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PHARMACOECONOMIC ANALYSIS OF HORMONE MEDICINES USED FOR IN VITRO FERTILIZATION

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Summary: A pharmacoeconomic evaluation of follitropin alpha (Gonal-F®), follitropin beta (Puregon) and menotropin (Menopur) to stimulate ovulation during the in vitro fertilization procedure has been performed. The results of the effectiveness analysis demonstrated the superiority of follitropins over menotropin in terms of the number of oocytes obtained, occurrence of pregnancy and live birth, all three taken as effectiveness criteria. There were no data to support statistically significant differences in effectiveness between follitropin alpha and follitropin beta. In this connection the main method of pharmacoeconomic analysis to compare follitropin alpha and menotropin was the "cost-effectiveness" analysis while for pharmacoeconomic evaluation of follitropin alpha and follitropin beta the "cost-minimization" analysis was applied. The results of "cost-effectiveness" analysis has shown that follitropin alpha (Gonal-F®) is more cost-effective across all three above criteria compared to Menopur. The "cost-minimization" analysis has revealed that administration of Gonal-F® instead of Puregon enables to save on treatment between 1,973 rubles and 4,861 rubles. Therefore, from the pharmacoeconomic standpoint, Gonal-F® is characterized as a dominant (strictly preferable) drug for ovarian stimulation during assisted reproductive technology (ART) as compared to Menopur and Puregon.

Key words: pharmacoeconomic analysis, IVF, follitropin alpha, follitropin beta, menotropin, Gonal-F®, Menopur, Puregon, "cost-effectiveness" analysis, "cost-minimization" analysis.

Introduction

The improvement of demographic situation in Russia is one of the priority directions in state policy declared by the country's leadership. The demographic determinants have been officially taken for effectiveness criteria which are used for the evaluation of performance of government executive bodies including ministries and healthcare departments. Birth rate is the most important demographic feature. On the other hand, infertility, from the healthcare standpoint, is one of the pressing issues that is in the way to increased birth rate. The results of recent epidemiological studies conducted in regions of Russian Federation to address this problem highlighted a wide occurrence of sterility thereby underscoring the importance of its treatment. Thus, for instance, the infertility prevalence rate among women in Trans-Baikal territory is over 15%, a critical level as defined by the WHO, reaching 24.9 % (22.3 % in towns and 25.8 % in villages) [13]. A questioning conducted among 1300 women of Buryat Republic has revealed that 64 respondents (4.9%) were primarily infertile and 169 (13%) were secondarily infertile [14].

Assisted reproductive technologies (ART) including in vitro fertilization (IVF) are amongst the most effective healthcare instruments to solve the infertility problem. The IVF process includes the oocyte retrieval from female ovaries and its subsequent artificial fertilization in vitro. The fertilized egg (the IVF embryo) is incubated for 2-5 days and subsequently transferred into the uterus to develop further. The IVF procedure is performed in specialist medical settings as an outpatient service or in day hospital.

The IVF procedure includes hormone treatment. Specifically, gonadotropin preparations are used at the step of the ovulation induction. Several medicinal

products (MP) for IVF containing different active ingredients for the ovulation induction are registered in Russian Federation that creates a problem with choosing the right MP. Considering restrictions on healthcare budgets, the choice of MP should take into account both medical particulars and therapeutic indications, also, the pharmacoeconomic profile of a medical technology used. The pharmacoeconomic analysis is an auxiliary decision-making tool which is widely used in both global and Russian healthcare practice. Moreover, in Russia the pharmacoeconomic evaluation of MP is recognized by Federal Law within the Decree of the RF Government N871 of 28.08.2014. "On approval of the regulations for preparation of the lists of drugs for medical use and the minimum range of drugs required for rendering medical care". The implementation of the pharmacoeconomic approach enables to choose medicinal products which use ensures the most effective resource allocation in healthcare. Within the framework of organization of the IVF procedure, the pharmacoeconomic evaluation also plays an important role enabling to determine treatment regimens with which the cost of target achievement (i.e., obtaining an oocyte, occurrence of pregnancy or live birth) is reduced to a minimum.

Literature search allowed us to find one national pharmacoeconomic study on the evaluation of the IVF procedure. The paper by Krysanov I.S et al. (2015) analyzed from the pharmacoeconomic standpoint the use of corifollitropin alpha and follitropin alpha along with ovarian stimulation protocol and GnRH antagonists [16]. This study has a number of assumptions which should be taken into account when interpreting the results. For instance, the study provides only a partial support for an inference that corifollitropin alpha and follitropin alpha are equally effective whereas the comparative efficacy analysis for corifollitropin alpha and follitropin alpha was not carried out, which predetermined the outcome of "cost-minimization" analysis. Besides, the above pharmacoeconomic study [16] did not include all available pharmaceutical forms. Thus, for instance, it provided the cost for only one dosage form of follitropin alpha (pen injector 300 IU №1) of all available on the market which could also have impact on the soundness of conclusion owing to cost differences between different pharmaceutical forms of a given MP.

In this regard we deemed it relevant to conduct a pharmacoeconomic evaluation of gonadotropin preparations used for ovulation induction within a long protocol for IVF. The study included follitropin alpha (Gonal-F®, Merck Serono), follitropin beta (Puregon, Organon N.B.) and menotropin (Menopur, Ferririg Pharmaceuticals A/S). The results of this pharmacoeconomic study may be of particular interest to public health officials responsible for implementation of the IVF programs, Heads of ART centers and physicians performing infertility treatments and IVF.

Methodologically, this study met the regulations and requirements of the pharmacoeconomic analysis and was characterized by retrospective design and horizon period that encompassed the duration of the IVF procedure. At the first step of pharmacoeconomic study we carried out the effectiveness analysis of studied MPs during which we used the evidence base that allowed direct comparison between medicinal products. Next, we calculated the

overall costs incurred for analyzed medications and IVF procedure. At the final step of pharmacoeconomic study we performed the pharmacoeconomic analysis of MPs using the “cost-effectiveness” analysis as a main method and “cost-minimization” as a particular case derived from the former approach. The results of pharmacoeconomic evaluation were subjected to a sensitivity analysis to verify their reliability considering variations of baseline parameters. No discounting of the pharmacoeconomic analysis results was carried out because of the short horizon period not exceeding one year.

Results of the effectiveness analysis of compared medicinal products

Considering that the effectiveness data derived from meta-analyses and large-scale clinical trials are the most reliable data, we conducted the information search by entering the following keywords into a search engine: “assisted reproductive technologies”, “follicle-stimulating hormone”, “menotropin”, “puregon”, “oocyte”, “pregnancy” and “birth”, that allowed us to select from over 300 publications the following clinical studies which included one meta-analysis and large-scale retrospective studies:

- Recombinant human follicle-stimulating hormone produces more oocytes with a lower total dose per cycle in assisted reproductive technologies compared with highly purified human menopausal gonadotrophin: a meta-analysis. Philippe Leheret, Joan C Schertz, Diego Ezcurra. Reproductive Biology and Endocrinology 2010, 8:112;
- Efficacy of recombinant human FSH in comparison to urinary hMG following a long down-regulation protocol – an analysis of 24,764 ART cycles in Germany. M. Ludwig, T. Rabe, K. Bühler, K. Diedrich, R. Felberbaum. Journal für Reproduktionsmedizin und Endokrinologie, 4/2004;
- Pregnancy rates in varying age groups after in vitro fertilization: a comparison of follitropin alfa (Gonal F) and follitropin beta (Follistim). Williams RS, Vensel T, Sistrom CL, Kipersztok S, Rhoton-Vlasak A, Drury K. Am J Obstet Gynecol. 2003 Aug;189(2):342-6.

Study	Design / Patient number	Ovulation induction protocols	Data reliability level
Ph. Leheret et al., 2010	Meta-analysis of 16 studies / 4040 patients	With GnRH agonists and antagonists	A
M. Ludwig et al., 2004	Large-scale retrospective analysis / 24 746 cycles	«Long» protocol with GnRH agonists	B
Williams R.S. et al., 2003	Retrospective analysis / 365 cycles	Protocol with GnRH agonists	B

The meta-analysis of Leheret P. et al., 2010 [1] included prospective randomized and pseudorandomized controlled studies which compared the effectiveness of hMG and rFSH in inducing superovulation within the IVF/ICSI programs, both in AR cycles with GnRH agonists and GnRH antagonists. Studies employing patients with polycystic ovary syndrome (PCOS) were excluded from the main analysis but retained for the sensitivity analysis. The meta-analysis included a total of 16 studies.

The main evaluation criterion was the number of oocytes obtained per each treatment regimen. The meta-analysis of 16 studies revealed that upon ovarian stimulation with follitropin preparations the average number of oocytes was 10.9 versus 9.4 obtained after stimulation with menotropins. The difference between the two (2.1 – standardized) appeared to be statistically significant (95% CI, range –2.83 ... –1.36; $p < 0.001$) and reflected the superiority of follitropin preparations. Therefore, the subsequent comparative analysis of follitropins and menotropins based on the number of oocytes obtained per stimulation cycle seemed appropriate both for cycles with GnRH agonists and GnRH antagonists.

The study of Ludwig et al., (2004) [2] was a retrospective analysis of 24764 cycles of ART which compared follitropins and menotropins in accordance with the GnRH agonist stimulation protocol. The analysis included women receiving treatment at 81 German centers for reproductive medicine in 2002. The results of analysis have shown that the amount of active ingredient of follitropin preparations per cycle, occurrence of pregnancy and birth was 2325, 8760 and 13185 IU, respectively, and that of menotropin preparations was 2827.5, 11258 and 18398 IU, respectively. The birth rate according to the analysis of Ludwig et al. (2004) was 16.9% for follitropins and 14.5% for menotropins.

Therefore, the results of meta-analysis and large-scale retrospective analysis revealed superiority of follitropins over menotropins for ovarian stimulation. During literature survey we found one paper which compared follitropin alpha and follitropin beta. A retrospective analysis by R.S. Williams et al. (2003) included 365 ART cycles which protocol employed ovulation induction using the GnRH agonists. There was no statistical difference in the frequency of success in achieving clinical pregnancy. In this connection, in the cited pharmacoeconomic study the authors made an assumption that the two above MPs were equally effective [3]. The results of effectiveness analysis are presented in Figure 1.

The results of effectiveness analysis of studied MPs have predetermined the choice of the further method of our pharmacoeconomic study. As there is a proven by others difference in effectiveness between menotropins and follitropins, for their comparative pharmacoeconomic evaluation we used the “cost-effectiveness” analysis. Based on the above assumption of equal effectiveness of follitropin alpha and follitropin beta, as can be judged from

Figure 1. Results of effectiveness analysis

a comparable frequency of achieved clinical pregnancy for both drugs, we further applied the “cost-minimization” analysis per one complete ART cycle for pharmacoeconomic evaluation of recombinant follitropins.

Results of cost analysis

The cost analysis factored in direct costs for the course of treatment with above MPs and costs for medical services according to the current standards of care for the ART [4]. The cost analysis was based on current prices for MPs indicated in State register of upper limit retail prices for vital and essential drugs (VAD) (+VAT), or in open electronic sources for the MP prices in case of their absence from the VAD register. The cost of medical procedures according to the standards of care for infertility using the assisted reproductive technologies [4] was calculated based on the tariffs of the Moscow city compulsory medical insurance fund (MC CMIF) [8], and in case of their absence, based on the data from Moscow center of ART [16].

Based on the cost of pharmaceutical forms (see Appendix №1), we calculated the average cost of one IU of each of compared MPs which was 16.97 rub., 17.20 rub. and 15.18 rub. for Menupur, Puregon and Gonal-F®, respectively (Fig. 2).

As reported by Ludwig W. et al. (2004), dosage of follitropin alpha or follitropin beta preparations per cycle was 2325 IU, and that of menotropins – 2828 IU. According to the standard of care for infertility with ART, and allowing for expert opinion, follitropin and menotropin dose per cycle did not differ from each other and, in accordance with the standard of care, was 2400 ME, whereas in expert opinion it varied between 1185 IU to 2835 IU with median value of 2010 IU (Fig. 4).

Based on the unit cost for active ingredient of each drug and their treatment course dose, we calculated the cost of the treatment course for each MP using equation 1:

$$Cost_H = Price_H \times D_K, \text{ where:} \quad (\text{Equation 1})$$

Cost – the cost of the treatment course for studied MP, in rub.;

Price – the average unit cost for active ingredient of MP (calculated as the arithmetic mean of unit costs for active ingredients of different pharmaceutical forms of a given medicinal product), in rub.;

Figure 2. Average cost of one IU of active ingredient of analyzed MPs.

The cost of each MP per one cycle was determined as the product of estimated cost of one IU of each MP multiplied to the number of corresponding IUs per cycle taken from the Ludwig et al. [2] study, current standard of care [4] or expert opinion. The expert opinion was obtained by questioning of 5 centers of reproductive medicine and was characterized by three point estimator, the minimum, median and maximum (Fig. 3).

D_K – treatment course dose of medicinal product in units of active ingredient (based on clinical trial data, ART national standard data and routine clinical practice data; several values of the course dose size have been taken into account).

	Min	Med	Max
Average dose of FSH preparations per cycle, IU			
Expert №1	1350	2025	2700
Expert №2	925	1600	2275
Expert №3	1800	2500	3200
Expert №4	1250	2125	3000
Expert №5	600	1800	3000
AVERAGE VALUE:	1185	2010	2835

Figure 3. Expert opinion over drug dosage per cycle (IU)

Figure 4. Drug dosage per cycle according to different sources

The costs for ovulation induction per ART cycle per one patient for each MP are shown in Figure 5. The cost values varied in a wide range depending on the baseline drug consumption data in IU per cycle (when meta-analysis of W. Ludwig et al., 2004, standard of care for infertility or expert opinion was used). Nonetheless, whatever the approach to calculate the treatment course cost, Gonal-F course was the least expensive while Puregon course was the most expensive. The cost of Menopur treatment course appeared to be the highest when calculated based on the meta-analysis of W. Ludwig et al. (2004) because of a significantly higher average dose (in IU) per menotropin stimulation course, i.e., 2828 IU.

The cost of treatment according to standard of care, calculated based on the tariffs of the Moscow city CMIF per separate medical services and procedures was 112811,55 rubles. Therefore, the total costs for ART including costs for medical procedures and MPs used for ovarian stimulation were as follows (depending on the source of data on the treatment course dose):

- Menopur from 132 924 rub. to 160 928 rub.
- Puregon from 133 988 rub. to 162 373 rub.
- Gonal-F® from 130 797 rub. to 155 840 rub.

Results of «cost-effectiveness» analysis

At the next step of the study, based on the effectiveness data and total cost of ART for each MP, we calculated the «cost-effectiveness» parameters which characterize the cost of health gain in terms of units of effectiveness for each of analyzed drugs, i.e., Menopur and Gonal-F®. The «cost-effectiveness» parameters were calculated using the following equation:

$$CER = \frac{Cost}{Eff}, \text{ where:} \quad \text{Equation (2)}$$

CER – «cost-effectiveness» ratio;

Cost – total costs for MP, in rub.;

Eff – MP effectiveness.

The calculated «cost-effectiveness» values based on selected effectiveness criteria are presented in Figures 6–8. As the main effectiveness criterion, we chose the number of obtained oocytes for each MP (Fig. 6) as this criterion directly reflects the results of ovulation induction during IVF. The «cost-effectiveness» value, i.e., the cost of each obtained oocyte, was lower for Gonal-F®. This result holds true for calculations based on standard of care (2400 IU per cycle for compared drugs) or on data from the meta-analysis of W. Ludwig et

al. (2004) where menotropin treatment course doses are considerably higher.

To date, the tasks that are to be solved in the course of IVF include the receipt of oocytes, their fertilization and transfer to the uterus. However, the ultimate task of the ART program funding from the standpoint of both State and patient, is to achieve pregnancy and successful childbirth. In this connection we carried out an analysis using as an effectiveness criterion the «frequency of success in achieving clinical pregnancy» (Fig. 7) as this criterion reflects a successful ART result in terms of realization of State healthcare guarantees over infertility treatment. As can be seen from Figure 7, the «cost-effectiveness» value is lower for Gonal-F® compared to Menopur regardless of the method used for cost estimation. In fact, it means that, under otherwise equal conditions, the cost and effectiveness of Gonal-F® enables to achieve each pregnancy at a lower cost.

Apart from that, we considered the value of the «frequency of live birth» parameter which is not directly related to ovulation induction alone. The interest to this parameter is associated with the notion that we can consider live birth as an eventual desirable outcome (end-point at the population level) for this healthcare technology. The study of W. Ludwig presents data on average amounts of required total doses of follitropins and menotropins per one birth, i.e., 13185 IU and 18398 IU, respectively. The «cost-effectiveness» parameters were calculated using this criterion as well (Figure 8) which appeared to be lower for Gonal-F® regardless of the cost estimation method, namely, standard of care (2400 IU per cycle for each drug), median value from expert opinion (2010 IU per cycle for each drug) and meta-analysis of 16 studies (2325 IU for follitropin or 2828 IU for menotropin per each cycle).

Lower «cost-effectiveness» values for Gonal-F® provides a pharmacoeconomic benefit over Menopur as the unit cost to deliver a desirable result with Gonal-F® is lower than with Menopur (i.e., the cost of one oocyte, cost of achieving of each pregnancy and cost of each live birth).

Results of «cost-minimization» analysis

A comparative pharmacoeconomic evaluation of Gonal-F® and Puregon was carried out using the «cost-minimization» analysis. This type of analysis implies that a correlation has to be drawn between the cumulative costs of studied drugs. The results of analysis have shown that the cost saving with Gonal-F® versus Puregon is between 1973 rub. and 4861 rub. per one ART cycle (Fig. 9).

Sensitivity analysis

Sensitivity analysis is a mandatory procedure within the pharmacoeconomic study and is used for the evaluation of stability and adequacy of obtained conclusions [3]. In this study we used one-way sensitivity analysis over the parameter of cost of Gonal-F®, which aimed at determining the degree of stability of pharmacoeconomic conclusions obtained for a given MP. We studied the impact of Gonal-F® price variation in the range $\pm 15\%$ on the results of pharmacoeconomic study, namely, the cost-effectiveness ratio and

Figure 5. Costs per drug per one ART cycle

Figure 6. The "cost-effectiveness" values based upon the number of obtained oocytes per cycle criterion

Figure 7. The "cost-effectiveness" values based upon the occurrence of pregnancy criterion

Figure 8. The “cost-effectiveness” values based upon the live birth criterion

Figure 9. Results of “cost-minimization” analysis

cost-minimization analysis results. Sensitivity analysis demonstrated that Gonal-F® prices across the range between -15% and +15% still have a lower “cost-effectiveness” ratio compared to Menopur and provide cost savings compared to Puregon.

Conclusions

The retrospective effectiveness analysis allowed us to reveal effectiveness superiority of follitropin over menotropin preparations, specifically, that with the former the average oocyte yield is 10.9 per cycle versus 9.4 oocytes per cycle for menotropins. Also, the two drugs significantly differed in the required number of units (IU) of active ingredient per ART cycle, pregnancy occurrence and birth, that was 2325, 8760 and 13185 IU for follitropins and 2829, 11258 and 18398 IU for menotropins, respectively. We found no evidence of difference in effectiveness between follitropin and menotropin preparations. For this reason the pharmacoeconomic analysis was conducted in several steps using the “cost-effectiveness” analysis to compare follitropins with menotropins and “cost-minimization” analysis to compare follitropin-alpha (Gonal-F®) with follitropin-beta (Puregon).

The calculation of the pharmacotherapy cost for each of compared drugs per one ART cycle was carried out using several methods. The results of analysis are given below:

- Menopur – 47 989 rub., 40 734 rub., 20 112 rub., 34 114 rub. and 48 117 rub. (according to the Ludwig study, standard of care established in the

Order of MH RF № 556n of 30.10.2012 and expert opinion presented as a minimum, median and maximum value);

- Puregon – 40 788 rub., 42 078 rub., 21 177 rub., 35 369 rub. and 49 561 rub. (according to the Ludwig study, standard of care established in the Order of MH RF № 556n of 30.10.2012 and expert opinion presented as a minimum, median and maximum value);
- Gonal-F® – 35 284 rub., 36 426 rub., 17 985 rub., 30 507 rub. and 43 028 rub. (according to the Ludwig study, standard of care established in the Order of MH RF № 556n of 30.10.2012 and expert opinion presented as a minimum, median and maximum value);

The cost according to standard of care for IVF calculated per individual medical procedures and services did not include drug cost, and was 112 812 rub.

Eventually, we calculated the cost-effectiveness ratio per each effectiveness criteria for Gonal-F® and Menopur. In this study we used several approaches to the evaluation of drug cost per dose and, accordingly, of drug pricing. Below we present the results of “cost-effectiveness” analysis based on the meta-analysis of Ludwig et al. (2004):

- Cost of obtaining one oocyte was 15 422 rub. for Gonal-F® and 19 234 rub. for Menopur;
- Cost of pregnancy occurrence was 633 346 rub. for Gonal-F® and 719 838 rub. for Menopur;

- Cost of birth was 953 273 rub. for Gonal-F® and 1 176 391 rub. for Menopur.

Different costs had an impact on the variability of “cost-effectiveness” parameter, but, eventually, have not affected on the analysis conclusions. Regardless of the cost evaluation method and drug dose, the analysis results allowed unambiguous interpretation (Figures 6,7,8), namely, the cost per unit of result for follitropins (Gonal-F®) is lower than for menotropins (Menopur).

Our “cost-minimization” analysis has revealed that administration of Gonal-F® instead of Puregon allows cost savings ranging from 1 973 rub. to 4 861 rub. (Fig. 9). A one-way sensitivity analysis over the parameter of cost of Gonal-F® demonstrated stability of the results obtained within the range of parameter variability [-15%; +15%].

Conclusion

In this pharmacoeconomic analysis Gonal-F® is characterized as a dominant (strictly preferable) drug for ovarian stimulation during the ART cycle, having a higher clinical effectiveness and lower cost-effectiveness as compared to Menopur and Puregon.

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Appendix №1. Prices of pharmaceutical forms of compared medicinal products.

INN	Trade name	Dosage form	Amount of active ingredient per dosage form	MA holder, manufacturer, packer	Price per package, rubles
Follitropin-alpha	Gonal-F	Lyophilized powder for solution for subcutaneous injection	75	Merck Serono SA, Swiss branch	941,49 rub.
Follitropin-alpha	Gonal-F	solution for subcutaneous injection	300	Merck Serono S.p.A., Italy	4 858,30 rub.
Follitropin-alpha	Gonal-F	solution for subcutaneous injection	450	Merck Serono S.p.A., Italy	7 192,44 rub.
Follitropin-alpha	Gonal-F	solution for subcutaneous injection	900	Merck Serono S.p.A., Italy	14 381,41 rub.
Follitropin-beta	Puregon	solution for subcutaneous injection	300	Organon N.B.	5 549,00 rub.
Follitropin-beta	Puregon	solution for subcutaneous injection	600	Organon N.B.	10 311,58 rub.
Follitropin-beta	Puregon	solution for subcutaneous injection	900	Organon N.B.	13 171,00 rub.
Follitropin-beta	Puregon	solution for intramuscular and subcutaneous injection	500	Organon N.B.	9 247,00 rub.
Menotropins	Menopur	Lyophilized powder for solution for subcutaneous injection	750	LLC Ferring Pharmaceuticals	12 808,58 rub.
	Puregon*	Pen-injector	791.5 rub.		