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Comparative study between agonist and antagonist protocols in PCOS patients undergoing ICSI: a cross-sectional study

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Abstract

Background: Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting 5–10% of women of reproductive age. The syndrome is surrounded by controversies regarding both its diagnosis and treatment. The introduction of long-acting GnRH agonists in the late 1980s revolutionized the approach to ovarian stimulation in assisted reproductive technologies by providing the means to downregulate endogenous pituitary gonadotropin secretion and thereby prevent a premature luteinizing hormone surge during exogenous gonadotropin stimulation. The relatively recent introduction of GnRH antagonists in clinical practice has provided another option for ovarian stimulation in IVF. The purpose of this study was to compare the efficacy of the fixed GnRH antagonist vs. GnRH agonist long protocol in patients with polycystic ovary syndrome treated by ICSI.

Results: There is a statistically significant difference between both groups in view of the received dose of gonadotrophin (1901.7 ± 400.6 vs. 1789 ± 368 with $p = .004$) and duration of stimulation (11.3 ± 0.8 vs. 10.3 ± 1.1 with $p = .017$). There is no significant difference between both groups in view of pregnancy outcome (37% vs. 32% with $p = .125$). There is a significant difference between both groups in view of ovarian hyperstimulation syndrome (OHSS) incidence where the rates were 15%, 6%, and 1.5% vs. 4.5%, 2.5%, and .05% with $p = 0.04$ for mild, moderate, and severe, respectively, form of OHSS in group 1 and group 2.

Conclusion: The antagonist protocol may be the preferred stimulation protocol for PCOS patients treated by ICSI in view of the reduction of OHSS incidence rates without compromising the pregnancy outcome.

Keywords: PCO, GnRH agonist, GnRH antagonist, ICSI, OHSS

Background

In 2003, a group of experts agreed for the diagnostic criteria of PCO to include oligo-anovulation, hyperandrogenism/hyperandrogenemia, and polycystic ovaries seen at ultrasound as the third diagnostic markers and to allow for a diagnosis of PCOS. If two of the three criteria were met and the same endocrinopathies were excluded, these are known as the Rotterdam criteria [1].

Polycystic ovarian syndrome (PCOS) is a significant cause of infertility for patients seeking assisted reproductive procedures and occurs in 4–12% of the general population [2].

The objective of the study was to evaluate which protocol is more effective in the prevention of ovarian hyperstimulation syndrome (OHSS) in a specific group of patients (i.e., PCO).

Advantages of antagonists are the shorter duration of the analog treatment, the shorter duration of stimulation with FSH, and the lower risk of developing ovarian hyperstimulation syndrome (OHSS) [3].

One advantage in the context of preventing OHSS may be the possibility of triggering ovulation with a short endogenous luteinizing hormone (LH) surge induced with a GnRH agonist adminstration instead of the prolonged LH action induced by the administration of hCG. In addition, with the standard "long agonist protocol," approximately 25 daily subcutaneous injections are needed, whereas antagonists require around 5 daily subcutaneous injections [4].

In this study, we compared two known protocols, long agonist and multiple-dose antagonist, for ovulation

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induction in PCOS patients with a primary goal of the estimation of OHSS incidence rates in addition to other ICSI outcomes such as the number of oocytes retrieved, fertilization, implantation, and pregnancy rates in both groups. It is well known that the comparison between agonist and antagonist had been previously reported in many studies, but we tried to emphasize the superiority of antagonist in the prevention of OHSS.

Previous studies did not account for various patient populations, especially PCOS patients, and so, we conducted this trial. Also, in this study, we used two arms of comparison in this group of patients, and this may add beneficial information about both types of stimulation particularly their effects on the occurrence of OHSS.

In other studies, there were differences in stimulation strategies between the study arms which could serve as uncontrolled confounders [5, 6].

The use of GnRH antagonists in IVF is characterized by both advantages and disadvantages as prevention of premature LH increase and is easier and takes less time. GnRH antagonists act within a few hours after their administration, and thus, they can be administered only when there is a risk for an LH surge. This is in contrast to GnRH agonists where pituitary downregulation occurs only after 7–10 days [7].

Women with polycystic ovary syndrome are also at increased risk for developing ovarian hyperstimulation when aggressively stimulated with exogenous gonadotropins. Both agonists and antagonists can suppress elevated circulating LH concentrations, but the smaller follicular cohorts observed in antagonist cycles may help to reduce the risk of ovarian hyperstimulation in women with polycystic ovary syndrome who tend to be high responders [8].

Methods

Subjects and place

This study was carried out in the ART Unit of International Islamic Center of Population Studies and Research (IICPSR), Al-Azhar University, between August 2012 and September 2014. Data of 400 patients diagnosed with polycystic ovaries enrolled in the study was revised and reported.

Inclusion criteria

The following are the inclusion criteria:

1. PCOS patients diagnosed according to Rotterdam and ASRM/ESHRE consensus criteria 2004, (presence of oligo/amenorrhea, clinical and or hormonal hyperandrogenism, and polycystic ovaries by ultrasound)
2. Age between 20 and 35 years
3. BMI < 30
4. Basal levels of FSH and LH hormones ≤ 10 IU/ml
5. Absence of pelvic pathology as endometriotic cysts, fibroids, and uterine abnormality such as a bicornuate uterus assessed by transvaginal ultrasound

Exclusion criteria

The exclusion criterion is patients in antagonist protocols who triggered by the agonist.

Statistical analysis

Package for Social Sciences (SPSS) for Windows version 20 (IBM, NY, USA) was used. Kolmogorov-Smirnov test for normality was applied to all measured variables. Student t test was used for the comparisons between quantitative variables; chi-square test was used for the comparisons between categorical variables. The sample size was estimated depending on α error = 5%, power of the study = 80%, and effect size that gave the minimally clinical effect using epi-info 7 software for the sample size calculation.

Methodology

Data file of a cohort of 400 PCOS patients was revised and subdivided into 2 equal groups according to the protocols prescribed: group 1 (n = 200) was stimulated by GnRH agonist long mid-luteal protocol, and group 2 (n = 200) was stimulated by fixed (day 7) antagonist protocol. In GnRH agonist long mid-luteal protocol (agonist group), triptorelin 0.1 mg (Decapeptyl 0.1, Ferring, Egypt) daily s.c. injection started on day 21 of the preceding cycle (3 days before the discontinuation of oral contraceptive pills (OCP) for 2 weeks), and complete downregulation was diagnosed if estimated E2 < 50 pg/ml. Then, recombinant FSH (rFSH), Gonal-F (follitropin b, Merck Serono, Egypt) s.c. injection was started at a dose of 150 IU/day (the dose was modified according to the response), and both the agonist and recombinant were continued until the day of triggering. In fixed GnRH antagonist protocol (antagonist group), rFSH was given starting from cycle day 2 in a dose of 150 IU daily (the dose was modified according to the response) to day 7 when antagonist (Cetrotide, cetrorelix 0.25 mg, Merck Serono, Egypt) s.c. daily injection was started, and both rFSH and antagonist were continued until the day of triggering. Coasting was decided in patients showing hyper response (> 15–20 follicles in each ovary and or E2 > 3500 pg/ml). As soon as three follicles with a mean diameter of ≥ 17 mm were reached, 5000 IU of HCG (Pregnyl, Organon, Netherlands) was administered i.m. once and 36 h before ovum pick up. Oocyte retrieval was performed assisted by transvaginal ultrasound-guided double-lumen needle aspiration. All embryos were transferred under abdominal ultrasound guidance. Luteal

phase support with 400 mg of micronized progesterone (Utrogestan Laboratoires Besins-International S.A., France) was initiated for 14 days after the embryo transfer. Embryo transfer was canceled, and elective embryo cryopreservation was performed in cases of early OHSS detected 3 days post-oocyte retrieval that could possibly lead to life-threatening OHSS [9] or in cases fulfilling one or more of the criteria for hospitalization [10].The primary outcome measure was the incidence rate of OHSS. Secondary outcome measures were the clinical pregnancy rate (CPR), number of oocytes retrieved, number of embryos transferred, fertilization rate, cancelation rate, duration of stimulation, total dose of stimulation, and E2 concentration on the day of HCG administration. Clinical pregnancy is defined as the presence of gestational sac with fetal heartbeat detected in 6–7 weeks of gestation.

Discussion

Many studies had been shown the difference between long agonist and antagonist protocols for non-PCOS patients treated with IVF/ICSI. In the current study, we had tried to clarify the efficacy of two commonly used protocols prescribed for this category of patients (PCOS patients).

Polycystic ovary syndrome (PCOS) is the most common cause of oligo-ovulation and anovulation both in the general population and among women presenting with infertility [11], being a common endocrine disorder affecting 5–10% of women in reproductive age [12].

The long GnRH agonist (GnRH-a) protocol is a conventional protocol, probably the most widely used throughout the world even now, allows a quite good predictability of the work in IVF units, implies a low cancelation rate, and allows to get a relatively high number of pre-ovulatory follicles of retrieved oocytes and, as a consequence, of embryos available for transfer, thus leading to a satisfactory pregnancy rate [13].

The relatively recent introduction of GnRH antagonists in clinical practice has provided another option for ovarian stimulation in IVF [13].The introduction of GnRH antagonists (GnRH-ant) in assisted reproductive technologies (ART) to prevent LH surge seemed to open up a new way towards a more “friendly IVF.” Unlike the indirect pituitary suppression induced by GnRH-a, GnRH-ant administration causes immediate and dose-related inhibition of gonadotropin release by competitive occupancy of the GnRH receptors in the pituitary [14].

In the current study, the data of 400 PCOS patients were collected and revised. The patients included were distributed into 2 equal groups (group 1, received long mid-luteal agonist protocol; group 2, received fixed antagonist protocol). ICSI was performed for all patients, and the data collected was analyzed anonymously.

Nine cases in group 1 and seven cases in group 2 were canceled. The causes of cancelation in group 1 were empty follicles in three cases, failed fertilization in two cases, and early OHSS in four cases. The causes in group 2 were empty follicles in two cases, failed fertilization in four cases, and OHSS in one case (Table 1).

Table 1 Comparison of cancelation rate and causes of cancelation in both groups

Parameters	Group 1	Group 2	*p* value
Cancelation rate	9 (4.5%)	7 (3.5%)	0.799
Causes of cancelation			
Empty follicles	3 (1.5%)	2 (1%)	
Failed fertilization	2 (1%)	4 (2%)	.611
OHSS	4 (2%)	1 (0.5%)	

There were no significant differences between both groups in view of cancelation rates (4.5% vs. 3.5% with $p = 0.79$) as well as causes of cancelation

There were no significant differences between both groups in view of age, BMI, and basal hormone levels (Table 2).

There was a significant difference between the groups when comparing the means of the total dose of rFSH given (means ± SD, 1901.7 ± 400 vs. 1789.7 ± 368.6 with $p = .004$ in group 1 and group 2, respectively) (Table 2 and Fig. 1). This result was similar to the previous studies done on non-PCOS patients [15, 16] whereas some researchers have shown a significant reduction in the number of used HMG in non-PCOS patients [17, 18] and PCOs patients who underwent treatment with GnRH antagonist [19]. The lower dose required with antagonist treatment may be explained by the difference in the behavior of stimulation between the agonist and antagonist protocols in that with agonist stimulation, the complete downregulation

Table 2 The baseline characteristics of the studied cases

Parameters	Group 1	Group 2	*p* value
[1]Age (years)	29. ± 4.2	28.5 ± 4.3	.0.09
BMI (kg/m^2)	27.2 ± 2.05	26.9 ± 2.06	.294
Basal FSH (μ/m)	7.7 ± 3.2	8.1 ± 2.0	0.141
Basal LH (μ/m)	7.0 ± 3.0	7.2 ± 2.6	0.413
Basal E2 (pg/ml)	37.0 ± 8.1	38.4 ± 7.7	0.069
Total dose of gonadotrophin	1901.7 ± 400.6	1789.7 ± 368.6	0.004*
Duration of stimulation	11.3 ± 0.8	10.3 ± 1.1	0.017*
E2 at hCG day	2672.3 ± 768.3	2528.7 ± 611.4	0.039*

There were no significant differences reported between both groups in view of patients' ages (means 29 vs. 28.5 with $p = 0.09$), BMI (means 27.2 vs. 26.9 with $p = 0.294$), and levels of basal hormones (means of FSH, LH, and E2 were, 7.7 vs. 8.1, 7 vs. 7.2, and 37 vs. 38, respectively, with p values = 0.141, 0.413, and 0.69) for groups 1 and 2, respectively). There were significant differences between both groups in view of the total stimulation dose (means, 1901.7 vs. 1789.7 with $p = 0.004$), the duration of stimulation (means 11.3 vs. 10.3 with $p = 0.017$), and the E2 levels at hCG day (means, 2672.3 vs. 2528.7 with $p = 0.039$) in groups 1 and 2

*Significant if $p \leq .05$. Independent *t* test and chi-square test were used for comparison

[1]Quantitative data was represented by mean and standard deviation, and qualitative data was represented by frequency and or percentage

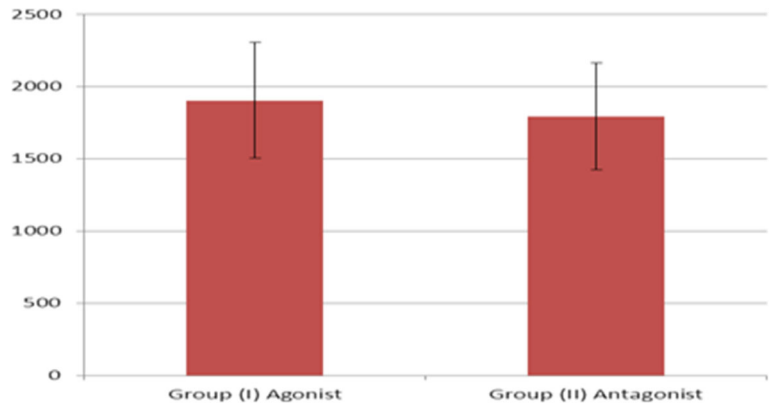

Fig. 1 Box plots representing the median and interquartile range (IQR) values for the doses of rFSH in both groups

required for starting treatment may provoke the depletion of endogenous FSH that may in turn requires augmentation of the gonadotrophin dosage. In antagonist protocol, stimulation with gonadotrophin started before giving antagonist when the levels of endogenous FSH still at the physiological levels that may support the given gonadotrophin, so lower doses were required.

In agreement with our results, many studies supported the finding of reduced stimulation dose in antagonist protocol if compared to agonist rendering ovarian stimulation less costly as in studies by Depalo et al. [7] and Johnston et al. [20].

There is a significant difference between both groups as regards the duration of stimulation by gonadotrophins where the mean ± SD is 11.3 ± 0.8 vs. 10.3 ± 1.1 with p = .017 for groups 1 and 2, respectively (Table 2 and Fig. 2). This result was similar to the result of two previous studies in non-PCOS patients [21, 22]. This also may be explained as mentioned above.

E2 levels estimated at hCG day are significantly different between both groups, i.e., lower levels are at the antagonist group (mean ± SD, 2672.3 ± 768.3 vs. 2528.7 ± 611.4 with p = .039) (Table 2 and Fig. 3).

There is no significant difference between the groups in view of the numbers of oocytes retrieved (mean ± SD, 18.7 ± 4.7 vs. 19.2 ± 3.9 with p = 0.267) (Table 3). The result of our study coincides with the results of the studies of Minaretzis et al. [16] and Hwang et al. [19] who stimulated PCOS patients for ICSI.

The fertilization rate (52% vs. 50% with p = .101) and pregnancy rate (37% vs. 32% with p = .125) for agonist and antagonist groups, respectively, were not significantly different (Table 3). These results were similar to the previous researches in non-PCOS [17, 18] and PCOS patients [19].

In our study, we used the clinical pregnancy rate (CPR) as the primary outcome because the CPR is achieved after ovarian stimulation and IVF represent very important outcome measures for any treatment

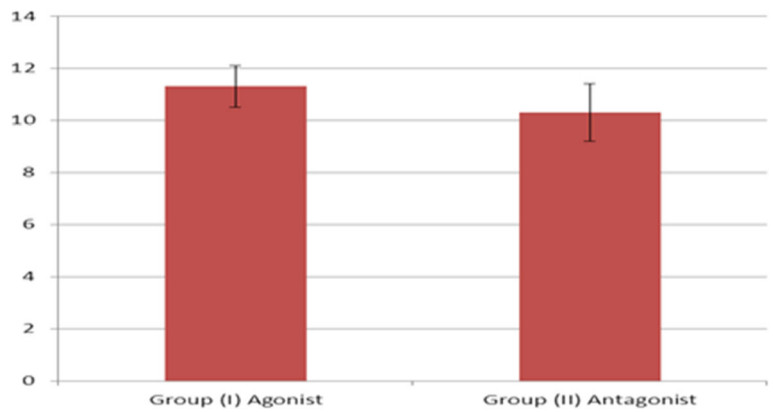

Fig. 2 Box plots representing the median and IQR values for the durations of stimulation in both groups

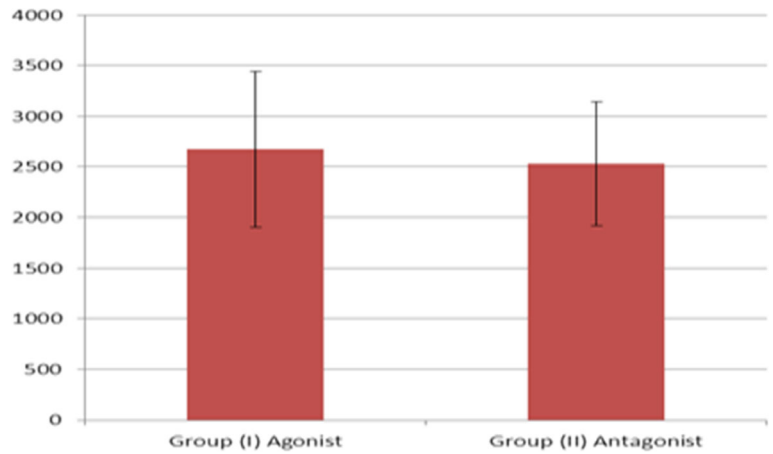

Fig. 3 Box plots representing the median and IQR for the levels of E2 concentrations in the day of hCG in both groups

protocol. There has been conflicting evidence in the literature regarding whether an antagonist protocol is as effective as the long agonist protocol with respect to the CPR and ongoing pregnancy rate (OPR). Significantly lower OPRs are observed in patients on fixed 6-day GnRH antagonist cycles [23].

The most recent review indicates that overall GnRH antagonists do not compromise the effectiveness and significantly prevent OHSS [3].

A meta-analysis of Haiyan et al. [24] included 9 RCTs with a total of 1142 women with PCOS and showed no significant difference between the antagonist and long agonist protocols with regard to CPR and OPR.

GnRH antagonist protocols came to be used more frequently in clinics in a wide range of patients, including patients with normal ovarian responses as well as patients with poor or high responses; this last group includes patients with PCOS.

All the above results are in agreement with those previously published by other contributors [18, 19, 25–29].

Previous studies have all agreed that the antagonist protocol is more patient-friendly and convenient [25, 30].

This convenience, added to the equal CPR compared to the agonist protocol, suggests that the antagonist protocol may be the most suitable stimulation regimen for PCOS patients.

A relatively recent RCT study done by Raffaella-Depalo et al. [31] and a retrospective cohort review by Johnston et al. [20] decided that GnRh antagonist is associated with a significantly lower incidence of grade II OHSS, requiring lower gonadotrophin amounts and a shorter duration of stimulation than GnRh agonist.

The role of an antagonist in the reduction of OHSS in PCOS patients may be attributed to the small follicular cohorts observed after exogenous stimulation. This is supported by a study of Fauser [8]. However, this proposal was not recorded in the current study.

There were significant differences between both groups in view of mild, moderate, and severe OHSS (15%, 6%, and 1% vs. 4.5%, 2.5%, and 0.55 with p = .04) in group 1 and group 2 (Table 4 and Fig. 4).

Our results are in agreement with the findings from previous studies in the general population [32, 33, 25]. These observations suggest that the use of GnRH

Table 3 Comparison of different ICSI outcomes in both groups

Parameters	Group 1	Group 2	*P* value
Number of oocytes retrieved	14.7 ± 4.7	12.2 ± 3.9	0.271
Number of embryos transferred	3.1 ± 1.0	3.0 ± 0.9	0.235
[1]Fertilization rate (%)	51.1%	49.9%	0.101
Pregnancy rate	71/191 (37%)	62/193 (32%)	.125

There were no significant differences between both groups as regards the number of oocytes retrieved (means, 14 and 12 with p = 0.271), the number of embryos transferred (means, 3.1 and 3 with p = 0.235), fertilization rate (51% vs. 49.95 with p = 0.101), and pregnancy rate (36% vs. 32% with p = 0.125) in groups 1 and 2

[1]Quantitative data was represented by mean and standard deviation, and qualitative data was represented by frequency and or percentage

Table 4 Comparison between the frequencies of different forms of OHSS in both groups

Parameters	Group 1	Group 2	*p* value
OHSS frequency (%)			
Mild	30 (15%)	9 (4.5)	
Moderate	12 (6%)	5 (2.5%)	.04*
Severe	3 (1.5%)	1 (0.5)	

Forty-five cases showed OHSS in group 1 [mild cases = 30 (15%), moderate cases = 12 (6%), and severe cases = 3 (1.5%)] while 15 cases showed OHSS in group 2 [mild cases = 9 (4.5%), moderate cases = 5 (2.5%), and severe cases = 1 case only (0.5%)] with significant difference between both groups as regards the incidence of all forms of OHSS (p value = 0.04)

*means significant if $p \leq .05$. Chi-square test were used for comparison

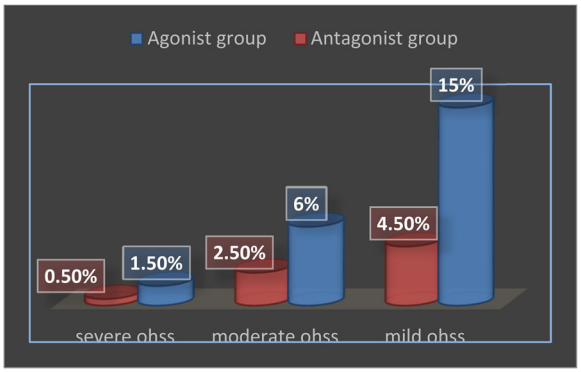

Fig. 4 Bar chart representing the percentages of different forms of OHSS in both groups

antagonists in the treatment of patients with PCOS results in a safer way of performing ovarian stimulation for IVF.

It is not, however, clear that the difference in the rate of OHSS in the two groups was associated with the number of oocytes retrieved. Despite the similar number of oocytes retrieved in the two groups, it cannot be excluded the number of small follicles, which did not yield oocyte but contributed to the incidence of OHSS.

Women receiving antagonists have been shown to have a lower incidence of ovarian hyperstimulation syndrome (OHSS). Assuming comparable clinical outcomes for the antagonist and agonist protocols, these benefits would justify a change from the standard long agonist protocol to antagonist regimens [32].

It should also be noted that the dose of hCG used for triggering final oocyte maturation in the current study was 5000 IU. This choice was made in order to reduce the occurrence of OHSS in this high-risk population. Consequently, regarding OHSS occurrence, the conclusions drawn in the current study might not be applicable in patients with PCOS in whom 10,000 IU hCG is used for triggering final oocyte maturation.

Conclusion

GnRH antagonist may be soon the preferred protocol for PCOS patients treated with ICSI in view of the reduction of the risk of OHSS, the less cost-effectiveness, and the short stimulation time without compromising the pregnancy outcome.

Abbreviations

CPR: Clinical pregnancy rate; GnRH: Gonadotrophin-releasing hormone; hCG: Human chorionic gonadotrophin; OHSS: Ovarian hyperstimulation syndrome; OPR: Ongoing pregnancy rate; PCOS: Polycystic ovary syndrome

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Authors' contributions

BM contributed to the study design, data collection, and statistical analysis. EH contributed to the data collection. EA contributed to the writing of the review and data analysis. EA contributed to the writing of the review and final revision. All authors have read and approved the final manuscript.

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Availability of data and materials

The data will not be shared because, it is the policy of our center.

Ethics approval and consent to participate

The study was approved by the University Medical Ethical Committee (registry number, GYN._199 Med.Research._0000199).

Consent for publication

All authors agreed for the publication at MEF journal.

Competing interests

The authors declare that they have no competing interests.

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