

# Management of a Nulliparous IVF Patient with a Declined Ovarian Reserve After Discovery of an Atypical Ovarian Endometriotic Cyst

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**Purpose:** Endometriosis (EM) is a common cause of infertility, and an ovarian endometriotic cyst may affect the ovarian reserve, ovulation, and endometrial receptivity. The majority of EM cases are benign; however, EM may also be prone to malignant transformation, associated with infiltrative growth, and recurrent or distant metastasis. In this study, we report the management of an atypical cyst discovered through ovarian endometriotic cyst puncture prior to controlled ovarian stimulation (COS).

**Case Presentation:** The patient required in vitro fertilization treatment due to EM and bilateral fallopian tube obstruction. Prior to initiating gonadotropin (Gn) treatment, the right ovarian EM cyst was punctured; cytological pathology of the obtained fluid revealed an atypical morphology. Subsequently, the case was discussed with the patient and ethically reviewed. Gn was initiated according to the patient's wishes, and six day-3 embryos were finally obtained and cryopreserved. Afterwards, laparoscopic cystectomy of the ovarian endometrioma revealed no malignant transformation. The patient achieved clinical pregnancy after resuscitation and transplantation of the embryo.

**Conclusion:** In summary, patients with EM-associated infertility are at risk of ovarian cancer formation when undergoing assisted reproduction treatment; therefore, this risk should be evaluated and minimized before initiating such treatment.

**Keywords:** ovarian cyst, endometriosis, atypical cyst, in vitro fertilization, cyst puncture

## Introduction

Endometriosis (EM) is the most common reason female patients request assisted reproduction, as it results in an infertility rate of as high as 30%–50%.<sup>1</sup> Ectopic endometrial tissue on the ovary is referred to as an ovarian endometriotic cyst, which is a common type of ovarian cyst. It may affect the ovarian reserve, ovulation, and the endometrial receptivity, resulting in infertility. Before assisted reproduction and surgical treatment for endometriosis are implemented, comprehensive assessment of ovarian cyst size and ovarian reserve should be conducted to determine the appropriate order in which these should be performed.

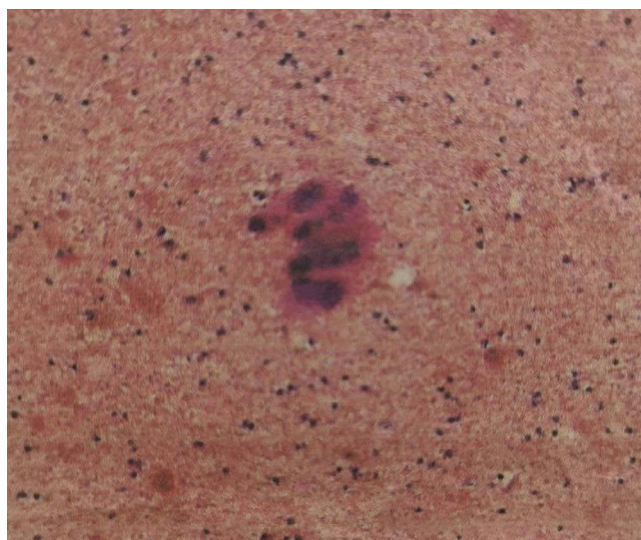
Cyst puncture is a surgical procedure commonly performed during the assisted reproduction process, whereas cystectomy should be avoided before assisted reproduction, especially for patients with a decreased ovarian reserve.<sup>2,3</sup> Cyst puncture preserves ovarian function and facilitates subsequent controlled ovarian stimulation (COS). Ultrasound-guided, transvaginal ovarian cyst puncture is associated with benefits such as little bleeding, low cost, and high patient acceptance; in addition, it reduces the risk of injury to normal ovarian tissues posed by cyst stripping surgery.<sup>4,5</sup> At the same time, it is a convenient technique for the ultrasonic counting of antral follicles and monitoring of follicle size, and has little influence on subsequent COS. Moreover, for infertile patients receiving assisted reproduction due to EM, particularly those who reject laparoscopic surgery, it reduces the risk of malignant transformation of EM and improves the clinical pregnancy rate.

After ovarian cyst puncture, fluid from the cyst should be subjected to cytological examination. To our knowledge, the management of a patient in whom an atypical ovarian endometriotic cyst was discovered prior to Gn administration, has not been reported. After approximately 20 years of performing assisted reproduction at our reproductive center, we report our first case of such a discovery upon cyst puncture before initiating COS for in vitro fertilization (IVF) treatment.

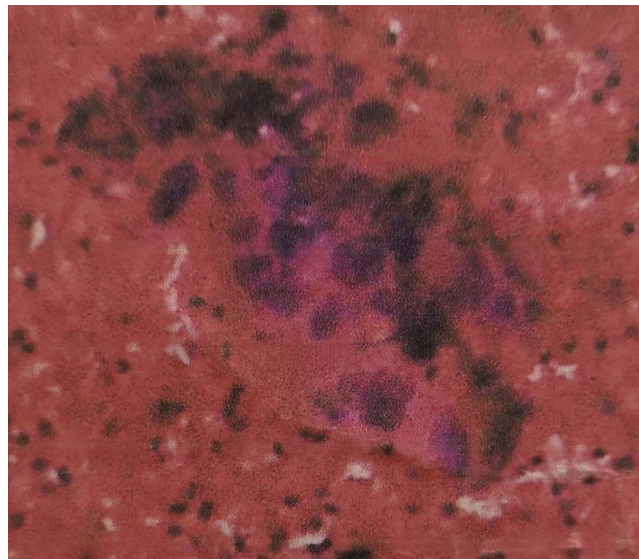
## Case Presentation

A 33-year-old female (G0P0) had attempted pregnancy for more than two years of regular, unprotected sexual intercourse. Her menstruation was regular, with normal ovulation and an anti-Müllerian hormone concentration of 1.03 ng/mL. Her basic endocrine parameters were as follows: follicle-stimulating hormone (FSH), 10.3 IU/L; luteinizing hormone (LH), 6.5 IU/L; and estradiol (E2), 127 pmol/mL. She had 5–6 antral follicles, experienced moderate dysmenorrhea, and had a CA125 concentration of 23.6 IU/mL. B-mode ultrasound revealed two dense, dot-like echoes of  $4.4 \times 3.5$  and  $1.8 \times 1.5$  cm, respectively, in the right ovary, consistent with chocolate cysts; hysterosalpingography revealed a normal uterus, distal obstruction of the right fallopian tube, and proximal obstruction of the left fallopian tube. The patient had no history of surgery and no known family history of malignancy. Gynecological examination revealed the following: a vulva typical of a nulliparous, sexually active female; smooth vaginal mucosa; no haphalgescic nodules in the posterior fornix; a smooth cervix; an anteverted, normal-sized uterus with fair activity; and in the right adnexa, a cyst the size of a hen's egg, exhibiting no tenderness. Semen examination of the husband revealed no abnormalities. Karyotype analysis was normal for both the patient and her husband. We diagnosed the patient with primary infertility; an ovarian endometriotic cyst; a pelvic inflammatory disease sequela (bilateral fallopian tube obstruction); and a declined ovarian reserve. Considering her declined ovarian reserve, surgery might have further reduced ovarian function.

We carefully explained the findings to the patient and her husband, and recommended IVF, to accumulate embryos, followed by surgical treatment, as necessary. As a result, the patient received luteal phase support via long-acting agonist treatment, according to our center's long protocol for ovarian stimulation. To be specific, we injected the patient with 1.5 mg triptorelin acetate. After 20 days, the down-regulation standard was achieved (E2, 98.2 pmol/mL; FSH, 3.23 IU/L; LH, 0.34 IU/L; progesterone, 0.48 pg/mL), and we proposed a change of regimen to Gn. We conducted a re-examination via ultrasound, which revealed that the cyst in the right ovary was approximately the same size as before. As the cyst interfered with antral follicle counting and would interfere with subsequent follicle monitoring, we recommended that the patient receives transvaginal ovarian cyst puncture. We used a 17G ovum aspiration needle to puncture the right ovarian cyst under transvaginal ultrasound guidance, and approximately 12 mL of a dark-brown, viscous liquid was extracted for cytological examination. We observed a small amount of epithelial cells against a background of abundant red blood cells (Figure 1). Its morphology was atypical (Figure 2).



**Figure 1** Abnormal epithelial cells discovered in the fluid obtained via ovarian endometriotic cyst puncture, against a background of abundant red blood cells.



**Figure 2** The abnormal epithelial cells exhibited hyperchromatic or faintly stained nuclei; there was an increased nuclear/cytoplasm ratio; the nucleoli were clear; and cells were dense, clustered, and formed multiple layers.

After receiving ethical approval and repeatedly communicating with the patient and her husband, they requested us to initiate IVF-assisted reproduction, to accumulate embryos, before surgical treatment of the cyst. Therefore, we initiated the 10-day COS process by injecting the patient with 300 IU human menopausal Gn. We retrieved eight metaphase-II oocytes, eight two-pronuclear oocytes, and six day-3 embryos, the latter of which were immediately cryopreserved. In the following month, we conducted laparoscopic cystectomy of the right ovarian endometriotic cyst. During surgery, we observed that the right ovary had increased in size to approximately  $7 \times 6 \times 4$  cm and contained multiple separated cysts, filled with a chocolate-like liquid. No abnormality was observed in the left adnexa. Postoperative histopathological results suggested a right ovarian endometriotic cyst. Three months after the surgery, frozen embryo transplantation (FET) was performed using two embryos, and an artificial FET cycle with down-regulation was adopted to successfully induce clinical pregnancy.

## Discussion

The majority of EM cases are benign; however, EM may also be prone to malignant transformation, associated with infiltrative growth, and recurrent or distant metastasis. New recent findings show that the glandular and stromal components of endometriosis originate from different sources. The epithelial components of endometriosis contain cancer-related mutations.<sup>6</sup> In a retrospective, observational cohort study conducted in the USA, recruiting 12,193 females evaluated for infertility, 13 infertile patients with EM were also diagnosed with ovarian cancer. Infertile patients with EM had a 2.72-fold increased risk of ovarian cancer in comparison with those without EM.<sup>7</sup> Benoit et al<sup>8</sup> reviewed 20,686 EM patients that were followed up for 11 years; the relative risk ratio of malignant transformation was 1:18 for EM patients compared to controls. Consequently, when a cyst is diagnosed as atypical through cytological diagnosis after ovarian EM cyst puncture, further histological examination should be performed to determine whether malignant transformation has occurred.

In the present case, cytopathological analysis of the fluid in the ovarian endometriotic cyst revealed a small amount of endothelial cells against a background of abundant red blood cells. Therefore, the possibility of a borderline ovarian tumor or a malignant tumor could not be excluded, and laparoscopic cystectomy was necessary for confirmation. However, this could not immediately be performed, as the patient was nulliparous and had a declined ovarian reserve. Embryo freezing should be proposed for fertility preservation, as a well-established option, because it is recommendable for married women with low ovarian reserve and advanced age.<sup>9</sup> For this patient, embryo cryopreservation was the optimal method to yield the highest probability of a successful clinical pregnancy. However, embryo cryopreservation poses several risks for patients with an ovarian EM cyst:

- (1) COS is required to obtain mature oocytes, a procedure of 2–4 weeks, which may delay tumor treatment.
- (2) Malignant transformation of EM may be related to an elevated estrogen level,<sup>10</sup> and COS increases the estrogen level *in vivo*.
- (3) A patient's body status after COS may reduce the success rate of endometriotic cyst surgery and negatively affect postoperative recovery.
- (4) Ovum aspiration may increase the risk of tumor metastasis and invasiveness, although laparoscopic surgery poses the same risk.
- (5) Further malignant transformation of an ovarian tumor cannot be excluded after FET.

Therefore, along with respecting the patient's wishes and reproductive counselling in the multidisciplinary management,<sup>11</sup> it is of particular importance to assess the possibility of malignancy before embryo cryopreservation. Multiple studies suggest that, for ovarian tumor patients requiring fertility treatment, ovarian tumor size, ultrasonic features of the tumor, and patient symptoms play a vital role in distinguishing benign and malignant tumors. Heidemann et al<sup>12</sup> discovered that the risk of malignant transformation of a cyst increased over time. Particularly, EM patients followed up over >10 years had the highest risk of malignant transformation. Kadan et al<sup>13</sup> and Thomsen et al<sup>14</sup> identified a larger cyst diameter as an independent risk factor of malignant transformation. With regard to our case, the patient had a lower risk of malignant transformation, in terms of cyst age and features. As far as cyst fluid analysis was concerned, the atypical nature of the cyst was not a specific indication of malignancy.<sup>15</sup> Normal cells are transformed to tumor cells through progressively acquiring epigenetic alterations and driver mutations, leading to alterations of tissue structure and cell morphology. Atypical EM (aEM) consists of cells that may be benign or malignant, exhibiting pale or hyperchromatic nuclei, and moderate to pronounced pleomorphism; in addition, an elevated ratio of nucleus to cytoplasm, together with crowding and stratification of tall epithelial cells, is observed.<sup>16</sup> Nonetheless, the concept of aEM is contentious and has been propounded by numerous authors for various diseases. Atypia is common in endometriotic cysts and is usually accompanied by pigment-rich macrophages, inflammation, increased fibrosis, and a loss of endometrioid stroma; such cysts may be caused by repetitive episodes of hemorrhaging.<sup>17</sup> In a review, Varma et al<sup>18</sup> stated that aEM was present in 12–35% of ovarian EM cases. Pathologists frequently depict nuclear atypia when they report such cases, although the term “aEM” may not be used. Czernobilsky and Morris<sup>15</sup> noted the possibility that aEM is reactive in nature, not necessarily associated with malignancy. Follow-up visits on patients with aEM have revealed no increase in the development of cancer.<sup>19–21</sup>

Nonetheless, when cytopathology reveals the atypical ovarian endometriotic cyst, patients are at risk of developing endometriosis-associated ovarian cancer (EAOC). Since Sampson first reported a case of EAOC in 1925,<sup>22</sup> a large number of studies have revealed that EM consists of similar genetic changes to that of ovarian cancer. Lu et al<sup>23</sup> revealed a genetic correlation coefficient of 0.4 for EM and ovarian cancer; EM was most closely correlated with ovarian clear-cell carcinoma. Wang et al<sup>24</sup> conducted a cohort study on 5945 EM patients and 23,780 non-EM cases in Taiwan and discovered that the former had an increased risk of ovarian cancer compared with the latter. Therefore, EM-associated malignant transformation has been widely acknowledged, and atypical cysts should not be disregarded.

Before conducting the procedure to confirm EAOC, it is necessary to communicate the risks of COS with patients. Numerous scholars have investigated the mechanisms of EM malignant transformation in terms of tissue pathology, metabolic disturbance, hormone and receptor malfunction, and molecular biology. However, no consensus has been reached, to date. For patients with suspected aEM, or a borderline or malignant ovarian tumor, it remains controversial whether COS is associated with the development of ovarian cancer. Modesitt et al<sup>10</sup> reported in 2002 that, among 21 EM malignant transformation patients, 13 had received hormone replacement therapy (primarily with estrogen). However, more recent large-scale studies indicate that medication for infertility is unrelated to ovarian tumor occurrence. Bjørnholt et al<sup>25</sup> retrospectively analyzed 96,545 infertile women in Denmark referred to fertility clinics from 1963 to 2006 and discovered that the risk of ovarian cancer was not related to the use of clomiphene citrate or Gn. Diergaarde et al<sup>26</sup> reviewed two large case–control studies and also revealed that ovarian stimulation therapy did not apparently increase the risk of ovarian cancer; however, they commented that it may have been too early to evaluate such a relationship, as most of the subjects had just reached the typical age of ovarian cancer development. Consequently, more large-scale studies with long follow-up times are required to accurately evaluate the relationship of assisted reproductive technology with ovarian cancer.



## Conclusion

In summary, patients with EM-associated infertility are at risk of ovarian cancer formation when undergoing assisted reproduction treatment; therefore, this risk should be evaluated and minimized before initiating such treatment. In some cases, patients may have a reduced ovarian reserve, increasing their urgency to achieve pregnancy. Where analysis of such a patient reveals a low probability of malignant transformation, the procedure should be:

- (1) Thorough communication,
- (2) Embryo accumulation,
- (3) And surgical management of ovarian endometriotic cyst, eg, cystectomy.

## Abbreviations

EP, ectopic pregnancy; IVF, in vitro fertilization; FET, frozen embryo transfers; REP, repeated ectopic pregnancy.

## Ethical Approval

Ethical approval was provided by the medical ethics committee of Chengdu Women's and Children's Central Hospital. The patient involved in this case report has been anonymized, and she acknowledges that she cannot be identified via the paper.

## Declaration of Patient Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflict of interest for this work.

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