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Original Research

hCG Administration in Luteal Rescue: Intracavitary or Subcutaneously in Agonist Induced Ovulation in IVF Cycles

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Abstract

Background: Ovarian hyperstimulation syndrome (OHSS) is characterized by collection of fluid in third spaces in *in vitro* fertilization (IVF) cycles and can result in the cancellation of the cycle and be fatal in 3 women out of 100,000. The aim of this study is to compare the admission of human chorionic gonadotropin (hCG) subcutaneously versus intracavitary during ovum pick-up (OPU) in agonist induced ovulation in IVF cycles in terms of pregnancy outcomes. **Methods**: This study was carried out in Kocaeli University Faculty of Medicine, Department of Obstetrics and Gynecology Assisted Reproductive Techniques Clinic as a retrospective study. 157 patients who underwent IVF treatment between January 2018 and February 2020, with $\geq$25 follicles detected in ultrasound and 1 mg of triptorelin acetate was administered for ovulation trigger, and 36 hours later of whom $\leq$20 oocytes were obtained in OPU were enrolled in this study. 109 patients who were administered 1500 IU of hCG subcutaneously belonged to Group 1, and 1500 IU hCG was administered intracavitary to 48 patients as Group 2. **Results**: Infertility causes, and characteristics of both groups were similar. Number of retrieved oocytes, Metaphase 2 (MII) oocytes and fertilization rates were similar in both groups. Implantation rate per embryo transferred was higher in the intracavitary group (p = 0.01). There was no significant difference for pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, livebirth rate and OHSS frequency between both groups. Twin pregnancy rate was significantly higher in the intracavitary group. **Conclusions**: Administration of 1500 IU hCG intracavitary at the time of OPU is associated with improved implantation rates when compared to subcutaneous hCG administration without a significant raise in OHSS occurrence. Prospective, randomized studies with bigger patient cohort are needed.

Keywords: *in vitro* fertilization; agonist trigger; luteal rescue; intracavitary hCG; subcutaneous hCG

1. Introduction

Merely 17% of the infertile couples are seeking hospital care amongst 48,500,000 couples that are estimated to be affected on global scale [1,2]. Pregnancy rates are increased in parallel to the number of follicles developed by controlled ovarian hyperstimulation (COH) and, of oocytes finally picked-up (OPU). While gonadotropin releasing hormone agonist (GnRHa) administration to trigger ovulation and mature follicles and, oocytes prior to OPU are getting more popular, in 75% of cycles, human chorionic gonadotropin (hCG) administration is still being preferred [3,4].

hCG is administered subcutaneously at a dose of 6000 units for normal weighting patients, and at 9000 to 12,000 units in obese and morbidly obese patients respectively. Together with its being the mainstay practice at *in vitro* fertilization clinics, it is not uncommon to encounter ovarian hyperstimulation syndrome (OHSS) characterized by collection of fluid in third spaces in lean or polycystic ovary syndrome (PCOS) patients with number of follicles more than 25, and with serum estradiol levels higher than 5000 pg/mL. When OHSS is fully developed, it leads to cycle and, embryo transfer cancelation, embryo freezing and, hospital admission in 9–38% of patients. It may be fatal in 3 women in 100,000 [5].

hCG is shown to support the first stage of implantation by increasing immune tolerance via inducing T- cell apoptosis and regulating the proteins that take part in implantation [6,7]. The studies have also showed that administering hCG into uterine cavity helped the maturation of endometrial secretions and increased the cell proliferation and, migration [8,9].

The best known and, applied way to avoid OHSS is to trigger ovulation by GnRHa instead of hCG. If >25 follicles develop in COH cases with antagonist protocol, OPU is performed 36 hours after the ovulation triggering is achieved by triptorelin acetate. If >20 oocytes are picked up, all oocytes are frozen. However, if <20 oocytes are retrieved, 1500 unit of hCG is administered subcutaneously or intracavitary, and then embryo transfer is done.

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In antagonist cycles, OPU is done in 36 hours after triggering with 1 mg triptorelin acetate or leuprolide acetate in the same way as done with hCG. This method is believed to be safe to avoid OHSS. However, it results in very low pregnancy rates [10]. The main reason for his failure is thought to be related to quick weaning of luteinizing hormone (LH) peak effect created by GnRHa administration, and deterioration of luteal phase functions. At this stage 1500 units of hCG is administered either subcutaneously or intracavitary to support luteal phase and, increase pregnancy rates without increasing OHSS risk significantly [11]. This method is named as "luteal rescue".

In our study, we aimed to compare the administration of hCG (1500 IU), either intracavitary or subcutaneously in cycles triggered by triptorelin acetate in terms of pregnancy outcomes and OHSS risk retrospectively.

2. Materials and Methods

This study is conducted retrospectively on the data obtained from the *in vitro* fertilization (IVF) patients administered to Assisted Reproductive Technologies Clinic of Obstetrics of Gynecology Department, at Kocaeli Medicine Faculty, Kocaeli University, between the dates January 2018 and February 2020, after obtaining ethical approval from Non-invasive Clinical Studies Ethical Committee of Kocaeli University, with the number of KÜ GOKAEK 2020/175.

The data of 161 patients, who yielded $<$20 oocytes at OPU after stimulation with follitropin-alpha (Gonal-F 450 IU, Merck, Serono, Italy), and 25 or more follicles (larger than 12 mm) bearing on both ovaries and triggered by 1 mg Triptorelin Acetate (Gonapeptyl 0.1 mg, Ferring, Kiel, Germany) were retrieved. Data of 4 patients were excluded from the study either if no pregnancy outcome data was found in the data base or could not be reached by telephone. 109 patients out of 157 who were administered 1500 IU of recombinant human chorionic gonadotropin (r-hCG) (Ovitrelle, 250 μg, Merck Serono, Darmstadt, Germany) subcutaneously at the time of OPU, were named as Group 1. Forty-eight patients who received hCG intracavitary were named as Group 2. By using a micropipette, 0.115 mL of the Ovitrelle solution equaling to a dose of 1500 IU choriogonadotropin alfa was obtained. Besides choriogonadotropin-alfa, Ovitrelle contains mannitol, methionine, poloxamer 188, diluted phosphoric acid and sodium hydroxide. It's not expected to have a toxic effect on the embryo since Ovitrelle was administered 3 to 5 days prior to the embryo transfer and the amount of the excipients is small. hCG administration is done by an embryo transfer catheter (FullEcho® Pro, Laboratoire CCD, Paris, France). In our clinic intracavitary hCG administration is preferred to the patients who were examined by ultrasound and deemed as with unfavorable cervix that may interfere embryo transfer, or to those with prior difficult transfer story in order to simulate a mock transfer before actual transfer is done. The decision whether to receive hCG intracavitary or not is let to be made by the patient herself. The pregnancy results of these two groups were compared in the current study.

Luteal phase support was given to all patients with 6 mg Estradiol Hemihydrate (Estrofem, 2 mg, Novo Nordisc, Istanbul, Turkey) orally and, 180 mg natural progesterone gel (Crinone 8%, Merc, Hertfordshire, UK) intravaginally. Embryo transfer is done at 3rd or 5th days according to their development status, and one or two embryos were transferred. The decision whether to transfer one or two embryos was done according to the age of patient, and to the number how many times she tried before. At 12th day after transfer, beta-hCG levels were obtained. It is regarded as positive if the result was $>$20 mIU/mL. Clinical pregnancy rates were obtained by observing fetal cardiac activity during ultrasound examination done at 6th week after last menstrual period to those with positive pregnancy test results. Ongoing pregnancy rates were collected if the pregnancy continued after 12th week. Fertilization rates were calculated by dividing fertilized oocyte number with the sum of two pronuclei (2PN) and pronuclei (PN) oocyte numbers. Implantation rate was calculated by dividing the number of gestational sacs observed during transvaginal ultrasound examination at 6th week after last menstrual period, by the number of transferred embryos.

Primary outcome measures were planned as difference in levels of beta-hCG, clinical pregnancy rates, ongoing pregnancy rates and, live birth rates between Group 1 and 2. Secondary outcome measure was planned as difference in severe or critical OHSS rates between groups.

Statistical analysis was done by using IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) software package. Normal distribution was evaluated by *Shapiro-Wilk* Test. Numerical variables that showed normal distribution was shown as $\pm$ standard deviation, whereas numeric variables that are not normally distributed were shown in median (25–75 percentile) and, categorical variables were represented in frequency (%). The difference between groups were tested by independent group *t-test* for normally distributed numerical variables, and by *Mann-Whitney-U* test for numerical variables that are not normally distributed, and, by *Yates and Monte Carlo Chi-Square* test for categorical variables. $p < 0.05$ was regarded as statistically significant for two sided hypotheses.

3. Results

The age, body mass index (BMI), pretreatment basal follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol (E2), thyroid-stimulating hormone (TSH) and, Anti-Mullerian hormone (AMH) levels were similar in both groups as shown in Table 1.

Most frequent infertility reason was anovulation as diagnosed in 71 (45.2%) patients. Other reasons were male factor, unexplained infertility, bilateral tubal blockage. In

Table 1. Characteristic features of Group 1 and Group 2.

	Group 1 (n = 109)	Group 2 (n = 48)	*p* value
Age (year) [a]	30 (22–40)	29 (23–37)	0.125
Body Mass Index (BMI) (kg/m^2) [b]	26.82 ± 6.14	26.15 ± 5.71	0.520
Basal FSH (mIU/mL)[a]	6.80 (2.04–10.75)	6.70 (1.46–12.30)	0.935
Basal LH (IU/L)[a]	5.70 (1.06–23.40)	6.60 (0.37–17.20)	0.979
Basal E2 (pg/mL)[a]	49 (10–823)	51 (10–211)	0.670
Basal TSH (mIU/L) [a]	1.95 (0.34–6.24)	1.58 (0.17–7.24)	0.241
Basal AMH (ng/mL) [a]	5.73 (1.20– 21.70)	5.82 (1–19)	0.612

Mann Whitney U Test was used. *p* value for statistical significance <0.05. [a]Data presented as mean (minumun–maximum). [b]Data presented as mean ± SD; FSH, Follicle-stimulating hormone; LH, Luteinizing hormone; E2, Oestradiol; TSH, Thyroid-stimulating hormone; AMH, Anti-Mullerian hormone.

Table 2. Distribution of the causes of infertility by groups.

	Group 1	Group 2	*p* value
Anovulation	48 (44%)	23 (47.9%)	
Male factor	34 (31.2%)	13 (27.1%)	
Unexplained Infertility	20 (18.4%)	9 (18.8%)	0.657
Bilateral tubal occlusion	7 (6.4%)	3 (6.3%)	
More than one reason	13 (8.28%)	8 (5.09%)	

Analyzed with the Pearson Chi-square Test. *p* value for statistical significance <0.05.

21 patients (13.3%) there were more than one factor involved. When infertility causes were compared, there was no any statistical difference between the groups ($p = 0.657$) (Table 2).

Other treatment characteristics were not different in both groups such as duration of recombinant follicle-stimulating hormone (rFSH) application, total rFSH doses, antagonist application duration, serum E2 and, progesterone levels and endometrial thickness measurements via transvaginal ultrasound examination at the hCG day when OPU was performed (Table 3).

When groups were assessed according to OPU and, fertilization characteristics, there was no any statistically significant difference in total oocyte numbers in both groups ($p = 0.620$) (14 *vs* 16) (Group 1 and 2 respectively). Metaphase 1 (MI) and Metaphase 2 (MII) oocyte numbers were also similar in both groups ($p = 0.311$ and $p = 0.449$, respectively). IVF or intracytoplasmic sperm injection (ICSI) rates were similar in both groups ($p = 0.465$) (10 *vs* 12). Number of fertilized oocytes ($p = 360$) (7 *vs* 7), fertilization rates ($p = 0.315$) (64.28% *vs* 76.9%), transferred embryo numbers were also similar in both groups (Table 4).

When implantation rates per cycle were assessed, there was a statistically significant difference between the groups ($p = 0.01$) (40.36% *vs* 62.50%). On the other hand, there was no significant difference in pregnancy rates ($p = 0.791$) (47.71% *vs* 50%). Although clinical pregnancy rate was higher in Group 2 (30.27% *vs* 39.58%); this difference was not statistically significant ($p = 0.254$). Similarly, ongoing pregnancy rate was again higher in Group 2 that did not reach a statistical significance (33.3% *vs* 27.52%) ($p = 0.461$). This trend with statistical insignificance also continued for live birth rates (33.3% *vs* 27.52%) ($p = 0.461$) (Table 5).

When pregnancy results per transferred embryo assessed by ultrasound were compared, implantation rate was statistically higher in Group 2 (49.18% *vs* 31.42%) ($p = 0.016$). But pregnancy rates assessed by serum beta-hCG, clinical pregnancy, ongoing pregnancy and live birth rates were similar in both groups ($p = 0.767$, $p = 0.259$, $p = 0.456$, $p = 0.456$) (Table 6).

Interestingly, there was a statistically significant difference between the groups in terms of multiple pregnancies as pregnancies in Group 2 were twins in 78.6%, while only 37% were multiple in Group 1 ($p = 0.012$) (Table 7).

Only 6 cases of OHSS developed in the entire study population. There was not any significant difference between the groups in terms of OHSS incidence per transferred embryo (2.9% *vs* 3.3%) ($p = 1.00$).

4. Discussion

While the number of patients admitted to IVF clinics has been on steady increase from past to present, new treatment protocols depending on the etiology of underlying pathology, have also been emerging reciprocally. Many different medical treatment protocols are applied at every step mainly during controlled ovarian hyperstimulation (COH), oocyte maturation, ovulation triggering and, luteal phase support. Standard protocols can also be modified according to parameters related to the underlying infertility cause, duration of infertility and patient age.

According to the current knowledge, it is well established that pregnancy rates increase as the number of follicles and retrieved oocyte numbers increase during COH cycles together with IVF-ICSI. On the other hand, it is also well known that the usage of agents during COH and, ovulation triggering in order to overcome the most common etiologic factor, namely ovarian dysfunction, may lead to OHSS that eventually cause cycle cancellation, significant

Table 3. Characteristics of treatment.

	Group 1	Group 2	*p* value
rFSH duration (day)	9 (6–18)	9 (7–13)	0.731
rFSH total dose (unit)	1687.5 (675–5062)	1706 (787–4050)	0.421
Antagonist duration (day)	5 (1–10)	5 (2–8)	0.313
E2 (pg/mL) on the day of hCG	2890 (527–4985)	3543 (1216– 4956)	0.103
Progesteron (ng/mL) on the day of hCG	0.95 (0.11–2.9)	1.07 (0.21–71)	0.295
Endometrial thickness (mm) on the day of hCG	11.5 (7.4–17.9)	11.3 (8–14.7)	0.818

Mann-Whitney U Test was used. Average (minimum–maximum) unless otherwise stated. *p* value for statistical significance <0.05. rFSH, Recombinant follicle-stimulating hormone; E2, Oestradiol.

Table 4. OPU and fertilization features of Group 1 and Group 2.

	Group 1	Group 2	*p* value
Number of oocytes collected on the day of OPU[a]	14 (3–20)	16 (6–20)	0.620[b]
MII oocyte number[a]	10 (1–20)	10 (3–19)	0.449[b]
MI oocyte number[a]	0 (0–9)	1 (0–3)	0.311[b]
IVF or ICSI performed oocyte number[a]	10 (1–20)	12 (3–20)	0.465[b]
Fertilized oocyte number[a]	7 (0–20)	7 (2–20)	0.360[b]
Fertilization Rate (%)	64.28 (16.6–75)	76.9 (46.1–100)	0.315[b]
Number of embryos transferred	1.28 ($\pm$0.45)[c]	1.27 ($\pm$0.45)[c]	0.726
Blastocyst stage embryo transferred patients n (%)	43 (39.4)	24 (50)	0.218[d]
Cleavage stage embryo transferred patients n (%)	66 (60.6)	24 (50)	0.218[d]
Excellent quality embryo transferred patients n (%)	33 (30.3)	16 (33.3)	0.713[d]
Good quality embryo transferred patients n(%)	39 (35.8)	18 (37.5)	0.836[d]
Single embryo transferred patients n (%)	78 (71.6)	35 (72.9)	0.862[d]
Double embryo transferred patients n (%)	31 (28.4)	13 (27.1)	0.862[d]

[a]Average (minimum–maximum). [b]Mann-Whitney U Test was used. [c]Median ($\pm$SD). [d]Pearson Chi-square test was used. *p* value for statistical significance <0.05. OPU, Ovum pick-up; MII, Metaphase 2; MI, Metaphase 1; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection.

morbidity and even mortality despite its being the mainstay of the whole therapy.

In COH cycles where gonadotropin releasing hormone (GnRH) antagonists are used, the administration of GnRHa reduces the risk of OHSS by leading to a short-lived endogenous LH surge that results in early lysis of corpus luteum [12]. Unfortunately, it is demonstrated that ongoing pregnancy rates are also decreased with GnRHa administration instead of only hCG to achieve oocyte maturation and, ovulation triggering [13]. Luteal phase defects that occur after triggering with GnRHa may be reduced by either high dose progesterone administration or low-dose adjuvant hCG application [14].

Many cytokines play role to create adequate nutritive environment for developing fetus via processes such as first interaction of blastocyte with endometrium, implantation, decidual differentiation of endometrium, invasion of endometrial vessel by trophoblasts. Developments in molecular studies show that the excretion of many cytokines and expression of many related molecules are defective in infertile women. But not a specific cytokine could be found to be defectively expressed in tissues or interstitial fluid [15]. In 2014, Perrier d'Hauterive *et al.* [16] demonstrated that hCG secreted from the blastocyte helps implantation by way of increasing Leukemia Inhibiting Factor (LIF) and also supports tolerance by inhibition of interleukin 6 (IL-6). Freis *et al.* [17] showed the levels of cytokines such as Interleukin-1 receptor antagonist (IL-1ra), macrophage inflammatory protein 1-alpha (MIP-1a) and, tumor necrosis factor-alpha (TNF-alpha) are significantly increased in patients with miscarriages who have significantly low levels of hCG .

The hCG hormone synthesized and secreted from the syncytiotrophoblasts stimulates the progesterone synthesis in the first trimester of pregnancy. When the importance of hCG in in early pregnancy and embryo implantation is considered, the administration of hCG to increase the success rates in assisted reproductive technology (ART) has been proposed [18].

In our current study, we aimed to retrospectively explore the pregnancy results and, OHSS rates of 159 patients who underwent COH protocol with antagonist administration and, underwent luteal rescue with both GnRH agonist and, intracavitary or subcutaneously administered r-hCG.

In a study done by Humaidan *et al.* [19], in 2005, it has been stated that positive pregnancy test rates, clinical pregnancy rates and implantation rates were better in group of patients when triggering was done only by hCG when

Table 5. Embryo transfer results per cycle.

	Group 1 (n = 109)	Group 2 (n = 48)	*p* value
Implantation rate (%)	40.36 (44/109)	62.5 (30/48)	0.010
Pregnancy rate (%)	47.71 (52/109)	50 (24/48)	0.791
Clinic pregnancy rate (%)	30.27 (33/109)	39.58 (19/48)	0.254
Ongoing pregnancy rate (%)	27.52 (30/109)	33.3 (16/48)	0.461
Live birth rate (%)	27.52 (30/109)	33.3 (16/ 48)	0.461

Pearson Chi-square test was used. *p* value for statistical significance <0.05.

Table 6. Embryo transfer results according to the number of embryos transferred.

	Group 1 (n = 140)	Group 2 (n = 61)	*p* value
Implantation rate (%)	31.42 (44/140)	49.18 (30/61)	0.016
Pregnancy rate (%)	37.14 (52/140)	39.34 (24/61)	0.767
Clinic pregnancy rate (%)	23.57 (33/140)	31.14 (19/61)	0.259
Ongoing pregnancy rate (%)	21.42 (30/140)	26.22 (16/61)	0.456
Live birth rate (%)	21.42 (30/140)	26.2 (16/61)	0.456

Pearson Chi-square test was used. *p* value for statistical significance <0.05.

Table 7. Comparison of subcutaneous and intracavitary groups in terms of single and multiple pregnancy.

	Group 1	Group 2	*p* value
Single pregnancy rate (%)	63 (17/27)	21.4 (3/14)	0.012
Multiple pregnancy rate (%)	37 (10/27)	78.6 (11/14)	

Pearson Chi-square test was used. *p* value for statistical significance <0.05.

compared with only GnRH analogue (busereline) administration in antagonist cycles.

In 2008, Shapiro *et al*. [20] postulated that administering low dose hCG (1000–2500 IU) together with GnRHa trigger increases pregnancy rates by protecting corpus luteum.

Although literature seems to settle on beneficial effects of hCG administration as a luteal rescue modality constituent, there also seems to be different perspectives on the best possible administration route, dosage and, timing of administration. While Stelling *et al*. [21] advocate that subcutaneous administration of hCG results in higher serum and, follicle fluid hCG levels, study done by Chan *et al*. [22] supports intramuscular route to result in higher levels. The serum levels are also believed to be influenced by the body mass index of the patients, leading less bioavailability in obese patients.

To further complicate the matter, there also seems to be a consensus about the risk of OHSS when hCG levels are increased either spontaneously or iatrogenically. With this perspective in mind, researchers tried to minimize the risk of OHSS by lowering hCG dose without losing its beneficial effect. Low dose intracavitary hCG administration is believed to overcome this problem. Mansour *et al*. [23] were the first researchers who published intracavitary hCG administration differing in terms of when to administer. There are studies and meta-analysis stating that administrating hCG within first 5–12 minutes of embryo transfer leads to high frequency uterine contractions and, consequently resulting in reduced live birth rates [24–26]. It is also stated that administering recombinant hCG is more potent in IVF cycles that prevents the apoptosis of decidualized endometrial stroma better when compared with hCG derived from urine [27,28].

In a study done by Hong *et al*. [29] in 2014, implantation and delivery rates were found to be similar between patients when intracavitary hCG administered and, not administered when the embryos were transferred at blastocyst stage. In the same study it is also stated that administering intracavitary hCG did not improve the results when fresh and frozen embryo cycles were evaluated. The researchers speculated that this failure to demonstrate improvement might be secondary to transferring blastocytes at their 5th or 6th days. At this stage of development embryo itself starts to secrete hCG. Similarly, in our study we included embryos transferred at both 3rd and 5th days. The reason of differences in implantation rates might be due to our blastocytes transferred at 3rd day.

In a review published by Craciunas *et al*. [18] in 2018, they evaluated the pregnancy results of administering intracavitary >500 IU hCG with <500 IU hCG and with patients not administered. They showed that the live birth rates were improved in the group of patients when ≥ 500 IU hCG intracavitary administered at cleavage stage. There were no differences between the groups when hCG was administered to patients whose embryos were transferred at 5th day. When it comes to when to administer hCG, in a review done by Kasum *et al*. [30], in 2016, the pregnancy rates were found to be around 50% when hCG was administered 30–36 hours before embryo transfer. This rate was almost the same result that we found in our study.

When primary outcome measures are considered, our study showed that implantation rates per cycle and per

transferred embryo were higher in intracavitary hCG patients (Group 2). There were no statistically significant differences in terms of positive pregnancy test at 12th day, clinical pregnancy rates, ongoing pregnancy rates, and live birth rates between groups. There was also no significant difference between subcutaneous and intracavitary hCG administration groups in OHSS rates as secondary outcome measure (3.7% *vs* 4.2%, $p = 1.00$).

5. Conclusions

Pregnancy chances are increased when higher quality embryos could be retrieved during ART cycles. Despite the increased usage of GnRHa for ovulation and oocyte maturation, the pregnancy results are shown to be worse than the cycles where GnRH and, hCG are used together for triggering. The OHSS caused by hCG limits the usage of itself as single agent. This handicap is the main factor that drives the researchers and physicians to develop new protocols utilizing both GnRHa and hCG together.

In our study the administration of 1500 IU hCG intracavitary and subcutaneously at OPU day to the patients who have increased risk for OHSS were compared in terms of pregnancy and, OHSS rates. Implantation and twin pregnancy rates were found to be increased in intracavitary group (Group 2). There was no statistically significant difference in pregnancy rates, clinical pregnancy rates, ongoing pregnancy rates and live birth rates. Also, the risk of OHSS were similar in groups.

There are studies focusing on the usage of GnRHa and, hCG to trigger ovulation and achieve oocyte maturation in different dosages and timing of administration, separate or co-usages and, with different GnRH formulations. Likewise, all the studies are conducted on different subsets of patients such as hyperresponders, normoresponders, hyporesponders. As to our knowledge we could not find any study comparing the subcutaneous and intracavitary usage of hCG.

Our study showed that in suitable patients the administration of hCG intracavitary instead of subcutaneously, improved implantation rate without imposing any increased OHSS risk. The prospective studies will hopefully shed more light on how hCG administration intracavitary support luteal phase and make endometrial receptivity changes. Since our study is done on limited number of patients in a retrospective way, new prospective, randomized studies done on homogeneous patient groups are needed.

Availability of Data and Materials

Datasets are available from the corresponding author on reasonable request after permission from the local authorities.

Author Contributions

LA—Conceptualization, data curation, statistical analysis, writing - original draft, methodology, investigation; ED—Conceptualization, supervision, data collection, methodology, validation; MÇK—Data curation, writing - review and editing; EK—Writing - review and editing, investigation, formal analysis, validation; HA—investigation, methodology, writing - review and editing, validation; EA—Manuscript revision, formal analysis, methodology, writing - review and editing, validation. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of Kocaeli University (approval number: 2020/175). Every patient involved in the study signed an informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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