

Pharmacotherapy Cost of Controlled Ovarian Hyperstimulation of *in Vitro* Fertilization—A Real Life Study

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Abstract

The aim of the current study is to analyze the cost of controlled ovarian hyperstimulation (COH) of *in vitro* fertilization (IVF) during the period 2009-2013 in a specialized gynecology clinic. It is a prospective, observational study and bottom up cost analysis of the COH pharmacotherapy of IVF. The data was collected for all women admitted to the clinic, therapeutic COH protocols, prescribed medicines and doses, average length of therapy and its cost. Statistical analysis is applied towards the pharmacotherapy and cost data. On average 136 (SD 21.92) women were admitted varying from 105 to 179 for 10.7 (SD 1.47) days. 11% were on long (GnRH agonist containing) therapeutic COH protocol and all other on short (GnRH antagonist containing). Therapeutic protocols include Follitropin- α IU (103 women at average dose of 1171 IU (SD 314.16)); Follitropin- β IU (299 women at average dose of 1634 IU (SD 423.5)); Urofollitropin 75 IU amp (243 women at average dose of 21.3 IU (SD 7.37)); urFSH + urLH 75IU:75IU/amp (354 women at average dose of 23.4 IU (SD 8.8)); cetrorelix amp 0.25 mg prescribed at 264 women at average dose of 3.84 IU (SD 1.32); ganirelix amp 0.25 mg for 299 women at average dose of 4.01 mg (SD 1.32); Human chorion gonadotropin for 535 women at average dose of 6752.52 IU (SD 1216.23); Nafarelin mcg/ml for 8 women at dose of 17,700 mcg (SD 10,725); triptorelinacetat 0.1 mg amp - 63 women at doses of 5.5 (SD 3.25) mg at 14 women and average dose of 7.5 mg (SD 2.5); clomiphene citrate and letrozole for 15 women at average dose of 8 mg (SD 2.4). The average cost of COH pharmacotherapy is varying among the years with highest value of 1803.776 (SD - 624.89) BGN in 2009. Controlled ovarian hyperstimulation of *in vitro* fertilization is cost and resource consuming procedure in regards to pharmacotherapy. Age and reason of infertility influence significantly the cost.

Keywords

Controlled Ovarian Hyperstimulation, *In Vitro* Fertilization, Pharmacotherapy, Cost Analysis

1. Introduction

Infertility is recognized as a growing problem worldwide with nearly 10% to 15% of couples not able to conceive a child [1]. Factors contributing to infertility could be from medical and social origin [2]-[4]. The infectious diseases, sexually transmitted diseases, anatomical and physiological factors have been described as medical factors in different studies [3]-[5]. Societal factors that contribute to the later women age when planning child birth are late marriage, carrier developing, and education [6]-[8].

In vitro fertilization (IVF) is considered a solution in lots of cases of infertility but its rate of success is not 100%, and significantly lowers as the age of the woman increases [7]-[13]. Controlled ovarian hyperstimulation (COH) is a principal beginning of IVF [14]. COH protocols changed with new medicines development and individualized approaches used by physicians. The changes of therapeutic approaches and appearance of new technologies that promise new success rate apply additional economic burdens [7]. Thus the factors contributing to the rate of success and its economic implications are a matter of concern for the health care payers and for the patients. Some studies show that the full coverage of the IVF pays off and other were trying to evaluate its economic implications at national level [15]. Success rate also differs among techniques and physicians experience. There is no economic analysis of the cost of IVF in Bulgaria that stimulate the interest towards this study [1] [16]-[21].

The aim of the current study is to analyze the cost of controlled ovarian hyperstimulation (COH) pharmacotherapy of *in vitro* fertilization during the period 2009-2013 in a specialized gynecology clinic in Sofia.

2. Materials and Methods

It is a prospective, observational analysis of the cost of COH pharmacotherapy of *in vitro* fertilization in a specialized gynecological clinic. The gynecological clinic is situated in Sofia and it is one of 10 biggest out of 26 specialized *in vitro* clinics in Bulgaria that is treating nearly 150 women per year. Medical center specializes in the treatment of all forms of female and male infertility, cryopreservation of reproductive cells, tissues and stem cells. *In vitro* Medical center “Dr. Dimitrov” is the only Bulgarian center approved as a member of the International Association of Private Assisted Reproductive Technology clinics and laboratories-APART.

During the period 2009-2013 the following data was collected for all women admitted to the clinic: information about the therapeutic protocols used, prescribed medicines and doses, average length of therapy and its cost.

Bottom up approach for the cost analysis is used. Frequency of prescribed hormones was reviewed. The COH pharmacotherapy cost is calculated after multiplying the prices of individuals unit of medicines used from every woman with the length of the therapy. Prices of medicines were taken from the Positive drug list in the year of observation.

Descriptive statistical analysis is applied towards the women demographic, pharmacotherapy and cost data. Via t-test, one way and two way ANOVA analyses was explored data correlations and statistical significance among the analyzed variables.

All prices are considered at the ex-change rate of 1 Bulgarian leva (BGN) = 0.95 Euro.

3. Results

3.1. COH Protocol Analysis

Two COH protocols are used in the clinical practice of IVF, which are named short (GnRH antagonist containing) and long protocol (GnRH agonist containing) (Table 1). The aim of the protocols is to stimulate the development of mature oocyte following consecutive daily application of hormonal medicines before the IVF. Selection of protocol depends on women characteristics, physician preferences, established therapeutic habits and in some cases on cost considerations.

3.2. Results of the Pharmacotherapy and Cost Analyses

In the observed clinic on average 136 (SD 21.92) women were admitted varying from 105 to 179 for average 10.7 (SD 1.47) days. Only 11% were on long therapeutic COH protocol and all other on short—Table 2. Women are almost equally distributed according to the sterility type with prevalence of primary sterility and cause of infertility within the years. The tube sterility is a leading cause in all years.

Table 1. Medicinal products used in short and long therapeutic IVF protocols.

Characteristic	Application
Short protocol	
Length of application	Applied 9 days on average + 3 additional 1 and 2 day FSH 3 and 4 day FSH + ganirelex 5 and 9 day FSH + 4 days ganirelex + hCG
Medicinal products	FSH Ganirelex human chorion gonadotropin (hCG)
Unit prices of medicines	FSH 75 IU 1 amp = 25.61 BGN or recombinant FSH 75 IU 1 amp = 340.35 BGN Ganirelex 1 amp = 56.11 BGN hCG 1500 IU = 1.68 BGN or 5000 IU = 5.60 BGN
Long protocol	
Length of application	Applied on average 16 days 7 days triptorelin 7 days triptorelin + FSH 2 days FSH
Medicinal products	triptorelin + FSH
Unit prices of medicines	triptorelin 14.29 BGN FSH 75 IU 1 amp = 25.61 BGN or recombinant FSH 75 IU 1 amp = 340.35 BGN

Note: *FSH—follicular stimulating hormone; hCG—human chorion gonadotropin; IU—international units; BGN—Bulgarian leva.

Table 2. Women demographic.

Characteristic	2009	2010	2011	2012	2013
N women	120	179	105	147	127
Age - N					
to 30	15	34	10	17	24
30 - 35	64	69	49	60	38
36 - 39	28	45	28	34	39
above 40	13	31	18	36	26
Sterility type - N (%)					
Primary	63 (52.5%)	119 (66.5%)	57 (54%)	81 (55%)	74 (58%)
Secondary	57 (47.5%)	60 (33.5%)	48 (46%)	66 (45%)	53 (42%)
Sterility cause					
Tubes	51	70	46	64	46
Endometriosis	6	6	2	3	2
LUFS*	1	1	2	7	7
Mail reason	38	66	31	37	35
PCOS*	2	3	0	1	0
Unknown	17	26	18	28	30
Combination	5	13	6	7	6
COH* - N (%)					
Long protocol		11 (6%)			
Short protocol	120 (100%)	168 (94%)	105 (100%)	147 (100%)	127 (100%)
Days on therapy (SD)	10 (SD 1.30)	11.6 (SD 2.6)	10.7 (SD 1.47)	10.7 (SD 1.58)	11.4 (SD 1.9)

*LUFS—Luteinizedunruptured ovary syndrome; PCOS—Polycystic ovary syndrome; COH—Controlled ovarian hyper stimulation; SD—standard deviation.

Therapeutic protocols include Follitropin- α IU (prescribed to 103 women at average dose of 1171 IU (SD 314.16)); Follitropin- β IU (prescribed to 299 women at average dose of 1634 IU (SD 423.5)); Urofollitropin 75 IU amp (prescribed to 243 women at average dose of 21.3 amp (SD 7.37)); urFSH + urLH 75IU:75IU/amp (prescribed at 354 women at average dose of 23.4 amp (SD 8.8)); cetrorelix amp 0.25 mg prescribed at 264 women at average dose of 3.84 IU (SD 1.32); ganirelix amp 0.25 mg prescribed at 299 women at average dose of 4.01 mg (SD 1.32)—**Table 3**.

Table 3. Prescribed pharmacotherapy and doses for COH of IVF.

Medicine/Year	2009	2010	2011	2012	2013
Follitropinalfa					
N of women	11	1	0	25	66
Average dose in IU (SD)	3454.55 IU (SD 1203.31)	2900 (SD 0)		1171 (SD 314.16)	1643.9 (SD 465.3)
Follitropin beta IU					
N of women	111	154	25	9	33
Average dose in IU (SD)	1862.55 (SD 660.94)	1643.95 (SD 441)	1634 (SD 423.5)	1388.9 (SD 645.68)	23.4 (SD 8.8)
Urofollitropin 75 IU amp					
N of women	5	29	63	113	78
Average dose in amp (SD)	13 (SD 4.4)	18.8 (SD 7.4)	21.3 (SD 7.37)	24.21 (SD 10.23)	23.4 (SD 8.8)
urFSH + urLH 75 IU:75 IU					
N of women	42	75	69	90	77
Average dose in amp (SD)	13.93 (SD 7.38)	13.5 (SD 8.84)	25.55 (SD 16.07)	26.55 (SD 17.98)	3.75 (SD 24.1)
cetrorelix amp 0.25 mg					
N of women	4	71	102	10	126
Average dose in mg (SD)	3.75 (SD 1.63)	4.61 (SD 1.65)	3.84 (SD 1.32)	3.79 (SD 1.3)	4.9 (SD 1.9)
ganirelix amp 0.25 mg					
N of women	116	57	0	0	0
Average dose in mg (SD)	3.35 (SD 1.17)	4.01 (SD 1.32)			
Human chorion gonadotropin					
N of women	119	177	103	136	125
Average dose in IU (SD)	7231.09 (SD 1634.42)	6963.06 (SD 1038.8)	6752.52 (SD 1216.23)	7088.23 (SD 1056.22)	6660 (SD 1109.4)
Nafarelin mcg/ml					
N of women	0	8	0	0	0
Average dose in mcg (SD)		17,700 (SD 10725)			
triptorelin 0.1 mg amp					
N of women	1	38	4	17	3
Average dose in amp (SD)	2	10.26 (SD 2.55)	5.5 (SD 3.25)	4.9 (SD 2.6)	11.7 (SD 11.6)
clomiphene 50 mg/tb					
N of women	7	6	0	5	1
Average dose in tb (SD)	11.14 (SD 2.20)	7.5 (SD 2.5)		8 (SD 2.4)	5 (SD 0)
letrozole 2.5 mg/tb					
N of women	4	8	1	0	0
Average dose in tb (SD)	8.5 (SD 3.5)	8.13 (SD 2.34)	10 (SD 0)		

*urFSH—Urinary Follicular stimulating hormone; urLH—Urinary Luteinizing hormone; IU—International units; SD—standard deviation.

Human chorion gonadotropin was prescribed to 535 women at average dose of 6752.52 IU (SD 1216.23); Nafarelin mcg/ml was prescribed at 8 women at dose of 17,700 mcg (SD 10,725); triptorelinacetat 0.1 mg amp prescribed at 63 women at doses of 5.5 (SD 3.25) mg at 14 women and average dose of 7.5 mg (SD 2.5); clomiphene citrate and letrozole for 15 women at average dose of 8 mg (SD 2.4)—**Table 3**.

The average cost of pharmacotherapy is varying among the years with highest value of 1803.776 (SD—624.89) BGN in 2009.

3.3. Statistical Analysis of Variables

ANOVA analysis shows that there is a statistical significant connection among the age groups of women and reason for infertility ($p = 0.0008$). Applying t-test analysis for within group differences show that all age groups differs statistically except the group of 30 - 40 years old women ($p = 0.51$). The degree of correlation among the age groups and reason of infertility is very high ($r = 0.796$ for primary infertility and $r = 0.842$ for secondary infertility).

The age of the women is correlated with the infertility ($r = 0.854$) and their number is increasing with the age as shows the ANOVA analysis ($p = 0.0001$).

Exploring the influence of the age of women and year of therapy through ANOVA analysis revealed that there is a statistically significant differences among the cost and age groups ($p = 0.000001$), as well as in years ($p = 0.0004$). There is a high correlation among the cost and age of the women (0.823).

The changes among the cost of pharmacotherapy and women age is shown on **Table 4**. ANOVA analysis shows that there is a statistical difference among cost of pharmacotherapy during the years for primary infertility ($p = 0.001$) and cost of pharmacotherapy per age group ($p = 0.004$) among the years ($p = 0.013$) for secondary infertility. Also the cost of pharmacotherapy is correlated with the age of the women ($r = 0.696$) and with the year of admittance ($r = 0.593$).

4. Discussion

Women who use the IVF are mainly outpatients during the stimulation protocols application [3] [4] [7]. Logically the resources that they use are pharmacotherapy, physicians, nurses and other medical staff labor cost. In this condition the COH pharmacotherapy is the cost limiting factor. The data from the clinic shows that the cost is mostly influenced by the use of recombinant FSH that increases the cost almost 10 times but it was with relatively limited utilization in some particular cases. Other national studies also found that the inclusion of recombinant products increase the cost considerably [19] [20]. Labor costs were not considered in this analysis but we do not expect them to influence the total cost due to the lack of changes in IVF tariffs.

Our study shows that the main factors that influence the cost of IVF are the age of the women, and reason for infertility. The limitation of the study is the fact that limited number of women was treated with long protocol which does not allow comparing the cost for long and short pharmacotherapy protocols. This might be explained

Table 4. Cost differences among age groups per infertility reasons.

	2009	2010	2011	2012
	Primary infertility			
Below 30	1571.29	1006.91	1408.52	1325.17
30 - 35	1608.97	1580.35	1295.09	1348.07
36 - 39	2038.06	1798.68	1627.99	1739.65
Above 40	2153.12	1721.86	1779.29	2152.56
	Secondary infertility			
Below 30	1927.04	1359.44	1089.24	1130.50
30 - 35	1619.28	1557.45	1273.96	1349.01
36 - 39	2130.81	1639.85	1882.97	1739.40
Above 40	2249.06	2213.93	1514.99	1811.82

with the physicians preferences to short COH protocols with the aim to decrease the patients stay and thus to influence the price. The shorter length of stay allows more patients to visit the clinic and to benefit the IVF thus decreasing the average cost of COH pharmacotherapy. Our study confirms the preference towards the short COH protocol in contrast to other studies [14] mostly with cost reasons but physicians are trying to individualize the therapy and to increase the respond to it.

5. Conclusion

In conclusion the COH of vitro fertilization is costly and resource consuming procedure having in minds the pharmacotherapy. Age and reason of infertility influence significantly the cost of IVF, as well as the use of recombinant products. To decrease the cost physicians tend to use frequently the short COH protocol.

Acknowledgements

The study was approved by the Ethical Committee of the Medical University of Sofia. All couples fulfilled informed consent. The informed consent is mandatory and include: description of all upcoming tests and procedures; description of possible risk; side effects of COH; success rates depending on the women age.

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