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ASSISTED REPRODUCTION TECHNOLOGIES

Laparoscopic excision of ovarian endometrioma does not exert a qualitative effect on ovarian function: insights from in vitro fertilization and single embryo transfer cycles

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Abstract
Purpose To evaluate whether laparoscopic excision of endometrioma exerts a qualitative effect on ovarian function.
Methods A retrospective analysis of oocytes retrieved in 25 cycles of 21 patients undergoing IVF treatment with controlled ovarian stimulation. The number of oocytes recovered from ovaries with a history of excision of endometrioma (E-Ov) were compared to those from contra-lateral healthy ovaries (H-Ov) as for the analysis of a quantitative effect of surgery. As for the analysis of a qualitative effect, 55 oocytes from E-Ov were compared to 128 oocytes from H-Ov in terms of normal fertilization rate and the rate of top-quality embryos per normally fertilized eggs. Furthermore, 10 embryos derived from oocytes recovered from E-Ov were compared to 24 embryos derived from oocytes from H-Ov in terms of clinical and on-going pregnancy rates per embryos in 34 single embryo transfer cycles.
Results Mean number of oocytes recovered from E-Ov was significantly smaller than that from H-Ov (2.2±2.0 vs. 5.1±3.3, P=0.009). There was no difference between oocytes from E-Ov and H-Ov as for normal fertilization rate (63.6 % vs. 69.5 %, P=0.43) and the rate of top-quality embryos (40.0 % vs. 49.0 %, P=0.34). Clinical and on-going pregnancy rates per embryos were also similar in embryos derived from oocytes recovered from E-Ov and H-Ov (40.0 % vs. 25.0 %, P=0.39 and 20.0 % vs. 20.8 %, P=0.96).
Conclusions The quality of oocytes recovered from the ovary with a history of laparoscopic excision of endometrioma is not inferior to the quality of oocytes from contra-lateral healthy ovary.

Keywords Laparoscopic excision · Ovarian endometrioma · Ovarian function · In vitro fertilization · Oocyte · Single embryo transfer

Capsule The quality of oocytes recovered from the ovary with a history of laparoscopic excision of endometrioma is not inferior to the quality of oocytes from contra-lateral healthy ovary.

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Introduction

Endometriosis affects up to 10 % of the women in reproductive age [1, 2], with 17–44 % of the women with endometriosis affected by endometrioma [3]. Since the women with endometriosis are often complicated with infertility [4–7], we should especially be careful about the ovarian function in making decision of therapeutic approach.

Laparoscopic excision has been a common surgical approach for endometrioma. However, concerns have been raised recently as for the detrimental effects of excision on ovarian function. Along with the emerging role of serum anti-Müllrerian hormone (AMH) level as a marker for the quantitative aspect of ovarian function [8], the expanding body of literature has been reporting a negative quantitative effect of excision with lower AMH levels after surgery [9, 10]. Although AMH levels are easy to measure, the reliability of AMH measured by current methods as a marker of ovarian reserve has been questioned by some authors [11, 12]. In addition, AMH levels do not necessarily reflect a quantitative effect of excision because this methodology cannot exclude a possible compensatory effect of intact gonad when the excised endometiroma is unilateral [13]. Above all, AMH levels do not provide any information on the qualitative effect of excision.

Another method to assess the ovarian function is to examine the ovarian response to controlled ovarian stimulation (COS). Especially, comparing the affected ovary and the contra-lateral healthy ovary of the same women with a history of excision of unilateral endometrioma is an efficient way to assess the effect of excision. This study design was applied to evaluate the effect of excision of endometrioma in 6 reports so far [14–19]. Five of them reported the lower numbers of co-dominant follicles and/or retrieved oocytes in affected gonads, suggesting a quantitative effect of excision [15–19]. The fate of the retrieved oocytes, that is, a qualitative effect of excision, was assessed only in one paper by Ragni et al. [17]. They showed the fertilization rate and the rate of high quality embryos were similar in oocytes from affected and contra-lateral ovaries, suggesting that excision of endometrioma does not exert a qualitative effect. Unfortunately, as they discussed, they failed to evaluate whether each embryo achieved implantation and pregnancy, the most reliable markers for the quality of an embryo, because more than one embryos were transferred in most cases.

Current lack of the evidence regarding a qualitative effect of excision of endometrioma drove us to conduct the present study comparing the oocytes from the ovary operated for endometrioma to those from the contra-lateral healthy ovary of the same patients. In addition, we took the advantage of our routine practice of single embryo transfer (SET), which enable us to examine the fate of each embryo. The main aim of the present study was to evaluate whether the past laparoscopic excision of endometrioma affects the developmental competence of oocytes recovered from operated ovary.

Material and methods

Cases were the patients who underwent in vitro fertilization (IVF) treatment with COS from May 2010 to April 2013 in our university hospital. Inclusion criteria were as follows: i) a history of laparoscopic excision of unilateral endometrioma over 3 cm in diameter; ii) no other history of intervention for ovaries than laparoscopic surgery mentioned in section i); iii) absence of endometrioma when COS for IVF was conducted; iv) absence of severe male factor which required testicular sperm extraction (TESE). 25 cycles of 21 patients fulfilled the inclusion criteria. All the patients received COS by daily injection of hMG (150–300 IU/day; HMG TEIZO or Gonapure; ASKA Pharmaceutical Co., Tokyo, Japan) with down-regulation by GnRH agonist (Nasanyl; Pfizer Japan., Tokyo, Japan) or antagonist (Ganirest; MSD K.K., Tokyo, Japan). When the leading follicle reached 18–20 mm in diameter, ovulation was induced by a single administration of hCG (10,000 IU; HCG Mochida; Mochida Pharmaceutical Co., Tokyo, Japan). Oocytes were retrieved 34 h after hCG administration.

Oocytes recovered from ovaries with a history of excision of endometrioma (E-Ov) were compared to those from contralateral healthy ovaries (H-Ov). For the analysis of a quantitative effect of surgery, the numbers of oocytes recovered from E-Ov and H-Ov were compared. For the analysis of a qualitative effect of surgery, the oocytes from E-Ov and H-Ov were compared as for normal fertilization rate per oocytes and the rate of top-quality embryos per normally-fertilized embryos. Confirmation of normal fertilization was performed 16–18 h after insemination by appearance of two pronuclei (PN). Top-quality embryos were defined as follows; i) if the embryos were transferred or frozen on day3, >/= 7 blastomeres and >/= grade II (Veeck criteria) on day 3 [20], or ii) if the embryos were cultured until day 5 or 6, >/=grade III and >/=BB (Gardner criteria) on day 5/6 [21]. Furthermore, the embryos from E-Ov and H-Ov were compared as for clinical and on-going pregnancy rates. For this analysis, the only SET cycles were included. Thirty-four embryos were transferred so far in 34 SET cycles. Confirmation of clinical pregnancy was performed by appearance of gestational sac in uterine cavity using transvaginal ultrasonography. On-going pregnancy was defined as pregnancy successfully continued beyond 12 weeks of gestational age.

The numbers of oocytes were compared using Mann Whitney *U* test. Categorical data were compared using Chi-square and Fisher's exact test. Mean values are reported with the SD. $P<0.05$ was considered as statistically significant and all reported *P* values are two-sided.

Results

25 cycles of 21 patients fulfilled the criteria. Table 1 shows the characteristics of the patients and IVF cycles. Mean age of the patients was 37.0±3.4 and mean number of oocytes recovered was 7.3±4.7. There is no cycle without recovered oocytes. Mean diameter of EMoma excised was 5.0±1.2 cm. The median interval between surgery and COS was 22 (IQR 8.8–78.8) months.

To address a quantitative effect, the numbers of oocytes recovered from endometrioma-excised (E-Ov) were compared to those of healthy (H-Ov) side of ovaries. Table 2 shows the results. Mean number of oocytes recovered from E-Ov was 2.2±2.0, which was significantly smaller than that from H-Ov, 5.1±3.3 ($P=0.009$). Moreover, 5 E-Ov (20 % of total E-Ov) yielded no oocyte, which was higher than 5 % of H-Ov, though the difference was not significant ($P=0.082$).

To address a qualitative effect, the oocytes from E-Ov and H-Ov were compared as for normal fertilization rate per oocytes and the rate of top-quality embryos per normally-fertilized embryos. Results were shown in Table 3. The oocytes recovered from E-Ov and H-Ov were same in normal

Table 1 Characteristics of the patients and IVF cycles

	Mean±SD (range), median (IQR), or number (%)
Age (year)	37.0±3.4 (30–43)
Diameter of the endometrioma excised (cm)	5.0±1.2 (4.0–7.0)
Laterality of endometrioma-excised ovary	
right	7 (33.3)
left	14 (66.7)
Interval between surgery and COS (months)	22 (8.8–78.8)
COS protocol	
Long protocol	4 (16.0)
GnRH antagonist protocol	21 (84.0)
Number of oocytes recovered	7.3±4.7 (1–18)
IVF technique used	
* conventional IVF	14 (58.3)
ICSI **	10 (41.7)

COS; controlled ovarian stimulation

* Out of 25 COS cycles, there was one cycle without performing IVF because only one degenerated oocyte was recovered.

** ICSI cycles include cycles performing ICSI for some oocytes and conventional IVF for the others.

fertilization rate (63.6 % vs. 69.5 %) and the rate of top-quality embryos (40.0 % vs. 49.0 %).

Next, for further analysis of a qualitative effect, clinical and on-going pregnancy rates per embryos derived from oocytes recovered from E-Ov and H-Ov were compared in 34 SET cycles. Embryos derived from oocytes recovered from E-Ov were described as E-Em and those from H-Ov as H-Em from now on. Table 4 shows the results comparing 10 E-Em and 24 H-Em. Neither clinical nor on-going pregnancy rate was different between E-Em and H-Em (40.0 % vs. 25.0 % and 20.0 % vs. 20.8 %, respectively).

Discussion

In the present study analyzing 25 IVF cycles with controlled ovarian stimulation, the number of oocytes recovered from the ovary operated for endometrioma was significantly smaller

Table 2 Ovarian response of endometrioma-excised (E-Ov) and healthy (H-Ov) side of ovaries

	E-Ov	H-Ov	P value
Number of oocytes recovered /ovary (Mean±SD)	2.2±2.0	5.1±3.3	0.009*
Cycles without oocytes recovered from unilateral ovary	5	1	
Failure of recovery /ovary (%)	20.0	4.0	0.082**

* Mann Whitney *U* test and

** Chi-square and Fisher's exact test was used, respectively.

Table 3 Normal fertilization rate and the rate of top-quality embryos of oocytes recovered from endometrioma-excised (E-Oo) and healthy (H-Oo) side of ovaries

	E-Oo	H-Oo	P value
Normally fertilized eggs / oocytes (%)	35/55 (63.6)	89/128 (69.5)	0.43
Top-quality embryos /Normally fertilized eggs (%)	14/35 (40.0)	44/89 (49.0)	0.34

Normal fertilization; confirmed by 2 pronuclei top-quality embryo; >/= 7cells and >/= grade II (Veeck criteria) on D3 or >/=grade III and >/= BB (Gardner criteria) on D5/6. Chi-square and Fisher's exact test was used.

than that from contralateral healthy ovary. The rates of normal fertilization, top-quality embryos, clinical pregnancy, and on-going pregnancy were not different between oocytes derived from endometrioma-excised and contra-lateral healthy ovary.

As for a quantitative effect of excision, our results were in line with the previous reports. As for the mechanisms by which the affected gonads yield the lower number of oocytes than contra-lateral healthy gonads, several theories have been proposed. One is the reduction in ovarian volume by simultaneous removal of normal ovarian cortex at surgery [22, 23]. Another is the reduction in vasculature due to hemostasis at surgery and/or inflammation induced by surgery [24, 25].

As for a qualitative effect of excision, the present study showed no deleterious effect of surgery in terms of achieving fertilization, quality of embryos, and achieving pregnancy. As far as our knowledge, the present study is the first paper in English literature evaluating the final fate of each oocyte recovered from endometrioma-excised and contra-lateral healthy ovaries, that is, whether each embryo achieved implantation and pregnancy. Analyzing the results of SET cycles in the present study made it possible to evaluate the final fate of oocytes. We expected that if excision of endometrioma has effects other than the reduction in ovarian cortex, such as the reduction in vasculature, it may also affect the quality of oocytes. Oocytes derived from poorly-vascularized follicles have reported to be associated with lower developmental competence, since an inappropriate microvasculature surrounding

Table 4 Clinical and on-going pregnancy rates per embryos from oocytes recovered from endometrioma-excised (E-Em) and healthy (H-Em) side of ovaries

	E-Em	H-Em	P value
Clinical pregnancy /embryos transferred (%)	4/10 (40.0)	6/24 (25.0)	0.39
On-going pregnancy /embryos transferred (%)	2/10 (20.0)	5/24 (20.8)	0.96

Clinical pregnancy; confirmed by a gestational sac in uterus on-going pregnancy; pregnancy continued beyond 12 weeks of gestational age. Chi-square and Fisher's exact test was used.

a follicle results in hypoxic intra-follicular conditions and reduced levels of oocyte metabolism [26, 27]. However, we did not detect any qualitative effects of excision. One reason might be that the effect of surgery on ovarian vasculature may be temporal, recovering at least in part in certain period after surgery. As for the long-term quantitative effects of excision, Sugita et al. conducted the study evaluating serum AMH levels for up to 12 months after surgery, showing that AMH levels can recover to some extent in some patients [28]. If excision exerts a qualitative effect in the same way as a quantitative effect, relatively long interval (median; 22 months) between surgery and COS in the present study might explain no qualitative difference between oocytes from endometrioma-excised and healthy ovary. However, in contrast to the paper by Sugita, some authors reported no recovery from quantitative damage exerted by excision of endometrioma, though their observation period were shorter than 12 months [29, 30]. The mechanisms by which the excision of endometrioma affects the ovarian function, together with whether the effect is temporal or sustained or even progressive, remain to be elucidated.

One limitation of the present study is the studied population. The present study only included patients undergoing IVF treatment. We should be careful in applying the results of the present study to all the patients with a history of laparoscopic excision of ovarian endometrioma. Another limitation is that the quality of oocytes retrieved in COS cycles was used as a surrogate marker for the quality of oocytes in whole ovary. However, given the current absence of a marker for the quality of oocytes in whole ovary, evaluating the fate of each retrieved oocyte in IVF treatment should be the best way at present to assess the qualitative aspect of ovarian function.

In conclusion, the results from the present study support the following observations: In cohort with the median interval of 22 months between surgery and IVF, (i) laparoscopic excision of ovarian endometrioma impairs the responsiveness of affected ovary to controlled ovarian stimulation, compared to the contra-lateral healthy ovary; and (ii) the quality of oocytes recovered from the ovary with a history of laparoscopic excision of endometrioma is not inferior to the quality of oocytes from contra-lateral healthy ovary.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Eskenazi B, Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin N Am. 1997;24:235–58.
2. Giudice LC. Clinical practice. Endometriosis N Engl J Med. 2010;362:2389–98.
3. Vercellini P, Chapron C, De Giorgi O, Consonni D, Frontino G, Crosignani PG. Coagulation or excision of ovarian endometriomas? Am J Obstet Gynecol. 2003;188:606–10.
4. Gupta S, Goldberg JM, Aziz N, Goldberg E, Krajcir N, Agarwal A. Pathogenic mechanisms in endometriosis-associated infertility. Fertil Steril. 2008;90:247–57.
5. Bulleti C, Coccia ME, Battistoni S, Borini A. Endometriosis and infertility. J Assist Reprod Genet. 2010;27:441–7.
6. Norenstedt SN, Linderoth-Nagy C, Bergendal A, Sjöblom P, Bergqvist A. Reduced developmental potential in oocytes from women with endometriosis. J Assist Reprod Genet. 2001;18:644–9.
7. Allegra A, Raimondo S, Volpes A, Fenale D, Marino A, Cicero G, et al. The gene expression profile of cumulus cells reveals altered pathways in patients with endometriosis. J Assist Reprod Genet. 2014;31:1277–85.
8. La Marca A, Sighinolfi G, Radi D, Argento C, Baraldi E, Artenisio AC, et al. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update. 2010;16:113–30.
9. Somigliana E, Ragni G, Infantino M, Benedetti F, Arnoldi M, Crosignani PG. Does laparoscopic removal of nonendometriotic benign ovarian cysts affect ovarian reserve? Acta Obstet Gynecol Scand. 2006;85:74–7.
10. Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2012;97:3146–54.
11. Rustamov O, Smith A, Roberts SA, Yates AP, Fitzgerald C, Krishnan M, et al. Anti-Mullerian hormone: poor assay reproducibility in a large cohort of subjects suggests sample instability. Hum Reprod. 2012;27:3085–91.
12. Ledger WL. Measurement of antimullerian hormone: not as straightforward as it seems. Fertil Steril. 2014;101:339.
13. Lass A. The fertility potential of women with a single ovary. Hum Reprod Update. 1999;5:546–50.
14. Loh FH, Tan AT, Kumar J, Ng SC. Ovarian response after laparoscopic ovarian cystectomy for endometriotic cysts in 132 monitored cycles. Fertil Steril. 1999;72:316–21.
15. Ho HY, Lee RK, Hwu YM, Lin MH, Su JT, Tsai YC. Poor response of ovaries with endometrioma previously treated with cystectomy to controlled ovarian hyperstimulation. J Assist Reprod Genet. 2002;19:507–11.
16. Somigliana E, Ragni G, Benedetti F, Borroni R, Vegetti W, Crosignani PG. Does laparoscopic excision of endometriotic ovarian cysts significantly affect ovarian reserve? Insights from IVF cycles. Hum Reprod. 2003;18:2450–3.
17. Ragni G, Somigliana E, Benedetti F, Paffoni A, Vegetti W, Restelli L, et al. Damage to ovarian reserve associated with laparoscopic

excision of endometriomas: a quantitative rather than a qualitative injury. Am J Obstet Gynecol. 2005;193:1908–14.
18. Duru NK, Dede M, Acikel CH, Keskin U, Fidan U, Baser I. Outcome of in vitro fertilization and ovarian response after endometrioma stripping at laparoscopy and laparotomy. J Reprod Med. 2007;52:805–9.
19. Almog B, Sheizaf B, Shalom-Paz E, Shehata F, Al-Talib A, Tulandi T. Effects of excision of ovarian endometrioma on the antral follicle count and collected oocytes for in vitro fertilization. Fertil Steril. 2010;94:2340–2.
20. Veeck LL. Preembryo grading and degree of cytoplasmic fragmentation. An atlas of human gametes and conceptuses: an illustrated reference for assisted reproductive technology. NewYork: Parthenon Publishing; 1999. p. 46–51.
21. Gardner DK, Schoolcraft WB. In vitro culture of human blastocysts. In: Jansen R, Mortimer D, editors. Toward reproductive certainty: fertility and genetics beyond. London: Parthenon Publishing; 1999. p. 378–88.
22. Alborzi S, Foroughinia L, Kumar PV, Asadi N, Alborzi S. A comparison of histopathologic findings of ovarian tissue inadvertently excised with endometrioma and other kinds of benign ovarian cyst in patients undergoing laparoscopy versus laparotomy. Fertil Steril. 2009;92:2004–7.
23. Muzii L, Bianchi A, Croce C, Manci N, Panici PB. Laparoscopic excision of ovarian cysts: is the stripping technique a tissue-sparing procedure? Fertil Steril. 2002;77:609–14.
24. La Torre R, Montanino-Oliva M, Marchiani E, Boninfante M, Montanino G, Cosmi EV. Ovarian blood flow before and after conservative laparoscopic treatment for endometrioma. Clin Exp Obstet Gynecol. 1998;25:12–4.
25. Wu MH, Tsai SJ, Pan HA, Hsiao KY, Chang FM. Three-dimensional power Doppler imaging of ovarian stromal blood flow in women with endometriosis undergoing in vitro fertilization. Ultrasound Obstet Gynecol. 2003;21:480–5.
26. Bhal PS, Pugh ND, Chui DK, Gregory L, Walker SM, Shaw RW. The use of transvaginal power Doppler ultrasonography to evaluate the relationship between perifollicular vascularity and outcome in in-vitro fertilization treatment cycles. Hum Reprod. 1999;14:939–45.
27. Borini A, Tallarini A, Maccolini A, Prato LD, Flamigni C. Perifollicular vascularity monitoring and scoring: a clinical tool for selecting the best oocyte. Eur J Obstet Gynecol Reprod Biol. 2004;115 Suppl 1:S102–5.
28. Sugita A, Iwase A, Goto M, Nakahara T, Nakamura T, Kondo M, et al. One-year follow-up of serum antimullerian hormone levels in patients with cystectomy: are different sequential changes due to different mechanisms causing damage to the ovarian reserve? Fertil Steril. 2013;100:516–22.
29. Biacchiardi CP, Piane LD, Camanni M, Deltetto F, Delpiano EM, Marchino GL, et al. Laparoscopic stripping of endometriomas negatively affects ovarian follicular reserve even if performed by experienced surgeons. Reprod BioMed Online. 2011;23:740–6.
30. Celik HG, Dogan E, Okyay E, Ulukus C, Saatli B, Uysal S, et al. Effect of laparoscopic excision of endometriomas on ovarian reserve: serial changes in the serum antimullerian hormone levels. Fertil Steril. 2012;97:1472–8.