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ANALYSIS OF OVARIAN HYPERSTIMULATION SYNDROME DEVELOPMENT USING DATA MINING

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A b s t r a c t

The aim of this study is to define the risk factors of ovarian hyperstimulation syndrome onset during assisted reproduction treatment using the in vitro fertilisation technique. Exploratory computer analysis of electronically stored data on assisted reproduction treatment cycles in clinical registry with the use of the data mining system.

The analysed file included data of 12527 monitored cycles from 1989 to 2003. Cycles which led to the development of the ovarian hyperstimulation syndrome were analysed (2456 cases, 19.6 % of cycles).

Both the ovarian hyperstimulation syndrome-complicated cases and cases without ovarian hyperstimulation were tested by the data mining method, which is designed to find statistically significant differences among the input attributes of the ovarian stimulation phase of therapeutic cycles. The observed differences between the input attributes were statistically tested and the value of statistical significance was evaluated.

A significantly higher incidence of a clinically important form of ovarian hyperstimulation syndrome development was observed among patients under 30 years old, who had been affected by the hyperstimulation syndrome in previous treatment cycles. We can predict a higher risk in patients with oligomenorrhoea and in cases of immunological and andrological sterility factors. A higher incidence of the clinically significant form of the hyperstimulation syndrome is noticed with stimulation protocols with highly effective gonadotropin hormones where the total dose of gonadotropins is greater than 1125 IU and the maximum 17-beta estradiol levels are greater than 20 nmol/l.

We have proved the applicability of the data mining system for the analysis of the risk factors with influence on the assisted reproduction treatment results. The data mining method can be used to define statistically significant relations among all attributes of the ovarian stimulation part of the therapeutic cycle and to define the risk factors of hyperstimulation syndrome occurrence.

K e y w o r d s

Ovarian hyperstimulation syndrome, Risk factors, Sterility treatment, Data mining

Abbreviations used

ACETN, frequency of failure analysis; ARDS, acute respiratory distress syndrome; ART, assisted reproduction technology; CC, clomiphene citrate; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hMG, human menopausal gonadotropin; HP,high-purified; IU, international units; IUI, intrauterine insemination; IVF, in vitro fertilization; OHSS, ovarian hyperstimulation syndrome; rFSH,recombinant follicle-stimulating hormone; SP/LP, Short protocol /Long protocol; VEGF, vascular endothelial growth factor; WHO, World Health Organisation

INTRODUCTION

Assisted reproduction technology (ART) in the Czech Republic has become an integral part of reproductive medicine and the techniques of in vitro fertilisation (IVF) have experienced great development. According to the outputs of the National Registry of ART in the Czech Republic (*1, 2, 3*), a similar situation is also observed in other countries of the European Union (*4, 5, 6*). From the prognostic point of view, ART is becoming a subject with growing importance.

The ovarian hyperstimulation syndrome (OHSS), especially its critical grade, is the most relevant and potentially dangerous iatrogenic complication of controlled ovarian stimulation in the infertility treatment by IVF techniques. OHSS is characterised by multiple cystic augmentation of the ovaries, hypogastric pain, haemoconcentration, and extravasation of the intravascular fluid with ascites or hydrothorax formation (*7*). The increase of capillary permeability is the main cause of secondary complications. A fully developed and critical OHSS can be accompanied by general deterioration of the patient's condition, renal failure with oliguria, hypovolemic shock, occurrence of thromboembolia, or acute respiratory distress syndrome (ARDS).

The main goal of the study is to define the risk factors of ovarian hyperstimulation syndrome onset during assisted reproduction treatment using the in vitro fertilisation (IVF) technique. Exploratory computer analysis of electronically stored data on assisted reproduction treatment cycles in clinical registry with the use of the database data mining system SHLUK. Processing of the acquired data with the ACETN method (Frequency of Failure Analysis).

MATERIALS AND METHODS

We reported 2456 cases of OHSS in 12527 performed stimulated IVF cycles (19.7 %) during the years 1989 – 2003. The following types of stimulation protocols were used:

Protocols without stimulation – natural cycles;
Protocols with clomiphene citrate (CC);
Protocols with CC + human menopausal gonadotropin (hMG);
Protocols with CC + follicle-stimulating hormone (FSH);
Protocols with agonists:
hMG/FSH + gonadotropin-releasing hormone (GnRH) – Short protocol/Long protocol (SP/LP)
FSH-high purified (HP) + GnRH – SP/LP
recombinant FSH (rFSH) + GnRH – SP/LP;
Protocols with antagonists:

rFSH + ganirelix
rFSH + cetrorelix.

The classification system of a clinical severity of OHSS for data mining (10) has four grades and arises from 17-beta estradiol laboratory levels in the patient's serum on the day of hCG application and from the number of oocytes retrieved through folliculocentesis in a stimulated ART cycle (*Table 1*).

According to our own system of OHSS classification the incidence of serious OHSS (614 cases, 4.9 %) and critical OHSS (488 cases, 3.9 %) is 8.8 % altogether. This incidence is influenced by the intensive hormonal support of folliculogenesis to retrieve a sufficient number of oocytes (*Table 2)*. All the 12257 stimulated IVF cycles were analysed by the SHLUK data mining system.

Table 1
Classification of ovarian hyperstimulation syndrome (OHSS)

Grade of OHSS	Rabau (1967) Major kriteria	Golan (1989) Major kriteria	Navot (1992) Major criteria	Hudeček (2004) Major criteria
Mild Grade I	laboratory evidence of OHSS only ovarian size ≤ 5x5 cm	ovarian size ≤ 10cm abdominal distension nausea, vomitus, diarrhoea		17βE2 max: 10–15 mmol /l ocytes No: <10
Moderate Grade II	abdominal distension ovarian size ≤12x12 cm	Addition ascites on ultrasound ovarian size ≥ 10cm		17βE2 max: 10–15 mmol /l oocytes No: 10–15
Severe Grade III	ascites or hydrothorax ovarian size ≥12x12 cm hemoconcentration with coagulation failure	additionClinical sign of ascites or hydrothorax (dyspnoe) ovarian size ≥ 12cm haemoconcentration, hypercoagulation, homeostasis failure, oliguria, renal insufficiency	various ovarian size increase ascites Hydrothorax haematocrit > 45 % leukocytes > 15.000 oliguria Creatinine > 100–150 mmol/l, creatinine clearence > 50 ml/min hepatic dysfunction	17βE2 max: 16–20 mmol /l oocytes No: 16–20
Critical Grade IV			various ovarian size increase excessive ascites or hydrothorax or hydropericard haematocrit > 55 % leukocytes > 25.000 oligo-anuria kreatinine > 160 renal insufficiency	17βE2 max: >21 mmol /l oocytes No: >21

Table 2

The frequency of ovarian hyperstimulation syndrome (OHSS) according to clinical and laboratory relevance

Grade of OHSS	OHSS No.	% / cycles (12 527)
Grade I	592	4,7 %
Grade II	762	6,1 %
Grade III	614	4,9 %
Grade IV	488	3,9 %
Total	2 456	19,6 %

Table 3

The test of significance (ACETN)

T(X) = (ui - cui) / sqrt (cui* (1-cui)) * sqrt (P)	The significance of the difference is described either by the p-value itself or by graphical symbols describing the value of ui as follows:
- -	strongly below the global average = statistically significant
-	below the average
.	approximately the average
+	above the average
+ +	strongly above the global average = statistically significant

Methods

With the use of the SHLUK data mining system, statistically significant relationships between the particular parameters of the IVF cycle and the potential risk factors of OHSS will be defined.

Both the OHSS-complicated cases and cases without ovarian hyperstimulation were tested by the ACETN data mining method, which is designed to find statistically significant differences among the input attributes of the ovarian stimulation phase of ART cycles. The differences observed between the input attributes were statistically tested and the value of statistical significance was evaluated (*Table 3*).

The ACETN method tests all theoretical combinations of the factor values that influence the result of the treatment. For each group, the method evaluates predefined indicators that characterise the success of the result. It also determines the statistical significance of the mean value deviation for the whole set. The database of numerical data on the phenomena under investigation contains the possible reasons (e.g. A, B, C) that assume the values of (a, b, c). The ACETN method successively generates all the possible expressions of the form:

if A=a $\wedge$ B=b $\wedge$ C=c, then U1=u1 (S1) $\wedge$ U2=u2 (S2)

where U1, U2 are the defined indicators, and u1, u2 their corresponding values characterised by the left side of the implication for a tested group. The values S1, S2 either symbolically or numerically denote whether the indicator Ui is the average or no average with respect to the basic set. Here is a description of the ACETN method:

Significant indicators (Ui) that characterise the group tested are defined.

The values cui of all the indicators Ui are computed for the whole basic set.

For a given set of possible reasons, all the combinations of the reasons are generated.

For each such combination, the following is computed:
the number (P) of cases,
the value of all the indicators (Ui = ui),
the test of significance of the difference between the global indicator cui and the indicator ui.
Finally, statistically significant differences are signalised.

According to the demand of the user, all the results or only the statistically significant differences are printed out in the form of a table containing all the indicators or in the form of hypotheses.

The test of significance

Since every group tested has an arbitrary number of cases (the value of P), test statistics T(X) are used for testing the significance of the differences.

$T(X) = (ui-cui) / sqrt (cui* (1-cui)) * sqrt (P)$

For carrying out the test, the following values are needed:

cui	...	the average value of the indicator in the whole basic set
ui	...	the average value of the indicator for the i-th group
P	...	the number of cases in the i-th group

Using these values, the p-value is determined for each group, which determines whether the probability ui can be considered as being the same as the probability cui, or whether ui significantly differs from the average probability. The testing rule is the following:

if	p-value > 0.05	then	ui = cui
	p-value ∈ <0.01, 0.05	then	it is an unconvincing interval
	p-value < 0.01	then	ui ≠ cui

The significance of the difference is described either by the p-value itself or by using graphical symbols that describe the value of ui (*Table 3*).

RESULTS

Statistically significant risk factors of ovarian hyperstimulation syndrome development:

- Age of patient
- Length of menstrual cycle
- Factor of sterility
- Incidence of OHSS in previous ART cycles
- Type of stimulation protocol
- Total dose of gonadotropins

1. *Age of patient and risk of OHSS*

Based on analysis, there is an evident key role of the patient's age in the development of OHSS. A significantly higher incidence of the ovarian hyperstimulation syndrome was observed among patients under 30 years old (*Table 4*). This group of patients is often represented by couples with a male factor of sterility. On the other hand, the incidence of OHSS, especially serious and critical grades, is significantly lower in the group of patients over 30 years old.

2. *Length of menstrual cycle and risk of OHSS*

The length and character of the menstrual cycle is the next predictive factor of OHSS development. Analysis focused on the type of the menstrual

Table 4

The incidence of clinically significant forms of ovarian hyperstimulation syndrome (OHSS)

ACETN (++)							**ACETN (- -)**					
Grade of OHSS	Age of patient (years)	Menstr. Cycle Length (days)	Factor of sterility	OHSS before	Stimulat. type	Dose (IU)	Age of patient (years)	Menstr. Cycle Length (days)	Factor of sterility	OHSS before	Stimulat. Type	Dose (IU)
Low Grade I	N.S.	27–29	Male Imunol.	1≤	HMG + GnRH SP/LP *	> 975	N.S.	N.S.	Ovarian	N.S.	Sine *	< 975
Middle Grade II	< 30	30–35	Male Imunol.	1≤	FSH + GnRH SP/LP *	> 975	> 35	N.S.	Ovarian	N.S.	CC *	< 975
Serious Grade III	< 30	30–35	Male Imunol.	1≤	rFSH + GnRH SP/ LP *	> 1125	> 30	N.S.	Ovarian	N.S.	HMG/ FSH *	< 975
Critical Grade IV	< 30	30–35	Male Imunol.	1≤	rFSH + Antagonist *	> 1125	> 30	22 - 27	Ovarian	N.S.	CC+ HMG/ FSH *	< 975

* all grades of OHSS

cycle proved a significantly higher incidence of the ovarian hyperstimulation syndrome among women with 30–35 days' cycles (*Table 4*). No protective influence of menstrual cycle with normal length was observed.

3. ***Factor of sterility and risk of OHSS***

Based on the data mining methods, a significantly higher incidence of the ovarian hyperstimulation syndrome was proved in cases of an immunological sterility factor – seropositive antibodies:

Anti – ovary Ig

Anti – sperm Ig

Anti – zona pellucida

Anti – cardiolipin IgG, IgA, IgM

Allergic intercourse reaction – IgE/S, Anti – latex, Anti – sperm, Anti – ejaculate, Anti – seminal plasma and sediment.

A significantly higher incidence of OHSS was noted in cases of an andrological factor of sterility according to WHO criteria (sperm count ≤20 mil/1ml, sperm motility ≤40 %, sperm morphology ≤40 %). A protective role of ovarian factors against OHSS development in stimulated ART cycles was proved by the data mining methods. In a group of low responders, women with hypergonadotropic hypoestrogenism according to serum levels of 17-β estradiol, LH and FSH on days 2 and 3 of menstrual cycle before initiation of stimulation, a significantly lower incidence of OHSS was observed (*Table 4*).

4. ***OHSS in previous ART cycles and risk of OHSS recurrence***

The data mining methods noted a significantly higher risk of repeated OHSS development in the group of patients with OHSS history of any grade in previous stimulated cycles (*Table 4*).

5. ***Type of stimulation protocol and risk of OHSS***

A significantly higher OHSS incidence was detected in therapeutic protocols with hMG/FSH+GnRH-SP/LP, FSH-HP+GnRH-SP/LP, rFSH+GnRH-SP/LP, and in protocols with rFSH /antagonists as compared with natural cycles, protocols with CC, and protocols with CC+hMG/FSH (*Table 4*).

6. ***Total dose of gonadotropins and risk of OHSS***

The total dose of gonadotropins used for folliculogenesis stimulation is closely associated with OHSS development. The data mining methods noted a significantly lower risk of OHSS in protocols with a total dose of gonadotropins under 975 IU. When the total dose of gonadotropins was greater than 1125 IU, a significantly higher risk of OHSS development was noted. Considering the frequent clinical

dosage over 1125 IU of gonadotropins in most therapeutical protocols – the so-called controlled ovarian hyperstimulation – the evaluation of other risk factors and careful monitoring of stimulation plays a key role (*Table 4*).

DISCUSSION

Current knowledge of the pathophysiology of OHSS points to an increase of capillary permeability. Disturbance of capillary permeability under the influence of released vasoactive substances produced by ovaries during ovarian stimulation plays a key role in OHSS development, in spite of the fact that there are more theories about the mechanism of OHSS pathogenesis and development and that they are still under research (*8*). Previous interest was focused on the role and the effect of histamine, serotonin, prostaglandins, and prolactin. The renin-angiotensin system, cytokines, interleukins, the tumour necrosis factor alpha, endothelin-1, and the vascular endothelial growth factor (VEGF) are thought to be aetiologically responsible at present. A dominant role of these systems in the change of capillary permeability explains most of the OHSS symptoms.

The incidence of OHSS is from 0.005 to 7 % in the low and middle grades of OHSS of stimulated cycles and from 0.008 to 10 % in the serious and critical grades of OHSS cycles with ovulation induced by gonadotropins. The wide scattering of OHSS incidence reflects non-uniform classifications of OHSS (*9*).

The classification criteria of the clinical grade of OHSS were changed greatly. *Rabauna's* (1967), *Galana's* (1989), and *Navot's* (1992) classifications arise from laboratory markers, ultrasound criteria, and clinical performance of a patient with already developed OHSS (*Fig 1*). These classifications do not reflect the parameters of a potential risk of the monitored attributes of a curative cycle itself, that means clinical and laboratory parameters which were monitored before the initiation of a treatment and during controlled ovarian stimulation. The classification of the clinical severity of OHSS for data mining has four grades and arises from 17-beta estradiol laboratory levels in the patient's serum on the day of hCG application and from the number of oocytes retrieved through folliculocentesis in a stimulated ART cycle. (*Table 1*.)

The existence of a clinical register of curative cycles of assisted reproduction on our department in an electronic form of the SW program PC PAR enables the solution of this problem. The database of the clinical register includes over 12500 curative cycles of 6000 patients of the Centre of Assisted Reproduction, Gynaecology and Obstetrics Department of the Faculty of Medicine of Masaryk University in Brno. The data volume and its electronic form provide an adequate source of information from the point of view of mathematical and statistical analysis. Thanks to a close co-operation with the information scientists from the Department of Electrical Engineering and Computer Science, Technical University of Ostrava (*10*), we were able to apply methods of data mining from the database of assisted reproduction

w(*11, 12*) and to use the knowledge gained to analyse and define risk factors of ovarian hyperstimulation syndrome development within the grant of the Ministry of Health of the Czech Republic, No. 7696–3.

The data analysis from the early beginning of assisted reproduction in the Czech Republic, when there was a lack of efficient gonadotropin preparations for the stimulation of folliculogenesis, shows a significantly lower incidence of all grades of OHSS. If we currently use antiestrogens (clomiphene citrate – CC), urine gonadotropins (human menopausal gonadotropin – HMG, the follicle-stimulating hormone – FSH) or their combinations in the induction of ovulation, we can notice a significantly lower risk of OHSS incidence. This type of stimulation has now been used in low doses, especially before intrauterine insemination (IUI). These preparations used in the conventional IVF protocols were replaced with highly purified (FSH-HP) and recombinant (rFSH) gonadotropins in a combination with GnRH analogues in a short or long protocol (SP/LP), or with GnRH antagonists.

The advantages and limitations of data mining analysis:

Analysis of multidimensional data by means of data mining represents a modern and progressive way of finding generally true cause-consequence relationships. Methods of data mining have been used in various fields not related to medicine, mainly in economics, sociology, etc., representing an alternative attitude to medical data evaluation.

The usage of these analytical methods is limited only by the sufficient size of the study database and its electronic form. The methods enable postulation in a shorter real time interval than do conventional clinical studies, of the basic hypotheses defining issues of particular speciality. The methods of multidimensional analysis automatically generate and formulate all theoretically possible hypotheses of a certain type and test them. Hypotheses with an adequate significance level are presented to analysts for further evaluation. These are mainly exploration analyses. They conduct reference data studies and discover new findings, provide answers with lower levels of significance, but also answer questions such as: “What is interesting and beyond the average about these data?”. As a result, they form hypotheses supported by researched data and present them for further verification and testing.

A causative treatment of OHSS still does not exist despite of extensive knowledge of the pathogenesis of this serious iatrogenic complication of the infertility treatment (*13*). What is available is only a symptomatic therapy of complications with an instability of the internal milieu and a limited variety of actions which alleviate the OHSS course. We must lay more stress on preventive movements and early diagnosis of incipient forms of the early ovarian hyperstimulation syndrome through ultrasound folliculometry. The possibilities of an effective prevention are limited by the fact that the generally valid classification criteria for OHSS severity rise from laboratory results and the clinical stage of a patient with an already developed syndrome, and it is usually very difficult to find laboratory results and overall parameters of the treatment of an ART cycle from the period before the treatment

initiation (*14*). The elementary step of an active prevention of OHSS development at high-risk patients is still focused on the particular patient's risk factors and the following correction of the type of stimulation protocol, doses of gonadotropins (*15*), and mainly careful monitoring of 17-β estradiol levels in the patient's serum (*16*) by a physician responsible for the conduction and course of the IVF treatment cycle.

CONCLUSION

As a high-risk patient, who is in a potential danger of a clinically significant form of OHSS development during the treatment course of assisted reproduction, is considered a woman of 30 years or younger, who was affected by OHSS in previous treatment cycles. We can predict a higher risk of OHSS development in women with 30–35 days' cycles and in cases of immunological and andrological sterility factors. A higher incidence of clinically significant forms of OHSS is noticed in stimulation protocols with highly effective gonadotropin hormones (hMG/FSH + GnRH-SP/LP, FSH-HP + GnRH-SP/LP, rFSH + GnRH-SP/LP, rFSH + GnRH/antagonists) where the total dose of gonadotropins is greater than 1125 IU.

The usage of data mining methods is limited by the sufficient size of a study database and its electronic form. The methods enable the postulation in a shorter real time interval than do conventional clinical studies, of basic hypotheses defining issues of particular speciality.

A c k n o w l e d g e m e n t

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OVARIÁLNÍ HYPERSTIMULAČNÍ SYNDROM V PROGRAMU ASISTOVANÉ REPRODUKCE – ANALÝZA RIZIKOVÝCH FAKTORŮ POMOCÍ DOLOVÁNÍ Z DAT

S o u h r n

Cílem práce bylo definování rizikových faktorů vzniku ovariálního hyperstimulačního syndromu v průběhu léčby neplodnosti technikami in vitro fertilizace. Explorační počítačová analýza elektronických dat o léčebných cyklech z klinického registru AR pomocí počítačového systému pro získávání znalostí z databází SHLUK. Rozbor dat metodou analýzy četnosti neúspěchů.

Bylo registrováno 2456 případů ovariálního hyperstimulačního syndromu v průběhu 12527 provedených stimulačních cyklů (19,7 %) za období 1989 – 2003. Výskyt klinicky závažného těžkého stupně OHSS (614 případů, 4,9 %) a kritického stupně OHSS (488 případů, 3,9 %) tvoří dohromady 8,8 %. Mírný a střední stupeň OHSS se vyskytuje celkem v 10,8 % případů stimulovaných cyklů.

Metoda ACETN analyzuje samostatně případy cyklů s rozvojem OHSS proti cyklům bez vzniku OHSS a hledá statisticky signifikantní rozdíly mezi vstupními atributy úvodní etapy „ovariální stimulace". Diskrepance mezi vstupními parametry úspěšných a neúspěšných případů jsou statisticky testovány testem významnosti a automaticky jsou zobrazeny signifikantní vztahy a rizikové faktory vzniku OHSS.

Statisticky signifikantně častější výskyt ovariálního hyperstimulačního syndromu byl zaznamenán u pacientek do 30 let věku a u pacientek s výskytem OHSS v předchozích cyklech AR, u pacientek s oligomenoreou a v případech imunologického a andrologického faktoru neplodnosti. Vyšší výskyt

klinicky závažných forem OHSS je zaznamenán ve stimulačních protokolech s gonadotropními hormony (hMG/FSH+GnRH-SP/LP, FSH-HP+GnRH-SP/LP, rFSH+GnRH-SP/LP, rFSH+GnRH/antagonisté), jejichž celková dávka přesahuje 1125 IU a maximální hodnota sérové hladiny 17- estradiolu je vyšší než 20 nmol/l.

Byla prokázána použitelnost systému pro dolování znalostí z dat SHLUK pro analýzu faktorů, které ovlivňují výsledky metod asistované reprodukce. Metoda umožňuje definovat statisticky významné vztahy mezi jednotlivými atributy etapy „ovariální stimulace" v léčebném cyklu AR a definuje rizikové faktory vzniku OHSS.

REFERENCES

1. *Ventruba P, Višňová H, Hudeček R.* Where is the aim of ART in Czech Republic? National Register of ART 1993 – 1996. Prakt Gyn 1997; 5 (Issue 5): 20–26.
2. *Ventruba P, Mardesic T, Pilka L, Crha I, Višňová H, Hudeček R.* Register of Assisted Reproduction: Results and analysis of complications. Čes Gynek 1998; 63: 39–41.
3. *Ventruba P, Višňová H, Hudeček R, Lokajová J.* 10 years of National Register of Assisted Reproduction in Czech Republic. Asist Reprod 2000; 10 (Issue 1): 5–6.
4. International Working Group for Registers on Assisted Reproduction: World Collaborative Report on In Vitro Fertilization. Preliminary Data for 1995. J Assist Reprod Genet 1997 (Suppl.): 251S–265S.
5. International Working Group for Registers on Assisted Reproduction: World Collaborative Report on In Vitro Fertilization. Preliminary Data for 1996. J Assist Reprod Genet 1999; 16 (Suppl.): 251S – 265S.
6. International Working Group Edit. Jones HW, Cohen J: IFFS – Surveillance 98. Hum Reprod 1999; 14: 251–265.
7. *Beerendonk CC, Van Dop PA, Braat DD, Mercus JM.* Ovarian hyperstimulation syndrome: facts and fallacies. Obstet Gynecol Surv 1998; 53 (7): 439–449.
8. *Elchalal U, Schenker JG.* The pathophysiology of ovarian hyperstimulation syndrome – views and ideas. Hum Reprod 1997; 12: 1129–1137.
9. *Aboulghar MA, Mansour RT.* Ovarian hyperstimulation syndrome: classification and critical analysis of preventive measures. Hum Reprod Update 2003; 9 (3): 275–289.
10. *Hudeček R, Huser M, Ventruba P, Šarmanová J.* Risk factors of ovarian hyperstimulation syndrome development in assisted reproduction. Prakt Gyn 2004; Issue 4: 6–10.
11. *Hudeček R, Ventruba P, Šarman Z, Šarmanová J, Solár T.* Data mining in assisted reproduction using methods for data analysis SHLUK and artificial neural network NEUL 3. Asist Reprod 2000; 10 (Issue 1): 10–11.
12. *Hudeček R, Ventruba P, Crha I, Šarmanová J, Šarman Z, Solár T.* Analysis of factors with influence on assisted reproduction outcome using system for data mining SHLUK. Čes Gynek 2001; 66: 270–276.
13. *Navot D, Relou A, Birkenfeld A.* Risk factors and prognostic variables in the ovarian hyperstimulation syndrome. Am J Obstet Gynecol 1993; 159: 210–215.
14. *Navot D, Bergh PA, Laufner N.* Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. Fertil Steril 1998; 58: 249–261.
15. *Delvigne A, Dubois M, Battheu B, et al.* The ovarian hyperstimulation syndrome in in–vitro fertilization: a Belgian multicentric study. II. Multiple discriminant analysis for risk prediction. Hum Reprod 1993; 18: 1361–1366.
16. *Delvigne A, Rozenberg S.* Preventive attitude of physicians to avoid OHSS in IVF patients. Hum Reprod 2001; 16: 2491–2495.