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Secondary predictors of ovarian hyperstimulation syndrome development

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Key words: ovarian hyperstimulation syndrome, prognosis, preovulatory follicles, oocytes, estradiol, vascular endothelial growth factor, interleukin-6.

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In the treatment of infertility by the method of fertilization *in vitro*, such a serious complication as ovarian hyperstimulation syndrome (OHSS) can occur. Primary predictors of OHSS development are widely used in practice while selecting controlled ovarian stimulation patterns. The identification and evaluation of secondary predictors of OHSS development is relevant.

Aim. To identify and evaluate secondary predictors of OHSS in women at high risk of OHSS.

Materials and methods. The study included 240 women at high risk of developing ovarian hyperstimulation syndrome, 63 of these women subsequently developed ovarian hyperstimulation syndrome, and 177 did not. To identify secondary predictors, a number of preovulatory follicles and oocytes was evaluated, estradiol levels, vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6) were defined in the blood serum and follicular fluid.

Results. Compared to women without OHSS, there was a statistically significant increase in the number of preovulatory follicles, oocytes, estradiol, VEGF, IL-6 in the blood serum and follicular fluid in OHSS patients. There was a direct correlation between the serum and follicular fluid levels of estradiol (r_s = 0.85; 95 % CI 0.80–0.89; P < 0.001), VEGF (r_s = 0.76; 95 % CI 0.69–0.81; P < 0.001) and IL-6 (r_s = 0.67; 95 % CI 0.58–0.74; P < 0.001). Secondary predictors of OHSS was the number of preovulatory follicles ≥30 for two ovary (sensitivity – 46.0 %, specificity – 91.0 %), the number of oocytes ≥19 (sensitivity – 87.3 %, specificity – 97.7 %), serum estradiol levels ≥4800 pg/ml (sensitivity – 74.6 %, specificity – 96.6 %) and estradiol in follicular fluid – ≥725000 pg/ml (sensitivity – 98.4 %, specificity – 97.7 %), serum VEGF ≥ 30 pg/ml (sensitivity – 76.2 %, specificity – 98.3 %) and VEGF in follicular fluid ≥500 pg/ml (sensitivity – 87.3 %, specificity – 97.2 %), IL-6 in serum ≥4 pg/ml (sensitivity – 65.1 %, specificity – 98.9 %) and IL-6 in follicular fluid ≥8.5 pg/ml (sensitivity – 90.5 %, specificity – 98.3 %), respectively.

Conclusions. The predictors of OHSS should be taken into account to reduce the risk of its development. In identifying secondary predictors of OHSS development, it is necessary to use preventive measures consisting in discontinuation of luteal phase support, vitrification of all embryos and their transfer in subsequent thawed cycles.

Ключові слова: синдром гіперстимуляції яєчників, предиктори, передовуляторні фолікули, ооцити, естрадіол, судинно-ендотеліальний фактор росту, інтерлейкін-6.

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Вторинні предиктори розвитку синдрому гіперстимуляції яєчників

Е. М. Айзятулова

Під час лікування безпліддя методом запліднення *in vitro* може виникнути таке важке ускладнення, як синдром гіперстимуляції яєчників (СГЯ). Первинні предиктори розвитку СГЯ широко використовують у практиці, обираючи схеми контрольованої оваріальної стимуляції. Актуальним є виявлення та оцінювання вторинних предикторів розвитку СГЯ.

Мета роботи – виявити та оцінити вторинні предиктори розвитку СГЯ в жінок із високим ризиком його розвитку.

Матеріали та методи. У дослідженні взяли участь 240 жінок із високим ризиком розвитку СГЯ, у 63 із них згодом розвинувся СГЯ, а у 177 – не розвинувся. Щодо визначення вторинних предикторів, оцінили кількість передовуляторних фолікулів і ооцитів, у сироватці крові та фолікулярній рідині визначили рівні естрадіолу, судинно-ендотеліального фактора росту (VEGF) та інтерлейкіну-6 (IL-6).

Результати. У пацієнток із СГЯ порівняно з жінками без СГЯ спостерігали статистично значуще збільшення кількості передовуляторних фолікулів, ооцитів, вмісту естрадіолу, VEGF, IL-6 у сироватці крові та в фолікулярній рідині. Встановили пряму кореляцію між показниками в сироватці крові та фолікулярній рідині вмісту естрадіолу (r_s = 0,85; 95 % CI 0,80–0,89; p < 0,001), VEGF (r_s = 0,76; 95 % CI 0,69–0,81; p < 0,001) і IL-6 (r_s = 0,67; 95 % CI 0,58–0,74; p < 0,001). Вторинними предикторами розвитку СГЯ є кількість передовуляторних фолікулів ≥30 на два яєчники (чутливість – 46,0 %, специфічність – 91,0 %), число ооцитів ≥19 (чутливість – 87,3 %, специфічність – 97,7 %), рівень естрадіолу в сироватці крові ≥4800 пг/мл (чутливість – 74,6 %, специфічність – 96,6 %) та естрадіолу в фолікулярній рідині – ≥725 000 пг/мл (чутливість – 98,4 %, специфічність – 97,7 %), VEGF у сироватці крові ≥30 пг/мл (чутливість – 76,2 %, специфічність – 98,3 %) і VEGF у фолікулярній рідині ≥500 пг/мл (чутливість – 87,3 %, специфічність – 97,2 %), IL-6 в сироватці крові ≥4 пг/мл (чутливість – 65,1 %, специфічність – 98,9 %) і IL-6 у фолікулярній рідині ≥8,5 пг/мл (чутливість – 90,5 %, специфічність – 98,3 %) відповідно.

Висновки. Для зниження ризику розвитку СГЯ необхідно враховувати предиктори розвитку цього синдрому. Виявляючи вторинні предиктори розвитку СГЯ, необхідно вживати превентивні заходи, що полягають у скасуванні лютеїнової підтримки, вітрифікації всіх ембріонів і їх перенесенні в наступних розморожених циклах.

Вторичные предикторы развития синдрома гиперстимуляции яичников

Э. М. Айзятулова

При лечении бесплодия методом оплодотворения *in vitro* может возникнуть такое тяжелое осложнение, как синдром гиперстимуляции яичников (СГЯ). Первичные предикторы развития СГЯ широко используют в практике при выборе схем контролируемой овариальной стимуляции. Актуальными остаются определение и оценка вторичных предикторов развития СГЯ.

Цель работы – установить и оценить вторичные предикторы развития СГЯ у женщин с высоким риском его развития.

Материалы и методы. В исследование вошли 240 женщин с высоким риском развития СГЯ, у 63 из этих женщин впоследствии развился СГЯ, а у 177 – нет. Для установления вторичных предикторов оценили количество предовуляторных фолликулов и ооцитов, в сыворотке крови и фолликулярной жидкости определили уровни эстрадиола, сосудисто-эндотелиального фактора роста (VEGF) и интерлейкина-6 (IL-6).

Результаты. У пациенток с СГЯ по сравнению с женщинами без СГЯ отмечено статистически значимое повышение числа преовуляторных фолликулов, ооцитов, содержания эстрадиола, VEGF, IL-6 в сыворотке крови и в фолликулярной жидкости. Отмечена прямая корреляция между показателями в сыворотке крови и фолликулярной жидкости содержания эстрадиола (r_s = 0,85; 95 % CI 0,80–0,89; p < 0,001), VEGF (r_s = 0,76; 95 % CI 0,69–0,81; p < 0,001) и IL-6 (r_s = 0,67; 95 % CI 0,58–0,74; p < 0,001).

Вторичные предикторы развития СГЯ: количество преовуляторных фолликулов ≥30 на два яичника (чувствительность – 46,0 %, специфичность – 91,0 %), количество ооцитов ≥19 (чувствительность – 87,3 %, специфичность – 97,7 %), уровень эстрадиола в сыворотке крови ≥4800 пг/мл (чувствительность – 74,6 %, специфичность – 96,6 %) и эстрадиола в фолликулярной жидкости – ≥725000 пг/мл (чувствительность – 98,4 %, специфичность – 97,7 %), VEGF в сыворотке крови ≥30 пг/мл (чувствительность – 76,2 %, специфичность – 98,3 %) и VEGF в фолликулярной жидкости ≥500 пг/мл (чувствительность – 87,3 %, специфичность – 97,2 %), IL-6 в сыворотке крови ≥4 пг/мл (чувствительность – 65,1 %, специфичность – 98,9 %) и IL-6 в фолликулярной жидкости ≥8,5 пг/мл (чувствительность – 90,5 %, специфичность – 98,3 %) соответственно.

Выводы. Для снижения риска развития СГЯ необходимо учитывать предикторы развития данного синдрома. При установлении вторичных предикторов развития СГЯ необходимо использовать превентивные меры, заключающиеся в отмене лютеиновой поддержки, витрификации всех эмбрионов и их переносе в последующих размороженных циклах.

Ключевые слова: синдром гиперстимуляции яичников, предикторы, преовуляторные фолликулы, ооциты, эстрадиол, сосудисто-эндотелиальный фактор роста, интерлейкин-6.

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Infertility is the most important medico-social problem not only in Ukraine, but throughout the world [1–4]. An effective method of infertility treatment is fertilization in vitro [1,5]. However, its widespread introduction into clinical practice does not only help to solve the problems of infertility, but also can be accompanied by severe complications that threaten the health and even the life of the patient [5,6]. One of these complications is ovarian hyperstimulation syndrome (OHSS) [5–10].

Despite the large number of studies on the given state, up to the present date, there is no perfect strategy that completely eliminates OHSS. At the same time, there are risk factors that can be taken into account in order to reduce the frequency of its development [7–10]. Primary predictors of OHSS development, including the number of antral follicles, antimullerian hormone levels, polycystic ovary syndrome, OHSS in previous cycles, young age and low body weight in patients are proved by many scientists and already widely used in practice while selecting controlled ovarian stimulation [7–10]. However, despite the implementation of preventive measures, the risk of developing OHSS remains because of the controlled ovarian stimulation. Therefore, identification and evaluation of OHSS secondary predictors allow to develop further tactics of patient treatment that will contribute to the reduction of OHSS cases up to complete elimination.

Aim

To identify and evaluate secondary predictors of OHSS in women at high risk of OHSS.

Materials and methods

The study included 240 women at high risk of OHSS development taking into account the primary predictors such as: the number of antral follicles more than 20, the content of antimullerian hormone 5.5 ng/ml and more, polycystic ovary syndrome, OHSS during previous in vitro fertilization attempts. Subsequently, 63 of these women developed OHSS and 177 did not.

An echographic study was performed using an ultrasound diagnostic system SSA-790A (APLIO-XG) (Toshiba, Japan) with transabdominal and transvaginal convex transducers.

Definition of estradiol, vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6) in the blood serum and follicular fluid were performed on the day of transvaginal follicle puncture. The follicular fluid was obtained from the dominant follicles, centrifuged for 5 minutes and separated from the blood cells. Using the electrochemiluminescent method and the reagents of Roche Diagnostics (Switzerland) company on an automated analyzer Cobas-e411 (Roche Diagnostics, Switzerland), estradiol concentration was determined; by immune-enzyme method using an immune-enzyme reader ImmunoChem-2100 (Hight Tehnology, USA), VEGF was investigated using the reagents of the company “BIO Tech Lab S” (USA) and IL-6 – of “Vector-Best” company (RF).

Statistical processing and the obtained data analysis were performed using the SPSS Statistics 22 software package. Since the most of the variables were not normally distributed, they were represented by the median (Me) and interquartile ranges – 25 and 75 percentiles (25; 75 %). The comparison of indicators between groups was performed using the non-parametric Mann–Whitney U test. To determine the direction and strength of a relationship between the variables the Spearman rank coefficient of correlation (r_s) and the 95 % confidence interval (95 % CI) was further calculated.

Binary logistic regression method was used to determine the boundary values of independent variables relative to the probability of OHSS occurrence. The prognostic test sensitivity (true positive result) and the specificity of the test (true negative result) were determined. The ROC-curves were represented. The value, which was diagnosed with a zero degree of prognosis, was depicted in the figures as a diagonal dashed line. Consequently, the more steeply curved ROC-curve (the maximum degree of prediction 1) was, the more accurate was the test results prediction.

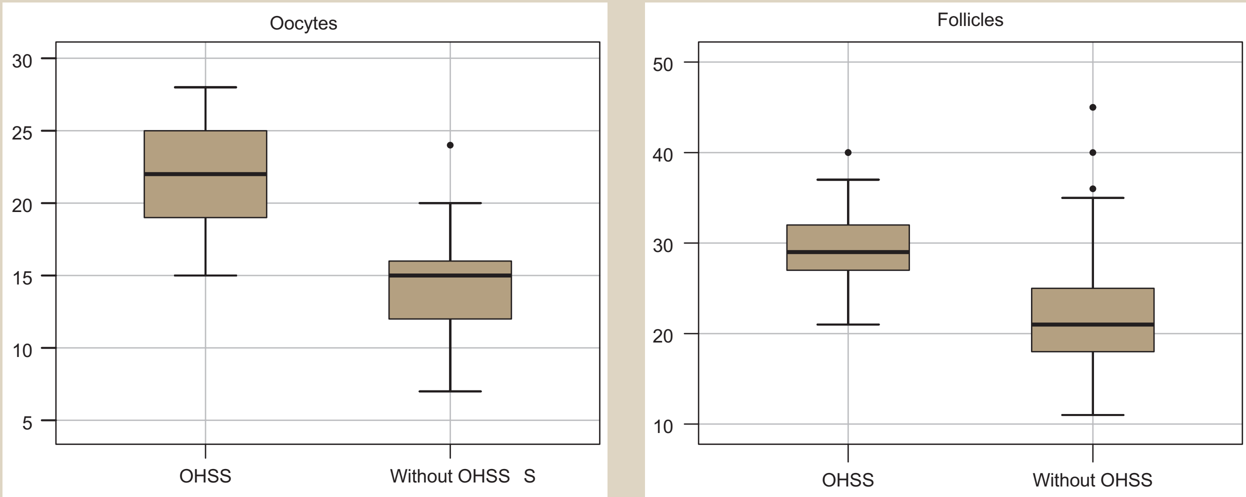

Fig. 1. The number of preovulatory follicles and oocytes in women with and without OHSS.

Results

While studying the characteristics of the corresponding ovarian response to controlled ovarian stimulation it was found that OHSS women had a statistically significantly higher number of preovulatory follicles than women without OHSS (29 (27; 32) versus 21 (18; 25); U = 1475, Z = 8.7, P < 0.001). The number of punctured follicles oocytes in OHSS women was also significantly higher than in those without OHSS (22 (19; 25) versus 15 (12; 16); U = 293, Z = 11.2, P < 0.001) (*Fig. 1*).

Determining the levels of biochemical parameters, it was found that estradiol content in OHSS women was statistically significantly higher than in those without OHSS, both in the blood serum (6540 (4730; 8121) pg/ml vs 2977 (2354; 3731) pg/ml; U = 238, Z = 11.3, P < 0.001), and follicular fluid 829000 (775700; 860000) pg/ml vs 268500 (92700; 446500) pg/ml; U = 123, Z = 11.5, P < 0.001). Determination of VEGF content also showed statistically significantly higher indicators in OHSS than without OHSS in the blood serum (58.0 (30.0; 142.8) pg/ml vs (17.5 (13.4; 21.4) pg/ml; U = 292, Z = 11.2, P < 0.001), and follicular fluid (602 (526; 674) pg/ml vs 272 (216; 364) pg/ml; U = 373, Z = 11.0, P < 0.001). A similar pattern was observed in the evaluation of IL-6 content, thus, the indications in OHSS women significantly exceeds those in women without OHSS in the blood serum (4.5 (3.7; 5.0) pg/ml vs 2.9 (2.4; 3.2) pg/ml; U = 1014, Z = 9.6, P < 0.001) and follicular fluid (11.8 (9.4; 18.2) pg/ml vs 6.1 (5.0; 6.8) pg/ml; U = 76, Z = 11.6, P < 0.001) (*Fig. 2*).

When calculating it was noted that estradiol content in the blood serum was strongly correlated with estradiol content in the follicular fluid (r_s = 0.85; 95 % CI 0.80–0.89; P < 0.001), the moderate correlation with VEGF (r_s = 0.76; 95 % CI 0.69–0.81; P < 0.001) and IL-6 (r_s = 0.67; 95 % CI 0.58–0.74; P < 0.001) was also noted (*Fig. 3*).

Correlation dependence between the follicular fluid and blood serum variables indicates a tendency to increase or decrease simultaneously, which, according to our opinion, in the case of unavailability of all laboratory values determination, makes it possible to determine only the indicators available in a particular laboratory, serum or follicular fluid.

By the method of binary logistic regression it was determined that the boundary value in OHSS was the preovulatory follicles number ≥30 for two ovarian, the sensitivity of the given predictor was 46.0 % and the specificity reached 91.0 %. The number of oocytes obtained after transvaginal puncture is one of the important predictors for OHSS occurrence. It was established that OHSS development could be assumed with the number of oocytes ≥19 with a sensitivity of 87.3 % and a specificity of 97.7 %.

In the course of a further study it was found that the boundary value for OHSS development was estradiol content in the blood serum ≥4800 pg/ml and in follicular fluid ≥725 000 pg/ml. The sensitivity for these predictors was 74.6 % and 98.4 %, the specificity was 96.6 % and 97.7 %, respectively.

The next indicator analyzed was VEGF, the boundary value of which for OHSS development corresponded to ≥30 pg/ml in the blood serum and ≥500 pg/ml in the follicular fluid. The sensitivity for these predictors was 76.2 % and 87.3 %, the specificity was 98.3 % and 97.2 %, respectively.

By the further analysis determined that the patients with IL-6 level in the blood serum ≥4 pg/ml and ≥8.5 pg/ml in the follicular fluid were classified as OHSS category. The sensitivity was 65.1 % and 90.5 %, the specificity – 98.9 % and 98.3 %, respectively.

Developing ROC-curves pointed to the high diagnostic efficiency of the considered predictors (*Fig. 4*). Thus, the area under the ROC-curve for preovulatory follicles was 0.87 (95 % CI 0.82–0.91), oocytes – 0.97 (95 % CI 0.95–0.99), estradiol content in the blood serum – 0.98 (95 % CI 0.96–0.99), estradiol in the follicular fluid – 0.99 (95 % CI 0.97–1.00), VEGF in the blood serum – 0.97 (95 % CI 0.95–1.00), VEGF in the follicular fluid – 0.97 (95 % CI 0.94–0.99), IL-6 in the blood serum – 0.91 (95 % CI 0.85–0.97), IL-6 in the follicular fluid – 0.99 (95 % CI 0.98–1.00), that is, all figures were approaching 1, 95 % CI, indicating the diagnostic value of the data indicators.

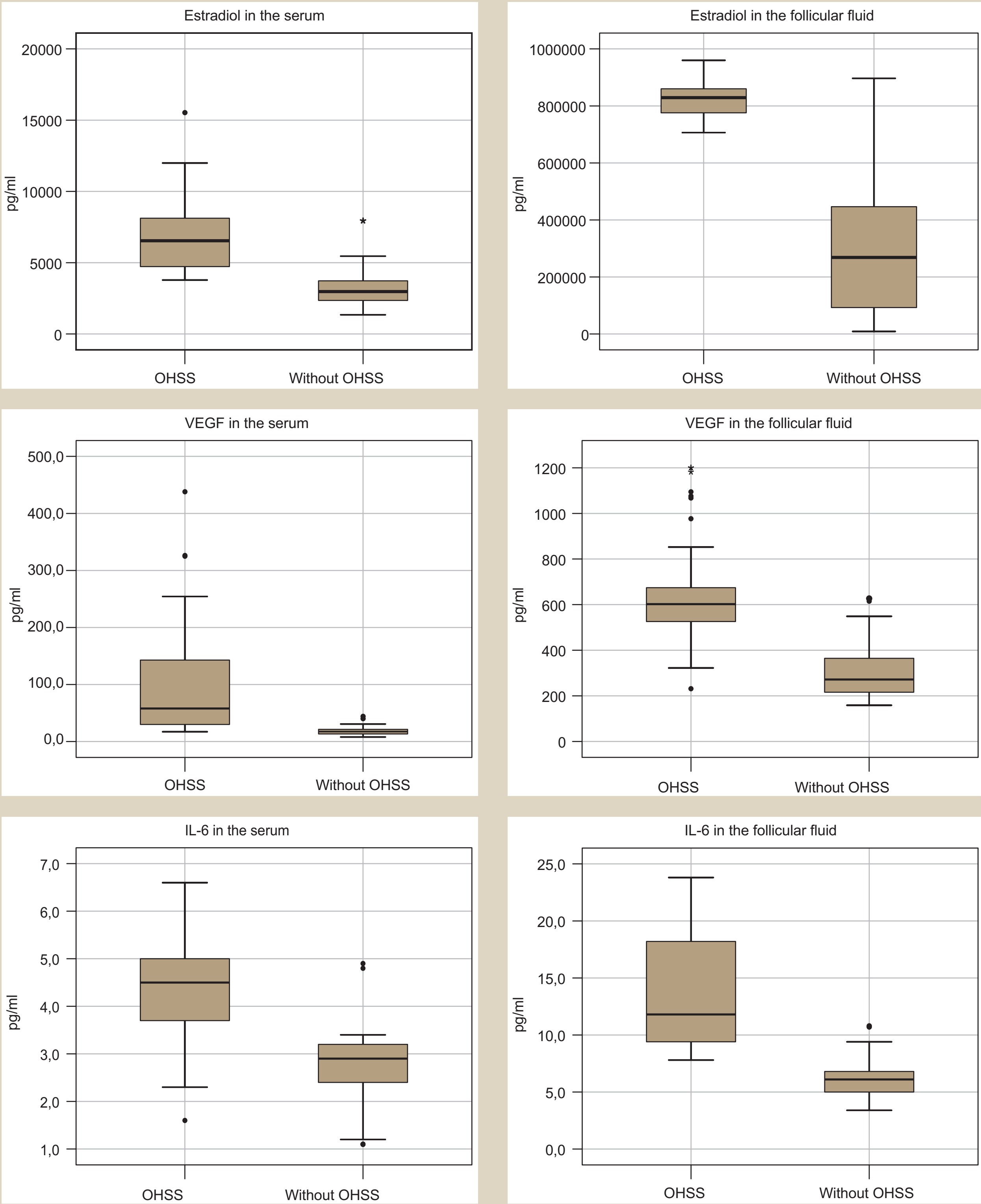

Fig. 2. The content of estradiol, VEGF and IL-6 in the blood serum and follicular fluid in women with and without OHSS.

Discussion

Thus, on the basis of the conducted study, secondary predictors of OHSS development include: the number of preovulatory follicles ≥30 per two ovaries, the number of oocytes ≥19, the level of estradiol in the blood serum ≥4800 pg/ml and in the follicular fluid – ≥725000 pg/ml, VEGF – ≥30 pg/ml and ≥500 pg/ml, IL-6 – ≥4 pg/ml and ≥8,5 pg/ml, respectively.

In identifying secondary predictors of OHSS development, the main management tactics for such patients is discontinuation of luteal phase support, vitrification of all embryos and their transfer in subsequent thawed cycles.

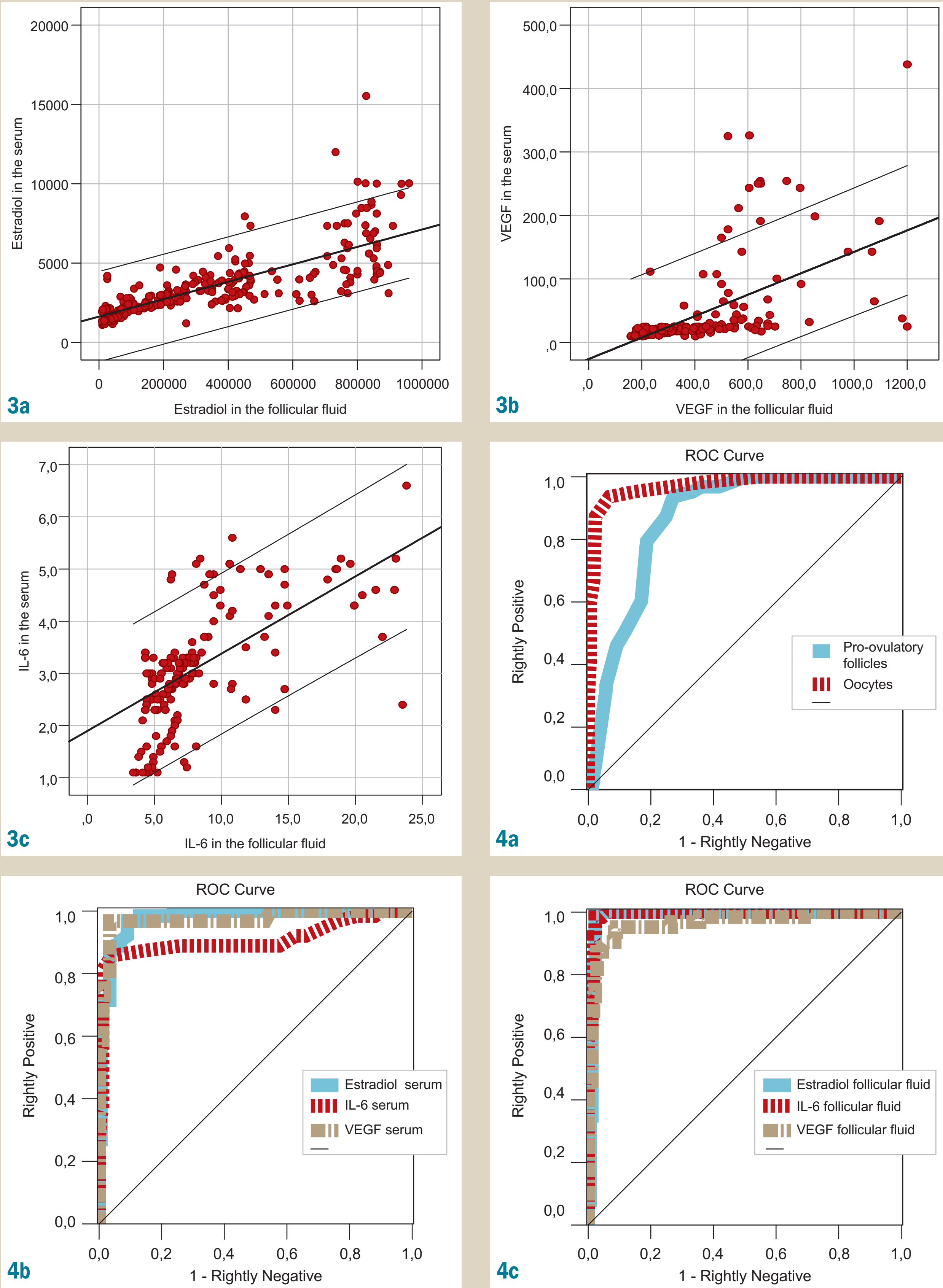

Fig. 3. Correlations between the content of biochemical parameters in the serum and follicular fluid.

Fig. 4. ROC-curves of secondary predictors of OHSS development.

Conclusions

1. The patients with OHSS demonstrate a statistically significant increase in the number of preovulatory follicles, oocytes, estradiol, VEGF, IL-6 in the blood serum and follicular fluid compared with the women without OHSS.

2. There is a direct correlation between the serum and follicular fluid levels of estradiol (r_s = 0.85; 95 % CI 0.80–0.89; P < 0.001), VEGF (r_s = 0.76; 95 % CI 0.69–0.81; P < 0.001) and IL-6 (r_s = 0.67; 95 % CI 0.58–0.74; P < 0.001).

3. Secondary predictors of OHSS development are the number of preovulatory follicles ≥30 per two ovaries, the number of oocytes ≥19, the level of estradiol in the serum ≥4800 pg/ml and in the follicular fluid – ≥725000 pg/ml, VEGF – ≥30 pg/ml and ≥500 pg/ml, IL-6 – ≥4 pg/ml and ≥8,5 pg/ml, respectively.

4. In identifying secondary predictors of OHSS development, the main management tactics for such patients is discontinuation of luteal phase support, vitrification of all embryos and their transfer in subsequent thawed cycles.

Conflicts of interest: author has no conflict of interest to declare.
Конфлікт інтересів: відсутній.

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