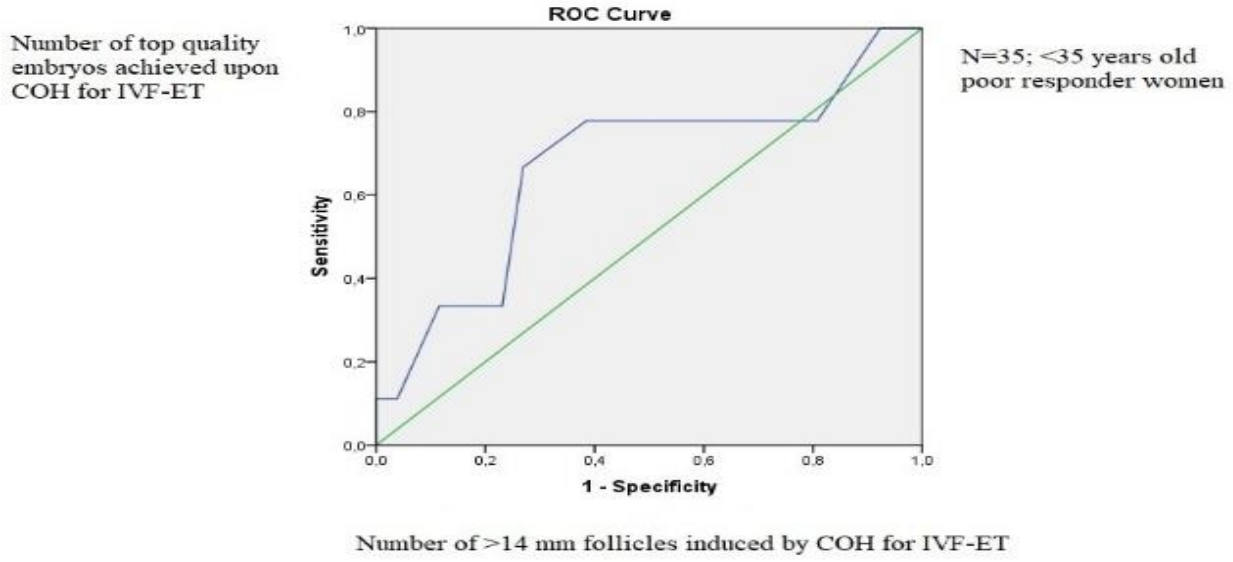

Figure 2. The receiver operating characteristic (ROC) curve analysis revealing a non-significant relationship between the number of >14 mm follicles induced during ovarian stimulation and top quality embryo achievement among <35 years old poor responder women (N=35; Area under curve: 0.67; p=0.13; %95 CI=0.44-0.89).

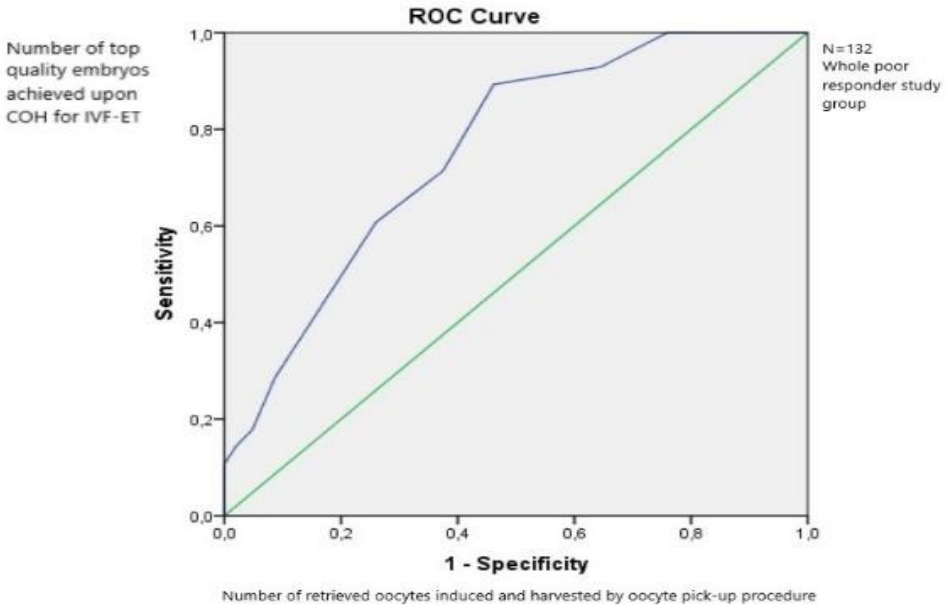

Figure 3. The receiver operating characteristic (ROC) curve analysis revealing a non-significant relationship between the number of >14 mm follicles induced during ovarian stimulation and top quality embryo achievement among whole study group (N=132; Area under curve: 0.75; p<0.001; %95 CI=0.61-0.92).

Discussion

The objective of the study was to determine the number of preovulatory (>14 mm) follicle numbers for the achievement of one TQE among poor responder patients. A positive statistically significant relationship has been found between the number of preovulatory follicles and achievement of one TQE for poor responder patients ≥35 years old unlike <35 years old counterparts. These results are consistent with the POSEIDON group's proposal highlighting that a lower number of oocytes are needed to achieve one euploid embryo for group 3 (<35 years old, poor ovarian reserve, good quality oocytes) low prognosis patient group (9). La Marca et al. developed a starting FSH dosage nomogram based on the woman's age and AFC as surrogate markers for ovarian reserve. Although not yet validated, the use of such a nomogram might increase the numbers of patients with a satisfactory oocyte yield while reducing the incidences of both poor and excessive ovarian responses to COH (10).

Recently, 'the ability to retrieve the number of oocytes necessary to obtain at least one euploid embryo for transfer in each patient' has been proposed by the "Patient-Oriented Strategies Encompassing Individualized Oocyte Number" (POSEIDON) group as a goal for COH. Additionally, a new concept of 'poor prognosis' has been defined for those patients undergoing assisted reproductive technologies to tailor treatment cycles based on their prognosis regarding patient characteristics, such as the woman's age, AFC, AMH level, and total numbers of harvested oocytes (11). The clinical utility of this concept has not yet been evaluated extensively.

Oocyte quality and subsequently formed embryo quality might be affected adversely by the use of high-dose gonadotrophins. In this way, the selection of poor-quality oocytes that would not have been selected during an unstimulated natural cycle has been proposed as an explanation for this phenomenon. However, the association between embryo quality and ovarian stimulation doses is prone to be confounded by the predisposition of older patients to receive higher doses of gonadotropins, and the higher incidence of a premature P rise caused by aggressive stimulation in fresh IVF–ET cycles (11). Additionally, aneuploidy rates are not different regarding the generated embryo numbers or ovarian stimulation status of the patient (12). Ho et al. proposed a modified natural cycle IVF with 'acceptable pregnancy rates, lower cost and lower risk of OHSS' as a reasonable first-line choice for good responders and as a second-line choice for poor responders with a history of low- and poor-quality oocyte yield with the use of standard COS protocols (11). In a multi-center randomized non-inferiority trial conducted among 394 patients, Youssef et al. demonstrated that a mild ovarian stimulation strategy was not inferior to conventional ovarian stimulation in terms of ongoing pregnancy rates, with shorter durations of stimulation, lower amounts of gonadotrophins needed, and lower costs. Based on these results, they recommended mild ovarian stimulation as a first-line treatment choice for women with poor ovarian reserves undergoing IVF (1).

Optimal utilization of competent oocytes/embryos and endometrial receptivity might be the biologically plausible advantages of mild ovarian stimulation protocols (13,14). Despite having fewer oocytes or embryos available with mild ovarian stimulation, cumulative pregnancy and live birth rates similar to those with conventional IVF have been demonstrated in previous studies (2,4,5,15-21).

Selection of the study group from the IVF-ET patients with low oocyte yield based on Bologna criteria is a strength of this study. However, retrospective design and the low number of patients seem to be the potential limitations of the study also. The utilization of different stimulation protocols is a limitation of the study. Despite utilization of three different ovarian stimulation protocols during IVF-ET procedures might have affected the pregnancy rates among the whole study group, the primary outcome measure of the study was determining the number of preovulatory (>14 mm) follicle number for the achievement of at least one TQE. Another limitation of the study is the lack of preimplantation genetic diagnosis analysis of the embryos reflecting chromosomal integrity of the embryos because of the retrospective nature of the study. Because, the majority of the study group has consisted of poor responder women older than 35 years old, cycle outcomes are better for patients with more than 4.5 preovulatory follicles of > 14 mm in size (Table 2). Despite the limitations emphasized above, the results of this study highlight the importance of inducing more preovulatory follicles for >35 years old poor responder women to achieve better cycle outcomes, unlike their younger counterparts.

Conclusion

In conclusion, much additional work needs to be done to identify the optimal ovarian response to achieve a healthy GQE regarding patient characteristics, such as ovarian reserve and chronological age. Development of dosing algorithms by using ovarian reserve markers and patient characteristics based on optimal ovarian response during IVF–ET procedures is needed. Large sample size randomized controlled trials comparing iCOS and conventional COS with the use of all relevant end-points, such as the burden of treatment, cost, patient preference, and cumulative chances for a healthy child are needed. Any clinical benefits of increased follicle numbers during COH among young (<35 years old) poor responders have not been observed, unlike their older (≥35 years old) counterparts. Possibly, milder stimulation protocols aimed at developing fewer dominant follicles should be selected for young poor-responder patients. Determining the exact number of stimulated follicles to achieve at least one 'good quality and euploid embryo' during COS for IVF–ET cycles for each patient might enable clinicians to use more patient-friendly stimulation protocols. The results of the present study suggest that clinicians should tailor the ovulation induction procedure during IVF-ET treatment to retrieve good quality oocytes/ embryos according to the woman's age and ovarian reserve.

Acknowledgments

We thank James Cummins, Ph.D., from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Funding sources

There is no financial support.

Conflict of interests

The authors declare that there is no conflict of interest.

Author contributions

All authors made substantial contributions to the conception, design, data acquisition, data analysis and interpretation of results of the study. All authors also drafted the work; revised it critically for important intellectual content; approved the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Surgical and medical practices were done by Hacer Cavidan Gulerman, Nafiye Yilmaz and Inci Kahyaoglu. Conception of the study objective was made by Serkan Kahyaoglu and Yaprak Ustun. Design, data collection and processing of the results of the study were made by Serkan Kahyaoglu. Analysis and interpretation of the results were made by Serkan Kahyaoglu, Hacer Cavidan Gulerman, Nafiye Yilmaz, Inci Kahyaoglu and Yaprak Ustun. Literature search and writing of the study were performed by Serkan Kahyaoglu.

Ethical issue

This retrospective study was conducted in a tertiary health center after obtaining permission for the research from the hospital's institutional review board. This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of Ankara Dr. Zekai Tahir Burak Women's Health Education and Research Hospital, University of Health Sciences who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted on 11/09/2017 with an "IRB approval number of 17" from the IRB of Ankara Dr. Zekai Tahir Burak Women's Health Education and Research Hospital, University of Health Sciences. This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate

Informed consent has been taken from all patients who have participated in this study.

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