

Case report

Development of endometrial stromal sarcoma in a patient undergoing in vitro fertilization: A case report

Tulsi Patel^{a,*}, Jessica N. Sosa-Stanley^b, Emily Evans-Hoeker^{a,c}, Janet L. Osborne^{a,d}^a Department of Obstetrics and Gynecology, Virginia Tech Carilion Clinic, United States^b Department of Obstetrics and Gynecology, Division of Minimally Invasive Gynecologic Surgery, St. Luke's University Hospital and Health Network, United States^c Department of Obstetrics and Gynecology, Division of Reproductive Medicine and Fertility, Virginia Tech Carilion Clinic, United States^d Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Virginia Tech Carilion Clinic, United States

ARTICLE INFO

Keywords:

Uterus
 Infertility
 Hormonal treatment
 Endometrial stromal sarcoma
 In vitro fertilization

ABSTRACT

Development of endometrial stromal sarcoma during in vitro fertilization (IVF) is rare. We encountered a case of endometrial stromal sarcoma (ESS) presenting as a new endometrial mass in a patient undergoing donor egg IVF, despite normal imaging and exams prior to and throughout treatment. To our knowledge, this is the only report describing the rapid growth of ESS during IVF treatment. When diagnosing an endometrial stromal sarcoma, it is important for the clinician and patient to be aware that full histologic inspection is required to distinguish it from a benign neoplasm. Given the need for a hysterectomy for definitive diagnosis, this case presents ethical challenges and potential for patient distress.

1. Introduction

Development of a potentially malignant, hormonally-sensitive mass in a patient undergoing fertility treatments creates a unique and challenging scenario. The physiological, emotional, and ethical implications for patients that desire reproduction and may be undergoing fertility treatment are complex in nature and may affect the provider's approach to the evaluation and management of these masses. Endometrial stromal sarcoma is a subset of the broader World Health Organization (WHO) classification of endometrial stromal neoplasms. It is a rare mesenchymal tumor, typically occurring in patients age 40–55 years old (mean 46 years), accounting for < 1% of all uterine malignant neoplasms and is most often high-grade with a high risk of metastasis and local recurrence (Desar et al., 2018 Feb). The subset classification of ESS is based on histology as well as the depth of invasion of the tumor into the myometrium and permeation into the lymphovascular spaces. It is morphologically indistinguishable from a benign endometrial stromal nodule; therefore imaging, sampling the lesion, and/or resecting the mass alone is not sufficient for diagnosis because myometrial assessment is necessary for categorization. The prognosis for low-grade ESS is favorable, and the five year survival rate (Stage I-II) is 90% (Desar et al., 2018; Xie et al., 2017). Most of these tumors are estrogen and progesterone receptor positive (60–100%), and thus, caution should be used when administering hormone therapy in a patient with an endometrial neoplasm (Laurelli et al., 2015). The

mainstay of treatment is a total abdominal hysterectomy and bilateral salpingo-oophorectomy, however, case reports suggest that fertility-sparing management with hysteroscopic resection and adjuvant hormonal therapy may be an option for young patients who desire future childbearing (Xie et al., 2017; Laurelli et al., 2015). We describe an unusual case of a rapidly growing, low-grade ESS discovered in a patient only 6-weeks after a biochemical pregnancy following donor egg IVF.

2. Case

A 45-year-old gravida 0 with a history of polycystic ovary syndrome (PCOS), obesity, and endometriosis initially presented for infertility evaluation and management. She had previously undergone fertility treatments including IVF with her own eggs without success in the remote past. After discussion of treatment options the patient opted for donor egg IVF. During the routine pre-IVF work-up she was found to have a normal uterus and ovaries on saline infusion sonohysterogram (Fig. 1). She underwent hormonal suppression with leuprolide followed by endometrial stimulation with oral and vaginal estradiol and intramuscular progesterone in oil. Total stimulation time was 3 weeks of unopposed estradiol in conjunction with leuprolide followed by 6 days of combined estradiol and progesterone therapy prior to embryo transfer. Estrogen and progesterone combination therapy was then continued from the day of embryo transfer until she was diagnosed with

* Address: Carilion Clinic Department of Obstetrics and Gynecology, 1906 Belleview Ave SE, Roanoke, VA 24014, United States.

E-mail address: tdpatel@carilionclinic.org (T. Patel).

<https://doi.org/10.1016/j.gore.2020.100541>

Received 26 September 2019; Received in revised form 20 January 2020; Accepted 23 January 2020

Available online 30 January 2020

2352-5789/ © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

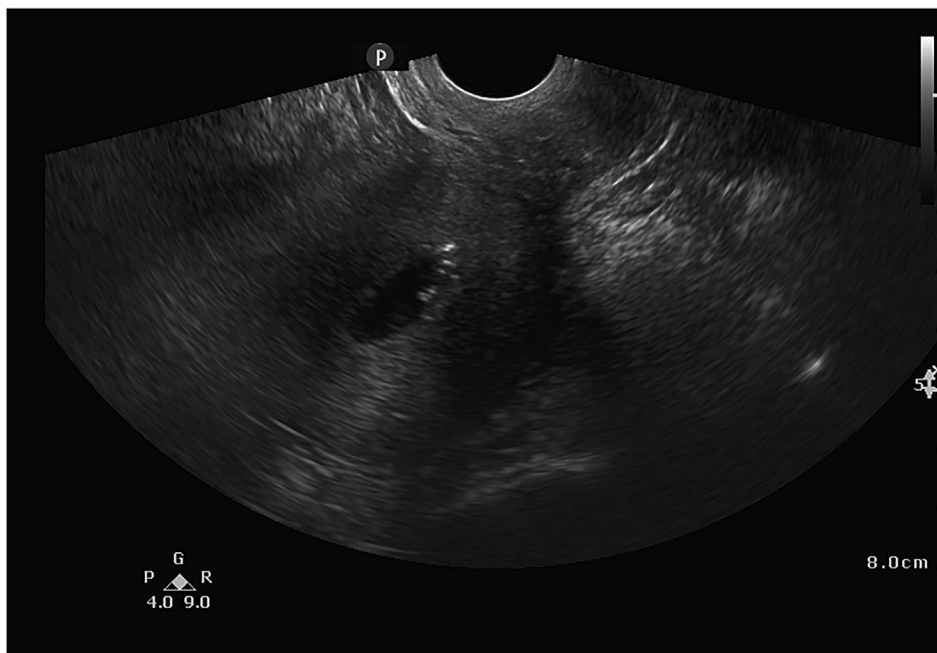


Fig. 1. Transvaginal ultrasound during saline infusion sonohysterogram prior to in vitro fertilization demonstrated normal appearing uterine cavity.

a biochemical pregnancy, accounting for a total of twenty one days of combined estradiol and progesterone therapy. As part of her monitoring during stimulation, she underwent 4 transvaginal ultrasounds which were normal. On the day of embryo transfer she had a normal trans-abdominal ultrasound and pelvic exam. She conceived, but subsequently had a biochemical pregnancy, which was managed expectantly by following beta-hcg values until they reached a non-pregnant level.

Twenty-three days after having vaginal bleeding and passage of fetal tissue, she presented for uterine cavity evaluation via office hysteroscopy prior to a planned frozen embryo transfer. Upon presentation for her hysteroscopy, she complained of vaginal bleeding and pelvic pain, which although are non-specific, are also the most common symptoms associated with ESS. On exam a 4 cm mass of friable, purple tissue delivering through the cervix was noted. Manipulation of this tissue resulted in heavy bleeding and thus she was taken to the operating room for resection of the cervical mass and dilation and curettage by reproductive endocrinology in conjunction with gynecologic oncology. Final pathology was inconclusive, but concerning for possible endometrial stromal neoplasm.

She subsequently underwent MRI, which demonstrated an endometrial nodule at the left fundal horn, extending into the myometrium, with mild heterogeneous enhancement (Fig. 2). There were no significant extrauterine findings, and the presence of invasion into the myometrium was not able to be determined. She then underwent hysteroscopic complete resection of the fundal tumor and curettage using the Truclear device (Fig. 3). Final pathology demonstrated a low-grade endometrial stromal neoplasm and secretory phase endometrium.

The patient underwent a formal consultation with gynecologic oncology, was counseled on the risks of a potential endometrial stromal sarcoma and was informed that the recommendation is typically for hysterectomy. She was counseled extensively on the risks of pursuing further fertility treatment in the setting of a possible uterine sarcoma. After multiple, extensive discussions with both reproductive endocrinology and gynecologic oncology, she underwent a robotic-assisted total laparoscopic hysterectomy with bilateral salpingo oophorectomy performed by gynecologic oncology. Pathology demonstrated a 1.7 × 1.7 cm low-grade endometrial stromal sarcoma infiltrating at least 9 mm into the myometrium (69% of total myometrial thickness) (Fig. 4). There was no infiltration of lymphovascular spaces or

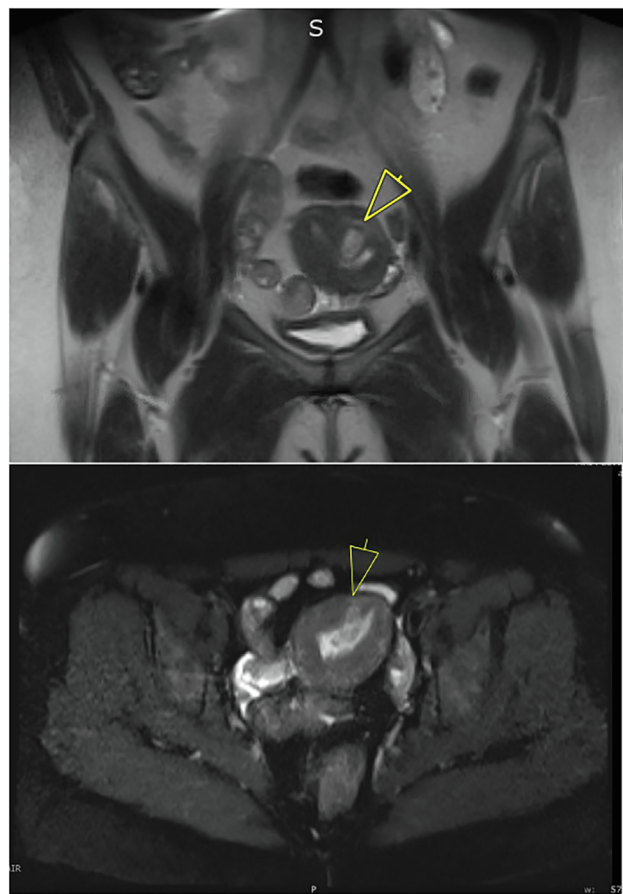


Fig. 2. MRI images demonstrating left fundal endometrial nodule extending into the myometrium.

involvement of cervix, parametria, fallopian tubes, or ovaries (Stage 1A). Thus, the patient was dispositioned to surveillance every 4–6 months for the first 3 years. Since her hysterectomy the patient has expressed interest in using a family member as a gestational carrier for

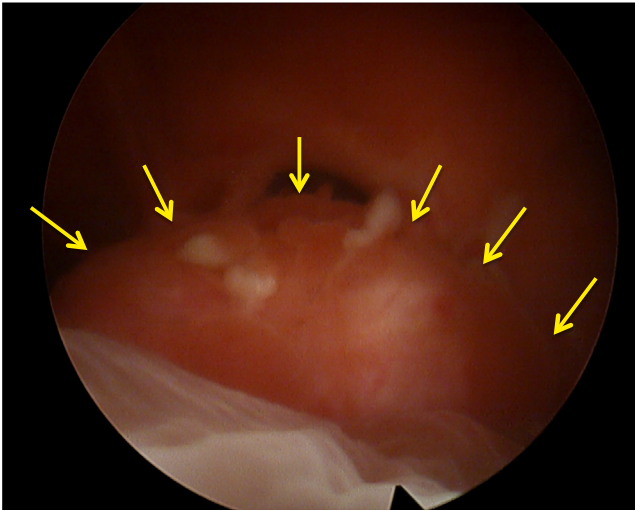


Fig. 3. Hysteroscopy demonstrating intrauterine fundal tumor.



Fig. 4. Specimen from robotic-assisted total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. Pathology demonstrated a 1.7×1.7 cm low-grade endometrial stromal sarcoma infiltrating at least 9 mm into the myometrium (69% of total myometrial thickness).

her remaining donor egg embryos and this process is currently underway.

3. Discussion

Patients with infertility, especially nulliparous patients, are known to have an increased risk of developing ovarian cancer, as well as uterine cancer in the setting of unopposed estrogen exposure (Louis et al., 2013). Fertility treatments such as ovulation induction agents and hormonal stimulations, as used in IVF, have sparked concern regarding

the risk of hormone sensitive cancers. A study by Venn et al found an increased incidence of uterine sarcoma (two cases of stromal sarcoma, two cases of leiomyosarcomas) between one and twelve years after receiving IVF treatment (Venn et al., 2001). However, there have been multiple meta-analyses that have not demonstrated a statistically significant increased risk of these malignancies (Schwarze et al., 2017; Saso et al., 2015). Although it has been established that hormonal therapies may be associated with the progression of ESS specifically, to date, an association with IVF and the effect of fertility treatments on disease progression have not been described.

Initial imaging obtained as part of the typical infertility work up allows early detection of an endometrial lesion; however, is not specific for the diagnosis of ESS. Suspicion should be raised if the tumor is rapidly enlarging or has an ill-defined margin, specifically on MRI, as this may help in the differentiation of a malignant stromal tumor from a leiomyoma with cystic degeneration (Kim et al., 2018). Low-grade ESS presents a diagnostic challenge, as it cannot be distinguished from a benign neoplasm without full histologic inspection of tumor-myometrial interface (i.e. hysterectomy specimen), which presents a significant dilemma for the patient who strongly desires fertility.

Due to the rarity of the disease, there is limited information on the various clinical presentations of low-grade ESS and there are no clear recommendations regarding treatment in patients desiring fertility. Management decisions have been mostly based on previous case reports (Kim et al., 2018; Jamea et al., 2017). Case series have demonstrated that hysteroscopic resection of low-grade ESS and adjuvant treatment with megestrol acetate, medroxyprogesterone acetate, gonadotrophin-releasing hormone (GnRH) analogues, or levonorgestrel-releasing intrauterine device have resulted in subsequent successful pregnancies in patients desiring a future pregnancy (Xie et al., 2017; Laurelli et al., 2015; Dong et al., 2014). However, until additional studies demonstrate favorable survival outcomes in the setting of conservative management, the mainstay treatment remains hysterectomy with bilateral salpingo-oophorectomy (Xie et al., 2017; Laurelli et al., 2015).

4. Conclusion

In summary, endometrial stromal sarcoma is rare, yet may develop in the setting of hormonal treatment, such as during in vitro fertilization. This case presentation is unique in that a rapidly developing mass occurred during donor egg IVF, despite normal imaging and exams prior to and throughout treatment. With a new rapidly growing endometrial mass, clinicians should include endometrial stromal sarcoma within the differential. In patients desiring future fertility, thorough counseling regarding the risks and benefits of conservative management (hysteroscopic resection and surveillance) versus definitive treatment (total hysterectomy and bilateral salpingo-oophorectomy) should be discussed.

Consent

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

Disclosure

The authors of this paper have no relevant disclosures.

Author contributions

1. Tulsi Patel participated in manuscript writing, medical record review, literature search and patient care.
2. Jessica Sosa-Stanley participated in manuscript writing, medical record review, literature search, and patient care.
3. Emily Evans-Hoeker participated in developing manuscript concept, manuscript writing, patient care, and acquisition of patient consent.

4. Janet Osborne participated in developing manuscript concept, manuscript writing, and patient care.

Declaration of Competing Interest

The authors of this paper have no relevant conflicts of interest relevant to the manuscript presented.

References

- Desar, I.M.E., Ottevanger, P.B., Benson, C., van der Graaf, W.T.A., 2018. Systemic treatment in adult uterine sarcomas. *Crit. Rev. Oncol./Hematol.* 122, 10–20.
- Xie, W., Cao, D., Yang, J., Jiang, X., Shen, K., Pan, L., Huang, H., Lang, J., You, Y., Chen, J., 2017. Fertility-sparing surgery for patients with low-grade endometrial stromal sarcoma. *Oncotarget* 8 (6), 10602–10608.
- Laurelli, G., Falcone, F., Scaffa, C., Messalli, E., Giudice, M.D., Losito, S., Gregg, S., 2015. Fertility-sparing management of low-grade endometrial stromal sarcoma: analysis of an institutional series and review of the literature. *Eur. J. Obstetr. Gynecol. Reprod. Biol.* 195, 61–66.
- Louis, L.S., Saso, S., Ghaem-Maghami, S., Abdalla, H., Smith, J.R., 2013. The relationship between infertility treatment and cancer including gynaecological cancers. *Obstetr. Gynaecol.* 15, 177–183.
- Venn, A., Jones, P., Quinn, M., Healy, D., 2001. Characteristics of ovarian and uterine cancers in a cohort of in vitro fertilization patients. *Gynecol. Oncol.* 82 (1), 64–68.
- Schwarze, J.E., Valdebenito, P., Ortega, C., Villa, S., Crosby, J., Pommer, R., 2017. Do women offered assisted reproduction technologies have a higher incidence of gynecologic cancer? A systematic review and meta-analysis. *JBRA Assist. Reprod. J.* 21 (2), 115–119.
- Saso, S., Louis, L., Doctor, F., Hamed, A.H., Chatterjee, J., Yazbek, J., Bora, S., Abdalla, H., Ghaem-Maghami, S., Thum, M.Y., 2015. Does fertility treatment increase the risk of uterine cancer? A meta-analysis. *Eur. J. Obstetr. Gynecol. Reprod. Biol.* 195, 52–60.
- Kim, T.H., Kim, J.W., Kim, S.Y., Kim, S.H., Cho, J.Y., 2018. What MRI features suspect malignant pure mesenchymal tumors rather than uterine leiomyoma with cystic degeneration? *J. Gynecol. Oncol.* 4.
- Jamea, G.A., Rikabi, A.C., Akkour, K., 2017. Primary low-grade endometrial stromal sarcoma arising in the vagina: a report of an unusual case and literature review. *J. Surg. Case Rep.* 11, 238.
- Dong, R., Yingxin, P., Mao, H., Ning, Y., Liu, P., 2014. Successful pregnancy following conservative management of endometrial stromal sarcoma: a case report. *Oncol. Lett.* 4, 1039–1042.