Systems Biology in Reproductive Medicine

ISSN: 1939-6368 (Print) 1939-6376 (Online) Journal homepage: https://www.tandfonline.com/loi/iaan20

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To cite this article: Ismail Guler, Ahmet Erdem, Yuksel Oguz, Funda Cevher, Mehmet Firat Mutlu, Nuray Bozkurt, Mesut Oktem & Mehmet Erdem (2017) The Impact of laparoscopic surgery of peritoneal endometriosis and endometrioma on the outcome of ICSI cycles, Systems Biology in Reproductive Medicine, 63:5, 324-330, DOI: 10.1080/19396368.2017.1332114

To link to this article: https://doi.org/10.1080/19396368.2017.1332114

Published online: 13 Jun 2017.

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SYSTEMS BIOLOGY IN REPRODUCTIVE MEDICINE
2017, VOL. 63, NO. 5, 324–330
https://doi.org/10.1080/19396368.2017.1332114

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RESEARCH ARTICLE

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The Impact of laparoscopic surgery of peritoneal endometriosis and endometrioma on the outcome of ICSI cycles

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ABSTRACT

Our objective was to assess the role of laparoscopic removal of ovarian endometriomas and ablation of peritoneal endometriosis on the outcome of intracytoplasmic sperm injection (ICSI) - Embryo Transfer cycles by comparing with the results of patients with untreated endometriomas and tubal factor without underlying endometriosis confirmed by laparoscopy. For this purpose, between 2002 and 2015, outcomes of 257 ICSI cycles of 150 patients, including 91 cycles of 48 patients in minimal endometriosis, 57 cycles of 25 patients in endometrioma removal, 65 cycles of 53 patients in non-operated endometrioma, and 44 cycles of 24 patients in tubal factor groups were retrospectively analyzed. Basal ovarian reserve was significantly lower, mean starting and total gonadotropin consumption was significantly higher, and mean serum E2 on the day of hCG injection, number of dominant follicles, number of retrieved total, and MII oocytes were all significantly lower in the endometrioma cystectomy group. Fertilization and embryo cleavage rates were also significantly the lowest in the endometrioma cystectomy group, whereas clinical pregnancy and live birth rates were comparable among all groups. The number of transferred embryos and duration of infertility were the most significant predictors of clinical pregnancy and live birth. Basal antral follicle count was also significant in predicting live birth.

ARTICLE HISTORY
Received 4 March 2017
Revised 1 April 2017
Accepted 2 April 201

KEYWORDS
Endometrioma; intracytoplasmic sperm injection; laparoscopy; peritoneal endometriosis; tubal factor

Introduction

Endometriosis is characterized by ectopic implantation and growth of endometrial stroma and glands [Macer and Taylor 2012]. The spectrum of the disease consists of minimal peritoneal to severe deep infiltrative endometriosis. Peritoneal lesions produce inflammatory mediators that may compromise fertilization and implantation via having toxic effects on sperm and decreasing endometrial receptivity, respectively [Duffy et al. 2014; Giudice and Kao 2004; Harb et al. 2013]. Inflammatory processes in the ovarian cortex causes early follicular activation and increased follicular atresia that may lead to diminished ovarian reserve and fertility potential in ovaries with endometriomas [Bulun 2014; Kitajima et al. 2014]. Fertilization, implantation, and pregnancy rates were all decreased in IVF cycles for endometriosis related infertility [Barnhart 2002].The presence of endometrioma is strongly related with decrease in ovarian reserve [Ata and Uncu 2015; Yang et al. 2015]. However, similar ovarian response to controlled ovarian hyperstimulation (COH) between ovaries in the same patients with unilateral endometrioma may indicate the inflammatory microenvironment of endometriosis is responsible for impairing ovarian response instead of endometrioma itself [Yang et al. 2015].

In subfertile patients with endometriosis, laparoscopic treatment is superior to diagnostic laparoscopy in terms of clinical pregnancy and live birth [Duffy et al. 2014]. Laparoscopic surgical removal also improves IVF outcomes in minimal-mild endometriosis [Opøien et al. 2011] and as well as in deep infiltrative disease [Bianchi et al. 2009]. However, the evidence is insufficient to support routine surgical treatment of endometriosis before IVF [Hamdan et al. 2015]. The stage of endometriosis is not well correlated with infertility [Practice Committee of the American Society for Reproductive Medicine 2012] and there is a necessity of further clarification of the specific impact of endometrioma alone or surgical treatment of endometriosis on IVF/ICSI outcomes [Hamdan et al. 2015].

So, we aimed to test the differences in COH and ICSI cycle outcomes between patients with untreated endometrioma, peritoneal endometriosis, removal of endometrioma, and diagnosis of tubal disease unrelated with endometriosis. Unlike previous studies in the literature, the cases of study groups were selected homogenously

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based on specific conditions of endometriosis other than the staging system that commonly refers to a wide range of the disease in any stage.

Results and discussion

In this study, we evaluated ICSI cycle outcomes of subfertile patients with specific presentations of endometriosis. Medical records of a total number of 257 ICSI cycles of 150 patients were found to be eligible for this design of the study. Study groups, including laparoscopically diagnosed and treated peritoneal endometriosis and endometrioma cystectomy and non-operated endometrioma consisted of 91 cycles of 48 patients, 57 cycles of 25 patients, and 65 cycles of 53 patients, respectively. The control group consisted of 44 cycles of 24 patients with laparoscopically confirmed tubal factor unrelated with endometriosis.

Table 1 shows the comparison of baseline variables and COH response characteristics among four groups and *post hoc* test results. Of baseline variables, basal FSH and E2 were significantly the highest (p = 0.001 and 0.006, respectively) and basal AFC was significantly lowest (p = 0.009) in the endometrioma cystectomy group. In the comparison of COH response parameters, mean starting and total dose of gonadotropins was significantly highest and serum E_2 on the day of hCG injection was significantly lowest in the endometrioma cystectomy group (p = 0.000). In concordance with this, the number of dominant follicles, the number of retrieved total, and MII oocytes were significantly lower in the endometrioma cystectomy group (p = 0.003, p = 0.002, and p = 0.004, respectively). Based on these results, a primary finding of our study was that history of endometrioma excision was related with compromised ovarian reserve and response to gonadotropins in comparison with other groups of endometriosis and tubal factor. Fertilization (p = 0.037 and p = 0.041, operated vs. non-operated endometrioma, and tubal factor, respectively) and embryo cleavage rates (p = 0.044) were also lowest in the operated endometrioma group that may indicate endometrioma excision pose some additional adverse effects on oocyte quality.

Comparison of cycle cancellation, clinical pregnancy, and live birth rates among groups are given in Table 2. Cycle cancellation rate was significantly lower in the non-operated endometrioma group than other groups (p = 0.004). In two group comparison between operated and non-operated endometrioma groups, cycle cancellation was significantly highest (p < 0.001) and clinical pregnancy per cycle and per embryo transfer (ET) was significantly lowest in the operated endometrioma group (p = 0.004 and p = 0.029, respectively). Whereas live birth rate per cycle and per ET did not show statistical significance (p = 0.072 and p = 0.182,

Table 1. Comparison of baseline data and controlled ovarian hyperstimulation response characteristics between study and control groups.

Variables (257 cycles of 150 Patients)	Peritoneal Endometriosis (1) (91 cycles of 48 Patients)	Operated Endometrioma (2) (57 cycles of 25 Patients)	Non-Operated Endometrioma (3) (65 cycles of 53 Patients)	Tubal Factor (4) (44 cycles of 24 Patients)	p Value
Age (years)	31.9 ± 4.6	32.5 ± 4.5	32.2 ± 4.7	33.8 ± 5.4	0.162
BMI (kg/m^2)	24.9 ± 3.7	23.3 ± 3.5	23.8 ± 4.5	25.5 ± 5.1	0.034
Basal FSH (mIU/ml)	6.7 ± 2.8 (2)	9.0 ± 4.4 (1,4)	6.9 ± 3.3	6.6 ± 2.2 (2)	0.001
Basal E_2 (pg/ml)	42.9 ± 26.8	54.0 ± 41.8 (3)	32.9 ± 20.2 (2)	49.1 ± 17.6	0.006
Antral follicle count	8.9 ± 5.4 (2)	6.0 ± 4.0 (1,3)	8.9 ± 5.2 (2)	7.9 ± 6.0	0.009
Duration of infertility (months)	89.8 ± 56.5 (3,4)	102.1 ± 72.0 (3,4)	62.5 ± 43.0 (1,2,4)	139.8 ± 76.3 (1,2,3)	<0.001
Duration of stimulation (day)	10.6 ± 2.8	11.2 ± 2.9	11.2 ± 2.3	10.2 ± 2.7	0.218
Starting dose of gonadotropins (IU)	282.4 ± 75.9 (2,4)	362.0 ± 99.8 (1,3)	298.4 ± 64.9 (2)	328.4 ± 78.7 (1)	<0.001
Total dose of gonadotropins (IU)	3400.3 ± 1903.9 (2)	4349.8 ± 1545.9 (1,3,4)	3128.0 ± 1325.6 (2)	3107.7 ± 1432.2 (2)	<0.001
Serum E_2 on the day of hCG injection (pg/mL)	1635.5 ± 1402.3 (4)	1258.8 ± 1012.2 (3,4)	2391.0 ± 1994.5 (2,4)	2603.5 ± 1994.5 (1,2.3)	<0.001
Serum LH on the day of hCG injection (mIU/mL)	2.4 ± 2.3	2.2 ± 2.6	2.4 ± 1.7	1.7 ± 1.3	0.618
Serum P on the day of hCG injection (ng/mL)	0.9 ± 0.6	0.9 ± 0.7	1.1 ± 0.9	1.07 ± 0.92	0.396
Number of ≥ 17 mm follicle count on the day of hCG injection	3.0 ± 2.3	2.0 ± 1.3 (3)	3.6 ± 2.1 (2)	3.0 ± 2.9	0.003
Number of 15-17 mm follicle count on the day of hCG injection	3.4 ± 2.7 (3,4)	2.9 ± 2.4 (3,4)	6.7 ± 4.5 (1,2)	5.6 ± 3.9 (1,2)	<0.001
Endometrial thickness at the day of hCG injection (mm)	11.9 ± 2.8	10.9 ± 2.4	11.5 ± 1.9	10.6 ± 2.5	0.024
Number of total oocytes retrieved	10.9 ± 8.2	7.1 ± 4.7 (4)	10.3 ± 8.1	13.6 ± 8.0 (2)	0.002
Number of MII oocytes retrieved	8.2 ± 6.6	5.8 ± 3.9 (4)	7.1 ± 5.4 (4)	10.4 ± 6.6 (2,3)	0.004
Fertilization rates (%)	71.4	66.8 (3,4)	73.6 (2)	73.6 (2)	0.274
Embryo cleavage rate (%)	93.2 (4)	92.2 (4)	95	96.5(1, 2)	0.044
Number of transferred embryos	2.8 ± 1.0 (3)	2.8 ± 0.9 (3)	2.0 ± 0.8 (1,2,4)	2.5 ± 0.9 (3)	<0.001

Data are mean ± SD, unless stated otherwise. BMI: body mass index; P: progesterone; E2: estradiol; FSH: follicle stimulating hormone; hCG: human chorionic gonadotropin. Superscript (n) indicates a statistically significant difference from Group (n) (p < 0.05).

Table 2. Comparison of cycle cancellation, pregnancy, and live birth rates between study and control groups.

Variables (257 cycles of 150 Patients)	Peritoneal Endometriosis (91 cycles of 48 Patients) [1]	Operated Endometrioma (57 cycles of 25 Patients) [2]	Non-Operated Endometrioma (65 cycles of 53 Patients) [3]	Tubal Factor (44 cycles of 24 Patients) [4]	*p* Value
Cycle cancellaton rate (*n*, %)	18, 19.8% [3]	14, 24.6% [3]	1, 1.5% [1,2,4]	9, 20.5% [3]	0.004
Clinical pregnancy rate, per cycle (*n*, %)	23, 25.3%	8, 14% [3]	24, 36.9% [2]	11, 25%	0.056
Live birth rate, per cycle (*n*, %)	16, 17.8%	7, 12.3%	15, 25.4%	8, 18.2%	0.195
Clinical pregnancy rate, per embryo transfer (n, %)	23, 31.5%	8, 18.6% [3]	24, 37.5% [2]	11, 31.4%	0.223
Live birth rate, per embryo transfer (*n*, %)	16, 21.9%	7, 16.2%	15, 25.9%	8, 22.8%	0.720

Superscript [(n)] indicates a statistically significant difference from Group (*n*) in comparison among two group ($p < 0.05$).

Table 3. Enter method of logistic regression analyses of variables to predict clinical pregnancy and live birth.

	Clinical Pregnancy			Live Birth		
Variables	Odds Ratio	95% Confidence Interval	*p*	Odds Ratio	95% Confidence Interval	*p*
Age	1.060	0.953-1.178	0.285	1.060	0.943-1.193	0.327
BMI	1.054	0.958-1.159	0.282	1.043	0.937-1.160	0.443
Basal antral follicle count	1.018	0.925-1.121	0.712	1.077	0.972-1.194	0.158
Duration of infertility	0.993	0.984-1.002	0.114	0.991	0.980-1.001	0.080
Number of total oocytes retrieved	1.038	0.963-1.119	0.327	1.025	0.946-1.111	0.548
Fertilization rates	1.003	0.983-1.024	0.756	1.004	0.979-1.029	0.757
Embryo cleavage rate	1.018	0.982-1.055	0.342	1.011	0.972-1.052	0.583
Number of transferred embryos	1.529	1.008-2.319	0.046	1.481	0.919-2.386	0.107
Presence of endometriosis	1.558	0.513-4.735	0.434	1.351	0.384-4.753	0.639
Cycle number [a]			0.930			0.936

BMI: body mass index. [a]Selected as categorical covariate for cycle dependencies.

respectively). However, one step comparison of four study groups with chi-squared ($\chi 2$) test with regard to clinical pregnancy and live birth rate did not reveal a statistically significant difference. This may result from comparison of a low number of cases that had clinical pregnancy and/or live birth in the study groups.

Actually, laparoscopic endometrioma cystectomy was proposed to improve IVF/ICSI cycle treatment outcomes by eliminating potential adverse effects of endometrioma on ovarian reserve, quality of oocyte and embryo, implantation, and pregnancy rates [Bulun 2014; Suzuki et al. 2005; Yanushpolsky et al. 1998]. In a prospective randomized study, ovarian responsiveness was found to be significantly decreased after three months from endometrioma cystectomy without improving pregnancy rates [Demirol et al. 2006]. Excision of endometrioma is strongly associated with a permanent decline in ovarian reserve as assessed by anti-Müllerian hormone (AMH) [Uncu et al. 2013]. This was also evidenced in experienced hands [Biacchiardi et al. 2011]. In a meta-analysis, Muzii et al. [2014] proposed that ovarian reserve may not be diminished after endometrioma excision if AFC is used to assess ovarian reserve instead of AMH. However, both AFC and AMH were found to be similar in assessing ovarian reserve after endometrioma excision in further evaluation of previous reports [Ata and Urman 2014].

Odds ratios (OR) of variables in predicting clinical pregnancy and live birth were given in Table 3. The final model of multivariate logistic regression analyses of variables with backward stepwise method revealed that the number of transferred embryos and duration of infertility were significant variables in predicting clinical pregnancy and live birth. Basal antral follicle count was also significant for predicting live birth (Table 4). These findings are consistent with the result of a comprehensive systematic review that concluded that the number of transferred embryos is one of the most important parameters to influence clinical pregnancy and live birth rates in IVF practice [Nardelli et al. 2014]. The importance of number of transferred embryos with regard to live birth rates was also confirmed in subfertility in a Cochrane meta-analysis [Pandian et al. 2013]. In addition, it was once again shown that duration of infertility and basal antral follicle count are the other important prognostic factors of ICSI cycles [Maignien et al. 2017; Pandian et al. 2013].

In subgroup regression analysis of variables, including age, cycle number (categorical covariate), antral follicle count, infertility period, number of total oocytes retrieved, fertilization rates, and number of transferred embryos among non-operated and operated endometrioma groups, the number of total oocytes retrieved was the most significant variable for predicting both clinical pregnancy and live birth (OR = 1.120, 95% CI:1.037-1.210, p = 0.004 and

Table 4. The final model after backward stepwise method of logistic regression analyses of variables to predict clinical pregnancy and live birth.

	Clinical Pregnancy		
Variables	Odds Ratio	95% Confidence Interval	*p*
Duration of infertility	0.992	0.985-0.999	0.024
Number of transferred embryos	1.486	1.031-2.142	0.034
	Live Birth		
Variables	Odds Ratio	95% Confidence Interval	*p*
Basal antral follicle count	1.090	1.003-1.184	0.042
Duration of infertility	0.052	0.991-1.000	0.052
Number of transferred embryos	1.441	0.931-2.230	0.101

Cycle number was selected as categorical covariate for cycle dependencies.

OR = 1.157, 95% CI:1.048-1.276, p = 0.004, respectively). Because the number of total oocytes retrieved was the most significant variable in predicting pregnancy and live birth among operated and non-operated groups, endometrioma cystectomy should not be performed if the aim is to improve IVF/ICSI outcome.

In most of the previous studies and meta-analyses evaluating the impact of endometriosis on IVF and ICSI outcomes, the patients were classified by using the ASRM endometriosis classification system. However, the extent of the disease varies in each stage of endometriosis and endometriosis-related infertility does not well correlate with the stage except in cases with involvement of fallopian tubes by advanced adhesions. This may resolve the inconsistent results of previous studies as well as meta-analysis. In a recent meta-analysis, the authors mentioned that the variability of their findings was significantly influenced by the great range of endometriosis at any stage [Harb et al. 2013]. It seems that the impact of surgery and endometriosis itself on IVF-ICSI outcomes should be assessed in more specific conditions of endometriosis until either the pathophysiology of endometriosis-related infertility or a better staging system is well established [Adamson and Pasta 2010; Practice Committee of the American Society for Reproductive Medicine 2012]. In another recent meta-analysis, the need for subgroup analyses, for example surgery for peritoneal endometriosis before IVF/ICSI, was also mentioned and planned to be examined in future [Barbosa et al. 2014].

The impact of pre-IVF treatment of peritoneal endometriosis was evaluated in a previous study in which ovarian response was found to be similar between first IVF/ICSI cycles after complete eradication of peritoneal endometriosis and diagnostic laparoscopy alone [Opøien et al. 2011]. However, laparoscopic ablation of visible peritoneal endometriosis improved first and cumulative implantation, pregnancy, and live birth rates. Consistently, our study revealed similar cycle cancellation, clinical pregnancy and live birth rates between laparoscopically treated peritoneal endometriosis and control tubal factor groups. Ovarian response to gonadotropin stimulation was also similar among laparoscopically ablated peritoneal endometriosis, tubal factor, and non-operated endometrioma groups.

In addition, our study revealed similar clinical pregnancy and live birth rates but a higher cycle cancellation rate in peritoneal endometriosis than in the non-operated endometrioma group. The finding of a higher cancellation rate may be related to a longer infertility period in the peritoneal endometriosis group. A recent meta-analysis concluded similar clinical pregnancy and live birth, as well as cycle cancellation rates with IVF/ICSI between peritoneal endometriosis and intact endometrioma alone [Hamdan et al. 2015]. However, the analyzed data was heterogeneous since, in one of two studies of that meta-analysis, the peritoneal endometriosis group consisted of stage I to IV endometriosis [Suzuki et al. 2005]. In addition, the other study included only 15 cycles of seven cases in the peritoneal endometriosis group [Kuroda et al. 2009].

For clarifying the specific impact of non-operated endometrioma alone on IVF/ICSI outcomes, it was found that the presence of endometrioma does not influence pregnancy and live birth rates despite significantly reducing the number of total and MII oocyte retrieved in the evaluation of the data of six and two studies, respectively [Yang et al. 2015]. Our study revealed a similar number of oocyte retrieved, fertilization and embryo cleavage rates, but a lower number of MII oocytes in comparison to the non-operated endometrioma with tubal factor group. Filippi et al. [2014] also showed similar ovarian responsiveness, oocyte quality, and fertilization and embryo cleavage rates between ovaries with and without endometrioma in women undergoing IVF cycle. However, controversial results regarding the role of endometrioma on ovarian

response and quality of oocytes and embryos were also reported [Benaglia et al. 2011; Reinblatt et al. 2011]. Possible additional complications of non-operated endometrioma, including spontaneous rupture, unintentionally puncture of endometrioma, or having difficulty in oocyte retrieval, pelvic infection, pain, and malignancy risk should also be addressed when counseling the patient.

In conclusion, the outcome of IVF/ICSI cycles in study groups mainly depends on the number of transferred embryos, duration of infertility, and the number of total oocytes retrieved that consequently reflects ovarian reserve. Laparoscopic endometrioma cystectomy may worsen IVF/ICSI outcomes by decreasing ovarian reserve and quality of oocyte and embryo.

Materials and methods

A retrospective cohort study was designed to compare the ICSI cycle outcomes of patients with diagnosis of minimal peritoneal endometriosis and endometrioma who underwent laparoscopic ablation of peritoneal lesions and unilateral or bilateral cystectomy, respectively, and of patients who were not operated for endometrioma prior to IVF at IVF Unit of Gazi University School of Medicine and Novaart IVF Center in the period between December 2002 and January 2015. The control group consisted of patients who underwent ICSI for tubal factor infertility without underlying endometriosis confirmed by laparoscopy. Approval of the Institutional Review Board and Ethics Committee of Gazi University Faculty of Medicine and informed consent were obtained. All recorded data were reviewed and ICSI cycles of patients with unexplained infertility without a diagnosis of endometriosis, endometriosis-related tubal factor, male factor infertility, history of laparotomy or oophorectomy for endometrioma, recurrent endometrioma, and severe male factors were excluded from the analyses. Bilateral endometrioma was found in 19 cycles of 7 cases and 11 cycles of 9 cases in operated and non-operated endometrioma groups, respectively.

All patients underwent pelvic examination, transvaginal ultrasonography, hysterosalpingography, basal antral follicle count (AFC), and hormonal tests before IVF cycle. Sperm analyses were performed in their male counterparts. Main indications for laparoscopy in the study and control groups were diagnostic laparoscopy for unexplained infertility, removal of endometrioma >3 cm and hydrosalpinx and diagnostic laparoscopy for tubal factor. The size of endometriomas ranged 17 mm to 51 mm in diameter in the non-operated endometrioma group.

In the technique of laparoscopic endometrioma cystectomy, ovarian cortex over endometrioma is incised, cyst is ruptured, and its content is aspirated. After inspection of cyst inside, traction and counter traction of cyst wall and ovarian cortex is performed to strip endometrioma with using blunt and sharp dissection, if necessary. Bleeders of a cyst bed is controlled with bipolar cautery. A 5 mm laparoscopic scissor, bipolar dissector, grasper, and an aspirator are the main instruments used in endometrioma cystectomy. There was not any surgical complication in the operated endometrioma group.

Controlled ovarian stimulation (COH) protocols were selected based on patients' age, basal antral follicle count, follicle stimulating hormone (FSH) level, body mass index (BMI), and previous COH characteristics. In normoresponders, either antagonist or long GnRH analog protocol were used. Microdose flare-up or antagonist protocols were used in poor responder patients. Gonadotropin dose was adjusted depending on ovarian response to stimulation that was monitored by serial transvaginal ultrasonography (TVU) and measurements of the level of serum E2. The endometrial thickness was also monitored by TVU. Oocyte retrieval was performed 36 h after hCG administration and fertilizations were all performed by ICSI regardless whether there was an absolute indication of ICSI. There was no instance of unintentionally puncturing of an endometrioma and any complication with this regard did not occur. Ultrasonography guided embryo transfer was performed after 48-72 h of oocyte retrieval. The number of transferred embryos was depended on patients' age and quality and the total number of formed embryos. All embryo transfers were in the fresh cycle.

Luteal phase was supported with intravaginal progesterone gel (90 mg/d) until a pregnancy was not evidenced or 10th week of gestation in pregnant women.

Serum level of beta-hCG was measured at 14th d after ET for testing pregnancy; and a clinical pregnancy was diagnosed with the presence of intrauterine gestational sac on sonography or pathology report indicating the products of conception in cases with abortion.

The primary outcome measures were clinical pregnancy and live birth rates. Gonadotropin consumption, duration of ovarian stimulation, the number of retrieved oocytes, fertilization, and embryo cleavage rates were considered as secondary outcome measures.

Statistical analysis was performed by using the Statistical Program for Social Sciences (SPSS, version 22.0, IBM, Chicago, IL, USA). Baseline data of the

patients were given as mean ± SD. Comparison of normally distributed parametric variables between groups was performed by one-way analysis of variance (ANOVA) with Bonferroni *post hoc* test. Non-normally distributed metric data were compared by Kruskal-Wallis with Mann-Whitney U tests. Distribution of parametric data was tested by Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical data was analyzed by chi-squared test. Both enter and backward LR stepwise methods of multivariate logistic regression analysis were used to determine the odds ratios and the effect of significant variables in predicting clinical pregnancy and live birth. Cycle number was used as a categorical covariate in the multivariate logistic regression analysis for cycle dependency. Collinearity was tested in multivariate logistic regression models by assessing the values of Variance Inflation Factors (VIF) of variables, which were all lower than 2.5 and ranged from 1.141 to 2.163 and from 1.122 to 2.118 in the logistic regression model for predicting clinical pregnancy and live birth, respectively. Statistical significance was accepted as $p < 0.05$.

Acknowledgment

We thank Gazi University for the support of this study.

Declaration of interest

We declare that all authors have no conflicts of interest.

Notes on contributors

Performed analyses and wrote the manuscript: IG, ME; Collected the data: YO, FC, MFM; Performed the ICSI cycles of cases: NB, MÖ, ME, AE.

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