ORIGINAL RESEARCH

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Recombinant FSH Versus Highly Purified Urinary FSH in Patients with Polycystic Ovary Syndrome Undergoing ICSI Cycles: A Prospective Randomized Study

ICSI Uygulanan Polikistik Over Sendromlu Hastalarda Rekombinant FSH ve Yüksek Saflaştırılmış Üriner FSH'nin Etkinliklerinin Karşılaştırılması

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Abstract

Objective: To compare efficacy and safety of recombinant follicule stimulating hormone (r-FSH) and highly purified urinary FSH (HP-uFSH) in polycystic ovary syndrome (PCOS) patients undergoing intracytoplasmic sperm injection (ICSI).

Method: This was a prospective randomized study conducted at Kocaeli University Faculty of Medicine, Department of Obstetrics and Gynecology, in vitro fertizilization (IVF) Unit. A total of 91 PCOS patients undergoing ICSI were randomly assigned to receive either r-FSH (n=46) or HP-uFSH (n=45) with a gonadotropin releasing hormone (GnRH) antagonist protocol. The main outcome measures were the number of mature oocytes retrieved, embryo quality, pregnancy rates, implantation rates.

Results: The number of mature oocytes retrieved, fertilization rates, the number of cryopreserved embryos were significantly higher in r-FSH group (p=0.024, p=0.023, p=0.026 respectively) while the total dose of FSH used was significantly lower in the same group (p=0.023). Pregnancy rates, clinical pregnancy rates were higher in r-FSH group although not

Öz

Amaç: ICSI uygulanan PCOS hastalarında rekombinant FSH (r-FSH) ve yüksek oranda saflaştırılmış üriner FSH'nin (HP-uFSH) etkinliğini ve güvenliğini karşılaştırmaktır.

Yöntem: Kocaeli Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı Tüp Bebek Ünitesi'nde yürütülen prospektif randomize bir çalışmadır. ICSI uygulanan toplam 91 PCOS hastası, bir GnRH antagonist protokolü ile r-FSH (n=46) ve HP-uFSH (n=45) almak üzere rastgele belirlendi. Ana sonuç ölçütleri; alınan olgun oosit sayısı, embriyo kalitesi, gebelik oranları, implantasyon oranlarıydı.

Bulgular: Alınan olgun oosit sayısı, döllenme oranları, dondurularak saklanan embriyo sayısı r-FSH grubunda anlamlı olarak daha yüksek (sırasıyla p=0,024, p=0,023, p=0,026), aynı grupta kullanılan toplam FSH dozu ise anlamlı olarak daha düşüktü (p=0,023). Gebelik oranları, klinik gebelik oranları r-FSH grubunda istatistiksel olarak anlamlı olmamakla birlikte daha yüksekti (sırasıyla %52,2'ye karşı %35,6, p=0,11, %37'ye karşı %28,9, p=0,41). Klinik gebelik başına genel tedavi maliyetleri, r-FSH

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statistically significant (52.2% versus 35.6%, p=0.11, 37% versus 28.9%, p=0.41 respectively). Overall therapy costs per clinical pregnancy were associated with a 9.94% increase in r-FSH group whereas costs per pregnancy were not different between groups.

Conclusion: r-FSH is superior than HP-uFSH in PCOS regarding fertilization rates, the number of mature oocytes retrieved and cryopreserved embryos, pregnancy rates although overall therapy costs per clinical pregnancy are higher.

Keywords: ART, HP-uFSH, PCOS, rec-FSH

grubunda %9,94'lük bir artışla ilişkilendirilirken, gebelik başına maliyetler gruplar arasında farklı değildi.

Sonuç: r-FSH, PCOS'de fertilizasyon oranları, alınan olgun oosit sayısı ve dondurularak saklanan embriyolar, gebelik oranları açısından HP-uFSH'den üstündür, ancak klinik gebelik başına genel tedavi maliyetleri daha yüksektir.

Anahtar kelimeler: ART, HP-uFSH, PCOS, rec-FSH

Introduction

Polycystic ovary syndrome is a challenging endocrine disorder clinically characterized by irregular menses, clinical/biochemical hyperandrogenemia, polycystic appearance of the ovaries on ultrasonography, and infertility (1). Pathophysiology still remains to be elucidated with a complex clinical background involving insulin resistance, hyperlipidemia, and a predisposition to certain malignancies.

Ovarian stimulation in infertile PCOS subjects is mostly complicated by under- or over- stimulation attributed to naturally narrow spectrum of follicular development in this group of patients (2).

Controlled ovarian stimulation (COH) as a primary part of IVF-ET is achieved by the implementation of exogenous gonadotropins in order to induce follicular recruitment and oocyte yield. FSH of different origins have been applied in clinical practice up to date. Urine derived gonadotropins having varying amounts of FSH together with urinary proteins have been available for years along with the drawbacks of requiring vast quantities of urine from multiple donors thus leading to discontinuity of the supply and batch-to-batch inconsistency (3). Recent advent of recombinant DNA technology using Chinese hamster ovary cells has provided recombinant FSH preparations with improved purity, higher specific activity, greater batch-to-batch consistency and independence of urine collection ensuring a constant FSH supply along with potentially higher medical costs (4,5). High purity is related to decreased immunogenicity thus conferring safety and tolerability (3,6).

Several comparative clinical trials and a meta-analysis have suggested better results with r-FSH in comparison with u-FSH during ART cycles in terms of pregnancy rates, oocyte quality and ovarian hyperstimulation syndrome (OHSS) whereas some others have reported contradicting conclusions in favor of u-FSH (7-15).

In the present study, we aimed to compare the efficacy and safety of rr-FSH (Follitropin α) and HP-uFSH (urofollitropin) in patients with PCOS, undergoing ICSI cycles.

Materials and Methods

A prospective randomized study was conducted at Kocaeli University, IVF Unit with a total of 91 PCOS patients undergoing ICSI. Written consents were obtained from all participants.

PCOS diagnosis was made according to the criteria of the Rotterdam ESHRE-ASRM-sponsored PCOS consensus workshop group (2004) when two out of three criteria were present: Oligomenorrhea (fewer than six menstrual periods in the preceding year) and/or anovulation; clinical and/or biochemical signs of hyperandrogenism; presence of ≥12 follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume (>10 mL) (16). Clinical evidence of hyperandrogenism was a Ferriman-Gallwey score (FG) of ≥8 indicating hirsutism (excessive growth of hair on androgen dependent body sites) and/or acne (17). Biochemical hyperandrogenism was defined as total testosterone and free androgen index >95th percentile for the control group studied, which were 3.8 nmol/L and 7% respectively. Any other etiologic factor leading to hirsutism and/or metabolic impairment such as type II diabetes mellitus, hyperprolactinemia, hypogonadotropic hypogonadism, thyroid disorder, congenital adrenal hyperplasia, androgen-secreting tumors and Cushing's syndrome, acromegaly and pharmacologic remedies were excluded by appropriate laboratory work-up. The subjects received no medications including oral contraceptives, antiandrogens or any other agent affective on carbohydrate metabolism for the last 3 months.

PCOS cases with primary infertility, age of 18-39 years, undergoing their first ART trial, without severe male factor, endometriosis and tubal factor, with a normal uterine cavity, in good medical and mental health condition, with a basal FSH level <10 IU/L, estradiol level <80 pg/mL and prolactin level <25 ng/mL were included in the study.

Exclusion criteria were the presence of uterine fibroids, endometriosis, endocrine, metabolic and any other medical disease, a body mass index (BMI) of >35 kg/m^2, ovaries inaccessible for oocyte retrieval, persistent ovarian cysts >15 mm, hydrosalpinx if it had not been surgically removed or ligated previously, any contraindication for pregnancy, any genital bleeding of unknown origin, neoplasia, impaired hepatic or renal function, any concomitant medication that might interfere study evaluation, alcohol or drug abuse, history of chemotherapy or radiotherapy, hypersensitivity to any preparation used during the study.

Power analysis of the study showed that when effect size was 0.3, a total of 88 patients were required to be randomized at alpha=0.05 and power of 80%. All the subjects were managed based on accepted principles of infertility practice. Standardized regimens for controlled ovarian hyperstimulation (COH), pituitary down regulation and ovulation triggering were instituted. Ninety-one PCOS subjects were randomized in order to receive GnRH antagonist protocol with r-FSH 225 IU/day (Gonal-f®,Serono,Switzerland) (n=46) and GnRH antagonist protocol with HP-uFSH 225 IU/day (Fostimon®, IBSA, Institut BiochemiqueSA, Lugano, Switzerland) (n=45). Randomization was done by means of a computer-generated randomization table and allocations were placed in consecutively numbered and sealed, opaque envelopes. Individualized step-down or step-up protocols were instituted and serial monitoring of ovarian response was assessed by ultrasonographic folliculometry and serum estradiol (E_2) assays. GnRH antagonist (Cetrotide® 0.25 mg, Serono, Switzerland) injections were started in a multidose flexible protocol as 14 mm follicle was determined by ultrasonography (USG). A single dose of 250 mcg human corionic gondotropin (hCG) (Ovitrelle®, Serono, Switzerland) was administered subcutaneously to trigger ovulation when 3 or more follicles were measured to be >17 mm and serum E_2 levels were increased approximately to 300-500 pg/mL per follicle larger than 17 mm. Transvaginal ultrasound guided oocyte retrieval under conscious sedation was performed 36 hours following hCG injection. Fertilization was assessed 17-18 hours after retrieval. One or two normally fertilized oocytes with the highest pronuclear score and the morphologic grade were considered for embryo transfer. Cleavage stage embryo transfers (in most cases 2 embryos) were carried out on day 3 or 5 under ultrasound guidance. Surplus embryos were cryopreserved. The luteal phase was daily supported by 8% progesterone gel (Crinone® 8% gel, Serono, Switzerland) initially for 14 days starting on oocyte retrieval day. A serum hCG pregnancy test was ordered in 12 days following embryo transfer.

Patient and cycle parameters were recorded, i.e. age, infertility etiology, infertility duration, BMI, baseline hormonal assessment of ovarian reserve (baseline FSH and E_2), IVF cycle stimulation protocol, duration of stimulation (days), total FSH amount (IU) for COH, number of follicles >15 mm on day of hCG, serum E_2 levels on day of hCG, serum estradiol levels following hCG injection, hCG day, day of embryo transfer, serum progesterone levels on hCG day, number of oocytes retrieved, number of mature oocytes, fertilization rates, quality of oocytes and embryos, number of transferred embryos, implantation rates and clinical pregnancy (CP) rates (CP-defined as intrauterine gestational sac visible on transvaginal ultrasound). Those variables were compared between two study groups. Cycle characteristics, embryology parameters and IVF outcome were defined. The primary outcome measures were the number of mature oocytes retrieved, embryo quality, pregnancy rates and implantation rates. Secondary outcome measures were duration of stimulation, total dose of gonadotrophins used, fertilization rates, embryo cleavage rates, cancellation rates and OHSS and multiple pregnancy rates and overall therapy costs.

Statistical Analysis

The collected data were processed using SPSS 11.0 (Statistical package for social sciences) software (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was analyzed by the Shapiro-Wilk normality tests. The continuous variables were expressed as mean ± standard deviation and compared by using the Student's t-test. Categorical data were expressed as numbers (percentages) and compared by X^2-test or Fisher's Exact test where appropriate. $p<0.05$ was considered to be statistically significant.

Results

Ninety-one PCOS subjects with an age range of 18-39 years were randomized in order to receive GnRH antagonist protocol with r-FSH 225 IU/day (n=46) and GnRH antagonist protocol with HP-uFSH 225 IU/day (n=45). Demographic data of the patients are shown in Table 1. Dysmenorrhea was significantly more common in the HP-uFSH group (p=0.043).

Hormonal data including (FSH, LH, estradiol, prolactin, TSH, free T_3 and free T_4) and fasting glucose, HbA1c levels did not differ significantly.

Table 1. Demographic data of the patients

Demographic data	r-FSH (n=46) (%, n)	HP- uFSH (n=45) (%, n)	p
Age (years)	28.2	29.8	NS
BMI (kg/m²)	24.5	24.4	NS
Duration of infertility (months)	76	89.9	NS
Hirsutism	67.4% (31)	53.3% (24)	NS
Galactorrhea	4.3% (2)	6.8% (3)	NS
Menses			
Regular	19.6% (9)	17.8% (8)	NS
Oligomenorrhea	47.8% (22)	37.8% (17)	NS
Hypomenorrhea	30.4% (14)	35.6% (16)	NS
Amenorrhea	2.2% (1)	4.4% (2)	NS
Acne	56.5% (26)	66.7% (30)	NS
Dysmenorrhea	28.3% (13)	48.9% (22)	0.043*
Dyspareunia	23.9% (11)	33.3% (15)	NS
Diabetes mellitus	6.5% (3)	0% (0)	NS
Thyroid disease	8.7% (4)	6.7% (3)	NS
Smoking	13% (6)	17.8% (8)	NS
Age of the partner	31.7	32.7	NS
Previous therapies			
CC	64% (9)	36% (5)	NS
CC+IUI	43% (9)	57% (12)	NS
Gonadotropin	50% (2)	50% (2)	NS
Gonadotropin + IUI	40% (13)	60% (20)	NS

BMI: Body mass index, CC: Clomiphene citrate, IUI: Intrauterine insemination, NS: Non-significant, *p<0.05 statistically significant

Table 2. Cycle characteristics of the patients

	r-FSH (n=46) (%, n)	HP u-FSH (n=45) (%, n)	p
Duration of stimulation (days)	9.8	9.9	NS
Total FSH dose used (IU)	2.494	2.872	NS
The first day of GnRH antagonist administration	8.2	8.2	NS
Duration of antagonist treatment (days)	4	4.1	NS
Coasting	6.5% (3)	0% (0)	NS
Folliculometry			
-Number of AF	21.8	20.1	NS
-Number of follicles 10-14 mm on hCG day	4.6	4.5	NS
	9.3	6.6	0.0001*
-Number of follicles 14-18 mm on hCG day	3.1	3.1	NS
-Number of follicles ≥18 mm on hCG day			
Estradiol level on day 6-7 (pg/mL)	1.212	1.159	NS
Estradiol level on hCG day (pg/mL)	2.590	2.416	NS
Basal endometrial thickness (mm)	5.06	4.1	NS
Endometrial thickness on hCG day (mm)	10.3	10.3	NS
Endometrial thickness on OPU day (mm)	10.7	10.7	NS
Endometrial thickness on transfer day (mm)	10.9	11.1	NS
hCG day	11.4	11.5	NS
OHSS	6.52% (3)	6.66% (3)	NS

OPU: Oocyte pick up, FSH: Follicle stimulating hormone, GnRH: Gonadotropin releasing hormone, AF: Antral follicle, OHSS: Ovarian hyperstimulation syndrome, NS: Non-significant, *p<0.05 statistically significant

Cycle characteristics and embryology data are demonstrated in Table 2 and Table 3, respectively. Number of follicles 14-18 mm on hCG day, number of oocytes retrieved, number of metaphase II oocytes, number of fertilized oocytes on day 1, number of cleaved embryos on day 2, and number of cryopreserved embryos were significantly higher in the r-FSH group (p<0.001, p=0.002, p=0.024, p=0.03, p=0.027, p=0.002, respectively).

OHSS complicated the cycles in 3 patients in each group. Only one case of the HP-uFSH group was moderate OHSS and was required to be hospitalized. Coasting was needed in 3 cases in the r-FSH group whereas no coasting was done in the HP-uFSH group. In 2 patients of the r-FSH group (due to no cleavage in 1 case and asynchronization in the other one) and in 6 patients of the HP-uFSH group (due to no fertilization in 3 cases, premature ovulation in 1 patient, asynchronization in 1 case and no cleavage in another one), embryo transfer was cancelled. ICSI outcomes of the groups are shown in Figure 1 and Table 4.

Fertilization rates (72% versus 63%), pregnancy rates [52.2% (24) versus 35.6% (16)], biochemical pregnancy rates [13.6% (6) versus 7.7% (3)], and CP rates [37% (17) versus 28.9% (13)] were found to be higher in the r-FSH group whereas multiple pregnancy rates [17.9% (7) versus 15.9% (7)] and implantation rates (21.3% versus 19.2%) were higher in the HP-uFSH group although none of the p-values demonstrated statistical significance.

Discussion

Recent advent of recombinant DNA technology has provided an alternative agent of ovarian stimulation to urine derived FSH preparations which are considered to be an important innovation in endocrine research area. In spite of several comparative studies which contribute to the growing body of evidence regarding this issue, which of the agents should be preferred for ovulation stimulation in IUI and ART cycles still remains to be clarified. Even the meta-analyses appear to suggest contradictory results.

Table 3. Embryology data of the patients

	r-FSH (n=44) (%, n)	HP u-FSH (n=39) (%, n)	p
Number of oocytes retrieved	19.1	12.5	0.002*
The rate of metaphase I oocytes	3.82	2.09	0.03*
The rate of metaphase II oocytes	13.9	9.7	0.024*
The rate of GV	2.3	1.6	NS
Number of good quality embryos (G1+G2)	2.7	3.0	NS
Number of G1 embryos (G1)	1.8	1.8	NS
Number of fertilized oocytes on day 1 (2 pn)	9.9	7.0	0.03*
Number of cleaved embryos on day 2	9.7	6.7	0.027*
The rate of embryo transfer	3.0 (n=44)	3.1 (n=39)	NS
Day of embryo transfer			
-Day 2 transfers	15.9% (7)	20.5% (8)	NS
-Day 3 transfers	63.6% (28)	71.8% (28)	NS
-Blastocyst transfer	20.5% (9)	7.7% (3)	NS
Cancelled transfer	25% (2)	75% (6)	NS
Easy transfer	86.4% (38)	97.4% (38)	NS
Cryopreserved embryos			
-Number of patients	22	9	0.003*
-Number of embryos	121	23	0.002*

GV: Germinal vesicle, G1: Grade 1, G2: Grade 2, NS: Non-significant, *p<0.05 statistically significant

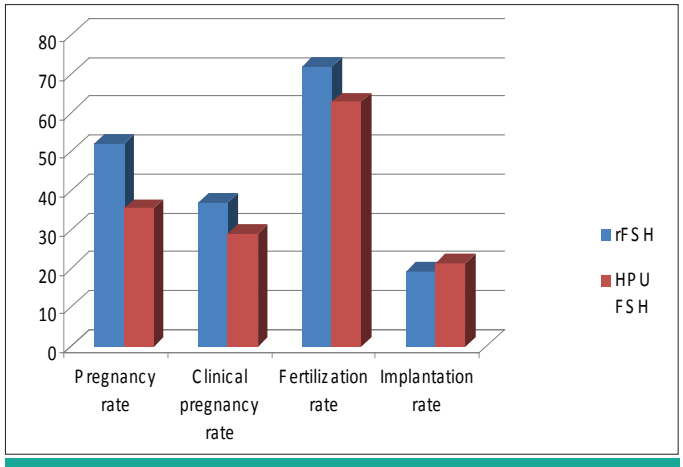

Figure 1. ICSI outcome of the patients

The meta-analysis of Daya and Gunby (7) pooling data of 12 randomized controlled studies compared treatment cycles of IVF/ICSI allocating 1.556 and 1.319 patients to r-FSH and u-FSH respectively in terms of cycle characteristics and IVF/ICSI outcome. Odds ratio for CP rate/cycle was 1.2 (95% confidence interval, 1.02-1.42, p<0.03) in favor of r-FSH thus concluding a significantly higher pregnancy rate with r-FSH in IVF/ICSI cycles (7). However, a Cochrane review of 4 randomized controlled trials comparing r-FSH and u-FSH in IUI cycles of PCOS patients demonstrated that there was no sufficient evidence to recommend one of those agents over the other (18).

Table 4. ICSI outcome of the patients

	r-FSH (n=44)	HP u-FSH (n=39)	p
Pregnancy rate	52.2% (24)	35.6% (16)	NS
Clinical pregnancy rate	37% (17)	28.9% (13)	NS
Biochemical pregnancy rate	13.6% (6)	7.7% (3)	NS
Multiple pregnancy rate	15.9% (7)	17.9% (7)	NS
Fertilization rate	72%	63%	NS
Implantation rate	19.2%	21.3%	NS

*p<0.05 statistically significant, NS: Non-significant

Several investigators comparing r-FSH and u-FSH in ART cycles in terms of efficacy and safety suggested higher efficiency in inducing multifollicular development with greater numbers of oocytes retrieved and embryos, higher embryo quality and decreased amount of total FSH used, shorter duration of stimulation in addition to higher rates of cryopreservation and pregnancy rates with the use of r-FSH (8-13). On the other hand, a group of other researchers have reported contradictory results. Mohamed et al. (14) compared those two preparations in older women undergoing ART cycles and found that oocyte retrieval and pregnancy rates did not differ significantly between groups and u-FSH appeared to be more cost-effective since the total amount of u-FSH used was lower than r-FSH in treatment cycles.

The results of clinical trials comparing r-FSH and u-FSH in IUI cycles also appeared to be controversial as they were in ART cycles. Some of them concluded that u-FSH was not less efficacious and safer than r-FSH in terms of ovulation rates, cycle cancellation rates, duration of stimulation, total dose of FSH used, OHSS and multiple pregnancy rates, pregnancy rates whereas the others reported better results with r-FSH in IUI cycles of patients with unexplained infertility and PCOS (1,19-22).

Another important issue to be considered with respect to the comparison of r-FSH and u-FSH is cost-effectiveness. Daya et al. (23) from UK, Silverberg et al. (24) from USA, and Romeu et al. (4) from Spain used Markov modelling to compare those two preparations in terms of therapy costs

and all concluded that r-FSH was found to be more cost-effective in their health care systems due to higher efficacy, decreased overall gonadotropin consumption, higher rates of cryopreservation, and need for fewer cycles to get one pregnancy. Only one group of researchers using the same Markov model found u-FSH to be more cost-effective (25). On the other hand, Revelli et al. (26) reported lower final economical costs per delivered baby with r-FSH since lower FSH dose used and slightly higher effectiveness of r-FSH in terms of delivered babies compensated for the higher costs per IU.

This great heterogeneity regarding the results of studies comparing r-FSH and u-FSH in either ART or IUI cycles may be attributed to different isoform profiles of FSH. Variable carbohydrate chains in size and structure, levels of sialylation and sulfation of FSH isoforms lead to significantly different ability of receptor binding and metabolic clearance thus causing variable *in vivo* biological activities (19). r-FSH contains higher proportions of less acidic forms whereas u-FSH presents a higher proportion of acidic forms. Less acidic isoforms are shown to bind to FSH receptors with a higher affinity. They are also associated with better proliferation of granulosa cells and estradiol production with faster circulatory clearance and a shorter half-life while acidic ones are more slowly cleared from the circulation (6).

Controversies regarding the efficacy and safety of different FSH preparations may be attributed to high purity and batch-to-batch consistency of r-FSH, varying patient selection criteria, pituitary suppression protocols, gonadotropin dose, administration route, and study design in addition to this varying isoform profile (14).

To the best of our knowledge, our study is one of the few prospective randomized studies to compare r-FSH and HP-uFSH in PCOS patients undergoing IVF/ICSI cycles (2). Aboulghar et al. (2) concluded that total dose of FSH used, duration of stimulation, number of retrieved oocytes, number of mature oocytes, number of transferred embryos, and ongoing pregnancy rates did not differ significantly. There were more fertilized oocytes, a higher fertilization rate, more top quality embryos, and more cryopreserved embryos in the HP-uFSH group. In our study, number of mature oocytes retrieved, fertilization rates, and number of cryopreserved embryos were found to be significantly higher in the r-FSH group while the total dose of FSH used was significantly lower in the same group. Pregnancy rates and CP rates were found to be higher in the r-FSH group although not statistically significant. Overall therapy costs per CP were associated with a 9.94% increase in the r-FSH group whereas costs per pregnancy were not different between groups. The duration of stimulation, the number of good quality embryos, implantation rates, OHSS, and multiple pregnancy rates did not differ significantly between two groups.

Conclusion

r-FSH was found to be more effective than HP-uFSH in PCOS patients undergoing ART cycles as it provides higher fertilization rates, higher numbers of collected mature oocytes and cryopreserved embryos, and lower FSH consumption. Pregnancy rates and CP rates were shown to be numerically higher with r-FSH. Although it is not statistically significant, it can be significant if the number of participants is increased. Higher overall therapy costs per CP with r-FSH should be considered as a major drawback. Further studies of cost-effectiveness using robust modelling procedures appropriate for each country's own health service systems and efficacy and safety trials involving a higher number of patients are required in order to get well-defined conclusions regarding this controversial subject.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethical Committee of Kocaeli University (approval date: 30.01.2009).

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.A., E.Ç., Concept: Ö.A., E.Ç., S.Ö.Ö.., E.D., Design: Y.C., B.A., E.Ç., S.Ö.Ö., Data Collection or Processing: S.Ö.Ö., Y.Ç., Analysis or Interpretation: E.D., Y.Ç., Literature Search: Y.C., B.A., E.D., Writing: Ö.A., Y.C., B.A., Y.Ç.

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