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ORIGINAL RESEARCH

Effects of Different Gonadotropin-Releasing Hormone Agonists on IVF/ICSI-ET Outcomes in Long Protocol: A Retrospective Study

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Background: Triptorelin acetate, leuprorelin and goserelin acetate were three commonly used gonadotropin-releasing hormone agonist (GnRH-a) formulations in IVF/ICSI-ET. However, current knowledge about the real-world effects on clinical outcomes of different GnRH-a formulations is limited. In this study, we aimed to compare the clinical outcomes of IVF/ICSI-ET using different GnRH-a formulations in long protocol during follicle phase.

Methods: This is a retrospective study. A total of 154 infertile women undergoing IVF/ICSI-ET in long protocol during follicle phase from September 2019 to December 2023 were assigned to three groups according to different GnRH-a formulations (A: triptorelin acetate; B: leuprorelin; C: goserelin acetate). The baseline information, ovulation induction outcomes and pregnancy outcomes were compared among three groups. Student's *t*-test, Pearson Chi-Square test or Fisher's exact test was used for statistical analysis appropriately.

Results: Groups A, B and C included 94, 36 and 24 patients, respectively. Compared with groups A and B, group C had significantly smaller total amount of gonadotropin (A vs B vs C: 2224.20±700.02 U vs 2266.67±884.01 U vs 1685.94±360.24 U) and shouter days of using gonadotropin (A vs B vs C: 11.61±1.91 days vs 11.83±2.48 days vs 9.50±0.98 days) ($P<0.05$). Among the three groups, group C had the best pregnancy outcomes with the highest implantation rate (A vs B vs C: 40.4% vs 32.7% vs 41.9%), clinical pregnancy rate (A vs B vs C: 41.7% vs 39.4% vs 57.9%), live birth rate (A vs B vs C: 32.5% vs 33.3% vs 52.6%) and the lowest miscarriage rate (A vs B vs C: 22.9% vs 15.4% vs 9.1%).

Conclusion: Goserelin acetate was found to have good pregnancy outcomes in IVF/ICSI-ET with small amount and shout using days of gonadotropin, but there is a lack of statistical significance when compared to the pregnancy outcomes of triptorelin acetate and leuprorelin. The findings need future confirmation in larger trials or meta-analyses.

Keywords: gonadotropin-releasing hormone agonists, IVF/ICSI-ET, triptorelin, leuprelin, goserelin

Introduction

Controlled ovarian hyperstimulation (COH) is an important procedure in the "in vitro" fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET) process, to regulate the function of the ovaries and prompt the ovaries develop multiple follicles synchronously in a single menstrual cycle, which aims to improve the egg harvest rate and the chance of conception.[1,2] Gonadotropin-releasing hormone agonist (GnRH-a) is one of the commonly used COH drugs, which is a synthetic gonadotropin-releasing hormone (GnRH) analogue.[3] GnRH pathway plays an important role in the hypothalamic-pituitary-gonadal axis of reproduction.[1,4] GnRH-a suppresses gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) secretion by mimicking the action of GnRH, thus promoting follicle development and the secretion of sex hormones.[3] Several randomized clinical trials (RCTs) have shown that gonadotropin plus GnRH-a improves pregnancy rates in IVF/ICSI-ET compared to no GnRH-a.[5]

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Long follicle phase is currently the mainstream COH protocol, which is easy to operate, can improve endometrial receptivity, reduce abortion rate and has been widely used in clinical practice in China.[6] The long follicle phase protocol generally down-regulates the endometrial receptivity using GnRH-a during the follicle phase to achieve better clinical outcomes of IVF/ICSI-ET.[4] Commonly used GnRH-a formulations for COH include goserelin, leuprorelin and triptorelin. A prospective randomized study found that patients who received leuprorelin had remarkably higher embryo implantation rate and pregnancy rate than triptorelin in COH.[7] However, current knowledge about the real-world effects on clinical outcomes of different GnRH-a formulations is limited.

RCTS are commonly considered the gold standard of drug evaluation. Nevertheless, strict inclusion criteria and quality control of procedures make it difficult to reproduce the results of RCTs in real world.[8] Real-world study uses real-world data from routine clinical work focusing on the efficacy and safety of a medical product.[9] Electronic health records, registries, bills and insurance data are common sources of real-world study.[9] A real-world study focuses on the evaluation of drug effect in real clinical settings.[8] We believe that real-world studies and RCTs are mutually complementary. Hence, we attempted to propose a real-world evaluation of different GnRH-a formulations as a complementary evidence for RCTs.

Currently, the differences in the efficacy of these GnRH-a formulations are still inconclusive. This study retrospectively analyzed the differences in clinical outcomes of different GnRH-a formulations in IVF/ICSI-ET and proposed a hypothesis that Goserelin acetate had better pregnancy outcomes than triptorelin acetate and leuprorelinin in IVF/ICSI-ET.

Methods

Patients and Study Design

This is a retrospective study. Infertile women undergoing IVF/ICSI-ET in long protocol during follicle phase from September 2019 to December 2023 at reproductive center of Huai'an First People's Hospital of Nanjing Medical University.

The inclusion criteria were as follows: 1) IVF/ICSI-ET assisted pregnancy for primary/secondary infertility; 2) no previous IVF/ICSI-ET history; 3) treating with long protocol during follicle phase; and 4) follow-up until pregnancy outcome. The exclusion criteria were as follows: 1) diagnoses of abnormal uterine morphology, including uterine malformations (mediastinum, unicornis, double uterus), submucosal fibroids, endometrial polyps, or uterine adhesions; 2) other conditions that may lead to infertility, such as hyperprolactinemia, abnormal and uncontrolled thyroid function; 3) pregnancy contraindications or diseases that have definite effects on pregnancy; and 4) chromosomal abnormalities in one or both spouses.

In this hospital, the most commonly used GnRH-a formulations were triptorelin acetate (Diphereline, Beaufort Ipsen Pharmaceutical, France), leuprorelin (Beiyi, Shanghai Lizhu Pharmaceutical, China) and goserelin acetate (Zoladex, AstraZeneca Pharmaceutical, England). The eligible patients were assigned to three groups according to their GnRH-a formulations: group A (triptorelin acetate), group B (leuprorelin) and group C (goserelin acetate).

Ethics

The study was conducted in accordance with the Helsinki Declaration of 1964 and approved by the ethics committee of Huai'an First People's Hospital of Nanjing Medical University (No. KY-2024-244-01). Study data were fully deidentified, and confidential information of patients was deleted, in accordance with the CIOMS/WHO International Ethical Guidelines for Health-related Research Involving Humans (2016), consequently, the study was deemed exempt from informed consent.

Protocols for IVF/ICSI-ET

From day 2 of menstruation, long-acting GnRH-a was administered through subcutaneous injection (3.75 mg triptorelin acetate; 3.75 mg leuprorelin; or 3.6 mg goserelin acetate). After 30 days, gonadotropin (Gonal-F; Merck Serono, Switzerland; Prilikon, Merck Pharmaceutical, China; Lishenbao, Livzon Pharmaceutical, China; Jinsaiheng, GeneScience Pharmaceutical, China; or human menopausal gonadotropin [HMG], Livzon Pharmaceutical, China) was administered 100–300 U/d to initiate ovulation according to the condition of follicles. When there were over two follicles of ≥ 18 mm in diameter, 5000 IU-10000 IU of HCG was administered. Oocytes were retrieved through transvaginal ultrasound-guidance after 36 hours. IVF or ICSI was administered based on sperm quality. A maximum of 2 embryos were transferred per cycle, and the remaining embryos

were cryopreserved according to the routine vitrification of the center. Transvaginal ultrasound was performed 28 days after transplantation, clinical pregnancy was diagnosed when the gestational sac and fetal heart beat were observed.

Clinical Outcomes

The baseline information, ovulation induction outcomes and pregnancy outcomes were compared among the three groups. In the process of ovulation induction, start-up amount of gonadotropin, total amount of gonadotropin, days of using gonadotropin, endometrial thickness on hCG day, hormone levels (including FSH, estradiol [E2], progestin [P] and LH) and mature oocytes retrieved were observed. Fertility rate (the number of zygotes of two pronuclei [2PN] divided by the number of yield oocytes), 2PN fertilization rate (the number of 2PN cleavage embryos divided by the number of 2PN zygotes), good-quality embryo rate (the number of embryos available for transfer, cryopreservation and extended culture to day 3 divided by the number of 2PN zygotes), blastocyst formation rate (the number of blastocysts divided by the number of day 3 embryos for extended culture), number of transplanted embryos were calculated.[10]

The primary pregnancy outcome was clinical pregnancy rate (CPR), and secondary pregnancy outcomes include the embryo implantation rate, live birth rate, miscarriage rate and premature birth rate.

Statistical Analyses

Quantitative variables were expressed as means ± standard deviations (SD) and were analyzed using Student's *t*-test. Qualitative variables were expressed as frequencies (percentages) and were analyzed using Pearson Chi-Square test or Fisher's exact test as appropriate. $P < 0.05$ was considered statistically significant. The statistical analysis was performed with the Statistical Package for Social Sciences version 26.0 (SPSS, Chicago, IL, USA).

Results

Baseline Information

As shown in Figure 1, a total of 154 eligible patients were finally included in the study. Group A included 94 patients, group B included 36 patients and group C included 24 patients. In Table 1, there were no significant statistical differences in mean women's age, spouse's age, women's body mass index (BMI), infertility years and infertility type (primary or secondary), assisted reproductive technology (IVF and/or ICSI). The total amount of gonadotropin (A vs B vs C: 2224.20±700.02 U vs 2266.67±884.01 U vs 1685.94±360.24 U) and days of using gonadotropin (A vs B vs C: 11.61±1.91 days vs 11.83±2.48 days vs 9.50±0.98 days) in groups A and B were significantly greater than in group C ($P < 0.05$). In terms of the hormone levels, the values of baseline E2 and LH on HCG day in group C were significantly different compared with other two groups ($P < 0.05$). All other characteristics were balanced among three groups.

Ovulation Induction Outcomes

As displayed in Table 2, the ovulation induction outcomes differed among three groups with non-significant difference, such as group A had the highest 2PN fertilization rate, good-quality embryo rate, blastocyst formation rate; group B had the highest fertility rate; and group C retrieved the most oocytes (all $P>0.05$).

Pregnancy Outcomes

Patients in group A underwent a total of 84 cycles and 109 transfers, patients in group B underwent a total of 33 cycles and 49 transfers, and those in group C underwent a total of 19 cycles and 31 transfers. According to Table 3, compared with groups A and B, group C had the highest pregnancy outcomes with the highest implantation rate (A vs B vs C: 40.4% vs 32.7% vs 41.9%), clinical pregnancy rate (A vs B vs C: 41.7% vs 39.4% vs 57.9%), live birth rate (A vs B vs C: 32.5% vs 33.3% vs 52.6%) and the lowest miscarriage rate (A vs B vs C: 22.9% vs 15.4% vs 9.1%) with non-significant difference (all $P>0.05$).

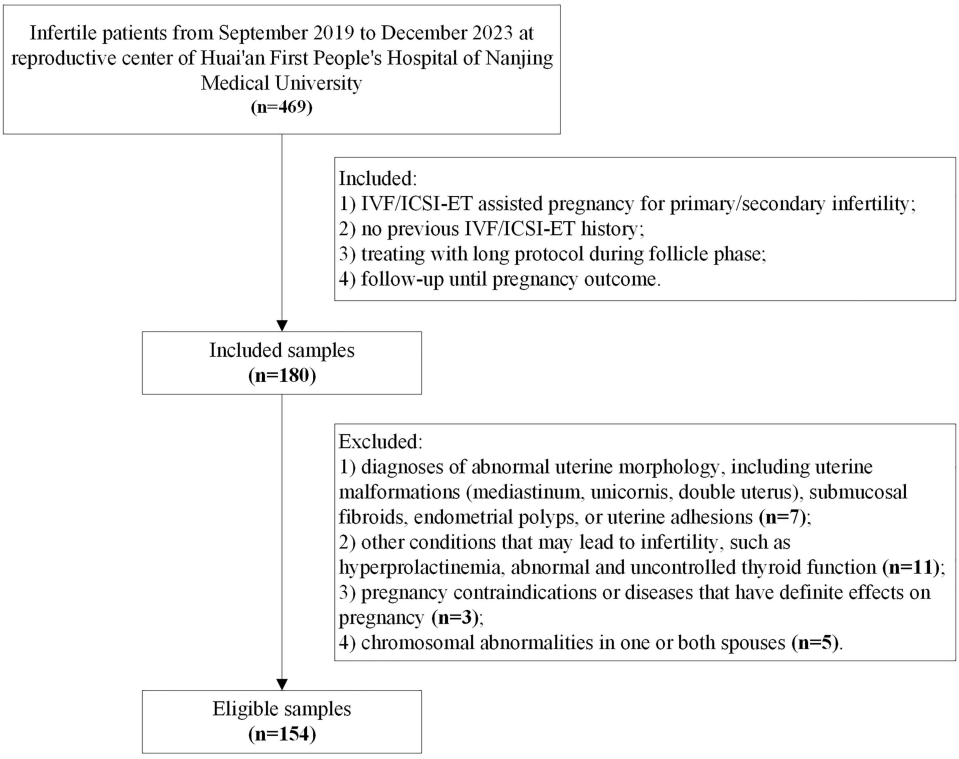

Figure 1 Workflow of patient enrollment.

Discussion

With the increasing application of IVF/ICSI-ET, GnRH-a regimens have been widely used for a long time, and the positive effect on live birth rate of GnRH-a has been proven.[11] Currently, triptolene and leuprorelin are commonly used in long follicular phase protocols, while goserelin is relatively rarely used in downregulation procedure.[12] In this study, we retrospectively collected four-year data of different GnRH-a formulations, in order to provide real-world evidence of the effects on clinical outcomes of IVF/ICSI-ET using different GnRH-a formulations. After analyses, we found that goserelin acetate show good pregnancy outcomes of IVF/ICSI-ET, specifically the implantation rate, clinical pregnancy rate, live birth rate and miscarriage rate, but no significant statistical differences were observed compared to triptorelin

Table 1 Baseline Information

Category	Variable		N (%) / Mean±SD			*P*-value[a]	*P*-value[b]	*P*-value[c]
			Group A (n=94)	Group B (n=36)	Group C (n=24)			
Demographic characteristics	Women's age, year		29.89±4.48	29.25±3.36	30.17±3.77	0.436	0.784	0.328
	Spouse's age, year		31.91±5.46	30.56±3.26	30.33±4.01	0.164	0.186	0.814
	Women's BMI, kg/cm^2		22.98±3.68	22.98±3.41	22.80±2.82	0.996	0.831	0.835
	Infertility duration, year		2.39±1.69	2.71±2.29	3.02±2.51	0.381	0.145	0.625
Treatments	Infertility type	Primary	56(60.9)	23(25.0)	13(14.1)	0.652	0.631	0.451
		Secondary	38(61.3)	13(21.0)	11(17.7)			
	Assisted reproductive technology	IVF	69(62.2)	24(21.6)	18(16.2)	0.741	0.955	0.748
		ICSI	14(58.3)	7(29.2)	3(12.5)			
		IVF+ICSI	11(57.9)	5(26.3)	3(15.8)			
	Gn_start-up dosage, IU		178.86±50.17	173.96±47.00	188.54±41.69	0.613	0.385	0.223
	Gn_total dosage, IU		2224.20±700.02	2266.67±884.01	1685.94±360.24	0.775	0.000	0.003
	Gn_duration, days		11.61±1.91	11.83±2.48	9.50±0.98	0.579	0.000	0.000

(*Continued*)

Table 1 (Continued).

Category	Variable	N (%) / Mean±SD			*P*-value[a]	*P*-value[b]	*P*-value[c]
		Group A (n=94)	Group B (n=36)	Group C (n=24)			
Hormone levels	FSH_baseline, U/L	6.66±2.38	6.55±2.64	6.26±1.58	0.809	0.436	0.638
	E2_baseline, pmol/L	74.36±207.63	113.45±366.05	47.08±62.48	0.446	0.527	0.384
	P_baseline, nmol/L	0.45±0.89	0.80±2.01	0.82±1.95	0.174	0.177	0.970
	LH_baseline, IU/L	5.74±3.10	5.89±4.08	6.61±4.47	0.817	0.264	0.519
	E2_HCG day, pmol/L	2650.46±1614.59	2753.19±1637.12	3648.92±2467.63	0.747	0.018	0.096
	P_HCG day, nmol/L	0.74±0.63	0.68±0.38	0.76±0.52	0.547	0.882	0.453
	LH_HCG day, IU/L	1.62±1.32	1.95±1.29	4.91±4.13	0.215	0.000	0.000
Other	Endometrial thickness_HCG day, mm	11.47±2.66	11.98±2.13	12.30±2.31	0.305	0.164	0.583

Notes: Group A= triptorelin acetate; group B= leuprorelin; group C= goserelin acetate. [a]Significant difference between groups A and B; [b]Significant difference between groups A and C; [c]Significant difference between groups B and C.
Abbreviations: N(%), number (percentage); SD, standard deviation; BMI, body mass index; IVF, "in vitro" fertilization; ICSI, intracytoplasmic sperm injection; Gn, gonadotropin; FSH, follicle-stimulating hormone; E2, estradiol; P, progesterone; LH, luteinizing hormone.

Table 2 Ovulation Induction Outcomes

	Group A	Group B	Group C	*P*-value[a]	*P*-value[b]	*P*-value[c]
Mature oocytes retrieved	9.86±4.19	10.08±4.82	11.04±5.92	0.796	0.263	0.494
Fertility rate (%)	64.73±21.49	66.83±22.16	55.98±22.12	0.622	0.079	0.068
2PN fertilization rate (%)	97.51±14.59	96.82±8.01	95.83±20.41	0.787	0.645	0.795
Good-quality embryo rate (%)	29.78±28.87	24.92±25.53	23.75±19.13	0.377	0.335	0.850
Blastocyst formation rate (%)	63.16±41.32	60.36±41.52	42.38±40.15	0.771	0.061	0.147
Number of transferred embryos	1.54±0.50	1.67±0.48	1.68±0.48	0.255	0.274	0.901

Notes: group A= triptorelin acetate; group B= leuprorelin; group C= goserelin acetate. Fertility rate=the number of zygotes of two pronuclei [2PN] divided by the number of yield oocytes; 2PN fertilization rate=the number of 2PN cleavage embryos divided by the number of 2PN zygotes; Good-quality embryo rate=the number of embryos available for transfer, cryopreservation and extended culture to day 3 divided by the number of 2PN zygotes; Blastocyst formation rate=the number of blastocysts divided by the number of day 3 embryos for extended culture. [a]Significant difference between groups A and B; [b]Significant difference between groups A and C; [c]Significant difference between groups B and C.
Abbreviation: 2PN, two pronuclei.

Table 3 Pregnancy Outcomes

	Group A	Group B	Group C	*P*-value[a]	*P*-value[b]	*P*-value[c]
Transfer cycles	84	33	19	–	–	–
Embryo implantation rate (%)	40.4(44/109)	32.7(16/49)	41.9(13/31)	0.355	0.875	0.400
Clinical pregnancy rate (%)	41.7(35/84)	39.4(13/33)	57.9(11/19)	0.822	0.199	0.198
Miscarriage rate (%)	22.9(8/35)	15.4(2/13)	9.1(1/11)	0.571	0.315	0.642
Premature birth rate (%)	11.4(4/35)	7.7(1/13)	9.1(1/11)	0.706	0.828	0.902
Live birth rate (%)	32.5(27/84)	33.3(11/33)	52.6(10/19)	0.934	0.100	0.172

Notes: group A= triptorelin acetate; group B= leuprorelin; group C= goserelin acetate. [a]Significant difference between groups A and B; [b]Significant difference between groups A and C; [c]Significant difference between groups B and C.

acetate and leuprorelin. It is noteworthy that the total amount of gonadotropin and duration of using gonadotropin were remarkably lower and shorter in patients using goserelin acetate than those using triptorelin acetate and leuprorelin. Herein, we inferred that goserelin acetate has good pregnancy outcomes in IVF/ICSI-ET with small amount and shout use of gonadotropin, but there is a lack of statistical significance when compared to the pregnancy outcomes of triptorelin acetate and leuprorelin. These findings need future confirmation in larger trials or meta-analyses.

A good pregnancy outcome requires an acceptable endometrium and a high-quality embryo. The important role of GnRHa in the endometrial/embryonic dialogue during early implantation has been reported et al found that GnRH can enhance endometrial receptivity and embryonic development.[13–16] GnRH and GnRH receptors are expressed in endometrium and embryo, and the expressions reach the highest levels during endometrial secretion and blastocyst expansion.[17–20] This suggests that GnRH-a has direct effect and functional role in the endometrium and embryo. Fujii et al suggested that giving GnRH-a during the luteal phase and early pregnancy had a positive effect on implantation and pregnancy outcomes.[21] Several meta-analyses demonstrated that in the fresh embryo transfer, the addition of GnRH-a during the luteal phase can considerably improve the rate of sustained pregnancy and live birth.[22–24]

The clinical outcomes in this study are partly consistent with previous studies. Parinaud et al found that leuprolide and triptorelin had similar pregnancy rates in IVF long-term suppression regimens.[25] Orvieto et al found that compared with triptorelin, leuprolide depot can significantly improve the implantation rate and pregnancy rate, but no effect on the quality of embryo based on a study of 26 samples.[7] In Cheung et al's study, the efficacy and safety of triptorelin and leuprorelin in down-regulating pituitary-ovarian function were similar.[26] Compared to leuprorelin, triptorelin had a longer duration of drug action, which benefits to be administered at longer intervals. In our study, goserelin acetate achieved good pregnancy outcomes of IVF/ICSI-ET with smaller amount and shouter use of gonadotropin than triptorelin acetate and leuprorelin, but the statistical significance needs to be verified in future research.

As far as we know, this is the first study of evaluating the clinical outcomes of triptolene, leuprorelin and goserelin in IVF/ICSI-ET based on real-world data. The effects of triptorelin and leuprorelin on IVF/ICSI-ET outcomes have been proven in a large amount of studies. In light of previous findings, goserelin is used to reduce estrogen levels in pre- or perimenopausal women, and protect ovarian function in cancer treatment.[27,28] Nowadays, goserelin is also used in IVF/ICSI-ET with similar mechanism of action to that of triptorelin and leuprorelin. Tapanainen et al demonstrated that goserelin can effectively induce pituitary down-regulation in IVF/ICSI-ET with few side effects.[29] Additionally, goserelin has longer half-life than triptolene and leuprorelin, which may help the sustained release of the drug to regulate the gonadotropin in the body. This may be one reason why goserelin regimen requires a small amount of gonadotropin to achieve good pregnancy outcomes. The mechanism of effects of goserelin on the clinical outcomes in IVF/ICSI-ET should be investigated more deeply in the future. Based on the results of this study, we may consider favoring the use of goserelin regimen in clinical practice for patients with gonadotropin intolerance or related side effects (such as abdominal pain and bloating).

Our study has several limitations. First, samples for the study began to be collected in September 2019, and the number of eligible samples after screening was limited. Further verification of our findings with larger sample size from multi-centers is needed. In addition, it is inevitable in real-world study that some variables are screened out due to high missing rates, may leading to a biased result. In future study based on real-world data, some statistical methods, such as multiple imputation and Markov Chain Monte Carlo, can be used to deal with missing data. Third, real-world study has noticeable demerits that it is non-experimental, causing inevitable interference of various confounding factors. This study did not control baseline differences in patient characteristics, due to the concern regarding potential reductions in sample size. In future study with sufficient sample size, confounding factors will be controlled by propensity scores matching, multiple regression and hierarchical analysis to reduce bias.[30] We also plan to conduct a RCT to control for potential confounding factors in the future. According to the principle of randomization, subjects are assigned to each group with the same probability, hence the potential confounding variables will be evenly distributed across the group. Forth, GnRH-a formulations should be selected not only by reference to the IVF/ICSI-ET outcomes, but also by comparing their efficacy through binding kinetics to GnRH receptors, duration of action and side effects. This is a research aspect we should concern and add relevant data in the future. Furthermore, in future research, we intend to evaluate more GnRH-a formulations, such as ganirelix, and evaluate more neonatal outcomes, such as malformation rate and Apgar scores.

Conclusions

In this study, we compared the real-world effects of three commonly used GnRH-a formulations in IVF/ICSI-ET. Our findings indicate that goserelin acetate has good pregnancy outcomes in IVF/ICSI-ET with small amount and shout use of gonadotropin, but there is a lack of statistical significance when compared to the pregnancy outcomes of triptorelin acetate and leuprorelin. This study may provide a comprehensive evaluation methodology in future study with large-scale

multicenter dataset, and help clinicians choose the proper COH regimen for patients with different situations, such as goserelin regimen for those with gonadotropin intolerance.

Abbreviations

COH, controlled ovarian hyperstimulation; IVF/ICSI-ET, "in vitro" fertilization/intracytoplasmic sperm injection and embryo transfer; GNRH-a, gonadotropin-releasing hormone agonist; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; RCTs, randomized clinical trials; HMG, human menopausal gonadotropin; E2, estradiol; P, progestin; 2PN, two pronuclei; CPR, clinical pregnancy rate; SD, standard deviations; BMI, body mass index.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Helsinki Declaration of 1964, and approved by the ethics committee of Huai'an First People's Hospital of Nanjing Medical University (No. KY-2024-244-01). Study data were fully deidentified, and confidential information of patients was deleted, in accordance with the CIOMS/WHO International Ethical Guidelines for Health-related Research Involving Humans (2016), consequently, the study was deemed exempt from informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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