Accepted Manuscript

Combination treatment of preoperative embryo cryopreservation and endoscopic surgery (surgery-ART hybrid therapy) in infertile women with diminished ovarian reserve and uterine myomas or ovarian endometriomas

Keiji Kuroda MD , Yuko Ikemoto MD , Asako Ochiai MD , Rie Ozaki MD , Yuko Matsumura MD , Shuko Nojiri , Koji Nakagawa MD , Rikikazu Sugiyama MD

PII: S1553-4650(19)30096-2
DOI: https://doi.org/10.1016/j.jmig.2019.02.008
Reference: JMIG 3750

To appear in: *The Journal of Minimally Invasive Gynecology*

Received date: 4 November 2018
Revised date: 10 February 2019
Accepted date: 13 February 2019

Please cite this article as: Keiji Kuroda MD , Yuko Ikemoto MD , Asako Ochiai MD , Rie Ozaki MD , Yuko Matsumura MD , Shuko Nojiri , Koji Nakagawa MD , Rikikazu Sugiyama MD , Combination treatment of preoperative embryo cryopreservation and endoscopic surgery (surgery-ART hybrid therapy) in infertile women with diminished ovarian reserve and uterine myomas or ovarian endometriomas, *The Journal of Minimally Invasive Gynecology* (2019), doi: https://doi.org/10.1016/j.jmig.2019.02.008

Original Article for *The Journal of Minimally Invasive Gynecology*

Combination treatment of preoperative embryo cryopreservation and endoscopic surgery (surgery-ART hybrid therapy) in infertile women with diminished ovarian reserve and uterine myomas or ovarian endometriomas

Keiji Kuroda, MD, Yuko Ikemoto, MD, Asako Ochiai, MD, Rie Ozaki, MD, Yuko Matsumura, MD, Shuko Nojiri, Koji Nakagawa, MD, Rikikazu Sugiyama, MD

From the Center for Reproductive Medicine and Implantation Research, Sugiyama Clinic Shinjuku, Tokyo, Japan (Drs. Kuroda, Nakagawa, and Sugiyama), Department of Obstetrics and Gynecology, Juntendo University Faculty of Medicine, Tokyo, Japan (Drs. Kuroda, Ikemoto, Ochiai, Ozaki, and Matsumura), Medical Technology Innovation Center, Juntendo University, Tokyo, Japan (Dr. Nojiri), and Clinical Research and Trial Center, Juntendo University Hospital, Tokyo, Japan (Dr. Nojiri).

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

Corresponding author: Keiji Kuroda, MD, PhD, Center for Reproductive Medicine and Implantation Research, Sugiyama Clinic Shinjuku, 1-19-6, Nishishinjuku, Shinjuku-ku, Tokyo, 160-0023, Japan
TEL: +81 3 53813000, FAX: +81 3 53814124, E-mail: kuroda@sugiyama.or.jp

Precis: Embryo freezing and endoscopic surgery in women with diminished ovarian reserve and myomas or ovarian endometriomas (Surgery-ART hybrid therapy)

ABSTRACT

Study Objective: To analyze the clinical outcomes and predictive factors for the therapeutic effect of

combination treatment of preoperative embryo cryopreservation and endoscopic surgery ('surgery-assisted reproductive technology [ART] hybrid therapy') in infertile women with diminished ovarian reserve (DOR) with uterine fibroids and/or ovarian endometriomas.

Design: A retrospective cohort study (Canadian Task Force Classification II-2)

Setting: Data from all patients who underwent surgery-ART hybrid therapy at Juntendo University Hospital and Sugiyama Clinic from 2014 to 2016 were analyzed retrospectively. We compared women who experienced livebirth (success group) and implantation failure or miscarriage (failure group) after surgery-ART hybrid therapy and evaluate the predictive factors for livebirth.

Patients: A total of 39 infertile women underwent surgery-ART hybrid therapy with 86 embryo transfer cycles.

Interventions: All women underwent ART treatment for embryo cryopreservation preoperatively, reproductive surgery and warmed embryos transfer after the postoperative contraceptive interval (surgery-ART hybrid therapy) for women with DOR (anti-Müllerian hormone < 1.0 ng/mL) and/or advanced reproductive age (>40 years) with uterine myomas and/or ovarian endometriomas who required surgery.

Results: Out of 39 women underwent surgery-ART hybrid therapy, one woman acquired no embryo after oocyte retrieval trials and gave up conceiving, 14 experienced childbirth (success group) and 24 (63.2%) experienced implantation failure or miscarriage (failure group) after surgery-ART hybrid therapy. Women in the success and failure groups were 40 (38-41) and 41.5 (41-42) years old [median (interquartile range)] ($p = .0318$) and had 2.5 (0.1-8.6) and 1.3 (0.1-4.2) ng/mL serum anti-Müllerian hormone levels [median (range)] ($p = .396$), respectively. The numbers of preoperative frozen embryos in the success and failure groups were 5.0 (4.0-6.0) and 2.0 (1.0-3.0), respectively ($p < .001$). There were no significant differences in surgical findings of myomas and endometriosis in the two groups. The 14 women who underwent successful surgery-ART hybrid therapy were significantly younger and had a larger number of cryopreserved embryos than the 24 who experienced hybrid therapy failure.

Conclusion: Successful surgery-ART hybrid therapy requires preoperative sufficient age-specific number of frozen embryos, establishment of ART treatment with stable pregnancy outcomes and skillful reproductive surgery and the strong wills of patients and doctors for pregnancy.

Keywords: Assisted reproductive technology; Endoscopic surgery; Fertility preservation; Myoma; Endometriosis

Female aging leads to decreased quality and quantity of oocytes [1-5]. Advance-aged women also are a high risk population for development of uterine tumor and endometriosis; therefore, the age at desire for childbearing currently overlaps with this period [6, 7]. Uterine disorders with uterine cavity distortion, such as submucosal myomas, interfere with embryo implantation, whereas based on assisted reproductive technology (ART) data with donated oocytes, the implantation rate is not decreased by aging without uterine tumor [8].

ART is the most effective infertility treatment; however, ART for aged women remains unsatisfactory due to low implantation and high miscarriage rates caused by diminished ovarian reserve (DOR) and uterine disorders [9]. Endoscopic surgery is to gold standard for women with uterine myomas and endometriosis; however, preoperative treatment, such as with a gonadotropin-releasing hormone (GnRH) analogue, has been demonstrated to improve surgical outcomes [10]. Regarding myomas, a postoperative contraception period also is needed due to myometrial wound healing to prevent uterine rupture during pregnancy [11, 12]. In endometriosis, oocyte loss is a serious issue of cystectomy for ovarian endometriomas [13, 14]. Therefore, it is debatable whether infertility treatment or surgery should be the first choice for aged reproductive women with uterine tumors and/or endometriomas. In 2009, we first reported successful live births after a combination of ART for embryo cryopreservation and surgery, named ‘surgery-ART hybrid therapy’ in advance-aged infertile women with multiple myomas [15].

We analyzed the clinical outcomes and predictive factors for the therapeutic effect of surgery-ART hybrid therapy.

Methods

Patient Selection

This study was approved by the local ethics committee of Juntendo University, Faculty of Medicine (No. 16-158) and Sugiyama Clinic (No. 16-001). We performed ART for embryo cryopreservation preoperatively and reproductive surgery (surgery-ART hybrid therapy) for 39 patients who met the following conditions: visiting Juntendo University Hospital between 2014 and 2016, informed consent by K.K., poor prognosis for successful pregnancy with DOR (anti-Müllerian hormone < 1.0 ng/mL) and/or advanced age (>40 years), uterine myomas and/or ovarian endometriomas requiring surgery, women who aimed to preserve >3–5 frozen embryos preoperatively at Juntendo University Hospital or Sugiyama

Clinic and laparoscopic surgery performed by K.K at Juntendo University Hospital.

Indication for Surgery

Regarding uterine leiomyomas, the indication for surgery were cases felt to be at high risk of implantation failure and complications during pregnancy. We assessed leiomyomas using magnetic resonance imaging, hysteroscopy and hysterography as appropriate. Submucosal or intramural myomas that protrude or compress into the uterine cavity cause implantation failure [16, 17]. In cases of intramural myomas, whether surgery should be done before pregnancy often is debatable. Intramural myomas with symptoms, such as abnormal uterine bleeding have a potential for obstruction of embryo implantation [16]. Therefore, we included them in the indication. For complications of pregnancy by leiomyomas, it is difficult to assess which uterine myomas increase the risk, because myomas have varied sizes, numbers and locations in the uterus and their volume may be changed during pregnancy [16]. In any case, when considering complications in pregnancy, such as pelvic pain with degeneration of myomas, miscarriage, preterm birth and postpartum hemorrhage, myomas >10 cm in diameter also are indicated for surgery [18].

In endometriosis, most endometriotic lesions are shrunken after pregnancy [19]. According to the European Society for Human Reproduction and Embryology (ESHRE) guideline, there is no evidence that cystectomy for ovarian endometriomas before ART treatment increases pregnancy outcomes in infertile women [20]. However, some large ovarian endometriomas are ruptured, developed abscess and grow with intratumoural decidual change [21]. Therefore, we decided that endometriomas >5cm in their greatest diameter are indicated for surgery.

Preoperative Cryopreservation of Embryos

Regarding preoperative embryo freezing, procedures for controlled ovarian stimulation, oocyte retrieval and in vitro fertilization (IVF)-embryo transfer (ET) have been described previously [22]. Briefly, in controlled ovarian stimulation approaches, clomiphene citrate-recombinant follicle-stimulating hormone (rFSH) or human menopausal gonadotropin (hMG), or GnRH antagonist cycles were chosen depending on the ovarian reserve status and previous ART data. In the clomiphene-rFSH or hMG cycle, infertile women received 50 mg clomiphene citrate (Clomid®, Fuji Pharma, Tokyo, Japan) once daily for 5 days starting at day 3 of the menstruation cycle, and 150–300 IU rFSH (Gonal-f®, Merck, Tokyo, Japan) or hMG (HMG Ferring, Ferring Pharmaceuticals, Tokyo, Japan) administered on cycle days 4, 6

and 8. In the GnRH antagonist cycle, 225–300 IU hMG was administered on consecutive days 3 to 6. On menstrual day 7, when dominant follicles ≥15 mm in diameter were confirmed, 0.25 mg GnRH antagonist (Cetrotede®, Shionogi & Co. Ltd., Tokyo, Japan) injection also was begun with the hMG injection. When dominant follicles ≥17 mm were confirmed, either 5,000 or 10,000 IU of human chorionic gonadotropin (Gonatropin®, Aska Pharmaceutical Co. Ltd., Tokyo, Japan) injection or 300 μg nasal buserelin acetate spray (Sprecur® nasal solution 0.15%, Mochida Pharmaceutical Co., Tokyo, Japan) was administered. Two days later, we aspirated follicles transvaginally and performed conventional IVF or intracytoplasmic sperm injection depending on spermatic findings and previous fertilization rates at Juntendo University Hospital or Sugiyama Clinic. Cleavage stage embryos at 2–3 days or blastocysts at 5–6 days after fertilization were recognized and cryopreserved once. Morphologically and developmentally competent embryos were defined as grades 1–3 of the Veeck classification and ≥6-cell embryos in cleavage stage at day 3 after fertilization and 5- or 6-day blastocysts after fertilization except for grade C in both the inner cell mass and the trophectoderm of the Gardner classification.

Laparoscopic Surgery

After embryo freezing, the GnRH agonist, Leuprorelin acetate (Leuplin®, Takeda, Tokyo, Japan) or Goserelin acetate (Zoladex® 1.8 mg depot; Kissei Pharmaceutical, Matsumoto, Japan), was injected every 4 weeks for 2–4 months as preoperative treatment and planned laparoscopic myomectomy or cystectomy.

An experienced surgeon (K.K.) performed all laparoscopic surgeries at Juntendo University Hospital. The surgical procedures for laparoscopic myomectomy and cystectomy have been described previously [22, 23]. Briefly, we usually performed the 4-puncture method with the patient under general anesthesia by endotracheal intubation in the lithotomy position. In myomectomy, vasopressin (20 IU in 1 mL diluted 100 times with saline) was infused between the myoma capsule and the normal muscle layer [24], and a horizontal incision was made above the myoma using a monopolar needle. The myoma was enucleated using a myoma screw. A 2–4-layer running 0 Polysorb (Tyco Healthcare, Tokyo, Japan) suture was used to close the myometrial layer to avoid forming a dead space. A mattress suture was used to close the serous layer. In ovarian cystectomy, we removed the ovarian cyst walls as a stripping method and closed the ovarian defect using 2-0 Polysorb purse string sutures. At operation, we examined the severity of endometriosis using the revised American Society for Reproductive Medicine (re-ASRM) score.

We decided that the postoperative contraceptive period after myomectomy was 6 months at Juntendo University Hospital to allow for wound healing of the uterine musculature. However, cryopreservation of

embryos was allowed after restart of menstruation during the contraceptive period. Regarding cystectomy, there was no need to have the contraceptive interval until ET. Afterwards, warmed embryos were transferred into the uterus using trans-vaginal ultrasound guidance.

Statistical Analysis

The data are presented as n (%) or median with interquartile range for quantitative and percentage for qualitative parameters. Shapiro-Wilk was used for evaluating normal distribution for quantitative data. Mann-Whitney U-test was applied in order to compare the parameters or independent samples. Categorical variables were compared with the Fisher's exact test. All statistical analyses were performed with GraphPad Prism ver.6.07 for Windows (GraphPad Software, San Diego, CA, USA). Statistical significance was defined as $P < 0.05$.

Our study design is a retrospective cohort study, using data from all patients who underwent surgery-ART hybrid therapy at Juntendo University Hospital and Sugiyama Clinic from 2014 to 2016 and compared women who experienced livebirth (success group) and implantation failure or miscarriage (failure group) after this therapy, analyzing statistically. Our study sample size is not enough to make conclusion, owing to the study feasibility, and our study results were preliminary and was an explored study, however, as the exploratory analysis, we believe our study results should be paid attention and have important clues for future direction of the study.

Results

A total of 39 women met the conditions of surgery-ART hybrid therapy and their characteristics are shown in Supplemental Table 1. One woman acquired no embryo after two oocyte retrieval trials and decided not to pursue further interventions. Fourteen (36.8%) experienced livebirth (success group) and 24 (63.2%) experienced implantation failure or miscarriage (failure group) after surgery-ART hybrid therapy (Fig. 1).

The characteristics of the patients in the two groups are shown in Table 1. The women in the success group [median (interquartile range)] were significantly younger than those in the failure group [40 (38-41) and 41.5 (41-42) years, respectively, p = .0318]. As for serum anti-Müllerian hormone levels [median (range)], there was no significant difference [2.5 (0.1-8.6) and 1.3 (0.1-4.2) ng/mL, respectively, p = .396]. Regarding embryo cryopreservation, the numbers of preoperative frozen embryos

in the success and failure groups [median (interquartile range)] were 5.0 (4.0-6.0) and 2.0 (1.0-3.0), respectively ($p < .001$), and the numbers of morphologically and developmentally competent embryos were 3.0 (2.0-5.0) and 1.0 (0-1.0), respectively ($p < .001$; Table 2). In particular, the number of frozen blastocysts in success group were significantly larger than that in failure group ($p < .001$). We recommended three to five frozen embryos preoperatively; however, 10 patients (41.7%) in the failure group obtained only one or two embryos.

The surgical findings are shown in Table 3. The success and failure groups [median (interquartile range)] had 3.5 (1.0-9.5) and 4.0 (1.0-8.5) uterine myomas ($p = .881$) with a diameter of 5.5 (2.0-10.0) and 8.0 (5.5-9.5) cm ($p = .234$), respectively. In endometriosis, there were no significant differences in the size of ovarian endometriomas and severity of endometriosis with re-ASRM scores. The findings of uterine myomas and endometriosis did not contribute to a success rate in surgery-ART hybrid therapy.

When comparing between 30 ET cycles in the success group and 56 in the failure groups, 1.1 transferred embryos per ET in both groups produced 73.3% (22 ET) and 10.0% (10 ET) clinical pregnancy rates and 46.7% (14 ET) and 0% (0 ET) livebirth rates, respectively (Table 4).

Discussion

Changes in the female lifestyle have led to a trend for later marriage. The aging of women has two critical problems for fecundity: decreased egg quality and quantity and an increased incidence of uterine disease and endometriosis. Aged oocytes are strongly associated with an increased rate of chromosomal anomalies, leading to a high incidence of reproductive failure, including implantation failure and pregnancy loss [9, 25-27]. Therefore, it is important to obtain embryos as early and as much as possible to optimize the odds of livebirth in advanced reproductive aged women with fibroids and/or endometriosis requiring surgery. Surgery-ART hybrid therapy minimizes degradation of time-dependent oocyte factors while a patient awaits surgery and recovers through upfront cryopreservation.

In this study, of 38 patients with advanced age or DOR, 14 achieved successful pregnancy after surgery-ART hybrid therapy (36.8%). The 14 women who underwent successful surgery-ART hybrid therapy were significantly younger and had a larger number of cryopreserved embryos compared to those who had surgery-ART hybrid therapy failure. We recommended three to five frozen embryos preoperatively; however, the average number of embryos was only 2.0 in the failure group. It is quite

difficult to predict the individual number of frozen embryos that can produce a sufficient livebirth rate. Most women do not have accurate information on female fertility decline with aging and age-specific pregnancy outcomes of IVF before ART treatment [28]. In our study, most of the patients had no experience with ART treatment; therefore, they might expect that preoperative frozen embryos can produce higher successful pregnancy rates, comparing to actual outcomes depending on their age. According to Japanese ART data in 2015, the clinical pregnancy rate of 36-year-old women is 37.2% per one ET cycle, including 21.6% for miscarriage, resulting in a 27.4% livebirth rate (Supplemental table 2) [29]. The livebirth rate for 40-year-old women is 16.0% per ET. In Japan, more than 80% of ET cycles are single embryo transfers; thus, the pregnancy outcomes per ET are approximate to those per single embryo. If 36-year-old women desire 50% or 80% cumulative livebirth rates, they must aim for three or six frozen embryos, respectively (Supplemental table 2). For 40-year-old women, four or nine embryos are needed, respectively. Counselling regarding livebirth rates and number of frozen embryos is based on this ART data. Although some countries, including Japan, have imposed restrictions on the use of chromosomal testing of embryos, frozen euploid embryos after preimplantation genetic testing must have a good prognosis for pregnancy in cases of surgery-ART hybrid therapy [30].

To increase the successful pregnancy rate with this therapy, maximum collection of oocytes preoperatively is important. However, in women with DOR, obtaining the ideal number of frozen embryos is difficult. To collect as many oocytes as possible, double stimulation during the follicular and luteal phases has been reported as the Shanghai protocol [31]. Lin et al [32] also reported that oocyte retrievals after ovarian stimulation during the luteal phase in women with poor ovarian response obtained a larger number of eggs and higher quality oocytes compared to those obtained during the follicular phase. Furthermore, in women with hypergonadotropic DOR, continuous clomiphene citrate and estradiol administration is an effective stimulation with a lower cancellation rate of oocyte retrieval and larger number of retrieved eggs [33]. To improve oocyte quality, supplementation with dehydroepiandrosterone (DHEA), a human growth hormone, resveratrol, melatonin, and myo-inositol during ART treatment may be an effective alternative [34-36].

We performed surgery for leiomyomas and endometriosis in cases with a high risk of implantation failure and complications during pregnancy; however, it is difficult to predict the increased risk of complications during pregnancy. Most ovarian endometriomas are shrunken after conception [19], but complications of endometriosis in pregnancy, including acute hemoperitoneum, are rare [37, 38]. Uterine

myomas are mainly enlarged during the first trimester of pregnancy; however, prediction of the likelihood to modify their size during pregnancy is also difficult [16, 39]. Furthermore, there is no evidence whether surgery would prevent the adverse effects of leiomyomas or endometriosis on pregnancy outcomes [38, 39]. Therefore, our indications for surgery were considered to be submucosal or intramural myomas that protrude into the uterine cavity, myomas >10 cm in diameter, and ovarian endometriomas >5 cm in diameter.

Surgery-ART hybrid therapy has advantages and disadvantages. Surgery-ART hybrid therapy can not only reduce the risk of implantation failure, but also the complications of pregnancy associated with uterine myomas and endometriosis, such as pregnancy loss, preterm birth and endometrioma rupture. By contrast, patients must undergo surgery and ART treatment; thus, causing a physical, temporal, and financial burden to the patients. In fact, most women in the failure group abandoned their desire to have a child after all frozen embryos had been transferred. Also, skillful surgical and IVF techniques are required in this therapy, therefore reproductive specialists and surgical experts can cooperatively treat the patients. In addition, surgery-ART hybrid therapy has no indication for patients with large myomas or endometriomas, which interfere with oocyte retrieval.

This study has some limitations. First, this is a retrospective cohort study. Second, we did not compare pregnancy outcomes in patients who underwent IVF treatment, surgery only, or no treatment. Third, the number of patients was small, which made it difficult to draw conclusions from the data.

Conclusion

To our knowledge, this is the first study of combination treatment consisting of preoperative embryo cryopreservation and endoscopic surgery in women with decreased ovarian function with myomas or endometriomas. Successful surgery-ART hybrid therapy requires preoperative cryopreservation of an age-dependent number of embryos, establishment of ART treatment with stable pregnancy outcomes and skillful reproductive surgery and the strong wills of patients and doctors for pregnancy.

Acknowledgements

We wish to thank all participating patients in study of surgery ART hybrid therapy. Keiji Kuroda was supported by JSPS KAKENHI Grant Number 18K09273.

References

1. te Velde ER, Pearson PL. The variability of female reproductive ageing. *Hum Reprod Update*. 2002; 8:141-154.
2. Schwartz D, Mayaux MJ. Female fecundity as a function of age: results of artificial insemination in 2193 nulliparous women with azoospermic husbands. Federation CECOS. *N Engl J Med*. 1982; 306:404-406.
3. van Noord-Zaadstra BM, Looman CW, Alsbach H, Habbema JD, te Velde ER, Karbaat J. Delaying childbearing: effect of age on fecundity and outcome of pregnancy. *BMJ*. 1991; 302:1361-1365.
4. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. *Hum Reprod*. 1992; 7:1342-1346.
5. Broekmans FJ, Soules MR, Fauser BC. Ovarian Aging: Mechanisms and Clinical Consequences. *Endocrine Reviews*. 2009; 30:465-493.
6. Payson M, Leppert P, Segars J. Epidemiology of myomas. *Obstet Gynecol Clin North Am*. 2006; 33:1-11.
7. Haas D, Chvatal R, Reichert B, et al. Endometriosis: a premenopausal disease? Age pattern in 42,079 patients with endometriosis. *Arch Gynecol Obstet.* 2012; 286:667-670.
8. Toner JP, Grainger DA, Frazier LM, Registry Res Comm SA. Clinical outcomes among recipients of donated eggs: an analysis of the US national experience, 1996-1998. *Fertil Steril*. 2002; 78:1038-1045.
9. Baird DT, Collins J, Egozcue J, et al. Fertility and ageing. *Hum Reprod Update*. 2005; 11:261-276.
10. Kongnyuy EJ, Wiysonge CS. Interventions to reduce haemorrhage during myomectomy for fibroids. *Cochrane Database Syst Rev*. 2007;24: Cd005355.
11. Nkemayim DC, Hammadeh ME, Hippach M, Mink D, Schmidt W. Uterine rupture in pregnancy subsequent to previous laparoscopic electromyolysis - Case report and review of the literature. *Arch Gynecol Obstet* 2000; 264:154-156.
12. Lieng M, Istre O, Langebrekke A. Uterine rupture after laparoscopic myomectomy. *J Am Assoc Gynecol Laparosc*. 2004; 11:92-93.
13. Matsuzaki S, Houlle C, Darcha C, Pouly JL, Mage G, Canis M. Analysis of risk factors for the removal of normal ovarian tissue during laparoscopic cystectomy for ovarian endometriosis. *Hum Reprod*. 2009; 24:1402-1406.
14. Kuroda M, Kuroda K, Arakawa A, et al. Histological assessment of impact of ovarian endometrioma and laparoscopic cystectomy on ovarian reserve. *J Obstet Gynaecol Res*. 2012; 38:1187-1193.

15. Kuroda K, Takeuchi H, Kitade M, et al. Surgery-assisted reproductive technology hybrid therapy: A reproductive procedure for an infertile woman of late reproductive age with multiple myomas. *J Obstet Gynaecol Res*. 2009; 35:827-831.
16. Marret H, Fritel X, Ouldamer L, et al. Therapeutic management of uterine fibroid tumors: updated French guidelines. *Euro J Obstet Gynecol Reprod Biol*. 2012; 165:156-164.
17. Pritts EA, Parker WH, Olive DL: Fibroids and infertility: an updated systematic review of the evidence. *Fertil Steril* 2009; 91**:**1215-1223.
18. Exacoustos C, Rosati P. Ultrasound diagnosis of uterine myomas and complications in pregnancy. *Obstet Gynecol*. 1993; 82:97-101.
19. McArthur JW, Ulfelder H. The effect of pregnancy upon endometriosis. *Obstet Gynecol Surv*. 1965; 20:709-733.
20. Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod.* 2014; 29:400-412.
21. Ueda Y, Enomoto T, Miyatake T, et al. A retrospective analysis of ovarian endometriosis during pregnancy. *Fertil Steril*. 2010; 94:78-84.
22. Kuroda K, Kitade M, Kikuchi I, et al. The impact of endometriosis, endometrioma and ovarian cystectomy on assisted reproductive technology. *Reprod Med Biol*. 2009; 8:113-118.
23. Takeuchi H, Kuwatsuru R. The indications, surgical techniques, and limitations of laparoscopic myomectomy. *JSLS*. 2003; 7:89-95.
24. Shimanuki H, Takeuchi H, Kitade M, Kikuchi I, Kumakiri J, Kinoshita K. The effect of vasopressin on local and general circulation during laparoscopic surgery. *J Minim Invasive Gynecol.* 2006; 13:190-194.
25. Pellestor F, Andreo B, Arnal F, Humeau C, Demaille J. Maternal aging and chromosomal abnormalities: new data drawn from in vitro unfertilized human oocytes. *Hum Genet*. 2003; 112:195-203.
26. Munne S, Alikani M, Tomkin G, Grifo J, Cohen J. Embryo morphology, developmental rates, and maternal age are correlated with chromosome abnormalities. *Fertil Steril.* 1995; 64:382-391.
27. Plachot M, Veiga A, Montagut J, et al. Are clinical and biological IVF parameters correlated with chromosomal disorders in early life: a multicentric study. *Hum Reprod*. 1988; 3:627-635.
28. Mac Dougall K, Beyene Y, Nachtigall RD. Age shock: misperceptions of the impact of age on fertility before and after IVF in women who conceived after age 40. *Hum Reprod*. 2013; 28:350-356.
29. Saito H, Jwa SC, Kuwahara A, et al. Assisted reproductive technology in Japan: a summary report for 2015 by The Ethics Committee of The Japan Society of Obstetrics and Gynecology. *Reprod Med Biol*. 2018; 17:20-28.

30. Coates A, Kung A, Mounts E, et al. Optimal euploid embryo transfer strategy, fresh versus frozen, after preimplantation genetic screening with next generation sequencing: a randomized controlled trial. *Fertil Steril* 2017; 107:723-730.e723.
31. Kuang Y, Chen Q, Hong Q, et al. Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol). *Reprod Biomed Online* 2014; 29:684-691.
32. Lin LT, Vitale SG, Chen SN, et al. Luteal Phase Ovarian Stimulation May Improve Oocyte Retrieval and Oocyte Quality in Poor Ovarian Responders Undergoing In Vitro Fertilization: Preliminary Results from a Single-Center Prospective Pilot Study. *Adv Ther* 2018; 35:847-856.
33. Kuroda K, Kitade M, Kumakiri J, et al. Minimum ovarian stimulation involving combined clomiphene citrate and estradiol treatment for in vitro fertilization of Bologna-criteria poor ovarian responders. *J Obstet Gynaecol Res* 2016, 42:178-183.
34. Vitale SG, Rossetti P, Corrado F, et al. How to Achieve High-Quality Oocytes? The Key Role of Myo-Inositol and Melatonin. *Int J Endocrinol* 2016; 2016:4987436
35. Gonda KJ, Domar AD, Gleicher N, Marrs RP. Insights from clinical experience in treating IVF poor responders. *Reprod Biomed Online* 2018; 36:12-19.
36. Liu MJ, Sun AG, Zhao SG, et al. Resveratrol improves in vitro maturation of oocytes in aged mice and humans. *Fertil Steril* 2018; 109:900-907.
37. Brosens I, Brosens JJ, Fusi L, Al-Sabbagh M, Kuroda K, Benagiano G. Risks of adverse pregnancy outcome in endometriosis. *Fertil Steril* 2012; 98:30-35.
38. Leone Roberti Maggiore U, Ferrero S, Mangili G, et al. A systematic review on endometriosis during pregnancy: diagnosis, misdiagnosis, complications and outcomes. *Hum Reprod Update* 2016; 22:70-103.
39. Vitagliano A, Noventa M, Di Spiezio Sardo A, et al. Uterine fibroid size modifications during pregnancy and puerperium: evidence from the first systematic review of literature. *Arch Gynecol Obstet* 2018; 297:823-835

Figure legends

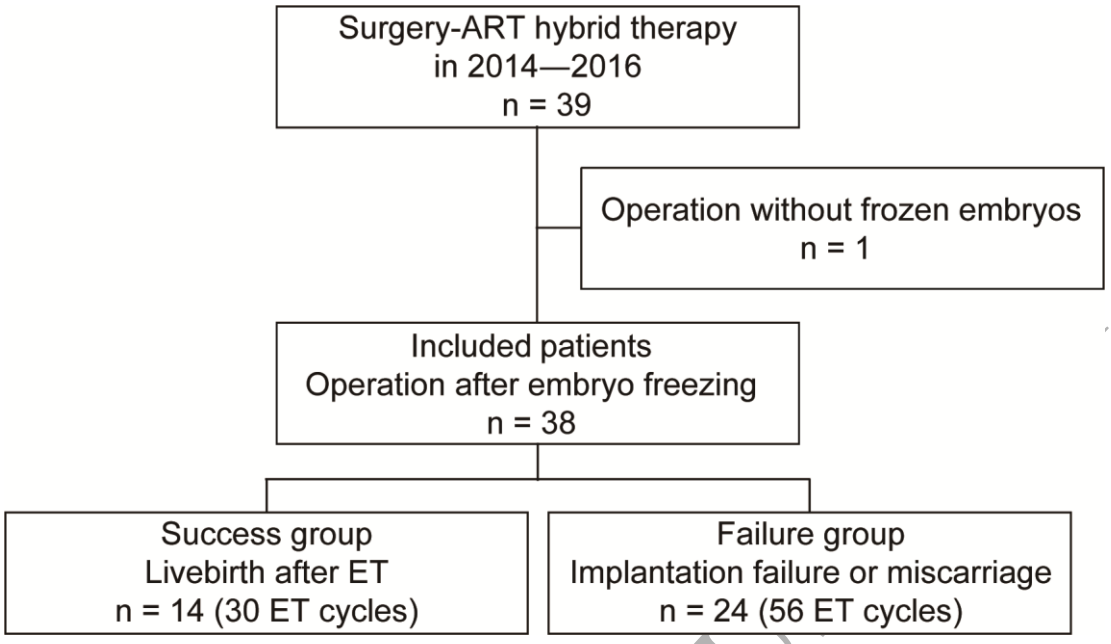

Figure 1. Flowchart of patients in surgery-ART hybrid therapy. A total of 39 women met the conditions of surgery-ART hybrid therapy. One woman acquired no embryo after two oocyte retrieval trials and unfortunately gave up her chance for childbirth. Of 38 women, 14 (36.8%) experienced childbearing (success group) after 30 embryo transfer (ET) cycles and 24 (63.2%) experienced implantation failure or miscarriage (failure group) after 56 ET cycles.

Table 1. Characteristics of patients

	Success group n = 14	Failure group n = 24	*P*
Age (years)*	40 (38-41)	41.5 (41-42)	*.0318*‡§
Pregnancy history*			
Gravida	0 (0-2)	0 (0-1)	.772§
Parity	0 (0)	0 (0)	1.000§
Duration of infertility (year)*	1.0 (1.0-8.0)	2.5 (1.5-4.0)	.134§
AMH (ng/mL) **	2.5 (0.1-8.6)	1.3 (0.1-4.2)	.396§
Indication for surgery†			
Myoma	12 (85.7)	24 (100)	.129¶
Endometriosis	6 (42.3)	10 (41.7)	1.000¶

AMH = anti-Müllerian hormone

* Variable, provided in median (interquartile range).

** Variable, provided in median (range).

† Variable, provided in n (%).

‡ Italic numbers indicate statistical significance.

§ Mann-Whitney *U* test

¶ Fisher's exact test

Table 2. Preoperative IVF and cryopreservation of embryos

	Success group *n* = 14	Failure group *n* = 24	*P*
Oocyte retrieval cycle*	3.0 (1.0-3.0)	2.0 (1.5-2.0)	.219§
Number of cryopreserved embryos*	5.0 (4.0-6.0)	2.0 (1.0-3.0)	< *.001*‡§
Cleavage embryo	2.0 (0-3.0)	2.0 (1.0-2.5)	.762§
Blastocyst	2.0 (1.0-5.0)	0 (0-0)	< *.001*‡§
Number of competent embryos*†	3.0 (2.0-5.0)	1.0 (0-1.0)	< *.001*‡§
Cleavage embryo	0.5 (0-1.0)	1.0 (0-1.0)	.891§
Blastocyst	2.0 (1.0-4.0)	0 (0-0)	< *.001*‡§
Embryo transfer cycle*	3.0 (1.0-3.0)	2.0 (2.0-3.0)	.726§

* Variable, provided in median (interquartile range).

† Competent embryos were defined as grades 1–3 of the Veeck classification and ≥6-cell embryos in cleavage stage at day 3 after fertilization and 5- or 6-day blastocysts after fertilization except for grade C in both the inner cell mass and the trophectoderm of the Gardner classification.

‡ Italic numbers indicate statistical significance.

§ Mann-Whitney *U* test

Table 3. Surgery findings during laparoscopy

	Success group	Failure group	*P*
Myoma	**n = 12**	**n = 24**	
Number of myomas*	3.5 (1.0-9.5)	4.0 (1.0-8.5)	.881†
Diameter of myomas (cm)*	5.5 (2.0-10.0)	8.0 (5.5-9.5)	.234†
Ovarian endometrioma	**n = 6**	**n = 10**	
Unilateral / Bilateral	4 / 2	7 / 3	1.000‡
Diameter of endometrioma (cm)*	6.0 (5.0-7.0)	7.0 (5.0-8.5)	.536†
Revised ASRM score (points)*	51.0 (30.0-120.5)	61.5 (32.0-108.0)	.915†

* Variable, provided in median (interquartile range).

† Mann-Whitney *U* test

‡ Fisher's exact test

Table 4. Pregnancy outcomes after frozen-warmed embryo transfer

	Success group n = 30	Failure group n = 56	*P*
Number of embryos transferred*	1.0 (1.0-1.0)	1.0 (1.0-1.0)	.934§
Clinical pregnancy rate†	22 (73.3)	7 (10.0)	*.014*‡¶
Livebirth rate†	14 (46.7)	0 (0)	*.006*‡¶

* Variable, provided in median (interquartile range).

† Variable, provided in n (%).

‡ Italic numbers indicate statistical significance.

[§] Mann-Whitney *U* test

[¶] Fisher's exact test