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Freeze-all policy versus luteal phase support with low dose of human chorionic gonadotrophin for high-responder patients undergoing intracytoplasmic sperm injection on pregnancy outcomes: a retrospective cohort observational study

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Abstract

Background: The literature has always controversies on the use of freeze-all policy in high-responder women performing intracytoplasmic sperm injection. In this article, we discuss the benefits of freeze-all policy on the incidence of pregnancy outcomes and the complications.

The main body of abstract: Freeze-all policy is applied to the intracytoplasmic sperm injection program by freezing of all embryos and delaying embryo transfer to another subsequent ovarian cycle, to decrease the incidence of ovarian hyperstimulation syndrome, especially in high-responder women. Unfortunately, freeze-all policy is correlated with an increase in the economic costs and more ICSI laboratory effort. Delayed embryo transfer (ET) is correlated with more anxiety among the patients. An alternative strategy is to perform fresh embryo transfer with more intensive luteal phase support to compensate for the negative effect of the GnRH agonist on the endometrial receptivity and luteal phase support.

Short conclusion: The freeze-all policy had better pregnancy rates with less incidence of moderate to severe hyperstimulation syndrome compared with original fresh embryo transfer in high-responder women performing intracytoplasmic sperm injection.

Keywords: Freeze-all policy, GnRH-antagonist protocol, GnRH-agonist trigger, Ovarian hyperstimulation syndrome, hCG

Background

Live birth rates have increased worldwide after improvement in ICSI [1]. Despite that, since the 2000, the live birth rate is still low with a stationary flat curve [2]. Also, ICSI still has several complications in which the ovarian hyperstimulation syndrome (OHSS) is still the most serious of them. The incidence of OHSS among high-risk women performing controlled ovarian hyperstimulation is about one-third of patients [3]. The incidence of OHSS has marked a decrease after increase use of the gonadotrophin-releasing hormone (GnRH) antagonist protocol [4]. When final oocyte maturation is carried out by

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a GnRH agonist instead of human chorionic gonadotrophin (hCG) as a triggering agent, the incidence of OHSS decreases [5].

The luteinizing hormone (LH) is an important hormone for final oocyte maturation, maintaining corpus luteum function and improving the secretion of progesterone hormone, growth factors that are involved in the process of embryo implantation and enhance placentation [6]. In ART, during controlled ovarian hyperstimulation (COS) to stimulate multiple follicular growth, the hypothalamic activity suppression by GnRH analogs/antagonists is mandatory to prevent a premature LH surge and retrieve multiple oocytes. The commonest triggering drug used for final oocyte maturation is hCG due to its strong biological activity and its long half-life [7]. Human chorionic gonadotrophin can preserve the function of multiple corpora lutea during the luteal phase period, to overcome hyperestrogenemia occurred in the preovulatory period during controlled ovarian hyperstimulation [8]. Progesterone hormone administration during the luteal phase is important for improving endometrial receptivity and for preventing early pregnancy loss [9].

High responders are women with high ovarian reserve as regarding anti-Mullerian hormone (AMH) and antral follicle count. In these patients, the use of exogenous hCG in the presence of state of hyperestrogenemia is correlated with a markedly increased incidence of ovarian hyperstimulation syndrome [10]. This is mostly due to ovarian overproduction of vasoactive substances in response to the stimulating effects of human chorionic gonadotrophin [11].

The use of "short protocols" with GnRH antagonists enables final oocyte maturation by GnRH agonist instead of exogenous human chorionic gonadotrophin as a triggering agent is correlated with decreased risk of ovarian hyperstimulation syndrome [12]. The endogenous LH released after a GnRH-agonist trigger actually has a short half-life duration with a negative impact effect on the corpus luteum function and decreased endometrial receptivity [13]. In fact, luteal phase defect occurred after GnRH-agonist trigger administration correlated with decreased implantation rate and clinical pregnancy rates even when exogenous progesterone hormone supplementation is used [14]. To overcome this problem, cycle segmentation (CS) strategy is used by freezing of all embryos and delaying their transfer to another subsequent ovarian cycle.

The incidence of OHSS with CS strategy is markedly decreased, whereas ICSI efficacy is preserved [15]. Unfortunately, CS strategy is correlated with increase economic costs and more ICSI laboratory work. Delayed embryo transfer (ET) is correlated with more anxiety among the parents. As alternatives to the CS strategy, luteal phase support by different pharmacological drugs after the GnRH-agonist trigger has been recommended. Among others, the supplementation of estrogen and progesterone at high doses [16] or the daily use of 1500 IU of exogenous human chorionic gonadotrophin started from the day of ovum pick up [17]. Favorable results have been noticed with the daily supplementation of a very small dose of exogenous human chorionic gonadotrophin (100 IU) during the luteal phase period, which was recommended in a small group of patients who performed GnRH-agonist trigger and original fresh embryo transfer [18].

The aim of this retrospective observational cohort study was to compare the ICSI outcome between cycle segmentation strategy and original fresh embryo transfer followed by a low daily dose of exogenous hCG in high-responder women treated by GnRH-analogue trigger. The primary outcomes were the clinical pregnancy rate, and secondary outcomes of the study were the implantation rate, live birth rate, and rate of OHSS.

Materials and methods

Study design

This is a retrospective observational cohort study was conducted at the ICSI Unit of Al-Hayat Fertility Center in Al Mansoura city, Egypt. The study was approved by the Institutional Review Board (IRB) of Al-Azhar University Faculty of Medicine (New Damietta) (00012367-21-5-009). Informed consent was waved as it is a retrospective cohort study. Three-hundred twenty-two patients who underwent ICSI from April 2018 to April 2021 at our center were screened for eligibility as shown in Fig. 1. We manually reviewed the recorded data of the screened patients.

All patients were classified as high responders when over-response to controlled ovarian stimulation was found, which was defined as the presence of about 18 follicles of 11 mm on the day of GnRH triggering [19], anti-Mullerian hormone (AMH) $\geq$ 3.36 ng/mL [20], or antral follicle count (AFC) more than 14 follicles [21].

Women who underwent controlled ovarian hyperstimulation for ICSI in a GnRH antagonist protocol cycle and mostly at high risk of ovarian hyperstimulation syndrome (OHSS) were divided into two groups:

- Group A: Performed fresh embryo transfer (ET) that included 78 patients.
- Group B: Performed cycle segmentation (freeze-all policy) that included 65 patients.

Both groups underwent final oocyte maturation by GnRH-agonist triggering followed by (group A), and

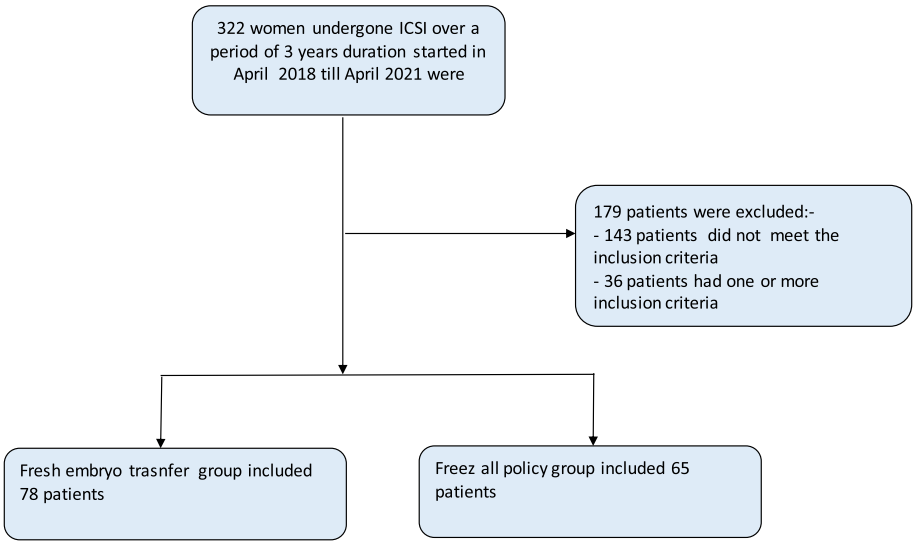

Fig. 1 Patients flowchart

luteal phase support was done, while in (group B), all the embryos were cryopreserved to be transferred in a subsequent artificial prepared cycle.

All patients in both study groups were screened for age, BMI, ovarian reserve by basal US (antral follicle count) and anti-Mullerian hormone (AMH), basal FSH, and LH. All patients in both study groups performed ICSI at the ART unite of AL-hayah fertility center in Egypt were screened during the period of controlled ovarian hyperstimulation by measuring serum estradiol level (E2) and folliculometry by transvaginal ultrasound every other day to detect ovarian response. Ovarian over-response to controlled ovarian hyperstimulation was considered by the presence of equal to or more than 18 follicles of 11 mm on the day of GnRH triggering.

Inclusion criteria

1. Female age > 18 < 38 years old
2. GnRH-antagonist suppression protocol with final oocyte maturation by GnRH-agonist triggering
3. Anti-Mullerian hormone (AMH) ≥ 3.36 ng/mL [20]
4. AFC more than 14 follicles [21]
5. The presence of equal or more than 18 follicles > 11 mm on the day of GnRH trigging [19]

Exclusion criteria

1. Important causes that could impaired implantation as hydrosalpinx, intrauterine synechiae, and submucosal fibroid
2. Embryo will undergo embryo biopsy as in FISH for sex selection.

Controlled ovarian hyperstimulation started after proof that the woman was not pregnant, and that she had basal serum levels of estradiol (< 50 pg/ml). Treating doctor decides daily dose of exogenous gonadotropins should be used depending on (age, BMI, ovarian reserve) highly purified urinary human menopausal gonadotropins (MenopurVR, Ferring Pharmaceuticals, St. Prex, Switzerland) used. Controlled ovarian hyperstimulation was monitored by transvaginal ultrasound and serum estradiol level (E2), starting on day 5 of stimulation and then every 1–2 days, depending on the patient's ovarian response to treatment. When at least one large follicle reached 15 mm in diameter, GnRH-antagonist suppression was done by daily injection of cetrorelix (CetrotideVR, Merck Serono Pharmaceuticals, Darmstadt, Germany). Final oocyte maturation and luteinization were triggered with 0.2 mg triptorelin (Decapeptyl 0.1 , Ferring Pharmaceuticals, St. Prex, Switzerland) when at least three follicles of larger than 17 mm were observed by transvaginal ultrasound.

A GnRH agonist was the best triggering drug to decrease the incidence of ovarian hyperstimulation syndrome (OHSS) associated with exogenous human chorionic gonadotrophin (hCG) triggering in high-responder women. Oocyte retrieval was performed 36 h after the GnRH-agonist administration under general anesthesia. ICSI was done, using the specimen of husband semen on the day of oocyte aspiration

Management of patients in both study groups

In group A (fresh embryo transfer group) following oocyte retrieval, the luteal phase support was done with a single injection of 1500 IU of exogenous human chorionic gonadotrophin (hCG) (Choriomoun, Ibsa, Lugano, Switzerland), 2 h after oocytes aspiration (because the endogenous LH released after a GnRH-agonist trigger actually has a short half-life duration with a negative impact effect on the corpus luteum function and decrease the endometrial receptivity) [13], followed by the administration of 400 mg of vaginal micronized progesterone (prontogest, Ibsa, Lugano, Switzerland) twice daily. The embryo transfer (ET) was carried out on days 3 or 5 of embryo development. The choice of transferred embryo's number one or two embryos was depended on the number of transferred embryo in previous cycle and the patient's age according to Belgian law. The remaining embryos were cryopreserved. The group B (freeze-all group) after oocyte retrieval no luteal phase support was done, in which all patient's embryos were cryopreserved on day 3 or on day 5. After that, patients in group B started exogenous estrogen hormonal therapy for endometrial preparation from the first day of the next menstrual cycle (2 mg of oral estradiol valerate) (ProgynovaVR, Bayer AG, Leverkusen, Germany) thrice daily for 10 to 13 days. Transvaginal ultrasound was carried out to assess endometrial development; when its thickness became more than 8 mm, 400 mg of vaginal-micronized progesterone (prontogest, Ibsa, Lugano, Switzerland) twice daily was administered to the treatment protocol. The frozen embryo transfer (ET) was done, considering the first day of exogenous progesterone therapy as the theoretical day of oocyte aspiration.

Study outcomes

The primary outcome measure is the clinical pregnancy rate at 7 weeks of gestational age, defined by the International Committee for Monitoring Assisted Reproductive Technology (ICMART) as the visualization of one or more gestational sacs (including an ectopic pregnancy) during transvaginal ultrasound [22]. The secondary outcome measures were the implantation rate (serum hCG was measured 14 days after embryo transfer) and live birth delivery (after 24 weeks) rates. Also, we evaluated the following complications and adverse results: the incidence of mild, moderate to severe OHSS (according to the criteria proposed by Golan and Weissman2009 [23] , clinical miscarriage and ectopic pregnancy (as defined by ICMART) [22] .

Statistical analysis and power calculation

Data analysis was done using IBM SPSS 28.0 (IBM Corp., Armonk, NY, USA) software for Windows. The normality of data distribution was tested using Shapiro–Wilk test. Parametric data were expressed as mean ± standard deviation with 95% confidence intervals and were analyzed using independent *t*-test categorical data and were expressed as number (percentage) and were analyzed using Fisher's exact test. Variable analysis was done by comparison between the two study groups. The sample size was chosen by selecting the eligible patients who had performed ICSI from April 2018 until April 2021; $p < 0.05$ is statistically significant.

Power analysis for the study

Using G software for Windows, a sample of 78 patients for fresh embryo transfer and 65 patients for freeze-all policy group achieved 95% power to identify a difference of 0.155 between the 2 groups using a 2-sided *z*-test at a significance level of 0.050.

Results

Of 322 patients who were screened for eligibility, 179 were excluded because either they did not meet the inclusion criteria ($n = 143$) or had one or more exclusion criteria ($n = 36$) (Fig. 1).

Patients, clinical, and hormonal characteristics

There was no significant difference between groups A and B regarding age, body mass index, AMH level, antral follicle count, basal FSH level, basal LH level, progesterone level, and the cause of infertility (Table 1).

Primary outcomes

The primary outcomes are shown in Table 2. In group A (fresh embryo transfer), the incidence of clinical pregnancy rate (24.35%) was significantly lower ($p < 0.001$) than group B (40%). The incidence of implantation rate in group A (28.20%) was significantly lower ($p < 0.001$) than group B (43.07%). The incidence of live birth rate in group A (17.94%) was significantly lower ($p < 0.001$) than group B (32.30%).

Complication and adverse outcome measures

The complication and adverse outcome measures are shown in Table 2. The incidence of clinical miscarriage in group A (26.05%) was significantly higher ($p < 0.001$) than group B (19.23%). In both groups, no patients developed ectopic pregnancy. The incidence of mild OHSS was comparable in both groups. The incidence of moderate to severe OHSS was significantly higher ($p = 0.023$)

Table 1 Patients clinical and hormonal characteristics

Clinical baseline characteristics	Group A ($n = 78$)	Group B ($n = 65$)	*p*-Value
Patients age in years	34.8 ± 4.3	34.6 ± 4.2	0.804
Patients BMI (kg/cm^2)	22.7 ± 3.6	22.6 ± 4.5	0.792
Antral follicle count	25.1 ± 6.8	27.1 ± 10.1	0.256
Basal FSH (UI/L)	6.5 ± 1.3	6.5 ± 1.6	0.904
Basal LH (UI/L)	6.7 ± 3.3	7.5 ± 3.3	0.148
AMH (ng/mL)	6.8 ± 2.8	7.4 ± 5.4	0.285
Progesterone level (ng/ml)	1.2 ± 0.23	1.1 ± 0.32	0.658
Causes of infertility			
PCOS	18 (23.07%)	14 (21.53%)	
Endometriosis	6 (7.69%)	5 (7.69%)	0.435
Male factor	35 (44.87%)	28 (43.07%)	
Unexplained infertility	19 (24.35%)	18 (27.69%)	

Data are presented as mean (SD), number, and proportion (%). *BMI*, body mass index; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *AMH*, anti-Mullerian hormone; *PCOS*, polycystic ovarian syndrome

Table 2 ICSI outcomes in the study groups

ICSI cycle outcomes	Group A ($n = 78$)	Group B ($n = 65$)	*p*-Value
Daily exogenous gonadotrophine dose (UI)	168.3 ± 38.7	165.7 ± 39.9	0.804
E2 level at day of trigger (Pg/Ml)	2330.2 ± 1025.1	3775.6 ± 2161.1	0.262
Endometrial thickness (mm)	10.3 ± 1.6	10.1 ± 1.9	0.814
Retrieved oocytes (*n*)	12.7 ± 3.2	14.1 ± 3.5	0.158
Mature oocytes (*n*)	10.2 ± 3.2	11.1 ± 3.7	0.711
Fertilization rate (%)	73.8	76.9	0.456
Embryo transfer (*n*)	1.2 ± 0.4	1.3 ± 0.4	0.684
Implantation rate (%)	22/78 (28.20%)	28/65 (43.07%)	< 0.001*
Clinical pregnancy rate/first ET%	19/78 (24.35%)	26/65 (40%)	< 0.001*
Live birth rate/first ET%	14/78 (17.94%)	21/65 (32.30%)	< 0.001*
Clinical miscarriage	5/19 (26.05%)	5/26 (19.2%)	< 0.001*
Ectopic pregnancy	0	0	
Mild OHSS	5/78 (6.41%)	5/65 (7.69%)	0.623
Moderate to severe OHSS	5/78 (6.41%)	0	0.023*

Data are presented as mean (SD), number, and proportion (%). *E2*, estradiol; *ET*, embryo transfer; *OHSS*, ovarian hyperstimulation syndrome. *$P < 0.05$ is statistically significant

in group A (6.41 %) than group B (0%). No patient who developed moderate to severe OHSS needed intensive care unit admission.

Discussion

The present study evaluated the balance between safety and efficiency of controlled ovarian hyperstimulation in the high-responder women at high risk of ovarian hyperstimulation syndrome (OHSS), by comparing the freeze-all strategy (cycle segmentation) with original fresh embryo transfer (ET) after GnRH-agonist triggering and luteal phase support. The results of this study showed that the implantation rate, clinical pregnancy rate, and live birth rate were better in cycle segmentation (freeze all) group with lower incidence of ovarian hyperstimulation syndrome (OHSS) when compared with original fresh embryo transfer group even with the daily supplementation of a low dose of human chorionic gonadotrophin (hCG) as a luteal phase support. The above can be explained by the endogenous LH release after a GnRH-agonist trigger has a short half-life duration with a negative impact effect on the corpus luteum function and decreases the endometrial receptivity [13].

In recent decade, "cycle segmentation" strategy has become more common which means the freezing of all patient embryos followed by thaw embryo transfer in another subsequent prepared cycles. The prevalence of "cycle segmentation" is mostly due to its efficacy in preventing ovarian hyperstimulation syndrome among "high-responder" women who include women with polycystic ovarian syndrome and those with marked responsiveness to controlled ovarian hyperstimulation [24]. These patients are starting a controlled ovarian hyperstimulation protocol with step-up policy in which a small dose of gonadotropin is used, plus the use of a GnRH antagonist to prevent premature LH surge.

Final oocyte maturation is obtained by administration of a single dose of GnRH agonist, which stimulate the release of an endogenous LH compared with the exogenous human chorionic gonadotrophin trigger; the GnRH-agonist-stimulated LH surge decreases the risk of ovarian hyperstimulation syndrome, but unfortunately, it has a short half-life and more biologically weaker, leading to inefficient corpus luteum function during the luteal phase period [25]. This problem can be solved when all embryos are cryopreserved and delayed embryo transfer to another subsequent artificial cycle. So, "cycle segmentation" strategy is effective in preventing OHSS and enhances endometrial gene expression and improves process of endometrial receptivity [25]. This is done by preventing hyperestrogenemic state and/or prevent premature progesterone elevation [26]. In fact, a controlled ovarian hyperstimulation has been correlated with impaired angiogenesis and poor placentation [27] and increase the instability of the microbacteria of the reproductive system [28]. All these factors can decrease the embryo implantation rate and clinical pregnancy rates. In fact, in specific subgroups of patient, cycle segmentation strategy has been correlated with higher implantation rates [29] and greater obstetric and perinatal outcomes [30], than the original fresh embryo transfer strategy. The application of cycle segmentation on patients not at high risk of ovarian hyperstimulation syndrome is still a controversy. Unfortunately, cycle segmentation strategy is correlated with increase economic coast, more ICSI laboratory work and marked psychological burden, and anxiety for the patients due to delayed embryo transfer. In the study done by Shapiro et al. [31], 70 patients that had subjected to elective cryopreservation of all their embryos showed obviously greater pregnancy outcome than 67 who undergo original fresh embryo transfer. However, the study had multiple limitations and biases regarding the small number of patients included in the study, the high clinical pregnancy rates in the cryopreservation cycles, and the presence of dual triggering drugs (referred as the effect of co-interventions). Roque et al. [32] conducted a comparative study as regarding the pregnancy outcome between original fresh embryo transfer and cycle segmentation strategy in correlation to the number of oocyte retrieved. There is no difference in pregnancy outcome between both groups (33% and 31%) in case of a small number of oocyte retrieved. However, better pregnancy outcome was observed among the cycle segmentation group than the original fresh transfer group when a large number of oocyte were retrieved (47% and 34%, respectively). This proves that cycle segmentation has no benefit in women with normal response to controlled ovarian hyperstimulation.

Large RCT carried out on (PCOS) patients (n¼ 1508) proved that there is a significant decrease in the incidence of ovarian hyperstimulation syndrome in the cycle segmentation group than the original fresh embryo transfer group (1.3% versus 7.1%, respectively) [33]. Also, cycle segmentation strategy showed higher live birth rate after the first embryo transfer when compared with original fresh embryo transfer cycles (49.3% versus 42%, respectively) in patients with PCOS. Actually, these studies correlated with the American Society for Reproductive Medicine recommendation, which recommends the cycle segmentation strategy in high-responder women as it increases the pregnancy outcome with lower incidence of ovarian hyperstimulation syndrome [34].

The main finding of this retrospective study is that the cycle segmentation strategy has better implantation rate, clinical pregnancy rate, and live birth rate, considering only the first embryo transfer than the original fresh embryo transfer with human chorionic gonadotrophin supplementation. This proves that a very small daily dose of exogenous human chorionic gonadotrophin although its safe as regarding the occurrence of ovarian hyperstimulation syndrome cannot compensate for negative effect on the luteal phase function produced by gonadotrophin-releasing hormone-agonist when used as a triggering drug.

As regarding safety issues, the strategy of original fresh embryo transfer with very little daily dose of exogenous human chorionic gonadotrophin administration was correlated with incidence of ovarian hyperstimulation syndrome (moderate to severe degree) 3.12%, which compares with the incidence of 3–6% reported in most ICSI cycles [35]. However, this incidence is still unsatisfactory, as one of the important objectives of ICSI is complete prevention of ovarian hyperstimulation syndrome.

The point of strength of this study is the comparison of the pregnancy outcome of ICSI among large number of

patients of high responders who underwent controlled ovarian hyperstimulation with GnRH-antagonist protocol, GnRH-agonist trigger, with good follow-up of all patients. The limitation of this study is the retrospective design; therefore, a randomized controlled trial is required to get more accurate results.

Conclusion

As described in this review, cycle segmentation strategy (freeze-all policy) had better pregnancy rate with less incidence of moderate to severe hyperstimulation syndrome compared with original fresh embryo transfer in high-responder women who performed intracytoplasmic sperm injection.

Abbreviations

CS: Cycle segmentation; ICSI: Intracytoplasmic sperm injection; OHSS: Ovarian hyperstimulation syndrome; GnRH: Gonadotrophine-releasing hormone; hCG: Human chorionic gonadotrophin; LH: Luteinizing hormone; COS: Controlled ovarian hyperstimulation; ET: Embryo transfer; PCOS: Polycystic ovarian syndrome; AFC: Antral follicle count; AMH: Anti-Mullerian hormone; BMI: Body mass index.

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Authors' contributions

EE, supervision and study design. EE, data analysis and interpretation of the results. EE, data collection. EE, study design and data analysis; AI, design. EE, manuscript preparation. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to (reason why data are not public) but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board (IRB) of Al-Azhar University, Faculty of Medicine (New Damietta) (00012367-21-5-009).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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