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Research Article

The trends of assisted reproductive technologies and cost for ovarian stimulation protocols in Ukraine

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Abstract

The prevalence of infertility has risen 2.9 times in recent years in Ukraine. The use of assisted reproductive technologies (ART) is needed. The State program for infertility treatment by budget funds was approved in Ukraine since 2004. However, funding for this program is enough only for 500–600 cycles per year, but ART centers conducted more than 27,000 cycles in 2018. This means that many women have to pay out-of-pockets.

Our research has shown that between 2000 and 2018, the number of ART clinics and the number of cycles, pregnancies, and children born increased significantly in Ukraine. The rate of ART cycles per 1 million population in Ukraine has increased from 226.9 to 655.3, but it is lower than the WHO recommended rate 800–1000 cycles per 1 million population. Changes in the structure of ART cycles for 2000–2018, the increase of ICSI, and egg donation cycles are shown. It requires an adequate supply by hormonal drugs for ovarian stimulation in ART centers.

Since 2004 Ministry of Health of Ukraine annually approved the list of medicines for State program of ART. Only 8 drugs were purchased by the state funds, which amounted for USD 227 438 in 2017, 2018.

A retrospective analysis of drug prescriptions in short and long stimulation protocols was performed. The frequency of drug prescriptions according to the ATC-classification based on medical records was determined, all prescriptions were accordance with the requirements of ART treatment standards in Ukraine. The costs of the three hormonal stimulation schemes, which were the most prescribing in ART center, were calculated. It was found that costs for hormonal schemes increased by 22–54% during 2015–2020, it significantly reduces the availability and affordability of ART for the population in Ukraine.

Keywords

infertility, assisted reproductive technologies, cost, ovarian stimulation, affordability

Introduction

In the world, infertility affects 15% of couples of reproductive age, amounting to as many as 186 million people (Agarwal et. al. 2015). According to the World Health Organization (WHO) data, over 10% of women are inflicted. There were women who have tried unsuccessfully, and have remained in a stable relationship for five years or more. WHO member countries have established a registry system to evaluate and monitor the effectiveness

of infertility treatment, implications of pregnancy, and health of treated women (https://www.who.int/reproductivehealth/topics/infertility/perspective/en/).

The results show that 50% of all cases of infertility are due to female factors alone, 20–30% are due to male factors, and the remaining 20–30% are due to a combination of male and female factors (Inhorn et. al 2015). According to reports in the 2006–2010, it was estimated that 6% of married females aged 15–44 years were infertile in the USA (Chandra et. al. 2013). Among reproductive couples the prevalence of infertility was 25.1% in China, 15.4% in Australia and 10–12% in Europe (Zhou et. al. 2018). About 1 million married couples suffer from infertility in Ukraine. The rate of infertility is 15–17%, it's higher comparing to the EU countries (Ukrainian association of reproductive medicine (Dakhno 2011).

The treatment of infertility has been improved over the past 4 decades by the implementation of assisted reproductive technology (ART). According to international data, more than 8 million children were born in the world after the birth of the first child Louise Brown in 1978 with ART (Norcross 2018). Based on CDC's 2017 Fertility Clinic Success Rates Report (CDC 2017), there were 284385 ART cycles performed at 448 reporting clinics in the United States and 78052 live born infants during 2017. Approximately 1.7% of all infants born in the United States every year are conceived using ART (https://www.cdc.gov/art/artdata/index.html).

In European countries performed amount 55% of all the ART cycles in the world; North America 20%; Asia 10%, and 15% – other regions (Adamson 2009). The European Society of Human Reproduction and Embryology (ESHRE) annually collected data from ART registers in European countries, including ART data from Ukraine. According to the data of ESHRE's report 2009, which published in 2013, in 21 countries a total of 399,020 ART cycles were performed on a population of 373.8 million, corresponding to 1067 cycles per million population (Ferraretti et al. 2013).

Statistical data of ESHRE's report of 2015, it was published in 2020, showed that in 38 countries which provided results through national registries or professional data societies offering ART services, a total of 849,811 cycles were performed (Geyter et. al. 2020). The leading countries among them were Spain (119,875 cycles), Russia (110,723), Germany (96,512), and France (93,918). In Ukraine, there were 18,286 cycles in ART centers. A total of 409,771 ART cycles were performed, corresponding to 1,432 cycles per million population (range: 727–3068 per million) in Europe (Geyter et. al. 2020). These data illustrate that the number of cycles reported that variability in treatment modalities in most European countries point towards the increasing impact of ART on reproduction in Europe.

Public funding for ART differs widely between countries in the world. The cost of IVF cycle (in vitro fertilization) is expensive and varies tremendously. In Japan, it is USD3,956, in Germany USD4,148. It is even higher, in the United States USD12,513, in Canada USD8,500, in the United Kingdom USD5,244. Many countries, such as the United Kingdom, incur strict restrictions and limitations on the provision of IVF treatment via public funding. The number of cycles funded is often limited for each person due to the cost involved. In Germany, it provides partial reimbursement to meet some of the cost of IVF treatment. Even with the provision of funding of up to 50%, three quarters of couples in Germany declined to proceed to IVF treatment (Teoh and Maheshwari 2014).

In Ukraine, the first child after IVF was born in Kharkiv on March 19, 1991. In October 2005, on the Reproductive health conference in Lviv, the Ukrainian Association of Reproductive Medicine (UARM) was registered. The UARM has generated reports on ART cycles and success rates and sent them to the ESHRE. Statistical ART data are collected according to a special form №41 "Report on assisted reproductive technologies", approved by the Order of Ministry of Healt of Ukraine, dated 10.12.2001 № 489. It's an objective assessment of the results of infertility treatment with ART in Ukraine (http://www.uarm.org.ua/en/).

For the first time in Ukraine, the use of ART for budget funds was approved in 2004 and has been in place since then. According to the Order of the Ministry of Health of 29.11.2004 N 579 "On approval of the Procedure for referral of women for the first course of infertility treatment by methods of assisted reproductive technologies on absolute indications for budget funds", it provided funding for the first course of infertility treatment by ART methods for women aged 19–40 years, carried out on absolute indications. Every year state budget funded 550–600 cycles (Dakhno 2011). Annually, the Ministry of Health of Ukraine approves a list of medicines that are purchased for ART state centers.

The high cost of ART, however, is the main barrier that prevents many benefits from this method to help infertility women. Patients in low income countries have to self-fund infertility treatments. Although the cost of ART treatment is variable among different countries, it is generally an expensive treatment for population in middle and low income countries. The price of medications used for ovarian stimulation is a major factor to the high cost of ART treatment. Most ART treatments are performed in private centers of Ukraine. There are strict restrictions and limitations on the provision of ART treatment via budget funding in Ukraine.

According to the WHO, data affordability refers to how easy or feasible an individual (society) finds it to pay for a medicine. It is a function of drug prices, insurance coverage, a family's financial circumstances, and, sometimes, the purpose of the drugs (Niëns 2012). Affordability of ART for individuals greatly differs in EU countries and low income countries.

The aim of the research was to analyze the dynamics of the number of ART cycles, pregnancies, and infants born alive for 2000–2018 in Ukraine; to identify changes in the types of ART cycles conducted for this period; to determine the prescriptions of drugs in the ovarian stimulation protocols according to real data from ART center.

We compared the costs on short protocols during 2015–2019. It also was conducted the cost analysis for three common used ovarian stimulation protocols and calculated an affordabilty ratio of ART in 2015, 2020 to assess the availibilty of ART to the population in Ukraine.

Materials and methods

Objects of this study were statistics data on infertility rates, number of ART cycles, pregnancies and infants born alive from "Information and Statistical Reference Book on Assisted Reproductive Technologies in Ukraine" (2020). We also used data from the "Fertility problems: assessment and treatment" (NICE Guidance 2017) (https://www.nice.org.uk/guidance/cg156); Order of the Ministry of Health of Ukraine No. 787 dated September 09, 2013 "On Approval of the procedure for the use of assisted reproductive technologies in Ukraine" (https://zakon.rada.gov.ua/laws/show/z1697-13). We analyzed the electronic database of stimulation protocols (short and long protocols included in Doctor ELEKS software) of women treated at the Medicover Medical Center, Lviv during 2017–2019. This medical center reports on ART cycles and is included in the "Information and Statistical Reference Book on Assisted Reproductive Technologies in Ukraine" that indicates good results of this center (https://medicover.ua/uk).

Research methods: system analysis, data synthesis and generalization of information, retrospective analysis of data on the number of ART cycles in 2000–2018, analysis of costs for ART. All protocols of ovarian stimulation were analyzed in Microsoft Excel 10. The costs were calculated on the retail price of medicines according to the electronic resource Apteka.ua (Ukraine) on 01.05.2020 (1 € = 29.9 UAH). We conducted a cost analysis for three hormonal stimulation protocols, based on the price of 1 tablet and cost per course per 1 patient, to determine less cost scheme for purchase of ART centers in Ukraine.

Results

According to national statistical reports, 12579 cases of female and 3712 of male infertility were registered in 2012. In 2017, 38168 cases of female infertility and 10945 cases of male infertility were registered. The prevalence of current infertility has increased in 3.0 times for the last five years in Ukraine. Therefore, there is a significant need to provide ART in Ukraine (http://www.uarm.org.ua/en/).

At the first stage of our study, we analyzed the dynamics of the number of ART cycles, pregnancies, and infants born alive during 2000–2018 in Ukraine. Analysis of statistic data included in "Information and Statistical Reference Book on Assisted Reproductive Technologies in Ukraine" showed that high growth in the number of ART rates during 2000–2018 years.

In 2000, 1143 treatment cycles (stimulated or not stimulated) were carried out for the treatment of infertility; in 2010–11144 cycles; in 2018–27654 cycles, respectively, in Ukraine. The growth rate was 9.75 for 2000–2010 and it was 2.28 for 2011–2018. In general, in 2000–2018, the number of ART cycles increased by 24.20 times in Ukraine.

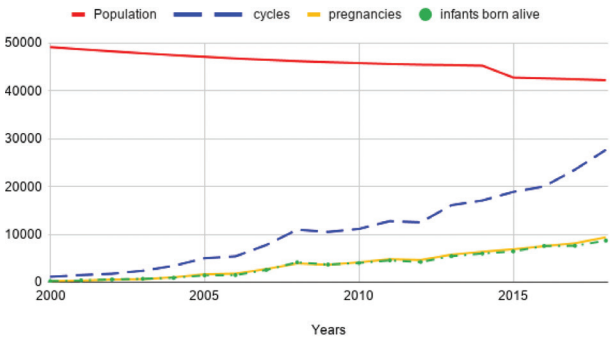

Figure 1. Population, ART cycles, pregnancies, infants born alive in Ukraine, 2000–2018.

The number of clinical pregnancies initiated under the ART cycles was 268 in 2000, the success ratio was 23.4%. It grew to 4165 pregnancies in 2010, the success rate was 37.4%. In 2018 the success ratio was 34.0%. There is an improvement in the ART treatment and these success rates are similar to the data in the European countries, and the ESHRE data were 25–27%. There were infants born alive 3702 in 2010, the growth rate was 14.2 times to 2000 year. In 2018, there were 8708 infants and the growth rate during 2010–2018 slowed to 2.4 times. Thus, a retrospective analysis of the statistic data of the ART-cycles, pregnancies, infants born alive showed that during 2000–2010 years, the success ratio and the growth ratio had the highest values in Ukraine. But this dynamics significantly decreased in 2010–2018. The slowdown in the growth rate of ART is influenced by many factors, the main of which are the population decline and immigration of people of reproductive age and by the limitation of economic availability of ART for the infertility couples and insignificant budget funding (Fig. 1).

We calculated the number of ART cycles per million population during 2000–2018. Our result illustrates that the number of ART cycles per million was 226.9 in 2000 year, 239.3 in 2009 and 655.3 in 2018, respectively. The rate of ART cycles per million population have risen gradually. It increased 2.9 times due to a growth of the number of ART centers and a decrease in the population of Ukraine over the past 20 years. According to WHO recommendations, the need of ART cycles is 800–1000 per million population. This means that in Ukraine there is still an insufficient providing by ART for the population.

Since 2004, there was approved the State Program for providing the first cycle of the ART by budget funds for women with absolute infertility (according to the Order of the Ministry of Health of Ukraine dated 11/29/2004 No. 579 "On approval of the procedure for referral of women to perform the first course of infertility treatment by methods of assisted reproductive technologies for absolute indications by budget funds") (Order of the Ministry of Health of 29.11.2004 N 579).

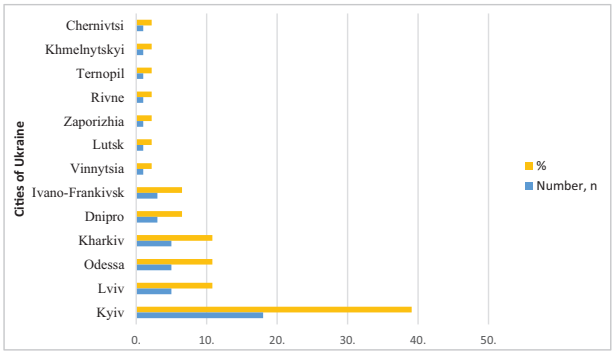

Figure 2. ART centers located in cities of Ukraine (2019).

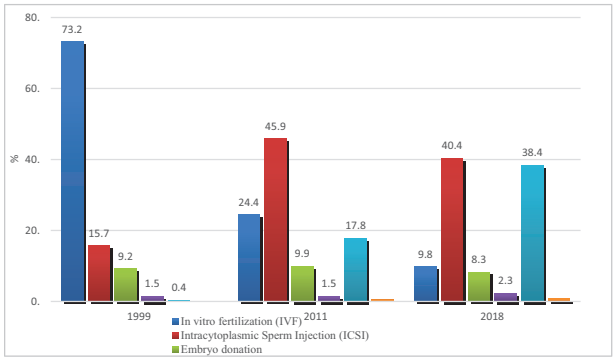

Figure 3. Structure of ART cycle types in Ukraine in 1999, 2011, 2018.

Annually the Ministry of Health of Ukraine approved the list of medicines for ART budget program. There are 8 medicines are purchased by the state funds. There are such medicines by INN: chorionic gonadotropin alpha, follitropin alpha 75 IU, 300 IU, follitropin beta, propofol, triptorelin, menotropin, ganirelix. There is a budget procurement for treatment of infertility which amounts for USD227,438 in 2017, 2018. There were 2849 women treated by State Program and 778 children were born in Ukraine on January 01, 2018 (https://eco-if.com.ua/derzhavna-prohrama). State funding for ART is insufficient for regulated categories of patients, so most women have to treat of infertility in private ART centers and to pay of ART out-of-pocket.

ART centers have been actively developing for the last 20 years in Ukraine. There are 46 ART centers, however, only five centers have state funding. In 2000, there were only 6 such ART centers. We found hat three state centers are located in Kyiv, one center is in Odessa and Ivano-Frankivsk. This placement of state centers reduces the availability of free ART cycles for population. Data from all centers form a "Report on Assisted Reproductive Technologies", which provides an opportunity to monitor the results of treatment cycles and to make an objective assessment of ART treatment results.

We studied the structure of the number of ART centers in 25 regions of Ukraine on 12/30/2019. It was established that a significant number, 39.1% of ART centers, were operating in the capital of Ukraine, Kyiv. There are 10.1% ART centers located in Lviv, Odessa, and Kharkiv. We found that 9 regions (Uzhhorod, Cherkasy, Sumy, Kirovohrad, Mykolaiv, Kherson, Poltava, Zhytomyr, Chernihiv) do not have any ART centers that perform ART, it is 36% of all regions (Fig. 2).

It should be cycles depending on the type of ART to determine the dynamics of the use of different types of ART cycles during 2000–2018 in Ukraine. We analyzed the structure of ART in 1999 the dominant share 73% were IVF cycles. In 2018 they occupy almost 10%, so the frequency of use IVF decreased 7.5 times. During the period of 2000–2018 in Ukraine, the number of egg donations increased significantly by 96 times from 0.4% to 38.4%, as well as ICSI cycles from 15.7% to 40.4%. However, embryo donation cycles remained a stable share 8–9% of the total number of cycles during 1999–2000 (Fig. 3).

Table 1. Age of women treated with ART in private medical center.

Age, years	Number of women prescribed stimulation protocols	
	n	%
21–25	4	5.1
26–30	17	21.8
31–35	37	47.4
36–40	15	19.2
41–45	5	6.4
46–49	0	0

The maximum costs in ART cycles are related to hormonal ovarian stimulation. At the next stage of study, we conducted analysis of the prescriptions in the ovarian stimulation protocols to determine the frequency and cost for hormonal medicines.

We analyzed the real data on the prescription of ovarian stimulation in a private medical center "Medicover Medical Center", which is located in Lviv. This ART center regularly submits statistical data on ART cycles to the Kyiv, which are included in ART Register of Ukraine. We analyzed 73 medical records of treated women, including 13 long and 60 short protocols during 2018–2019. The age characteristics of treated women were determined. We found that the largest group consisted of women aged 31–35 years (47.44%). However, infertility treatment was performed for 5% of women aged 21–25 years (Table 1).

A frequency analysis showed that 39 trade names were prescribed in ART stimulation protocols, which corresponds to 23 INN medicines. Totally, 788 appointments were made to patients. We established the absolute number of prescriptions of medicines in ART stimulation protocols, according to the ATC-classification, which is presented in Table 2.

Thus, leaders of appointments were complex vitamins; progesterone, it is recommended by both the Ukrainian protocol and international guidelines; it was also acetylsalicylic acid. Distribution of medicines according to the ATC-classification showed, that the largest share of all names of medicines of these groups are the following: A11E – complex vitamins (22.58%), G03 – progestogens (14.47%), and B01 antiplatelet medicines (12.32%).

We analyzed and compared the costs for ovarian stimulation protocols commonly used for the treatment of IVF/ICSI patients. The direct costs of gonadotropins per cycle were calculated from individual data, multiplying the cost

Table 2. Frequency of appointments in ART long and short protocols.

INN	ATC-cod	Number of appointments, n	Frequency of appointments, %
ovarian stimulation treatment			
Progesterone	G03DA04	114	14.47
Ganirelix	H01CC01	54	6.85
Follitropin alfa	G03GA05	51	6.47
Triptorelin	L02AE04	30	3.80
Choriogonadotropin alfa	G03GA08	27	3.42
Human menopausal gonadotropin	G03GA02	25	3.17
Cetrorelix	H01CC02	20	2.54
Chorionic gonadotropin	G03GA01	16	2.03
Follitropin beta	G03GA0	7	0.88
Estradiol	G03CA03	4	0.51
Corifollitropin alfa	G03GA09	2	0.25
Follitropin alfa/ Lutropin alfa	G03GA30	1	0.13
adjuvant treatment			
Comb drug (polyvitamini)	A11E A	178	22.58
Acetylsalicylic acid	B01AC06	97	12.32
Colecalciferol	A11CC05	51	6.47
Methylprednisolone	H02AB04	47	5.96
Dietary Supplements		43	5.46
Immunoglobulins	J06B A02	11	1.39
Folic acid	B03B B01	5	0.63
Nadroparin calcium	B01AB06	2	0.25
Enoxaparin sodium	B01AB05	1	0.13
Ethi1nylestradiol + Drosperinone	G03AA12	1	0.13
Methformin	A10BA02	1	0.13
Total		788	100.00

of a single IU by the weighted means of IU used per cycle. The cost of three short stimulation protocols was calculated, which were most often prescribed according to the real data of medical records (Table 3).

According to the Table 3, the cost for the stimulation protocol ranges from UAH19,249 to 44,165 (€644–1477), the average cost is UAH31,707 per one woman.

We also compared the cost of ovarian stimulation protocols per woman in 2015 and 2020. It was concluded that the increase of cost was 21.9%–53.9%, which is due to the rising of the prices of medicines on the Ukrainian market in the last years (Fig. 4).

It was found that the cost of ovarian stimulation protocols has increased by 22–53% over the past 5 years, it reduces the availability of ART for the population. According to the WHO recommendations for calculating the availability and affordability of medicines for ART, the costs of ART schemes are not affordable, as the average salary per month is UAH12,264 (€410.1) on 12/01/2019 (https://tradingeconomics.com/ukraine/wages).

There is a need to increase funding for the ART state program to guarantee the covering of ART cycles for women to improve their affordability in Ukraine.

Discussion

The cost of ART varies across Europe and prices for hormonal stimulation schemes are rising. In Bulgaria, costs for schemes of hormonal ovarian stimulation with

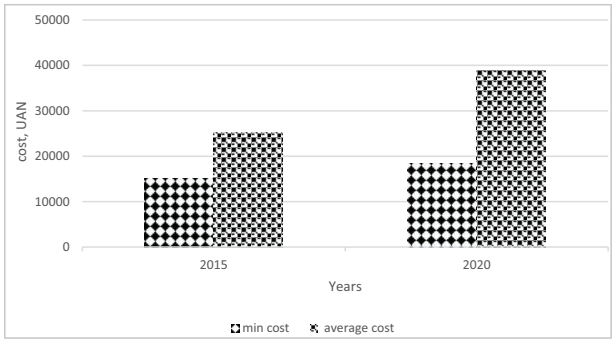

Figure 4. Dynamics of the cost of ovarian stimulation protocols (ovarian stimulation) in 2015, 2020.

rFSH and rFSH and urFSH were 1615.69–1964.52 BGN (Petrova et. al. 2016; Benbassat et. al. 2017). The results indicated that the GnRH-agonist protocol is the cost-effective one, with smaller cost per live-born child.

In Spain, cost minimization analysis (Barrenetxea et. al. 2018) showed that treatment with corifollitropin alfa resulted in a lower pharmacological cost compared with rFSH (€757.25–950.30, respectively), creating a saving of approximately 20%. The results illustrated that corifollitropin alfa reduced the cost for ovarian stimulation in comparison with daily administration of doses ≥ 250 IU rFSH, regardless of the additional days required (average €223).

The use of a minimal stimulation protocol with lower gonadotropin provides the onset of pregnancy in the same way as the use of stimulation therapy with antagonists, but is more affordable and cost-effective substitute for the patient for poor ovarian responders (Pilehvari et al. 2016).

There are no government ART programs in China. The cost of tree-based therapy regimens for the long protocol using GnRH antagonists was $16,970.85, and with agonists was $2,902.24. The GnRH-agonist protocol has been found to be more cost-effective (Jing et. al. 2020) .

Our research has shown that in Ukraine there are 46 ART centers, however, only 5 centers have budget funding. These public centers provide a free first ART cycle by budget funds for women with absolute infertility. It was revealed that in 9 regional cities (36% of regions) there are no any ART center. The main share of all ART centers (39%) is concentrated in the capital of Ukraine, Kyiv.

It was found that during 2000–2010 ART had the highest growth dynamics, however, in 2011–2018 the dynamics of growth has slowed only 2.5 times with regard to demographic, economic, social aspects.

The obtained results showed significant changes in structure of ART cycle types in Ukraine in the last 2 decades. There is a trend to increase the number of ART cycles such as ICSI, egg donation, and a significant decrease of IVF cycles. The observed pattern allows to determine and plan the volume of hormonal drug supply for ART centers.

Analysis of 73 protocols of ovarian stimulation showed that already 5% of women aged 21–25 were treated for infertility. It requires increased attention and the need for early diagnosis of infertility in young women under 25 years of age who need ART. It should be noted that there

Table 3. Costs of short ovarian stimulation protocols in ART.

International onproprietary name	Trade name, dose	Dose and package	The cost of package	Number of treatment	Cost, UAH	Cost, EUR
Protocol 1						
Follitropin Alpha	Gonal-F 150 IU	75 IU №1	700.00	11 days	15400.00	515.05
Cetrorelix	Cetrotide 0.25 mg/ml	0.25 mg / ml №7	7700.00	3 days	1100.00	36.79
Triptorelin	Diphereline 3.75 ml	3.75 ml №1	1961.80	1 day	1961.80	65.61
Acetylsalicylic acid	Cardiomagnyl 75 mg	75 mg №30	113.96	11 days	113.93	3.81
Methylprednisolone	Metypred 4 mg	4 mg №30	127.84	5 days	127.84	4.28
Comb drug (polyvitamini)	Neurorubine	B1 200 mg B6 50 mg B12 1 mg	249.71	5 days	249.71	8.35
Colecalciferol	Decristol D3	5600 IU	295.68	11 days	295.68	9.89
Cost of scheme					**19248.96**	**643.77**
Protocol 2						
Corifollitropin alfa	Elonva 150 IU	150 IU №1	11900.00	1 day	11900.00	397.99
Ganirelix	Orgalutran 0.25 mg /0.5 ml	0.25 mg / 0.5 ml № 5	3503.40	3 days	2102.04	70.30
Chorionic Gonadotropin	Pregnyl 10 000 IU	5000 IU № 1	495.69	1 day	991.38	33.16
Human menopausal gonadotrophin	Merional 75 IU, 150 IU	75 IU №10 150 IU №10	6500.00 11000.00	6 days 3 days	3900 3300	130.44 110.37
Estradiol	Divigel 1 g	gel 0.1% / 1 h, №10	183.98	10 days	183.98	6.15
Acetylsalicylic acid	Cardiomagnyl 75 mg	75 mg №30	113.96	10 days	113.93	3.81
Dietary Supplements	Folio	B9 400 mgr KI 200 mgr	220.79	30 days	220.79	7.38
Immunoglobulins	Bioven 50 mg	50 mg	3947.32	1 day	3947.32	132.02
Cost of scheme					**26659.44**	**891.62**
Protocol 3						
Triptorelin	Diphereline 3.75 ml	3.75 ml №1	1961.80	1 day	1961.80	65.61
Follitropin Alpha	Gonal-F 225 IU	300 IU / 0.5 ml №1	3350.00	9 days	30150.00	1008.36
Follitropin beta	Puregon 50 IU	100 IU / 5 ml№5	4500.00	8 days	3600.00	120.40
Cetrorelix	Cetrotide 0.25 mg/ml	0.25 mg 0.5 ml №7	7700.00	3 days	1100.00	36.79
Choriogonado-tropin alfa	Ovitrelle 250 mgr/0.5 ml	0.25 mg / 0.5 ml №1	2000.00	1 day	2000.00	66.89
Acetylsalicylic acid	Cardiomagnyl 75 mg	75 mg №30	113.96	10 days	113.93	3.81
Comb drug (polyvitamini)	ELEVIT PRONATAL	Comb drug	717.07	30 days	717.07	23.98
Immunoglobulins	Bioven 50 mg	50 mg	3947.32	1 day	3947.32	132.02
Methylprednisolone	Metypred 4 mg	4 mg №30	127.84	5 days	127.84	4.28
Metformin	Metformin	500 Mg №30	151.00	10 days	151.00	5.05
Colecalciferol	Decristol D3	5600 IU	295.68	30 days	295.68	9.89
Cost of scheme					**44164.64**	**1477.08**

were no women of older reproductive age 45–49 years. This indicates that women of advanced maternal age are less likely to seek ART treatment in Ukraine.

It was found that 66.7% of women were urban and 33.3% rural population, depending on the place of residence. Thus, current situation showed, that 2 times more urban women than rural are treated with ART. It may indicate that urban women, who live in cities, are more informed and they have higher financial possibilities for ART treatment.

We established that in 73 protocols of ovarian stimulation were used only 12 INNs, namely progesterone, ganirelix, follitropin alfa, triptorelin, choriogonadotropin alfa, human menopausal gonadotrophin, cetrorelix, chorionic gonadotropin, follitropin beta, estradiol, corifollitropin alfa, follitropin alfa/ lutropin alfa. The rate of the frequency was 44.52% of all appointments.

We conducted that an additional drugs used in ART for adjuvant treatment, such as polyvitamins, acetylsalicylic acid, colecalciferol, methylprednisolone, dietary supplements, immunoglobulins, folic acid, nadroparine calcium, enoxaparine sodium, ethinylestradiol + drosperinone, methformin. We found that the frequency rate was 55.48% of all appointments. The frequency rate of additional medicines (adjuvant therapy) is high, this trend leads to an increase in the cost per patient and indicates the need to optimize the appointment for the improvement of ART affordability.

The other studies, conducted for short stimulation protocols, showed that the cost per cycle was UAH15,145–25,227 in Ukraine (Horbachevska 2015; Piniazhko 2016). We found that the cost of ovarian stimulation protocols has significantly increased by 22–53% over the past 5 years. The detected trend significantly decreases the affordability of ART for the population in Ukraine, because many patients pay out of pocket and public funding is limited.

The obtained results illustrate that the cost for the short stimulation protocols (ovarian stimulation treatment) are €617.39–1298.06, on average €957,50 per patient in Ukraine. It was also found that cost for adjuvant treatment is UAH 2,534.60 (€84.77) per patient.

It also reduces the affordability of ART treatment for patients in Ukraine.

According to the WHO recommendations for calculating the affordability of medicines are used the costs per one month of treatment regarding an average salary per month for each country. According to WHO data, the affordability ratio for treatment regimen should be less than 1.0.

We calculated the affordability of ART for patient as the ratio of cost per ovarian stimulation cycle to the average salary of two family members. In Ukraine the average salary was UAH12,264 (€410.1) on 12/01/2019 (https://tradingeconomics.com/ukraine/wages).

We calculated the ART affordability ratios in 2015 and 2020 years. We established, that in 2015, the direct costs of ART protocols were UAH15,145–25,227 (€506.52–843.71), the average salary was UAH4299 (€143.78) on 06/01/2015. The calculated affordability ratio was 1.76–2.93, it indicated the low affordability for couples in 2015.

In 2020, the cost of ART schemes was UAH18461.80–38811.99 (€617.39–1298.06) per one patient, the average salary was UAH11579 (€ 387.25) on 06/01/2020. The calculated availability ratio is 0.79–1.68, which means that the costs of ART cycles are more affordable in relation to the average salary in Ukraine in 2020. However, this affordability ratio is higher than 1.0, which recommended by WHO. So it is advisable to increase funding for the State program for infertility treatment in Ukraine to improve accessibility for low-income families and to guarantee the covering of ART cycles for patients

Analysis of cost studies of hormonal ovarian stimulation schemes has shown that these costs in Ukraine are similar to those data in Europe. Pharmacoeconomic studies are needed to identify the cost-effective medicines that provide lower costs for treatment in order to rationally use of budget funds and to improve availability, affordability, and acceptability of ART for population in Ukraine.

Conclusions

Statistical data on the prevalence of infertility in Ukraine indicates increasing in 2.9 times for the period 2012–2019. The use of assisted reproductive technologies (ART) have risen according to needs of population. Over the 20 years it showed a continuing expansion of the number of ART centers and ART cycles, and pregnancies, alive born children respectively in Ukraine. The ratio of ART cycles per 1 million has risen from 226.9 to 655.3 during 2000–2018. Currently, 39% of ART centers are located in the Kyiv, but 36% of regions do not have any ART center, which reduces access to ART treatment for population in these regions, especially in the quarantine period. The number of ART cycles significantly increased during 2000–2019. State program for ART covered only 550–600 cycles, it is insufficient for the population in Ukraine.

Cost per the course of ovarian stimulation for the short stimulation protocol was UAH19,249 to 44,165 (€644–1477), on averages UAH31,707 per one woman in the ART private center in 2020. The cost for ovarian stimulation has increased by 22–53% over the past 5 years, it reduces the availability of ART for the population. The calculated affordability ratio of ART was 1.76–2.93 in 2015, that was higher than WHO recommendations. In 2020 the affordability ratio of ART is lower 0.79–1.68 indicating better affordability of ART for patients. Budget funding for ART program is needed to be increase and improve accessibility for infertile families in Ukraine.

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