Gynecology and Minimally Invasive Therapy 5 (2016) 161–165

Contents lists available at ScienceDirect

Gynecology and Minimally Invasive Therapy

journal homepage: www.e-gmit.com

Original article

Effect of ovarian dermoid cyst excision on ovarian reserve and response: Insights from *in vitro* fertilization

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ARTICLE INFO

Article history:
Received 9 November 2015
Received in revised form
27 December 2015
Accepted 21 January 2016
Available online 23 February 2016

Keywords:
dermoid cyst
in vitro fertilization–embryo transfer
ovarian reserve

ABSTRACT

Study objective: To investigate the impact of an ovarian dermoid cyst or dermoid cyst surgery on ovarian reserve in patients undergoing *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI).
Design: We performed a retrospective cohort study by using the records of patients with a history of ovarian dermoid cyst who underwent IVF/ICSI between 2009 and 2013. The antral follicle count (AFC) obtained by transvaginal ultrasound during controlled ovarian hyperstimulation of IVF/ICSI, total number of basal follicles [i.e., basal antral follicle count (B-AFC)], and dominant follicles greater than 1.4 cm [i.e., dominant antral follicle count (D-AFC)] were calculated between the different groups.
Patients: We included 260 patients with a history of dermoid cyst excision and 23 patients with a dermoid cyst who underwent IVF/ICSI. Two hundred and eighty-three matched patients without a dermoid cyst and ovarian surgery history were included.
Intervention: None.
Measurements and main results: The B-AFC was significantly smaller in the dermoid cyst group than in the matched control group ($p = 0.030$). The B-AFC and D-AFC were both significantly smaller for the previously operated ovary than for the contralateral nonoperated ovary ($p = < 0.001$), and both were smaller in the ovary with a teratoma than in the other teratoma-free ovary with a mean reduction of 40.5% and 38.8%, respectively ($p = 0.018$ and $p = 0.004$, respectively). The B-AFC and D-AFC were significantly fewer in ovaries treated by open surgery than in ovaries treated laparoscopically ($p = 0.031$ and $p = 0.028$, respectively). There was no significant difference in the main IVF outcomes between the two groups or the subgroups.
Conclusion: Our results suggest that ovarian dermoid cyst excision could significantly reduce ovarian reserve to a similar extent as the cyst itself. The presence or resection of dermoid cysts will not affect the main IVF outcomes.

Background/Introduction

A mature ovarian cystic teratoma, also called a dermoid cyst, is the most common ovarian tumor in women of reproductive age and constitutes up to 20% of all ovarian tumors.[1] Despite its high prevalence, studies are scarce concerning its effect on ovarian reserve and its treatment strategy in infertile patients, although one previous study showed an increased prevalence of infertility among women with mature cystic teratomas.[2]

Conflicts of interest: The authors have no conflicts of interest to declare relevant to this article.

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http://dx.doi.org/10.1016/j.gmit.2016.01.005

The management of ovarian dermoid cysts in infertile women raises the following questions: (1) does surgical treatment of a dermoid cyst impact the ovarian reserve? (2) does a dermoid cyst and its resection impair the prognosis of assisted reproductive technologies (ARTs)? and (3) does the cyst damage the surrounding ovarian tissue? Until recently, definitive data have rarely been available to clarify these issues. Few studies have specifically investigated residual ovarian function after laparoscopic excision of dermoid cysts, especially in association with infertility. Kim et al[3] reported no difference in the serum levels of anti-Müllerian hormone (AMH) between women with mature cystic teratomas and age-matched and body mass index (BMI)-matched controls. They speculated that mature cystic teratomas do not significantly affect ovarian reserve, whereas stage IV endometriomas may be closely associated with decreased ovarian reserve. The effects of surgical treatment are often more harmful to the ovarian reserve, compared to the cyst itself. Surgical treatment of the dermoid cyst seems to affect the antral follicle count (AFC). Urman et al[4] reported that the AFC decreased more than 10% 6 months after cystectomy for endometriomas, compared to the preoperative count. Somigliana et al[5] declared that the laparoscopic excision of nonendometrioid benign ovarian cysts, which included only seven cases of dermoid cyst, was associated with significant injury to the ovarian reserve.

Purpose/Aim

The aim of the present study was to evaluate the impact of excising an ovarian dermoid cyst on ovarian reserve and the response to ovarian stimulation.

Materials and methods

We performed a retrospective cohort study that involved the collection of data from the electronic records of women who underwent *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) between January 2009 and December 2013 in the Center for Reproductive Medicine at Shandong Provincial Hospital Affiliated to Shandong University (Jinan, China). Patients were monitored and managed in accordance with standardized clinical protocols used at the hospital. We initially included 304 patients who were previously diagnosed with a dermoid cyst by postoperative pathologic examination or by transvaginal ultrasound scan (TVS). Twenty-one patients were excluded because they met the following exclusion criteria: (1) dermoid cyst recurrence after surgery, (2) history of adnexectomy, or (3) previous ovarian surgery. If an included patient underwent several oocyte retrieval cycles, only the first cycle was included. Two hundred and sixty patients who had a history of dermoid cyst resection and 23 patients who had a dermoid cyst but no resection were finally included in Group 1. The control group (Group 2), which comprised women without fibroids, was matched to the study group by the following criteria: (1) age (± 1 year), (2) number of cycles, (3) type of infertility (i.e., primary or secondary), (4) presence of tubal disease (as diagnosed by a history of ectopic pregnancy or tubal obstruction) or history of tubal surgery, (5) history of surgery for endometrial polyps, (6) presence of male factors (oligospermia, asthenospermia, azoospermia), (7) presence of polycystic ovary syndrome,(8) type of protocol used for controlled ovarian hyperstimulation (COH), and (9) presence of endometriosis or adenomyosis. We required exact matching for criteria 1–3. For criteria 4–9, we attempted to match individuals as closely as possible. For most individuals, we were able to match at least three of these criteria. Researchers performing the matching were blinded to the IVF/ICSI outcomes. If multiple patients matched the criteria, one patient was chosen at random. All patients underwent routine COH. Day 3 AFCs before starting ovarian stimulation (i.e., the B-AFC) and the number of dominate follicles (D-AFC) that were greater than 1.4 cm at the time of human chorionic gonadotropin (hCG) administration were calculated. Detailed TVS monitoring before and during IVF/ICSI cycles was systematically applied and recorded; it had comparability with ultrasound assessment.

To avoid a large difference in number when comparing women who had surgery and women who did not have surgery (260 women vs. 23 women), we only included patients who had laparoscopic cystectomy into Group 1.1 and included patients who had no surgical management on the ovary into Group 1.2. This comparison was more acceptable because the ratio of the case numbers was lowered to 108:23, and the evaluation of open surgery for just the removal of an ovarian cyst was less meaningful. In both subgroups, the total number of B-AFC and D-AFC in each ovary was compared. The pregnancy outcomes such as cancellation, clinical miscarriage, clinical pregnancy rate (CPR), and delivery rate (DR) were compared.

Moreover, in the unilateral surgery subgroup, the difference in the AFC numbers between women who underwent an open surgery approach and laparoscopic approach was also measured. In our paper, $\triangle 1$ = (AFC on the nonsurgery side of the ovary) − (AFC on the surgery side of the ovary). $\triangle 2$ = (AFC on the teratoma-free side of the ovary) − (AFC on the teratoma side of the ovary). To clarify whether the impact is related to the surgical procedure and/or to a prior cyst, we compared the values between $\triangle 1$ and $\triangle 2$. A schematic diagram of our study is shown in Figure S1.

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) while taking into consideration the match between each case woman and her control. Normally distributed data were presented as the mean and standard deviation. Abnormal distribution data were presented as the median (interquartile range). For continuous variables, the difference between the mean of the patients and the mean of the controls was computed and tested using a *t* test for paired comparisons. For proportions, the Chi-square test or Fisher's exact test were applied. The Kruskal–Wallis nonparametric test, followed by the Mann–Whitney *U* test, was applied for non-normal distributive data. A two-tailed $p < 0.05$ was considered significant.

This study was approved by the Institutional Review Board of Shandong University (Jinan, China). Written informed consent was obtained from the participants at the time of their presentation for IVF/ICSI treatment.

Results

Two hundred eighty-three patients fulfilled the inclusion criteria and were paired with 283 matched controls (Figure 1). The characteristics of the patients and the ovarian stimulation outcomes are shown in Table 1. Group 1 comprised patients who had undergone ovarian dermoid cyst resection unilaterally ($n = 203$) or bilaterally ($n = 57$) and 23 patients who still had a dermoid cyst during IVF/ICSI. Group 2 included 283 matched controls without a dermoid cyst or cystectomy. The oocyte retrieval procedure was successful without complications. There was no report of teratoma torsion or peritonitis during or after oocyte retrieval. No torsion was reported during the pregnancies. Table 1 shows no significant differences in most of the items compared. However, the mean B-AFC (in the left and right ovaries) was significantly smaller in Group 1 than in Group 2 (13.9 ± 7.1 vs. 15.9 ± 8.1; $p = 0.030$). The median number of good quality embryos transferred was significantly higher in Group 2 than in Group 1 (2 embryos vs. 1 embryo; $p = 0.029$). There were no differences between the two groups in the main IVF outcomes such as the CPR and DR (Table 2). The clinical miscarriage rate was slightly higher in Group 1 than in

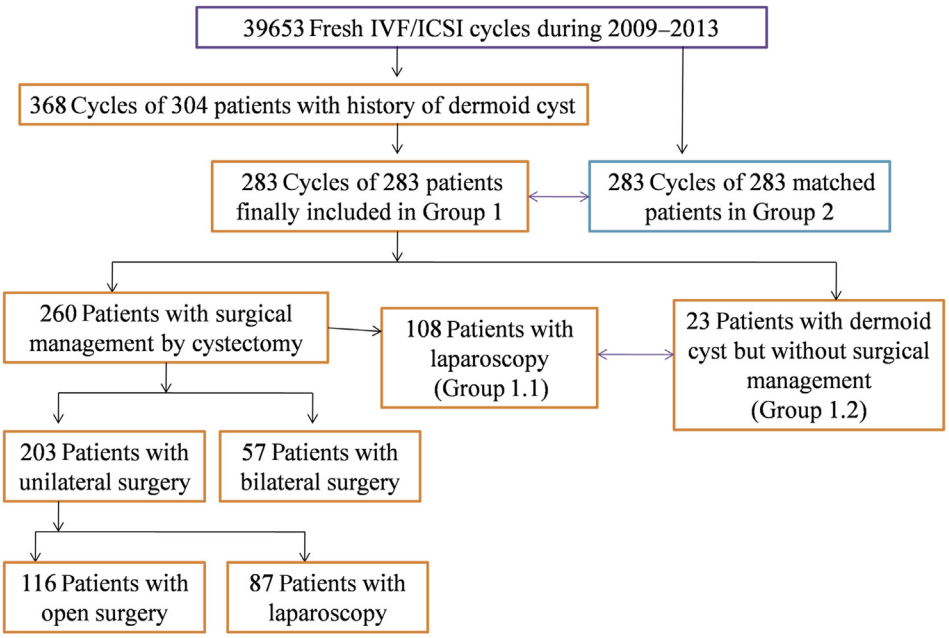

Figure 1. A schematic of the database searching pathway and the group divisions. ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization.

Table 1
The baseline characteristics of the patients and the *in vitro* fertilization outcomes of Groups 1 and 2.

Item	Group 1	Group 2	*p*
Patients (*n*)	283	283	
Age (y)	30.9 ± 4.6	30.8 ± 4.5	NS
Body mass index (kg/m^2)	23.4 ± 3.7	23.1 ± 3.4	NS
Day 3 serum FSH (IU/mL)	7.2 ± 2.8	6.9 ± 2.5	NS
Day 3 serum E2 (pg/mL)	43.9 ± 33.1	41.4 ± 33.1	NS
B-AFC (left + right ovary)	13.9 ± 7.1	15.9 ± 8.1	0.030
Starting dose of Gn	190 ± 48	183 ± 45	NS
Total dosage of Gn per cycle (IU)	2210 ± 975	2068 ± 779	NS
Mean number of oocytes retrieved	11.8 ± 6.9	12.6 ± 6.6	NS
Good quality embryo transferred (Mann–Whitney *U* test) [a]	1 (0, 2)	2 (0, 2)	0.029
Mean number of embryos transferred	1.5 ± 0.5	1.5 ± 0.5	NS

B-AFC = basal antral follicle count; D-AFC = dominant antral follicle count; E2 = estradiol; FSH = follicle stimulating hormone; Gn = gonadotropin; Group 1 = patients who had a dermoid cyst + prior surgery; Group 2 = patients who had dermoid cyst + no prior surgery; IFV = *in vitro* fertilization; NS = not significant.
[a] The mean number of good quality embryos transferred is 1.0 in Group 1 (i.e., dermoid cyst + prior surgery). The mean number of good quality embryos transferred is 1.1 in Group 2 (i.e., dermoid cyst + no prior surgery).

Table 2
The IVF/ICSI outcomes in Group 1 and Group 2.

Item	Group 1	Group 2	*p*	OR
Cancellation rate	37/283 (13.1)	39/283 (13.7)	0.805	0.94 (0.58–1.53)
Clinical miscarriage rate	29/159 (18.2)	17/140 (12.1)	0.088	1.75 (0.92–3.33)
CPR per started cycle	159/283 (56.2)	141/283 (49.8)	0.130	1.31 (0.93–1.80)
DR per started cycle	109/283 (38.5)	102/283 (35.7)	0.356	0.66 (0.27–1.62)

Data are presented as the n/N (%), unless otherwise indicated.
CPR = clinical pregnancy rate; DR = delivery rate; Group 1 = patients who had a dermoid cyst + prior surgery; Group 2 = patients who had dermoid cyst + no prior surgery; ICSI = intracytoplasmic sperm injection; IVF = *in vitro* fertilization; OR = odds ratio.

Group2 (18.2% vs. 12.1%; $p = 0.088$), but without significance. The mean size of a dermoid cyst in Group 1.2 was 2.2 ± 1.3 cm. We could not present the size of the dermoid cysts before surgery in Group 1.1.

Table 3 shows the comparison of the AFC between the bilateral ovaries. The characteristics of patients and the ovarian stimulation outcomes are shown in Table 1. In Group 1.1, the mean B-AFC was 8.4 ± 4.2 follicles in the control ovary and 5.8 ± 4.3 follicles in the previously operated ovary ($p = < 0.001$). The D-AFC was 6.0 ± 3.5 follicles in the control ovary and 3.8 ± 3.3 follicles in the previously operated ovary ($p = < 0.001$). This decrease in the B-AFC corresponded to a mean reduction of 31% (95% confidence interval, 24.5–37.5%) and the decrease in the D-AFC corresponded to a mean reduction of 35% (95% confidence interval, 24.5–45.7%). The B-AFC

Table 3
The antral follicle count comparison between the bilateral sides of the ovaries.

Item	B-AFC	D-AFC
One side (203 patients in Group 1.1)		
Surgery side	5.8 ± 4.3	3.8 ± 3.3
Nonsurgery side	8.4 ± 4.2	6.0 ± 3.5
p	< 0.001	< 0.001
Nonsurgery (23 patients in Group 1.2)		
Teratoma side	5.3 ± 3.8	3.7 ± 2.3
Nonteratoma side	8.9 ± 6.2	6.0 ± 4.1
p	0.018	0.004
Surgery type		
Open surgery side of the ovary (116 patients)	5.2 ± 4.5	3.3 ± 3.0
Laparoscopy side of the ovary (87 patients)	6.5 ± 3.8	4.4 ± 3.6
p	0.031	0.028
Surgery & teratoma		
△1 [a]	3.61 ± 6.78	2.35 ± 3.52
△2 [b]	2.60 ± 3.92	2.18 ± 3.95
p	0.489	0.843

B-AFC = basal antral follicle count; D-AFC = dominant antral follicle count.
[a] △1 = (AFC on the nonsurgery side of the ovary) − (AFC on the surgery side of the ovary).
[b] △2 = (AFC on the teratoma-free side of the ovary) − (AFC on the teratoma side of the ovary).

on the ovary subjected to open surgery (116 patients) was significantly less than that of the ovary subjected to laparoscopic surgery (87 patients; $p = 0.031$), although no significant difference existed between the nonoperated sides in the two groups ($p = 0.262$). In Group 1.2, the B-AFC and D-AFC in the ovary with a teratoma were both significantly lower than in the other teratoma-free ovary ($p = 0.018$ and $p = 0.004$, respectively) with a mean reduction of 40.5% (95% confidence interval, 7.6–73.7%) and 38.8% (95% confidence interval, 13.6–64.1%), respectively.

However, the decrease in the B-AFC and D-AFC in the previously operated ovary is a combined effect of the impact of surgery and the dermoid cyst itself (Figure S1). Therefore, a comparison of △1 and △2 could, to some extent, show the real effect of surgery on ovarian reserve. This result showed that the decrease in the B-AFC and D-AFC caused by dermoid cyst resection or the dermoid cyst itself did not reach significance ($p = 0.489$ and $p = 0.843$, respectively). This finding may indicate that dermoid cyst resection does not impact ovarian reserve, as evaluated by AFC.

To explain the aforementioned results, we re-evaluated the pathologic results of the thin cortex above dermoid cyst from several patients. We found fibrosis and a loss of cortex-specific stroma in the stretched cortex. We also collected the ultrasound results of several women in our clinics. We found that the AFC of the deromoid cyst side was lower than that of the tumor-free side (Figure S2). Table S2 shows no differences between Group 1.1 and Group 1.2 in the main IVF outcomes such as CPR and DR.

Discussion

Several studies[6,7] have advocated a relationship between endometriosis, infertility, and reduced ovarian reserve. Ovarian response may be reduced in some women who have undergone surgery for endometriomas. However, few studies have evaluated dermoid cysts with regard to the aforementioned issues. In this study, we demonstrated that surgical excision of an ovarian dermoid cyst significantly decreases the AFC, compared to the AFC of the nonoperated side. Moreover, an existing teratoma could also significantly reduce the AFC and ovarian function, based on the analysis of Group 1.2. Therefore, a dermoid cyst itself or its surgical resection could also lower the ovarian reserve, similar to an endometrioma. There were no significant differences in the main IVF outcomes between the dermoid cyst group (i.e., Group 1) and the matched control group (i.e., Group 2), or between the surgery subgroup (i.e., Group 1.1) and nonsurgery subgroup (i.e., Group 1.2). Our results indicated that teratoma resection may not significantly impact the main IVF outcomes.

In Group 1, the presence of an ovarian dermoid cyst was confirmed ultrasonographically. We excluded patients with recurrent dermoid cysts, a history of adnexectomy, and previous surgeries on the other ovary because these surgeries could have influenced the AFC comparison and added confounding factors to our results.

The mean B-AFC in Group 1 was significantly smaller than in Group 2, which could prove that surgery had a harmful effect to some extent on ovarian reserve. Our finding indicated that, like endometriosis, a dermoid cyst itself could reduce ovarian reserves. Kitajima et al[8] evaluated the histologic features of ovarian cortical tissue in endometriomas and found significantly lower follicular density, compared to the cortical tissue of the contralateral normal ovary. They also found fibrosis and a loss of cortex-specific stroma in endometrioma tissues. Our study also had similar results. We preliminarily demonstrated an association between tissue alterations in the dermoid cyst and reduced ovarian reserve. We speculated that the mechanical stretching of the enlarged ovary cortex induced by the dermoid cyst could also cause fibrosis and loss of follicles. This factor may explain our results of significant AFC reduction in ovaries with a dermoid cyst, compared to the tumor-free ovary; however, this phenomenon needs further detailed pathological investigation.

The mean size of the dermoid cyst in Group 1.2 was very small. The accuracy of the AFC measurement in the presence of an ovarian cyst is questionable, although a small size may increase the accuracy. For example, based on Figures S2C and S2D, we could clearly distinguish between the tumor and the AFCs. Our data showed that damage to the ovary reserve was related to the surgical procedure and to the dermoid cyst. Almog et al[9] compared AFCs in ovaries harboring different types of cysts with the contralateral normal ovaries and found that a dermoid cyst does not influence the AFC.

Our study showed that a laparoscopic approach was preferable to open surgery in protecting ovarian function. One study[10] of 55 patients who underwent laparoscopic surgery for dermoid cysts, which measured 2–15 cm, found residual ovarian parenchyma 6–12 months later, even when no parenchyma was visible before surgery. The proportion of open surgery was high and was possibly related to the lagging deployment of laparoscopic surgery in China. However, the laparoscopic technique is increasingly becoming widespread. Surgical management by laparoscopic cystectomy could help to prevent potential complications such as rupture, torsion, or malignancy during IVF/ICSI and later pregnancy.

Surgeons should protect ovarian function carefully by retaining as much ovarian tissue as possible. There are many reports[7,11] that state that hemostasis by bipolar coagulation after stripping an endometrioma reduces ovarian reserve to a greater extent than suturing, as determined by serial AMH levels. Therefore, suturing may be a better hemostatic choice after stripping out an ovarian endometriomas. In our study, we did not have detailed information on whether electrocoagulation or suturing was used. However, we believe that the same consideration with regard to endometriomas should apply to dermoid cyst excision. Thermal and mechanical injury to the ovary should be avoided. Physicians should keep in mind that any operation on the ovary compromises ovarian function. Potential deleterious mechanisms are the accidental removal of any ovarian tissue during cystectomy, damage inflicted on the ovarian stroma, and vascularization by surgery-related local inflammation and electrosurgical coagulation during hemostasis.[5]

The evidence from our study is inconclusive concerning whether dermoid cysts should be removed in infertile women

planning IVF. Caspi et al[12] reported the results of ovarian stimulation and IVF in the presence of dermoid cysts and found no effects related to the presence of a cyst or the parameters of stimulation or IVF, based on the data of only six patients with dermoid cysts. A systematic review[13] recently showed that surgery for endometrioma does not significantly affect ovarian reserve, as evaluated by AFC. In our study, we demonstrated no significant differences in the ovarian stimulation parameters and main IVF/ICSI outcomes between the two groups, whereas surgical resection does harm the ovarian reserve. Complications such as cyst torsion, infection, hemostasis, or malignant transformation can arise in women with a dermoid cyst undergoing ART; therefore, laparoscopic ovarian cystectomy sometimes may first be recommended for women, especially when the dermoid cyst is large and the ovarian reserve is good. However, if a small dermoid cyst (usually < 5 cm) is discovered just before IVF with no symptoms or signs of malignancy, we believe that the correct choice is to continue with IVF and continue monitoring the cyst, especially if the ovarian reserve is not good.

Our study has the following strengths. First, the 260 patients studied were the largest reported sample. Second, the matching procedures were a very important strength of this study. The control group (i.e., Group 2) was specifically chosen to eliminate confounding variables. As far as we know, few previous studies were as strictly and systematically controlled for age, number of cycles, comorbidities, and other confounding factors as our study was. Third, this study had a within-patient comparison of the ovary undergoing unilateral surgery with the unoperated ovary. We compared the bilateral sides of the ovarian follicles to eliminate individual bias. Fourth, we found that the main IVF outcomes may not be impacted by whether the teratoma is resected. We speculated that mature cystic teratomas could cause simple mechanical tissue stretching and significantly affect ovarian reserve. There is no current consensus on the management of dermoid cyst before ART; therefore, our study may help in this issue.

Some limitations of our research should be noted. This was a retrospective study and therefore it may have a selection bias. Data were collected from one IVF center, but there was no control in the manner in which the surgeries were performed. Most of our included patients had their surgery in other hospitals; therefore, we do not know how much normal ovary was removed in each patient. We also could not present clearly the surgical techniques. We do not know whether the difference in ovarian reserve was only because of the surgery or because of the history or the presence of a dermoid cyst. It is possible that there was a difference before the surgery. We only analyzed the cross-sectional data of the AFC. There was no prestimulation follow up of ovarian function. We did not use AMH because we used within-patient comparisons and because AMH, which more accurately evaluates ovarian function, represents the whole bilateral ovarian function. We did not standardize the timing of the ovarian reserve measurements relative to the surgery. It would not have made a difference for the control-versus-case study (because it was the same person), although a well-designed randomized controlled trial on this aspect is needed to generate the best evidence while overcoming the pitfalls of observational studies.

Our study showed that, after a teratoma resection, the AFC is significantly lower on the operated side than on the nonoperated side. Surgical excision of an ovarian dermoid cyst may significantly decrease ovarian function to a similar extent as the cyst itself; thus, its adverse effect on ovarian reserve is not a core issue. Whether a teratoma is resected may not impact the main IVF outcomes. In view of the aforementioned facts, laparoscopic ovarian cystectomy may sometimes be recommended first for women, especially when the dermoid cyst is large and the ovarian reserve is good. However, for most patients with a dermoid cyst presenting for ART, ovarian surgery should be avoided if there are no proper indications such as malignant transformation, especially when the ovarian reserve is poor.

Acknowledgments

We are very grateful to our patients and volunteers from Shandong University in data collecting. This study was financially supported by the State Key Program of National Natural Science Foundation of China (Beijing, China) (81430029), the National Natural Science Foundation of China (Beijing, China) (81571414), and Science Research Foundation Item of No-earnings Health Vocation (Beijing, China) (201402004).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.gmit.2016.01.005.

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