Am J Transl Res 2014;6(2):163-168
www.ajtr.org /ISSN:1943-8141/AJTR1312008

Original Article

Surgical treatment for endometrioma does not increase clinical pregnancy rate or live birth/ongoing pregnancy rate after fresh IVF/ICSI treatment

Xiyuan Dong[1], Rui Wang[1], Yu Zheng[1], Ting Xiong[1], Xiuhua Liao[2], Bo Huang[1], Hanwang Zhang[1]

[1]Reproductive Medicine Center, Tongji Hospital, Tongji Medicine College, Huazhong University of Science and Technology, Wuhan 430030, China; [2]Reproductive Medicine Center, Women and Children's Hospital of Fujian Province, Fuzhou, 350000, China

Received December 16, 2013; Accepted December 31, 2013; Epub January 15, 2014; Published January 30, 2014

Abstract: The impact of surgical treatment for endometrioma prior to assisted reproductive treatment (ART) on pregnancy outcomes remains controversy. The aim of this study is to investigate whether surgery provides benefits in subsequent ART outcomes. We retrospectively analyzed the data of 292 patients who underwent their first attempted IVF/ICSI treatment at fertility center in a university hospital, from 2011 to 2013. The primary outcomes included clinical pregnancy rate (CPR), live birth/ongoing pregnancy rate (LB/OPR). Although patients with no history of surgery and with visual endometriomas during IVF/ICSI treatment had fewer antral follicles (9.3±4.9 vs. 11.0±5.3, *P*=0.046), and required higher dosage of gonadotropin (3122.8±1118.1 vs. 2741.7±1096.0, *P*=0.043) when compared to patients who underwent surgery for endometriomas and without visual endometriomas during IVF/ICSI, the CPR and LB/OPR was not significantly affected (OR=0.771, 95%CI=0.398-1.495, and OR=1.043, 95%CI=0.526-2.069, respectively). In conclusion, surgical treatment does not significantly improve pregnancy outcomes in patients who plan to take IVF/ICSI treatment.

Keywords: Endometrioma, IVF, ICSI, surgery, clinical pregnancy rate, live birth/ongoing pregnancy rate

Introduction

Endometrioma is ectopic endometrial cyst located on the ovary and is a manifestation of advanced stage endometriosis [1]. It is widely accepted that endometrioma is associated with infertility. However, the underlying mechanism is not well understood. It has been suggested that endometrioma might induce inflammatory reaction, impair follicle-genesis and ovulation in the ipsilateral ovary [2, 3].

Surgery is often used in patients with endometrioma for both diagnostic and therapeutic purpose. Traditional clinical practice believes that surgery may remove the endometrial cyst, restore the anatomical disturbance, and improve the ovarian response and Assisted Reproductive Treatment (ART) outcomes. However, this opinion lacks clinical evidence. Meta-analyses showed that surgical management of endometrioma does not significantly effect IVF pregnancy rates or ovarian response [4, 5]. Furthermore, removal of endometrioma may also damage normal ovarian tissue and lead to subsequent reduced ovarian response [6, 7]. Therefore, the impact of surgery for endometrioma on ART outcomes remains a controversial issue.

In order to investigate whether surgery for endometrioma prior to ART improves pregnancy outcomes, we compared IVF/ICSI outcomes in women without previous surgery and with visual endometrioma, outcomes in operated women who had recurred endometrioma during IVF/ICSI, and outcomes in operated women without visual endometrioma during IVF/ICSI.

Materials and methods

This was a retrospective, non-interventional, single-center, cohort study. Analysis was carried out on 292 IVF/ICSI cycles completed at

Reproductive Medicine Center, Tongji Hospital in the period from January 2011 to June 2013. The study was approved by the Institutional Review Board of Tongji Hospital.

Patient population

All patients undergoing their first autologous IVF/ICSI attempt during the study period, with ovarian endometrioma or with history of surgical treatment for ovarian endometrioma, and without any other known infertility factor besides endometriosis, were considered for analysis. We excluded cycles involving oocyte cryopreservation, semen preserve, blastocyst transfer, in vitro maturation, and natural cycles. A total of 338 patients were identified. Further, we excluded cycles not resulting fresh embryo transfer, thus 292 patients were included. All patients were telephone-followed up to at least 12th week of gestation to obtain delivery or ongoing pregnancy data. No patients were lost to follow up.

Patients were divided into three groups. Group A consisted of 68 patients with ovarian endometrioma who had not received surgical treatment prior to IVF/ICSI treatment. Ovarian endometrioma was diagnosed by transvaginal ultrasound [8]. There were 71 patients in Group B who had undergone laparoscopic cystectomy for endometrioma but had ultrasound diagnosed endometrioma present during the treatment cycle. Group C included 153 patients who had undergone surgery and had no endometrioma present during the treatment.

Clinical protocols

Down-regulation, Controlled Ovarian Hyperstimulation (COH), follicle aspiration, Fertilization in Vitro, embryos culture, and embryo transfer were implemented as previously published [9, 10]. Briefly, treatment was initiated with one of the following down-regulation protocols: long GnRH-agonist protocol, dual suppression protocol with oral contraceptive pills (OCP) and GnRH-agonist, GnRH-antagonist protocol, and prolonged GnRH-agonist protocol. COH with gonadotropin was started with rFSH or uFSH with or without hMG. The starting dose of gonadotropin was 150-300IU/d based on the age, AFC, basal FSH, and BMI. Gonadotropin dose was adjusted according to ovarian response, assessed by serum estradiol (E2), progesterone (P), luteinizing hormone (LH), and serial ultrasound scans. When at least 2-3 follicles developed with diameter of ≥18 mm, 10,000 IU hCG was given to trigger the maturation of follicles. Oocytes were retrieved transvaginally 34-36 hours after hCG injection. Fertilization method included IVF, ICSI, and 50% IVF + 50% ICSI. Main variables in assessment of embryo included the cleavage rate, equality of blastomeres, the degree of fragmentation, and mononuclearity in blastomeres [11]. Good-quality embryo was defined as ≥4 cells on day 2 or ≥6 cells on day 3, equal or less equal, fragmentation <20%, and with no multinucleated blastomeres. Usually, no more than two best-quality embryos were transferred on the day 2 or 3 after oocyte retrieval, and excessive available embryos were cryopreserved for subsequent FET cycles. Injections with 60mg P intramuscularly were administrated as luteal phase support from the day of oocyte retrieval.

Outcomes measurements

Primary outcomes were clinical pregnancy rate (CPR) and live birth rate/ongoing pregnancy rate (LBR/OPR). Biochemical pregnancy was defined as a pregnancy with transient hCG increase (>20IU/L) but does not develop into a clinical pregnancy. Clinical pregnancy was diagnosed when serum hCG level reached >20IU/L and gestational sac was visualized on ultrasound 5-7 weeks after transfer. Implantation rate was defined as the number of gestational sacs present on ultrasound scan 5-7 weeks after transfer divided by the number of embryos transferred [12]. An ongoing pregnancy was defined as a pregnancy with a positive fetal heartbeat after 12 weeks of gestation.

Statistical analysis

SPSS software (version 19.0, SPSS Inc., Chicago, Illinois) was used for statistical analysis. The continuous data were given as mean ± SD. Groups were compared with one-way analysis of variance (ANOVA) and Dunnett post hoc test. Categorical variables were present as percentage and number. Comparison was conducted with chi-square test and the Fisher exact test. Multiple logistic regression analysis was made to adjust potential confounders (age, BMI, infertility type, duration of infertility, FSH, AFC, down-regulation type, fertilization method), and to assess independent effects of predictors (OCP vs. non-OCP, duration and dosage

Table 1. Demographics and clinical characteristics

	Group A	Group B	Group C
No. of cycles	68	71	153
Age (year)	31.1±4.2	30.0±3.1	30.4±4.4
Infertility type			
Primary infertility (%)	72.1 (49/68)	70.4 (50/71)	64.1 (98/153)
Secondary infertility (%)	27.9 (19/68)	29.6 (21/71)	35.9 (55/153)
Duration of infertility (year)	4.7±4.0	3.6±2.7	4.3±3.1
BMI (kg/m^2)	19.1±5.9	19.6±5.9	20.5±5.0
Basal FSH level (mIU/mL)	7.5±2.9	7.7±3.6	7.2±4.0
Basal LH level (mIU/mL)	4.1±1.6	4.3±2.3	4.1±2.3
Basal E2 level (pg/mL)	59.9±36.8	56.7±32.0	52.8±30.8
AFC	9.3±4.9[a]	10.2±5.5	11.0±5.3
Day 3 endometrial-thickness (mm)	5.3±2.5	5.1±2.0	4.9±2.4

Note: [a]: *P*=0.046.

of gonadotropin, No. of oocytes retrieved, No. of available embryos, No. of good-quality embryos, No. of embryos transferred, endometrial-thickness, E2, P) on CPR and LBR/OPR. Missing data were removed per analysis. A *P* value <0.05 was considered statistical significant.

Results

Demographic data and clinical characteristics were shown in **Table 1**. Patients in group A had fewer antral follicles than patients in group C (9.3±4.9 vs. 11.0±5.3, *P*=0.046). No differences were found regarding age, infertility type, duration of infertility, BMI, basal FSH, basal LH, basal E2, and day 3 endometrial-thickness.

COH performance and embryo parameters were present in **Table 2**. There were no differences in respect with pretreatment protocol, down-regulation type, and fertilization method. Patients in the three groups required similar days of ovarian stimulation. However, the dosage of gonadotropin in group A was higher when compared to group C (3122.8±1118.1 vs. 2741.7±1096.0, *P*=0.043). The number of oocytes retrieved, the number of follicles >14 mm, endometrial-thickness, E2, P on the day of hCG were comparable among the three groups. Regarding embryos, no difference was found, in terms of the number of embryos transferred, the number and rate of day 3 good-quality embryos, the number and rate of available embryos, and fertilization rate.

Pregnancy results after fresh IVF/ICSI treatment was illustrated in **Table 3**. The biochemical, implantation rate, CPR, and LBR/OPR were similar among the three groups. After adjusting confounding factors and other variables, still no differences were found regarding CPR (group A: OR=0.771, 95%CI, 0.398-1.495; group B: OR=1.437, 95%CI, 0.658-3.137) and LBR/OPR (group A; OR=1.043, 95%CI, 0.526-2.069; group B: OR=1.453, 95%CI, 0.646-3.267).

Discussion

The present study retrospectively analyzed the data of 292 patients. The results showed that patients without previous surgery and with visual endometrioma before ART had fewer antral follicles, and required higher dosage of gonadotropin. However, the oocytes and embryos were not significantly affected. Irrespective of whether surgery before ART was used, and whether endometrioma was present, IVF/ICSI yielded similar pregnancy results in the three groups.

The role of surgical treatment in the management for endometrioma is a subject of ongoing debate. European Society of Human Reproduction and Embryology recommends ovarian cystectomy when the endometrioma is ≥4 cm [13]. However, a study with large sample size reported lower pregnancy rate and live birth rate in patients with visual endometrioma, in whom 78% had surgery history [14]. Numerous recent studies comparing patients with and without surgical intervention for endometrioma before ART reported that surgery lacks the ability to improve ovarian response and pregnancy outcomes [7, 8, 15]. There was also evidence suggesting that presence of endometrioma during ART treatment is not associated with reduced embryo quality [16]. Our result was in general agreement with their findings. A study comparing IVF outcomes in patients with endometriomas and those with simple ovarian cysts concluded that removal of endometrioma provides no benefit [17]. A recent study showed that the presence of endo-

Table 2. COH and embryo parameters

	Group A	Group B	Group C
No. of cycles	68	71	153
OCP pretreatment (%)	30.9 (21/68)	28.2 (20/71)	35.9 (55/153)
Down-regulation type			
Long agonist protocol (%)	61.8 (42/68)	53.5 (38/71)	62.7 (96/153)
Antagonist protocol (%)	13.2 (9/68)	15.5 (11/71)	7.8 (12/153)
Prolonged agonist protocol (%)	25 (17/68)	31.0 (22/71)	29.4 (45/153)
Fertilization method			
IVF (%)	75.0 (51/68)	76.1 (54/71)	75.8 (116/153)
ICSI (%)	22.1 (15/68)	16.9 (12/71)	19.6 (30/153)
Half-ICSI (%)	2.9 (2/68)	7.0 (5/71)	4.6 (7/153)
Duration of gonadotropin (day)	11.0±3.0	10.6±3.1	10.7±2.3
Dosage of gonadotropin (IU)	3122.8±1118.1[a]	2954.7±1216.1	2741.7±1096.0
No. of follicles >14 mm	9.0±4.9	7.1±4.3	8.8±4.2
Endometrial-thickness on hCG day (mm)	12.1±2.7	11.7±2.4	11.2±3.0
Serum E2 level on hCG day (pg/mL)	3711.7±2284.3	3614.8±2692.5	3623.5±2175.3
Serum P level on hCG day (ng/mL)	1.0±0.5	1.1±1.0	1.0±0.5
No. of oocytes retrieved	9.0±5.5	8.3±4.8	9.5±5.0
No. of day 3 good-quality embryos	3.8±3.1	3.8±3.2	4.1±3.2
No. of available embryos	3.3±1.8	3.2±1.9	3.5±2.0
No. of embryos transferred	1.9±0.4	1.9±0.4	1.9±0.3
Fertilization rate (%)	60.7 (371/611)	64.6 (379/587)	58.8 (858/1460)
OR (95%CI)	0.922 (0.760-1.118)	0.782 (0.641-0.954)	1.000
D3 high-quality embryo rate (%)	70.1 (260/371)	71.5 (271/379)	72.7 (624/858)
OR (95%CI)	1.138 (0.871-1.489)	1.063 (0.812-1.391)	1.000
Available embryo rate (%)	59.8 (222/371)	60.2 (228/379)	61.7 (529/858)
OR (95%CI)	1.079 (0.841-1.384)	1.065 (0.831-1.364)	1.000

Note: [a]: P=0.043.

Table 3. Pregnancy results after fresh IVF/ICSI cycle

	Group A	Group B	Group C
No. of cycles	68	71	153
Biochemical pregnancy (%)	2.9 (2/68)	2.8 (2/71)	2.6 (4/153)
OR (95%CI)	0.886 (0.158-4.957)	0.926 (0.166-5.178)	1.000
Implantation rate per transfer (%)	34.4 (45/131)	30.8 (41/133)	28.3 (83/293)
OR (95%CI)	0.755 (0.486-1.174)	0.887 (0.567-1.387)	1.000
CPR per transfer (%)	51.5 (35/68)	45.1 (32/71)	43.1 (66/153)
Crude OR (95%CI)	0.715 (0.403-1.269)	0.925 (0.525-1.629)	1.000
Adjusted[a] OR (95%CI)	0.771 (0.398-1.495)	1.437 (0.658-3.137)	1.000
LBR/OPR per transfer (%)	42.6 (29/68)	35.2 (25/71)	37.9 (58/153)
Crude OR (95%CI)	0.821 (0.459-1.468)	1.123 (0.625-2.019)	1.000
Adjusted[a] OR (95%CI)	1.043 (0.526-2.069)	1.453 (0.646-3.267)	1.000

Note: [a]: Adjusted for confounding factors (age, BMI, infertility type, duration of infertility, FSH, AFC, down-regulation type, fertilization method) and variables (OCP vs. non-OCP, duration and dosage of gonadotropins, No. of oocytes retrieved, No. of available embryos, No. of good-quality embryos, No. of embryos transferred, endometrial-thickness, E2, P).

metrioma does not induce systemic nor local inflammatory reaction, which also supports the argument against surgery before IVF [3].

Our finding has a clinical implication in tailoring treatment strategy for management of endometrioma associated infertility. Base on the

results of our study, surgery before ART does not elevate the likelihood of pregnancy or live birth. On the contrary, surgery may impair the ovarian reserve [18, 19], and increase the risk of poor ovarian response [20]. Moreover, laparoscopy may result in surgery complications, increase cost of treatment, and prolong time to pregnancy. Our finding adds evidence against surgical treatment for endometrioma in patients with endometrioma associated infertility.

Limitation of the present study is its retrospective nature. Selection, bias, and confounding factors may interfere with the results, nevertheless these factors were adjusted by multiple regression analyses. The sample size of our study is relatively small. Therefore, prospective randomized controlled trial is needed to confirm this finding.

In conclusion, surgical treatment for endometrioma does not significantly improve ovarian response and embryo-quality. It also lacks the ability of increasing chances to achieving pregnancy or live birth. Therefore, it should be cautious to use surgical treatment for endometrioma. Direct IVF/ICSI treatment can be considered as the first treatment in patients with endometrioma.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hanwang Zhang, Reproductive Medicine Center, Tongji Hospital, Tongji Medicine College, Huazhong University of Science and Technology, Jiefang avenue 1095#, Wuhan, 430030, China. E-mail: hwzhang@tjh.tjmu.edu.cn

References

[1] Flyckt R, Soto E and Falcone T. Endometriomas and assisted reproductive technology. Semin Reprod Med 2013; 31: 164-172.

[2] Macer ML and Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. Obstet Gynecol Clin North Am 2012; 39: 535-549.

[3] Opoien HK, Fedorcsak P, Polec A, Stensen MH, Abyholm T and Tanbo T. Do endometriomas induce an inflammatory reaction in nearby follicles? Hum Reprod 2013; 28: 1837-1845.

[4] Tsoumpou I, Kyrgiou M, Gelbaya TA and Nardo LG. The effect of surgical treatment for endometrioma on in vitro fertilization outcomes: a systematic review and meta-analysis. Fertil Steril 2009; 92: 75-87.

[5] Benschop L, Farquhar C, van der Poel N and Heineman MJ. Interventions for women with endometrioma prior to assisted reproductive technology. Cochrane Database Syst Rev 2010; CD008571.

[6] Al-Azemi M, Bernal AL, Steele J, Gramsbergen I, Barlow D and Kennedy S. Ovarian response to repeated controlled stimulation in in-vitro fertilization cycles in patients with ovarian endometriosis. Hum Reprod 2000; 15: 72-75.

[7] Demirol A, Guven S, Baykal C and Gurgan T. Effect of endometrioma cystectomy on IVF outcome: a prospective randomized study. Reprod Biomed Online 2006; 12: 639-643.

[8] Garcia-Velasco JA, Mahutte NG, Corona J, Zuniga V, Giles J, Arici A and Pellicer A. Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case-control study. Fertil Steril 2004; 81: 1194-1197.

[9] Xu B, Li Z, Zhang H, Jin L, Li Y, Ai J and Zhu G. Serum progesterone level effects on the outcome of in vitro fertilization in patients with different ovarian response: an analysis of more than 10,000 cycles. Fertil Steril 2012; 97: 1321-7, e1-4.

[10] Dong X, Liao X, Wang R and Zhang H. The impact of endometriosis on IVF/ICSI outcomes. Int J Clin Exp Pathol 2013; 6: 1911-1918.

[11] Papanikolaou EG, D'Haeseleer E, Verheyen G, Van de Velde H, Camus M, Van Steirteghem A, Devroey P and Tournaye H. Live birth rate is significantly higher after blastocyst transfer than after cleavage-stage embryo transfer when at least four embryos are available on day 3 of embryo culture. A randomized prospective study. Hum Reprod 2005; 20: 3198-3203.

[12] Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E and van der Poel S. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. Hum Reprod 2009; 24: 2683-2687.

[13] Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A and Saridogan E. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod 2005; 20: 2698-2704.

[14] Opoien HK, Fedorcsak P, Omland AK, Abyholm T, Bjercke S, Ertzeid G, Oldereid N, Mellembakken JR and Tanbo T. In vitro fertilization is a

successful treatment in endometriosis-associated infertility. Fertil Steril 2012; 97: 912-918.
[15] Benaglia L, Bermejo A, Somigliana E, Faulisi S, Ragni G, Fedele L and Garcia-Velasco JA. In vitro fertilization outcome in women with unoperated bilateral endometriomas. Fertil Steril 2013; 99: 1714-1719.
[16] Reinblatt SL, Ishai L, Shehata F, Son WY, Tulandi T and Almog B. Effects of ovarian endometrioma on embryo quality. Fertil Steril 2011; 95: 2700-2702.
[17] Kumbak B, Kahraman S, Karlikaya G, Lacin S and Guney A. In vitro fertilization in normoresponder patients with endometriomas: comparison with basal simple ovarian cysts. Gynecol Obstet Invest 2008; 65: 212-216.
[18] Urman B, Alper E, Yakin K, Oktem O, Aksoy S, Alatas C, Mercan R and Ata B. Removal of unilateral endometriomas is associated with immediate and sustained reduction in ovarian reserve. Reprod Biomed Online 2013; 27: 212-216.
[19] Raffi F, Metwally M and Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. J Clin Endocrinol Metab 2012; 97: 3146-3154.
[20] Bongioanni F, Revelli A, Gennarelli G, Guidetti D, Delle Piane LD and Holte J. Ovarian endometriomas and IVF: a retrospective case-control study. Reprod Biol Endocrinol 2011; 9: 81.