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ORIGINAL ARTICLE

Reduced ovarian hyperstimulation syndrome risk with Follitropin-δ in ovarian stimulation

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Summary

Introduction: Ovarian stimulation (OS) during assisted reproductive technology (ART) carries the risk of ovarian hyperstimulation syndrome (OHSS). The risk is increased in polycystic ovary syndrome (PCOS). Recombinant DNA technologies have brought new generations of gonadotropins, such as Follitropin-δ. Individualized Follitropin-δ dosing, based on patient's body weight (BW) and Anti-Müellerian hormone (AMH), reduces OHSS risk.

Aim: To compare the prevalence of OHSS and the efficacy of OS with individualized Follitropin-δ and standard dosing with old generation gonadotropins in women with PCOS.

Material and methods: Case-control study encompassed 24 women stimulated with individualized Follitropin-δ dosing (Study Group) and 48 women with standard old generation gonadotropin dosing (Control Group). The inclusion criterion was PCOS. The exclusion criteria included other causes of infertility. Study participants were matched according to age, BW, AMH, and smoking status.

Results: Prevalence of moderate (0% vs. 5.9%) and severe (0% vs. 17.6%) OHSS were significantly lower in Study Group (p=0.009). Duration of OS (9.06±1.53 vs. 10.00±1.13 days, p=0.01) and total gonadotropin dose (1,117.95±234.90 vs. 1,940.33±501.20 IU, p<0.001) were significantly lower in Study group. The number of good quality embryos was significantly higher in Study group (3.33±1.13 vs. 2.20±0.96 embyos, p<0.001).

Conclusion: The prevalence of moderate and severe OHSS is lower in OS with individualized Follitropin-δ dosing compared to standard dosing with older generations of gonadotropins. The effectiveness of OS in the study groups did not differ significantly, except for the shorter duration of OS, a lower applied total gonadotropin dose and significantly higher number of good quality embryos, which were recorded in Study group.

Keywords: prevalence, good quality embryos, gonadotropin dose

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INTRODUCTION

Excessive multifollicular growth during ovarian stimulation (OS) in assisted reproductive technology (ART) is common in women with polycystic ovary syndrome (PCOS), often leading to ovarian hyperstimulation syndrome (OHSS), a challenging iatrogenic complication (1). OHSS stirs a general concern in ART, which disturbs both women's physical and mental health and increases the risks regarding adverse pregnancy outcomes (2). Results from the observational study highlight the significance of PCOS as a risk factor for OHSS, showing a marked difference in OHSS prevalence between women with and without PCOS. Among women with PCOS, 22.1% experienced OHSS, compared to less than 5% in those without PCOS (3). Consequently, prevention of OHSS in women with PCOS is very important for the safety of OS treatment.

The initiation of recombinant DNA technologies in the field of reproductive medicine caused a fast development of novel medications, and enabled transition from standardization to individualization regarding the choice and dosage of gonadotropins (4). This advancement in gonadotropin production also enabled the generation of proteins through biological processes, resulting in high-purity medications produced at large scales with consistent composition. Follitropin-δ, the newest and unique gonadotropin, is produced from a host cell line of human origin, while previous recombinant gonadotropins were derived from a host cell line of Chinese hamster. Additionally, it has a diverse pharmacokinetic profile from other gonadotropins because of higher levels of 2.6-linked sialic acid and tri- and tetra-sialylated glycans. This leads to more effective action of gonadotropin-δ compared to other gonadotropins (4), lower clearance (5), and a risk/benefit ratio considered to be positive including headache and OHSS (6). Furthermore, it comprises unique approach by individualizing the gonadotropin dosage based on body weight and ovarian reserve, allowing individualized therapeutic approach and decreasing the risk of OHSS (4).

Several years ago, Follitropin-δ was introduced in clinical practice in ART procedures in Serbia. Involvement in such practice is gradually increasing. However, real-world studies regarding Follitropin-δ, that reflect current practices with respect to how patients react to treatment in terms of safety, tolerance and efficacy in Serbia and South-East Europe are missing. Therefore, this observational match case-controlled study aimed to enhance medical knowledge regarding safety and efficacy of individualized Follitropin-δ in population of women with PCOS in Serbia. We aimed to evaluate the prevalence of OHSS and efficacy of OS in women treated with individualized Follitropin-δ dosing and in women who were treated with standard gonadotropin dosing.

MATERIAL AND METHODS

Subjects

Study participants were women who underwent ART at two clinics in Belgrade financed by the Republic Fund of Health Insurance of the Republic of Serbia. One clinic is a public university clinic and the other one is a private ART clinic. Both are located in Belgrade, the capital of the Republic of Serbia, both perform ART procedures financed by the Republic Fund of Health Insurance, and they are both considered to be referral centers for ART for the entire country. The inclusion criteria were: PCOS identified following Rotterdam criteria, fresh autologous cycle, age between 18 and 45 years. The exclusion criteria included obesity and any other infertility cause. The approval for this study was obtained from the Institutional review board (No. of decision 05006-2022-16004).

Methods

Retrospective observational analysis (matched case-controlled study) with carefully selected homogeneous group of patients assessed prevalence of OHSS and ART outcomes in women with PCOS stimulated with individualized Follitropin-δ dosing and with conventional gonadotropin dosing. After applying inclusion and exclusion criteria, anonymized data of two groups of women with PCOS undergoing OS were analyzed. The Study group encompassed women who received individualized Follitropin-δ dosing (individualized dosing group), the Control group received standard gonadotropin dosing (standard dosing group). In total, 24 women treated with Follitropin-δ were matched in terms of age, AMH, body weight, and smoking status with 48 patients who had been treated with standard gonadotrophin dosing.

The primary study outcome was the prevalence of OHSS, both regarding the prevalence of OHSS in general and regarding the prevalence of different severity of OHSS (mild, moderate, severe). The diagnosis of OHSS and various degrees of severity of OHSS were assessed by Golan criteria and classification (7). Secondary study outcomes were the duration of OS, the total dosage of applied gonadotropin, the total number of retrieved oocytes, the number of metaphase II oocytes (MII), the total number of obtained embryos, and the number of good quality embryos (GQE) and clinical pregnancy rate (CPR).

The approval for this study was obtained from the Institutional review board (No. of decision 05006-2022-16004).

Statistical analysis

Depending on the type of data, the data are presented as counts (percents) or mean+/–standard deviations. For comparisons between study groups, parametric tests

Table 1. Clinical characteristics of study participants

	Study group	Control group	p
Age (years)	32.67±3.21	32.63±3.14	0.958*
Infertility duration (years)	2.42±1.12	2.51±0.95	0.345*
Previous delivery/deliveries	0%	10.4%	0.162¶
Previous misscariages	20.8%	18.8%	1.000¶
Menarche (years)	12.60±1.39	13.37±1.79	0.069*
Cycle length (days)	33.13±9.05	32.40±7.35	0.719º
FSH - day 3 (IU/l)	5.97±1.43	5.70±1.75	0.515*
LH - day 3 (IU/l)	8.26±3.72	6.46±3.10	**0.033***
Estradiol - day 3 (IU/l)	139.77±62.48	179.37±88.78	0.068º
AMH (ng/ml)	5.78±.25	5.74±3.23	0.929º
Antral Follicle Count	25.67±1.46	25.42±1.22	0.446*
Right Ovary volume(cm3)	12.68±0.41	12.66±0.33	0.835*
Left Ovary volume (cm3)	12.76±0.44	12.71±0.34	0.572*

Data are expressed as mean±SD or as percentages. * – t-test was used to test the differences; ¶ - Fisher's exact test was used to test the differences; º - Mann-Whitney test was used to test the differences

Table 2. Outcomes of OS in study groups

	Study group	Control group	p
Duration of OS (days)	9.06±1.53	10.00±1.13	**0.01º**
Gonadotropin dose	1,117.95±234.90	1,940.33±501.20	**<0.001***
Serum E2 (pmol/l) trigger day	6512.60±1.39	7813.37±1.79	0.069*
No of periovulatory follicles	10.96±4.81	11.17±3,18	0.849*

Data are expressed as mean±SD or as percentages. * – t-test was used to test the differences; º - Mann-Whitney test was used to test the differences

(Student's t-test and Fisher's exact test) and non-parametric tests (Mann Whitney test, Chi-square test) were used. Multivariate logistic regression was employed as a statistical method to account for confounding factors. All data analyses were performed using the statistical software SPSS (IBM corp.). All p values less than 0.05 were considered significant.

RESULTS

Characteristics of women with PCOS treated with individualized Follitropin-δ and those treated with standard gonadotropin dosing are presented in **Table 1**. A significant difference between the groups was only found regarding serum LH levels on day 3 of the cycle, being lower in standard dosing group.

The outcome of OS treated with individualized Follitropin-δ or standard gonadotropin dosing are presented in **Table 2**. The duration of OS and applied gonadotropin dose were significantly lower in Study group.

Table 3 presents data on the outcomes of oocyte pick-up and ART results in the individualized Follitropin-δ dosing group compared to the standard gonadotropin dosing group. The number of germinal vesicles and atretic oocytes were significantly higher in standard gonado-

Table 3. ART outcomes in study groups

	Study group	Control group	P
Retrieved oocytes	10.50±5.09	10.25±3.24	0.828*
Metaphase II oocytes	5.79±3.06	5.06±2.57	0.291*
Metaphase I oocytes	1.71±2.39	1.46±1.73	0.618º
Germinal vesicle oocytes	0.37±0.92	1.10±1.51	**0.009º**
Atretic oocyte	0.04±0.20	0.88±1.06	**<0.001º**
Total No of Embryos	6.33±2.87	5.17±2.79	0.169º
No of Good Embryos	3.33±1.13	2.20±0.96	**<0.001º**
Clinical pregnancy rate	29.17%	34.8%	0.057¡

Data are expressed as mean±SD or as percentages. To test the differences: * – t-test was used t; º - Mann-Whitney test was used; ¡ - Chi-square test was used

Table 4. Prevalence of OHSS in study groups

	Study group	Control group	p
OHSS	7 (29.2%)	17 (37.0%)	0.515¡
Severe OHSS	0 (0.0%)	1 (5.9%)	
Moderate OHSS	0 (0.0%)	3 (17.6%)	**0.009** º
Mild OHSS rate	7 (100%)	14 (76.5%)	

Data are expressed as absolute numbers and as percentages (in brackets). To test the differences: º - Mann-Whitney test was used; ¡ - Chi-square test was used

tropin dosing while the number of obtained good quality embryos was significantly higher in individualized dosing group. **Table 4** presents the prevalence of OHSS, including overall cases and the distribution among different grades, within the study groups. Although the prevalence of OHSS in general did not differ significantly, the prevalence of different grades differed significantly, prevalences of moderate and severe forms were lower in individualized dosing group.

DISCUSSION

To the best of our knowledge, our study is the first to compare the prevalences of OHSS in the population of women with PCOS in Serbia and the region of South-East Europe stimulated with individualized Follitropin-δ dosing and with standard gonadotropin dosing. Results from our matched case-controlled study represent real-world data from Serbia during routine healthcare reproductive medicine care, generated through data obtained from electronic records from our clinics. Our data is in line with randomized control trials (RCT) evaluating this issue in general population of women undergoing ART in Japan (8) and also in the population of women with PCOS in Poland (9).

Regarding the efficacy of OS, we found significantly lower applied gonadotropin dose in women with individualized Follitropin-δ dosing, which is in accordance with the study performed by Gazzo et al. (10) and by Kovacs et al. (11). Furthermore, a significantly shorter duration of OS was present in individualized Follitropin-δ dosing group. This is in contrast with RCT performed by Qiao et al. (12). By default, participants in a randomized controlled trial (RCT) follow a strictly controlled treatment regimen based on a specified study protocol. In contrast, our study utilizes real-world data (RWD) derived from various electronic health and medical records, reflecting less regulated and more diverse treatment options. Furthermore, Qiao et al. performed a study in Asian population and the inclusion criteria considerably differed from our inclusion criteria, while they included women diagnosed with tubal and unexplained infertility as well as minimal and mild endometriosis. The aforementioned facts may explain the discrepancies between the results of their RCT and our matched case-control study. Still, when compared to other RWD, our duration of OS was shorter. Thus, mean duration of OS (9.06 days) was noticeably shorter than OS duration obtained from RWD DELTA study (13). This marked difference could be explained by the fact that in our study other causes of infertility rather than PCOS were excluded from the study, while in DELTA study all kinds of infertility causes other than anovulatory PCOS were included.

This study has some limitations. Follitropin-δ was introduced a few years ago, and the number of women stimulated with this new medication is gradually rising; however, the overall population of these women remains small. Besides, in order to avoid potential confounding factors that may influence ART outcomes, we applied very strict inclusion and exclusion criteria which resulted in narrowing down the selection of potential study participants. For the aforementioned reasons, the number of study participants is small and we acknowledge this as a study limitation. Furthermore, the study sample was small to evaluate different PCOS phenotypes among study participants, and that is another limitation of the study. Different PCOS phenotypes mirror the diversity of ovarian response to OS and risks in developing OHSS (14).

This study has its strengths as well. Rigorous exclusion and inclusion criteria lead to avoidance of possible confounding factors. Furthermore, external validity is another study strong point. As previously mentioned, both clinics involved in this study are considered to be referral centers for ART in the Republic of Serbia and neighboring countries. Therefore, women undergoing ART in those clinics could be considered as representative population of infertile women in the region.

CONCLUSION

Our study demonstrated excellent safety performances of OS with individualized Follitropin-δ dosing. These performances were better than OS with standard gonadotropin dosing, since the prevalence of moderate and severe OHSS is significantly higher in OS with standard gonadotropin dosing. In unison, ART outcomes between study groups did not differ significantly. The real-world data (RWD) on the safety profile of ovarian stimulation with individualized Follitropin-δ dosing in Serbia, provided by this observational matched case-control study, align with the findings of previously published clinical trials and global real-world studies. However, some data

regarding efficacy of OS are in contrast with RWD and RCT. Therefore, larger studies are needed to deliver more reliable data concerning the issues evaluated in this study.

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Disclosure of interest

Milan Perovic was a speaker for MERCK, FERRING Pharmaceuticals, Alkaloid and Laboratoire INNOTECH International

Author Contributions

- The conception or design of the work: Milan Perović, Nebojsa Zečević
- The acquisition, analysis, and interpretation of data: Milan Perović, Nebojša Zečević, Dragana Bojović-Jović, Tatjana Nožić Zečević, Ana Nikolić
- Preparing the manuscript draft: Milan Perović, Nebojsa Zečević, Dragana Bojović-Jović, Tatjana Nožić Zečević, Aleksandar Stojsavljević, Ana Nikolić
- Interpretation of revised version of manuscript: Milan Perović, Nebojša Zečević, Dragana Bojović-Jović, Tatjana Nožić Zečević, Aleksandar Stojsavljević, Ana Nikolić

Ethical approval was obtained from the Institutional Review Board (Decision No. 05006-2022-16004).

REFERENCES

1. Ovarian Stimulation TEGGO, Bosch E, Broer S, et al. ESHRE guideline: ovarian stimulation for IVF/ICSI† [published correction appears in Hum Reprod Open. 2020 Dec 29; 2020(4): hoaa067. doi: 10.1093/hropen/hoaa067]. Hum Reprod Open. 2020; 2020(2): hoaa009.
2. Vembu R, Reddy NS. Serum AMH Level to Predict the Hyper Response in Women with PCOS and Non-PCOS Undergoing Controlled Ovarian Stimulation in ART. J Hum Reprod Sci. 2017;10(2):91-94. doi:10.4103/jhrs.JHRS_15_16.
3. Doroftei B, Ilie OD, Anton N, Marcu OA, Scripcariu IS, Ilea C. A Narrative Review Discussing the Efficiency of Personalized Dosing Algorithm of Follitropin Delta for Ovarian Stimulation and the Reproductive and Clinical Outcomes. Diagnostics (Basel). 2023;13(2):177. doi:10.3390/diagnostics13020177.
4. Palomba S, Caserta D, Levi-Setti PE, Busnelli A. Efficacy and safety of follitropin delta for ovarian stimulation in vitro fertilization/intracytoplasmic sperm injection cycles: a systematic review with meta-analysis. J Ovarian Res. 2024;17(1):60. Published 2024 Mar 14. doi:10.1186/s13048-024-01372-w.
5. Olsson H, Sandström R, Grundemar L. Different pharmacokinetic and pharmacodynamic properties of recombinant follicle-stimulating hormone (rFSH) derived from a human cell line compared with rFSH from a non-human cell line. J Clin Pharmacol. 2014;54(11):1299-1307. doi:10.1002/jcph.328.
6. Koechling W, Plaksin D, Croston GE, Jeppesen JV, Macklon KT, Andersen CY. Comparative pharmacology of a new recombinant FSH expressed by a human cell line. Endocr Connect. 2017;6(5):297-305. doi:10.1530/EC-17-0067.
7. Golan A, Ron-el R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. *Obstet Gynecol Surv*. 1989;44(6):430-440. doi:10.1097/00006254-198906000-00004.
8. Ishihara O, Arce JC; Japanese Follitropin Delta Phase 3 Trial (STORK) Group. Individualized follitropin delta dosing reduces OHSS risk in Japanese IVF/ICSI patients: a randomized controlled trial. *Reprod Biomed Online*. 2021;42(5):909-918. doi:10.1016/j.rbmo.2021.01.023.
9. Višnová H, Papaleo E, Martin FS, Koziol K, Klein BM, Mannaerts B. Clinical outcomes of potential high responders after individualized FSH dosing based on anti-Müllerian hormone and body weight. *Reprod Biomed Online*. 2021;43(6):1019-1026. doi:10.1016/j.rbmo.2021.08.024.
10. Gazzo I, Bovis F, Colia D, Sozzi F, Costa M, Anserini P, et al. Algorithm vs. clinical experience: controlled ovarian stimulations with follitropin-delta and individualised doses of follitropin-alpha/beta. *Reprod Fertil*. Published online February 1, 2024. doi:10.1530/RAF-23-0045.
11. Kovacs P, Jayakumaran J, Lu Y, Lindheim SR. Comparing pregnancy rates following ovarian stimulation with follitropin-Δ to follitropin -α in routine IVF: A retrospective analysis. *Eur J Obstet Gynecol Reprod Biol*. 2023; 280:22-27. doi:10.1016/j.ejogrb.2022.11.006.
12. Qiao J, Zhang Y, Liang X, Ho T, Huang HY, Kim SH, et al. A randomised controlled trial to clinically validate follitropin delta in its individualised dosing regimen for ovarian stimulation in Asian IVF/ICSI patients. *Hum Reprod*. 2021;36(9):2452-2462. doi:10.1093/humrep/deab155.
13. Porcu-Buisson G, Maignien C, Swierkowski-Blanchard N, Rongières C, Ranisavljevic N, Oger P, et al. Prospective multicenter observational real-world study to assess the use, efficacy and safety profile of follitropin delta during IVF/ICSI procedures (DELTA Study). *Eur J Obstet Gynecol Reprod Biol*. 2024; 293:21-26. doi:10.1016/j.ejogrb.2023.12.011.
14. Cela V, Obino MER, Alberga Y, Pinelli S, Sergiampietri C, Casarosa E, et al. Ovarian response to controlled ovarian stimulation in women with different polycystic ovary syndrome phenotypes. *Gynecol Endocrinol*. 2018;34(6):518-523. doi:10.1080/09513590.2017.1412429.

SMANJEN RIZIK OD HIPERSTIMULACIJE JAJNIKA USLED PRIMENE FILOTROPINA DELTA TOKOM STIMULACIJE JAJNIKA

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Sažetak

Uvod: Stimulacija jajnika (OS) u sklopu vantelesne oplodnje (VTO) nosi rizik od sindroma ovarijalne hiperstimulacije (OHSS). Ovaj rizik je naročito izražen kod žena sa sindromom policističnih jajnika (PCOS). Rekombinantnim DNK tehnologijama stvorene su nove generacije gonadotropina, kao što je folitropin delta, koje individualizovanim doziranjem na osnovu vrednosti Anti-Milerovog hormona (AMH) i telesne mase (tm) pacijenta smanjuju rizik od OHSS-a.

Cilj: Upoređivanje prevalence OHSS-a i efikasnosti OS-a individualizovanim doziranjem folitropinom delta i standardnim doziranjem starijim generacijama gonadotropina u populaciji žena sa PCOS.

Metode: U studiji kontrole slučajeva radnu grupu činile su 24 žene stimulisane individualizovanim doziranjem folitropinom delta, a kontrolnu 48 žena koje su stimulisane standardnim doziranjem starijim generacijama gonadotropina. Studijski kriterijum za uključivanje bio je PCOS, a za isključivanje ostali uzroci infertiliteta. Ispitanice radne grupe uparene su sa ispitanicama kontrolne grupe na osnovu AMH, tm, godina starosti i pušačkog statusa.

Rezultati: U radnoj grupi prevalenca umerenih (0% vs. 5,9%) i težih (0% vs. 17,6%) formi OHSS-a značajno je manja (p=0,009) u odnosu na kontrolnu grupu. Trajanje OS (9,06±1,53 dana vs. 10,00±1,13 dana, p=0,01) i primenjena doza gonadotropina (1,117.95±234,90 vs. 1,940.33±501,20 IU, p<0,001) značajno su manji u radnoj grupi. Broj dobijenih embriona visokog kvaliteta veći je u radnoj grupi (3,33±1,13 vs. 2,20±0,96, p<0,001).

Zaključak: Prevalenca umerenih i težih formi OHSS-a manja je kod OS individualizovanim doziranjem folitropinom delta u odnosu na OS standardnim doziranjem starijim generacijama gonadotropina. Efikasnost OS u studijskim grupama nije se značajno razlikovala, osim kraćeg trajanja OS, manje ukupne primenjene doze gonadotropina i znatno većeg broja dobijenih visokokvalitetnih embriona, a koji su zabeleženi kod OS individualizovanim doziranjem folitropinom delta.

Ključne reči: prevalenca, kvalitetni embioni, doza gonadotropina

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