

IMPACT OF DIFFERENT INFERTILITY DIAGNOSES ON THE COST OF OVARIAN HYPERSTIMULATION AND CLINICAL OUTCOMES IN IVF/ICSI CYCLES

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Abstract

The aim of this study was to analyze the impact of different infertility diagnoses on the cost of ovarian stimulation and clinical outcomes in IVF/ICSI cycles. The study was performed in specialized gynecology clinic in Bulgaria and included 640 patients undergoing IVF/ICSI cycles during the period 2016–2020. We found that there were statistically significant differences in mean controlled ovarian hyperstimulation (COH) cost for male factor, tubal factor, and unexplained infertility. The results have shown that the cost of COH statistically differs for male factor patients without live birth. In terms of IVF/ICSI outcomes, the results demonstrate that clinical pregnancies and live births depend on infertility reason. In conclusion, the cost of COH therapy depends on infertility reasons and differs for groups with achieved clinical pregnancies and live births. There was an evidence that higher cost is connected with higher birth rate and lower miscarriages but it strongly depends on infertility reasons.

Key words: in vitro fertilization, infertility, clinical pregnancy, live birth

Introduction. Infertility affects 10–15% of the general population in reproductive age in the Western countries and 9% worldwide [1]. In Europe the prevalence is 10%, followed by USA (8–15%), Australia (15.4%) and Russia (8–17.5%) [2]. Almost 45% of infertility cases are due to women reproductive disorders (female factor), 40% due to male disorders (male factor), and 15% lay down in both partners [3].

In vitro fertilization – Embryo Transfer (IVF-ET) is the most often-applied technique in clinical practice as assisted reproductive technology (ART). Controlled ovarian hyperstimulation (COH) is the first stage of most IVF/ICSI procedures. The goal of COH is optimal number of grown eggs that could lead to sufficient number of quality embryos [4].

In addition to the individual characteristics of the patients, the costs and availability of medicines are also important factors for COH. Studies reported that treatment with rFSH products leads to a significant increase in costs of COH [5,6]. A Cochrane review concluded that differences in clinical effectiveness and safety between all gonadotrophins for COH are very unsubstantial. Clinical choice of gonadotrophins should depend on availability, convenience and costs [7]. Economic evaluation of two large randomized clinical trials in UK demonstrates that higher success rate would be achieved at lower costs with cheaper gonadotrophins [8]. Analysis in Egypt showed that for every 100 000 cycles performed, additional 34 238 IVF/ICSI procedures and 4565 clinical pregnancies might be possible if COH used cheaper gonadotrophins. Expensive treatment could result in a lower number of cycles of IVF/ICSI treatment, especially if patients are paying for it [9].

We aimed to study the relation between the cost of COH protocols, different infertility diagnoses and IVF/ICSI results as clinical pregnancy and live birth rate.

Materials and methods. We conducted a prospective study at a specialized gynecology clinic in Bulgaria for the period 2016–2020. The study included 640 patients undergoing IVF/ICSI cycles. It was approved by the Ethical Committee at the Medical University, Sofia. All couples fulfilled informed consent that included: description of all tests and procedures, possible risks, side effects of COH, success rates depending on the woman's age [10]. Number of live births were also registered. The patients were stimulated with GnRH-antagonist protocol and only fresh IVF/ICSI cycles were performed. Three main GnRH-antagonist protocols were used for COH according to gonadotropins used: protocol with recombinant follicle stimulating hormone (rFSH) and urinary follicle stimulating hormone (urFSH); protocol with urFSH alone and protocol with rFSH alone. GnRH antagonist used in all protocols was cetrorelix. The choice of protocol was based on age, habitat, ovarian reserve, Body Mass Index, presence of polycystic ovary syndrome (PCOS), ovarian response to previous stimulation (if available), price of medicines.

According to cause for infertility, patients were divided into five groups:

- Male factor – the diagnosis was based on the sperm analyses performed according to the criteria of WHO.
- Tubal factor – patients with removed fallopian tubes, bilateral occlusion or stenosis of fallopian tubes.
- Endometriosis – III-IV grade AFS, diagnosed by laparoscopy, ultrasound

exam, computerized tomography (CT) scan or magnetic resonance imaging (MRI).

- Luteinized unruptured follicle syndrome (LUFs) diagnosed by ultrasound for at least three menstrual cycles.
- Unexplained infertility – four or more negative intrauterine inseminations, when there was no other reason for infertility.

Micro costing approach was used for COH cost calculation. The COH pharmacotherapy cost was calculated after multiplying the prices of individual units of medicines used from every patient by the length of the therapy. Prices of medicines were taken from the Positive Drug List in the year of observation [11]. All prices are expressed in national currency (BGN) at the exchange rate of 1 BGN = 0.51 Euro.

Statistical analysis. Descriptive statistical analysis was applied towards the patients characteristics, and cost data. Kruskal–Wallis, and frequencies analyses were used to explore the correlations and statistical significance among the analyzed variables. Statistical significance was established at $p < 0.05$.

Results. Relationship between different infertility diagnoses and cost of COH. In 32% of patients, the infertility was attributed to male factor, in 19.9% was undefined and in 48.1% was due to female disorders (Table 1).

T a b l e 1
Characteristics of the explored subgroups and COH cost

| Infertility reason | N of patients | COH cost | | | | |
|-------------------------|---------------|----------|-------------------|----------|----------|---------------------|
| | | Mean | 95% CI | SD | SEM | Normal distribution |
| Male factor | 207 | 1642.471 | 1546.608–1738.335 | 699.5712 | 48.6236 | 0.000 |
| Tubal factor | 277 | 1664.866 | 1579.013–1750.719 | 711.1473 | 43.6032 | 0.0000184 |
| Endometriosis | 19 | 1642.411 | 1282.517–2002.304 | 746.6901 | 171.3024 | 0.588 |
| LUFs | 18 | 1801.567 | 1479.804–2123.330 | 647.0354 | 152.5077 | 0.416 |
| Unexplained infertility | 119 | 1572.358 | 1444.526–1700.189 | 727.9485 | 64.5950 | 0.000000717 |

The average cost of COH was highest in patients with LUFs and lowest for patients with unexplained infertility, but without statistical significance between groups ($p = 0.5308$).

We divided patients into two subgroups – with and without clinical pregnancy achieved. The mean cost for the group with clinical pregnancy accounts for 1489.813 (SD630.5754) BGN, while for patients without clinical pregnancy it accounts for 1701.072 (SD729.5290) BGN ($p = 0.0006$).

Including also the infertility factor, we found that statistically significant are the differences in mean COH cost for male factor, tubal factor and unexplained infertility ($p = 0.0123$) (Table 2).

T a b l e 2

Number of clinical pregnancies and live birth per subgroup

Legend:

- 1 – Infertility reason
- 2 – N of patients
- 3 – N of patients without clinical pregnancies
- 4 – Mean cost of COH for patients without clinical pregnancies (SD)
- 5 – N of clinical pregnancies
- 6 – Mean cost of COH for patients with clinical pregnancies (SD)
- 7 – N of live birth (multiple pregnancies)
- 8 – Mean cost of COH for patients with live birth (SD)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|-------------------------|-----|-----|------------------------|----|------------------------|---------|------------------------|
| Male factor | 207 | 151 | 1709.594 (733.8263) | 56 | 1461.481 (564.5025) | 38 (12) | 1444.263 (519.3397) |
| Tubal factor | 277 | 200 | 1678.732 (727.3774) | 77 | 1630.830 (673.0372) | 53 (17) | 1561.633 (658.1338) |
| Endometriosis | 19 | 13 | 1731.623 (680.0837) | 6 | 1449.117 (911.9235) | 3 (1) | 1446.730 (297.1263) |
| LUFS | 18 | 12 | 1876.612 (590.0821) | 6 | 1651.477 (785.3947) | 4 (0) | 1839.670 (927.7874) |
| Unexplained infertility | 119 | 87 | 1705.400 (759.1600) | 32 | 1177.388 (437.0177) | 20 (2) | 1044.534 (285.2191) |

No differences were established dividing the patients into two subgroups – with and without live births ($p = 0.9312$). Further subdividing according to infertility reason statistically differs the cost of COH for male factor and COH cost of patients without live birth ($p = 0.0123$).

Relationship between different infertility diagnoses and clinical pregnancy. The total number of clinical pregnancies was 177 (27.8%). We found the highest clinical pregnancy rates in the group with LUFS, followed by the groups with endometriosis. The patients with tubal and male factor have equal pregnancy rate. The lowest pregnancy rate was observed in the group with unexplained infertility (Table 3).

The relationship between different infertility diagnoses on the one hand, and live births and miscarriages on the other is presented in Table 3.

Discussion. The cost of COH was lower in cases when clinical pregnancy was achieved compared with unsuccessful procedures. Probably the group with successful clinical pregnancies was with favourable characteristics in terms of infertility factor, age, etc. Our study confirmed that the reason for infertility influenced the cost of COH protocols.

The findings that COH cost did not differ between live birth and no live birth subgroups but differs when subgrouping according to infertility reason supports the necessity of such kind of subgroup analyses. In many countries, including Bulgaria, in vitro fertilization is financed by public budget and such findings

T a b l e 3

Clinical pregnancy rates, miscarriages rates and live birth rates according to infertility reason

| Characteristics | Infertility reason | | | | |
|--|--------------------------|--------------------------|-------------------------|-------------------------|--------------------------|
| | Male factor | Tubal factor | Endometriosis | LUFs | Unexplained infertility |
| <i>N</i> of patients | 207 | 277 | 19 | 18 | 119 |
| Clinical pregnancy rate per cycle (%) | 27.1 (<i>n</i> = 56) | 27.8 (<i>n</i> = 77) | 31.6 (<i>n</i> = 6) | 33.3 (<i>n</i> = 6) | 26.7 (<i>n</i> = 32) |
| - per total number of clinical pregnancies % | 31.6 | 43.5 | 3.4 | 3.4 | 18.1 |
| Miscarriages rate (%) | 32.1 (<i>n</i> = 18) | 31.2 (<i>n</i> = 24) | 50 (<i>n</i> = 3) | 33.3 (<i>n</i> = 2) | 37.5 (<i>n</i> = 12) |
| Live birth rate (%): | | | | | |
| - per cycle % | 24.2 | 26.0 | 21.1 | 22.2 | 18.5 |
| - per live birth children % | 32.9 | 47.4 | 2.6 | 2.6 | 14.5 |
| Total number of live births | 50 | 72 | 4 | 4 | 22 |
| 95% CI | 21.0–33.2 | 23.5–34.4 | 08.56–54.6 | 09.21–57.5 | 17.5–32.9 |
| Standard error (%) | 3.095 | 2.786 | 10.96 | 11.43 | 3.868 |

could benefit from the allocation of financial resources to subgroups with a high success rate and a corresponding cause of infertility.

When excluding the groups with LUFs and endometriosis our findings showed that patients with tubal factor were with higher COH cost, higher live birth rate and fewer miscarriages. Patients with unidentified infertility had lower COH cost, lower live birth rate, lower number of clinical pregnancies and higher number of miscarriages. The difference in the COH cost between the two groups was 517 BGN (258 EUR). We consider these findings the original contribution of this work. We found no other pharmacoeconomic evaluations or cost analysis of COH and its relation to different infertility reasons.

Our results demonstrated that the highest frequency of clinical pregnancies was in the group of patients with LUFs, followed by those with endometriosis, but those were very limited number of patients. The patients with tubal and male factor had similar pregnancy rate. We observed the lowest pregnancy rate in the group with unexplained infertility. Our results are similar to those of other studies, that found that the women with endometriosis had a higher or similar pregnancy rate than women with tubal, male [12, 13] and unexplained infertility [14].

Contrary to our findings, studies show that patients with endometriosis-related infertility have significantly reduced levels of clinical pregnancy – almost half of that of women with other indications for IVF [15, 16]. A number of studies have found a higher incidence of miscarriages in patients with endometriosis than in those with other infertility factors [12, 13, 16]. We achieved similar results, reaching 50% of miscarriages in the group with endometriosis. We suppose these

results could be attributed to poor ovary/embryo quality or lower implantation rates in patients with endometriosis.

We found the highest live birth rate in the group with tubal factor and the lowest in the group of unidentified infertility, unlike another study, that reported equally live birth rates to tubal factor and to unexplained infertility [16]. Yet another study showed that there was no significant difference in live birth rates between endometriosis, tubal and male infertility [12].

Conclusion. The cost of COH therapy depends on infertility reasons and differs for groups with achieved clinical pregnancies and live birth children. In general, there is evidence that higher costs are associated with higher birth rates and lower miscarriages, but this is highly dependent on the causes of infertility. Clinical outcomes also depend on the causes of infertility.

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