RESEARCH

Soft ovarian stimulation protocol in polycystic ovary syndromes women inspired by gonadotropin stimulated intrauterine insemination cycles converted to rescue IVF: time to shift the focus "retrospective study"

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Abstract

Background Polycystic ovary syndrome (PCOs) women usually exhibit a high luteinizing hormone (LH) and hypersensitivity to exogenous gonadotropins stimulation which is a tremendous risk to ovarian hyperstimulation syndrome (OHSS). Since the pathophysiology of PCOS is mysterious, an aetiological approach to the treatment is difficult and should be individually designed. These features affect the outcome of treatment including ovulation and success rate. Also, PCOS women who have difficulty conceiving, frequently experience substantial treatment burden, risk, and psychological distress. Recently, a renewed interest has emerged in patient-friendly, low-risk, and less costly IVF treatments. Our study proposed a new soft protocol in PCOS ovrian stimulation without prior pituitary desensitization followed by fresh embryo transfer. Patients and methods: a retrospective cohort study was conducted between January 2018 to December 2021, including 48 out of 325 women with PCOS who underwent gonadotropin-stimulated intrauterine insemination cycles but due to unexpectedly high response with risk of multiple pregnancies and OHSS, they had been shifted to a rescue IVF and fresh embryo transfer. The primary outcomes were biochemical pregnancy, implantation rate, clinical pregnancy, rate of miscarriage, OHSS, and multiple pregnancies. Secondary outcomes were the endocrinological profiles, gonadotropin dose, and duration of stimulation. This study aims to evaluate the outcomes in the conversion of high-response gonadotropin intrauterine insemination (IUI) cycles to "rescue" in vitro fertilization (IVF/fresh embryo transfer) regarding implantation rates, pregnancy rates, and ovarian hyperstimulation syndrome (OHSS).

Results This study used a low dose gonadotropin injections (2.1 ± 1.4) for an average duration of (9.1 ± 1.2) and showed a high success pregnancy rate: biochemical pregnancies (56.2%), implantation rate (50.2%), clinical pregnancy rate (49.9%), and miscarriage rate (8.5%). Multiple pregnancies occurred in (6.6%) and OHSS(4.4%) only in a mild form.

Conclusion Our study revealed that ovarian stimulation without prior pituitary suppression in high responders was feasible to improve the implantation rate and alleviate profound OHSS without compromising the pregnancy outcomes. This encourages all fertility specialists to implement this new protocol with expected high responders as an alternative to the conventional cycle segmentation protocol: GnRH agonist-antagonist IVF/freeze-all strategy.

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Introduction

Polycystic ovary syndrome (PCOS) is a highly prevalent endocrinological disorder with a heterogeneous spectrum of ovulation dysfunction, polycystic ovary morphology, and hyperandrogenism. Globally, PCOS prevalence is up to 8–13% of the general population. (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) defined PCOS by the presence of two out of the three following diagnostic criteria: hyperandrogenism, polycystic ovaries with ≥ 12 small follicles between 2 and 9 mm, and/or an ovarian volume of 10 ml and oligo-/anovulation [1, 2]. Based on those criteria, PCOS prevalence might be as high as 18% among women of reproductive age including all different phenotypes [3]. The causation of PCOS is likely that both genetic and environmental factors contribute to its development and severity [4, 5]. Herein, the Middle East area prevalence of PCOS is high up to 35–40% of the general population; and it is responsible for 70–80% of anovulatory infertility [6].

Ovarian response of those categories of women depends on individual heterogeneity during controlled ovarian hyperstimulation. Severe ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening iatrogenic complication, and occurs almost exclusively in the presence of sustained LH activity as seen after hCG triggers in ART cycles [7]. Many studies tackled OHSS prevention strategies, e.g;decreasing the hCG dose for the ovulatory trigger, antagonist protocol, using gonadotropin-releasing hormone (GnRH) agonists for the trigger, and employing a freeze-all strategy. Despite these strategies, OHSS still albeit occurs [8, 9]. The predictive factors of ovarian sensitivity of PCOS patients to gonadotrophins include fasting blood insulin, anti-Mullerian hormone (AMH), baseline follicular stimulating hormone(FSH), age, and body mass index (BMI). Evaluation of different PCOS subpopulations, such as lean, ovulatory, and/or non-hyperandrogenic women, may not explain the comprehensive data or the clinical risk of infertility [10]. The previous studies highlighted that although the number of retrieved oocytes from PCOS patients undergoing in vitro fertilization (IVF) is quite high, yet poor oocyte quality, low fertilization rate, and high miscarriage rate are still severe problems. It is pointed out that the quality of embryo and oocyte could be hurdled by prolonged ovarian stimulation. Moreover, gonadotropin-stimulated IUI cycles remain an option for those who cannot afford or fulfill the indications of IVF. Similarly, when doing stimulated IUI cycles they might exhibit hype response and be at increased risk for OHSS and multiple pregnancies. Among hyper-responders, where follicular recruitment is excessive, a decision should be made to either cancel the cycle or allow a rescue IVF [11].

Since the outcome of the IUI cases who had a rescue IVF/ET was promising. This retrospective study could propose a simple ovarian stimulation protocol to be used in the predicted high responders including small doses of gonadotrophins and avoiding pituitary down-regulation by using an agonist or antagonist [12–14]. Alternatively, non-steroidal anti-inflammatory (NSAID) is used to prevent premature LH surge [15]. This protocol will minimize the risk of OHSS and multiple pregnancies. We acknowledge the patient's wishes for a fresh cycle embryo transfer. Thus, we can improve options in PCOS diversity of patients in suggestions that might be able to improve patient satisfaction. Our study attempts to address these issues and concerns and provides a simple personalized stimulation protocol with a better safety profile without compromising pregnancy outcomes. This protocol is a new strategy worth exploring in the high responders PCOS women planning for IVF by shifting the focus from antagonist-agonist protocol with frozen embryo transfer to milder stimulation protocol with fresh embryo transfer. We hypothesize that lacking pituitary suppression improves oocyte quality, endometrial receptivity, and pregnancy outcome. This retrospective cohort trial was performed to evaluate the efficacy of soft ovarian stimulation protocol used in high responders planned to gonadotropin IUI and converted to rescue IVF/ET to alleviate the risk of multiple pregnancies and OHSS as a surrogate marker for PCOs women who intended to have a FRESH cycle IVF without compromising the success rate.

Patients and method

Study design

A single-center retrospective cohort study.

Sitting

This cohort analysis of PCOS patients undergoing gonadotropin-stimulated IUI cycles between January 2018 and December 2021 in a large private (RMS/IVF) center in Egypt.

Methodology

Study participant

This study included 48 out of 325 women between 20 and 37 years of age with a diagnosis of PCOS opt for gonadotropin-stimulated IUI due to failure to conceive spontaneously with a reasonable semen analysis parameter. The diagnosis of PCOS was made according to the 2003 Rotterdam consensus, in which at least 2 out of 3 of the following criteria were met [1]: (1) oligo- and/or anovulation; (2) biochemical and/or clinical evidence of hyperandrogenism; or (3) polycystic ovarian morphology on ultrasound. The following diseases were excluded: other etiologies of hyperandrogenism and ovulatory dysfunction, including congenital adrenal hyperplasia, androgen-secreting tumors, hyperprolactinemia, and thyroid disease. Patients' informed consent stating the risks of different protocols were signed by patients undergoing controlled ovarian hyperstimulation in concordant with our center's Keep Performance Indicators (KPI). All study data were collected by authorized staff. Retrospective data collection from medical records notes and electronic files between January 2018 and December 2021.

Controlled ovarian stimulation

Our unit protocol is an initial daily dose of rec FSH (Gonal F, Gonapure-MINA PHARMA) ranging between 75 IU to 225 IU was administered according to the patient's age and ovarian reserve tests, on day 2 of spontaneous menstruation or progesterone withdrawal bleeding for 4 days. The dose was adjusted on day 5 according to the evident ovarian response. Followed by ovulation trigger using subcutaneous injections of 10,000 IU hCG when a leading follicle reached 18 mm size or more. All patients were screened during the stimulation period through serial sonography (follicular growth and endometrial thickness) and estradiol level measurement. An excessive response was defined as having more than 4 follicles 17–20 mm on the day of planned HCG administration. These hyper responder cases were counseled to be converted to in vitro fertilization and embryo transfer (IVF-ET) to eliminate the risk of multiple pregnancies and OHSS. To avoid the risk of premature LH surge, non-steroidal anti-inflammatory (NASID) was used (Borutaren Sapo; Novartis, Australia) two separate doses of 25 mg diclofenac rectal suppositories at 8 and 14 h before oocyte retrieval. Contraindications included NSAID allergy, asthma, peptic ulcer, or inflammatory bowel disease. The final oocyte maturation and triggering were achieved through hCG ((single dose of Choriomon, IBSA 10000 IU) followed by oocyte retrieval according to ultrasound and biochemical guidance. Oocyte retrieval was performed at 34.5 h following hCG triggering. After oocyte retrieval, any immature (metaphase I or germinal vesicle) oocytes were observed for up to 12 h until most matured spontaneously. Mature (metaphase II) oocytes were inseminated by conventional IVF or intracytoplasmic sperm injection and normally fertilized 2 pronuclear zygotes were cultured individually in 20 ml of cleavage-stage medium (SAGE; USA) until day 2 or 3. All embryos were cultured at 37 °C under a gas phase of 5% O_2, 5% CO_2, and 90% N_2 with full humidity in a water jacket, and small multi-gas incubators (Astec; Japan). All patients underwent fresh embryo transfer on day 3 or 5 depending on embryo quality. Either single embryo or double embryo transfer was done in all women according to the women's age, number, and quality of the embryo. Finally, standard luteal support of vaginal progesterone (Cyclogest ®; Actavis, Barnstaple, UK, 400 mg/daily) starting the day after oocyte retrieval for 2 weeks [11, 15]. The primary outcome in this study was biochemical pregnancy rate, implantation, and clinical pregnancy which was defined by the presence of fetal heart activity by transvaginal ultrasound at 4 and 6 weeks after embryo transfer. The secondary outcome was to measure the risk of OHSS (classified as mild, moderate, or severe according to the RCOG Guideline; Royal College of Obstetricians and Gynaecologists, 2016.

Statistical analysis

Data retrieved: duration of ovarian stimulation, number of gonadotropins injections, number of the oocyte (17–20 mm), endometrial thickness, peak of estradiol, number of oocytes, number of embryos, and clinical pregnancy outcome. The data were summarized by mean, and standard deviation. For validation we compared our results to a cohort of conventional long agonist protocol who showed a high response during the stimulation, we used an unpaired t test with a two-tailed p value to establish statistical significance, which was defined by convention to be established by p values < 0.05.

Results

Among 325 gonadotropins-stimulated IUI cycles, 85 cases developed ovarian hyper response and opted to rescue IVF/ET; however, due to financial constraints, only 48/85 (56.4%) agreed and consented to IVF/ET (Fig 1). The demographic parameter of the participant was plotted in Table 1. The study group included 56.4% of hyper responders' cases of IVF and embryo transfer was done in 45 cycles, resulting in biochemical pregnancies rate of 26/48 (56.2%), an implantation rate of 13/26 (50%), a clinical pregnancy rate of 12/26 (46.1) %, and a miscarriage rate of 2/26 (8%). Multiple pregnancies occurred in 3/45(6.6%). cancellation due to non-fertilization was 3/48 (6.2%). finally, only mild OHSS was evident in (4.4%) of cases after IVF-ET (Table 2). The mean duration of
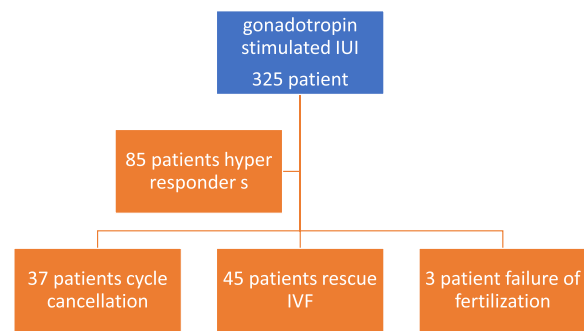
Fig. 1 Flow chart of the study

Table 1 Demographic characteristics of the patients

Parameters	Mean ± SD
Age	29.7 ± 3.2
BMI	27.6 ± 4.2
Duration of infertility	3.2 ± 1.3
Parity	1.2 ± 0.6
Associated co-morbidity	
Hypothyroidism	7.1 ± 3.2
Type 2 diabetes mellitus	10.3 ± 2.1
Hypertension	2.5 ± 1.5

Table 2 The pregnancy outcomes

Pregnancy outcome	Percentage %
Biochemical pregnancy rate	26/48 (56.2%)
Implantation rate	13/26(50 %)
OHSS rate	
Mild	4.4 %
Moderate	0 %
Severe	0 %
Clinical pregnancy rate	12/26 (46.1%)
Multiple pregnancies	3/45(6.6%)
Miscarriage rate	2/26 (8 %).

IVF/ICSI in vitro fertilization/intracytoplasmic sperm injection; *ET*, embryo transfer. The quantitative and qualitative variables are presented as mean (standard deviation) and number (percentage), respectively, recombinant follicle-stimulating hormone; *hCG*, human chorionic gonadotropin; *ET*, and embryo transfer. OHSS, ovarian hyperstimulation syndrome the data are presented as mean (±standard deviation)

Table 3 The pharmacological doses, hormonal levels, and ultrasound markers

Parameters	Mean ± SD
Duration of COS	9.2 ± 1.2
Gonadotropin injection dosage	2.1 ± 1.4
Estradiol E2 level (pg./ml)	2359 ± 34
Progesterone level on the day of hCG pg/ml	0.79 ± 0.5
Progesterone level on the day of ET pg/ml	55.6 ± 7.1
Endometrial thicknesses (mm)	9.03 ± 2.9
Retrieved oocyte	6.6 ± 2.8
2 pronucleus stage	7.3 ± 1.9
Quality of embryo on D3	4.1 ± 1.3
Number of embryo transfer	2.1 ± 0.3

opted for a planned IVF and showed a hyper response during the stimulation.

Table 4

The mean dose of gonadotropin used per cycle was higher in the control group, with an average of 2236 international units (IU) of follicle stimulation hormone (FSH) compared to 525 IU ± 37.5of FSH in the "rescue" IVF group. The results showed statistical differences between both groups in terms of retrieved oocyte count in the control IVF group 19.2 ± 3.8 compared to 6.6 ± 2.8 in the study group *p* value 0.0088*. Despite a smaller number of oocytes retrieved in the studied group, biochemical pregnancy, and clinical pregnancy were significantly higher than the control group *p* value < 0.0001*. Multiple pregnancies were statically higher in the control group along with severe OHSS *p* value < 0.0001* (Table 5).

Discussion

PCOS is enigmatic and still not fully understood. ovarian Stimulation in cases of PCOS is tricky because the response is unpredictable and dosage adjustment is challenging. Throughout IVF cycles the use of ovarian stimulation aims to induce multi-follicular development; however, this is associated with an increased risk of ovarian hyperstimulation syndrome (OHSS), especially in women with PCOS [7]. The existing evidence suggests that a personalized protocol for ovarian stimulation based on serum AMH, or antral follicle count could balance the benefits between superovulation and risks (OHSS). The widely used method to prevent OHSS is cycle segmentation using antagonist protocol, GnRH agonist triggering followed by frozen embryo transfer, nevertheless moderate to severe OHSS still occurs albeit [16].

Throughout our study, we noted that stimulation of the ovaries with small doses of gonadotrophins without

stimulation was 9.2 ± 1.2 days the average gonadotropin used during the stimulation was 2.1 ± 1.4 injections daily (Table 3).

To verify our results, we compare the rescue converter group to a matched cohort of 101 PCOs women who

Table 4 Comparison of cohort characteristic rescue IVF with the control group of IVF hyper responders

Cohort characteristics

	Study group "rescue" IVF	Control group IVF hyper-responders	*p* value
Number	48	101	–
Average age (range)	29.1 (20–34)	31.85 (26–43)	0.294
Basal day 3 FSH	7.1 (4.9–8.2)	6.2 (4.9–7.1)	0.4834
Infertility indication (%)			
Unexplained	0	15.2	–
Moderate male factor	0	41.7	
Ovulatory	48	14.2	
Tubal	0.0	22.2	
Combined	0.0	7.7	
Luteal phase support	Micronized progesterone 400/daily	Micronized progesterone 200 mg TID	–
		17β-estradiol 2 mg TID	–
Embryo transfer	**Day 3**	**Day 3**	–

Table 5 The pregnancy outcome between hyper responder rescue IVF and control group IVF hyper responders

Results

	Study group "rescue" IVF	Control group IVF hyper-responders	*p* value
Number	48	101	
Duration of stimulation (days)	9.2 ± 1.2	10.4 ± 2.3	0.6324
Dose of gonadotropin/cycle	$525\,IU \pm 37.5$	$2236\,IU \pm 241$	< 0.0001*
Type of gonadotropin			
r-FSH	100%	75.3%	–
Mixed	0.0%	22.2%	–
hMG	0.0%	2.5%	–
# Oocytes	6.6 ± 2.8	19.2 ± 3.8	0.0088*
#Embryos transferred (ET)	2 (1–3)	2 (1–3)	1.000
Implantation rate (IR)	50	37.6	0.0047*
Biochemical pregnancy rate (PR)/cycle	56	46.4	< 0.0001*
Ongoing clinical pregnancy rate (CPR)/cycle	50.0	40.1	< 0.0001*
Ongoing clinical pregnancy rate/transfer (CPR/ET)	50.0	32.9	< 0.0001*
% Severe OHSS	0 %	4.9%	< 0.0001*
% Multiple pregnancies	6.6	22.0	< 0.0001*

a prior pituitary suppression in addition to prevention of premature LH surge by adding non-steroidal anti-inflammatory resulted in a better outcome and a milder form of OHSS complication. This protocol was tested in IUI-gonadotropin stimulated cycles, converted to IVF/ET to reduce the risk of multiple pregnancies and OHSS. Retrospectively, this data was analyzed and compared to a cohort of PCOs women with conventional IVF mid-luteal agonist protocol who experienced hyper response to gonadotropin doses during the treatment cycle. Based on our results, we could adopt this friendly minimal stimulation protocol as a surrogate successful strategy in PCOs women planned for IVF/ET. The added values of this protocol are fewer gonadotrophins injections, decreasing the financial burden, eliminating the risk of OHSS, and improving the pregnancy outcome and patient satisfaction by transferring to a fresh cycle with a comparable high pregnancy rate.

Ovulation induction with gonadotropin-stimulated IUI is accepted as an effective modality of treatment for PCOS subfertility; however, it could result in a multiple pregnancy rate of up to 29% [17]. With superovulation,

a safe alternative to cycle cancellation could be to convert an IUI cycle to IVF-ET, thereby reducing the multiple pregnancy rate [18]. Additionally, Conversion prevents the complete financial loss and frustration of a canceled cycle by maintaining a pathway toward a possible pregnancy. Previous studies have reported that ovarian down-regulation protocols such as GnRH agnosit, antagonist, or progesterone-primed cycles resulted in improved oocyte numbers, embryo quality, embryo number, and implantation and pregnancy rates [15, 16, 19–21]. However, the present study suggests that the lack of downregulation in gonadotropin IUI cycles does not appear to be detrimental to embryo development, as the implantation rate of embryos in the cases was quite high (50%). Our target of avoiding multiple pregnancies and OHSS by converting patients to IVF-ET was sub-optimally achieved [17, 18, 22, 23]. There were three cases of multiple pregnancies (6.6%) and two cases of mild OHSS (4.4%), with all the OHSS cases in patients with multiple gestations (Table 2). Nevertheless, this incidence in our population might have been higher if the cycles had continued. One explanation for the high twin rates is that the cases had a higher response and usually had an excellent quality oocyte, embryo, and implantation rate. Our result was concordant with Antman et al. results on conversion OI/IUI cycles to IVF, fertility sterility, 2002 studied 719 multiple reported 33% pregnancy rates after their patients had undergone an average of 2.67 cycles each [8, 19]. This paper supports the previous work of Nisker et al. (1994) and Antman et al. (2002) that good responders converted from gonadotrophin IUI cycles to IVF-ET cycles can experience good clinical pregnancy and delivery rates (57 and 48%, respectively) [14]. The cost associated with IVF "rescue" is an important issue, which may impede the undertaking of this practice in many centers. Though cycle cancellation can also prevent the occurrence of OHSS, it poses significant financial burdens on the patients, especially in regions and centers where IVF is not funded. A study comparing "rescue" IVF to conventional IVF in PCOs and non-PCOs populations, theorizes that lower doses of gonadotropin between the "rescue" IVF group and control groups might be due to ovarian down-regulation in the control groups [15]. This dose difference results in an added cost for hyper-responsive patients on standard IVF programs. Rescue IVF cycles seem therefore to require a milder stimulation protocol that is cost-effective compared with the standard strategy for IVF. In addition, the psychological burden of cycle cancellation is a real concern for patients and IUI providers. An added benefit of the practice of "rescue" IVF is that it reduces the emotional stress of couples.

Given our results, it seems to be promising that women undergoing gonadotropin-stimulated IUI who converted to IVF would do as well as robustly responding patients who underwent planned, down-regulated IVF cycles even with a better outcome. furthermore, non-steroidal anti-inflammatory drugs (NSAID) may efficiently delay or even prevent follicular rupture by blocking cyclooxygenase 2, which has a key role in the ovulatory process [16, 19].

The short-term, low-dose, post-trigger NSAID application decreased the rate of premature LH surge and managed a higher proportion of cycles to reach embryo transfer [20, 21, 24]. In the context of natural IVF, NSAID was applied successfully by Kadoch et al. (2008) to diminish the rate of unwanted premature ovulation. In their retrospective, observational study, an NSAID was non-randomly used in one-third of 255 natural IVF cycles and it was associated with a significantly diminished rate of premature ovulation (6% versus 16%) and a non-significantly higher clinical pregnancy rate per initiated cycle (13% versus 6%). Although their findings are completely in line with the present study, NSAIDs were used in a high-dose regimen (150 mg indomethacin/day) over a course of several days concomitantly with a daily GnRH antagonist to control the LH surge (Kadoch et al., 2008) [25]. Similarly, to the present study, pregnancy rates were not adversely affected (and in some studies implantation rates were increased) and miscarriage rates were comparable supporting the safety of NSAID administration in the peri-implantation period. This might be related to the fact that a 25-mg NSAID dose is used twice with a 6-h interval initiated by the time of oocyte retrieval and does not have any potential negative effect afterward.

Limitation of our study includes a retrospective nature and the lack of a control group of high-responder gonadotropin IUI patients who went through with IUI cycle completion. Physicians should be aware that converted patients potentially have less resistant infertility and better embryo quality than the cohort of patients who undergo IVF after gonadotropin IUI failure. Therefore, it may be worth transferring a single embryo to those patients. The findings are representative of one population at one center, and as such, may not be generalizable

Conclusion

Based on present results stimulation of the ovaries with small doses of gonadotrophins without a prior pituitary suppression along with prevention of premature ovulation using non-steroidal anti-inflammatory, resulted in better outcomes and less severe OHSS form. Improving the patient's convenience through transfer in a fresh cycle with a high pregnancy rate and less psychological disturbance.

Recommendation

Prospective randomized controlled studies with larger sample sizes and basic research should be performed in the future.

Appropriate treatment guidelines based on well-constructed clinical trials are needed to address the issue.

Future studies are needed to ascertain the underlying cause of this observation.

Abbreviations

PCOS　　Polycystic ovary syndrome
hCG　　 Human chorionic gonadotropin
FSH　　 Follicular stimulation hormone
LH　　　 Luteinizing hormone
IVF　　　In vitro fertilization
IUI　　　 Intrauterine stimulation
OI　　　 Ovulation induction
OHSS　　Ovarian hyperstimulation syndrome.

Authors' contributions

ANA contributed to the conception of research, data collection, analysis, and drafting of the manuscript. AMA contributed to data collection and analysis and revision of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate

Did not apply due to its retrospective nature and to the fact that study data was consistently anonymous.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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