

Uterine smooth muscle tumour of uncertain malignant potential and in vitro fertilization treatment in an infertile patient

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Triantafyllidou Olga¹, Kastora Stavroula Lila^{2,3} ,
Georgios Kounidas², Papazian Maria¹ and Vlahos Nikolaos¹

Abstract

The term smooth uterine muscle of uncertain malignant potential (STUMP) indicates a group of uterine smooth muscle tumours that cannot be diagnosed unequivocally as malignant but does not fulfil the criteria for leiomyoma, or its variants. In this case, we present a woman treated for infertility who presented with an asymptomatic cervical mass, diagnosed as STUMP after three cycles of controlled ovarian stimulation. We reviewed the literature with particular emphasis on the effects of STUMP upon fertility, up-to-date guidance regarding the management of patients' wishing fertility-sparing approaches and obstetric outcomes. To the best of our knowledge, this is the first case report of STUMP in a patient that has undergone multiple in vitro fertilization treatments as well as the first to provide a putative biological basis for the efficacy of gonadotropin-releasing hormone agonists, in this patient group.

Keywords

Obstetrics/gynaecology, oncology, genetics, bioinformatics

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Introduction

The smooth muscle neoplasms are categorised as benign (leiomyomas), malignant (leiomyosarcomas) or smooth muscle tumours of uncertain malignant potential (STUMP), according to displayed characteristics including mitotic activity and proliferating capacity, cytological atypia and coagulative or tumour cell necrosis.¹ The term STUMP indicates a group of uterine smooth muscle tumours that cannot be diagnosed unequivocally as malignant and raises concern that the lesion may behave in a malignant fashion.¹ Nonetheless, the term 'atypical leiomyoma' has been incompatibly employed to include diverse entities, including STUMP, which does hold a risk of recurrence, as well as leiomyoma with bizarre nuclei, which does not pose such a risk when appropriately classified.¹ Occasionally smooth muscle tumours may exhibit significant mitotic activity without cellular characteristics of malignancy.²

The clinical presentation and imaging modalities have not been proven adequate to distinguish STUMPs from other

neoplastic entities. The symptoms of uterine STUMPs are similar to those of leiomyomas including vaginal bleeding, anaemia, abdominal pain or discomfort, dyspareunia, dysuria and other features of a pelvic mass.^{3,4} Accurate STUMP diagnosis can only be achieved by pathology evaluation of retrieved hysterectomy or myomectomy samples.¹ The Stanford criteria of STUMP diagnosis include at least two of the following: diffuse moderate to severe atypia, a mitotic

¹2nd Department of Obstetrics and Gynaecology, Aretaieion Hospital, University of Athens, Attica, Greece

²School of Medicine and Applied Sciences, University of Aberdeen, Aberdeen, UK

³Department of Acute Medicine, Aberdeen Royal Infirmary, NHS Grampian, Aberdeen, UK

Corresponding Author:

Kastora Stavroula Lila, Department of Acute Medicine, Aberdeen Royal Infirmary, NHS Grampian, Ward 101, Foresterhill Health Campus, Foresterhill Road, Aberdeen AB25 2ZN, UK.

Emails: Stavroula.kastora@abdn.ac.uk; stavroula.kastora@nhs.scot



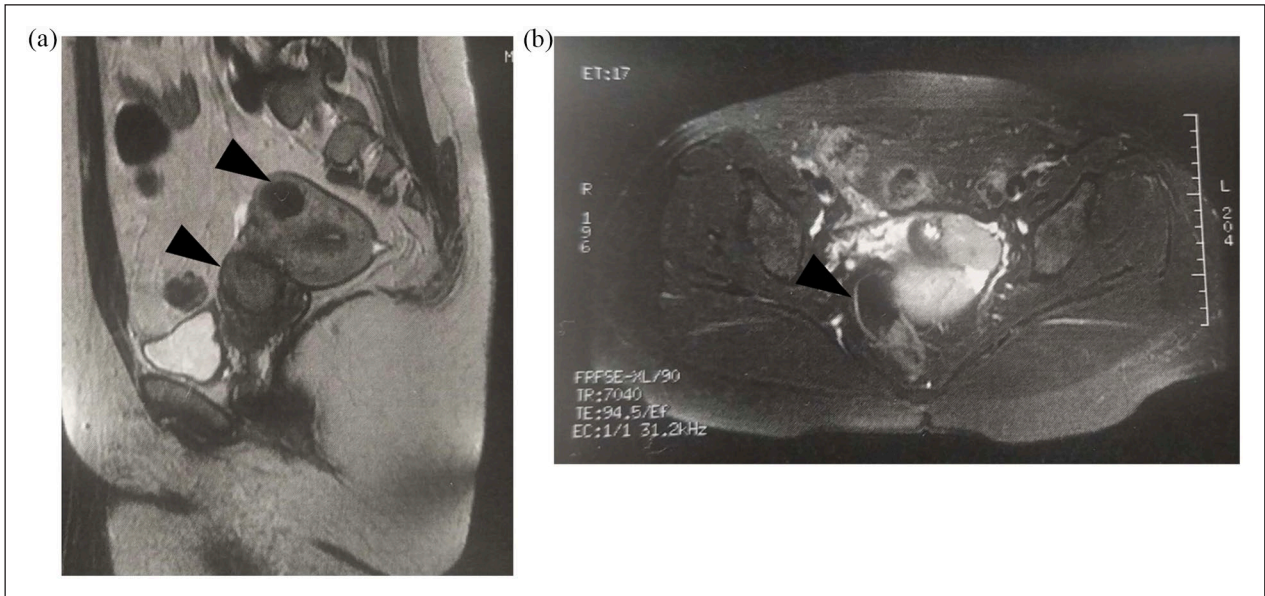


Figure 1. Patient MRI findings: (a) sagittal and (b) transverse sections. Patient identifiable information has been removed from the images. Black arrows indicate areas of interest.

count of at least 10 mitotic figures or 10 high power fields and tumour cell necrosis.^{3,4}

Consequently, diagnosis, surgical management, and follow-up of this neoplasm remains controversial, especially in pre-menopausal women who desire fertility. As the proliferation index of STUMP remains obscure due to the mixed cytological phenotypes, all tumours that have been categorised as STUMP should be considered as having some recurrence potential, even in cases where complete hysterectomy with an intact corpus has been performed.^{3,5} Consequently, while tumours without cytologic atypia and tumour cell necrosis but with a recorded high mitotic index carry a low risk of recurrence 8.7%, tumours without cytologic atypia and low mitotic index with recorded tumour cell necrosis carry a risk of recurrence as high as 26.7%.² Regardless of mitotic index, a tumour with high cytological atypia and necrosis should be classified as malignant leiomyosarcoma, according to Stanford criteria.⁵ Here, we report a case a woman treated for infertility who presented with an asymptomatic cervical mass, diagnosed as STUMP after three cycles of controlled ovarian stimulation (COS).

Case report

A 37-year-old nulliparous Caucasian woman was admitted to the IVF centre due to infertility. Her initial assessment including clinical examination, transvaginal ultrasound and biochemical profile revealed poor ovarian reserve (anti-Müllerian hormone (AMH) 0.8 ng/mL, follicle-stimulating hormone (FSH) 12.2 mIU/mL, estradiol (E2) 42 pg/mL, antral follicle count (AFC) 4 on Day 3 of menstrual cycle). The sperm count of her spouse was of normal range and good motility. She

reported regular cycles and no other co-morbidities were recorded or known to the patient. Within the first year of her presentation, she underwent three cycles of COS, using a fixed gonadotropin-releasing hormone (GnRH) antagonist stimulation protocol with 300 IU of gonadotropins. Briefly, ovarian stimulation was initiated on Day 3 with 300 IU of human Menopausal Gonadotropins (hMG; Menopur; Ferring Pharmaceutical Hellas AE). She was re-evaluated on Day 5 of stimulation (Day 8 of the cycle), when a transvaginal sonogram was performed to evaluate follicular growth and serum E2 levels were re-measured. On Day 6 of stimulation or when a leading follicle reached a diameter of 14 mm, a commercially available GnRH antagonist, Cetrorelix acetate 0.25 mg/day, was initiated (Cetrotide; Merck Serono Hellas AE). Patient had serial evaluations as required per protocol. When at least two follicles reached an average diameter of 18–20 mm, final oocyte maturation was triggered with 10,000 IU of human chorionic gonadotropin (hCG; Pregnyl; Organon Greece Inc). Oocyte Pick Up (OPU) was carried out 34–36 h later. The patient underwent routine intracytoplasmic sperm injection (ICSI) based on the limited number of available oocytes. Three embryo transfers were carried out with no success.

Six months after her last embryo transfer, the patient presented for evaluation prior to her fourth attempt. A transvaginal ultrasound on Day 3 was performed as usual and revealed a 5 cm cervical asymptomatic mass with possible diagnosis of leiomyoma, which was not previously recorded. Magnetic resonance imaging (MRI) images confirmed the finding with extension above the cardinal ligament, projecting in the peritoneal cavity (Figure 1). The patient underwent laparoscopic evaluation which confirmed the presence of a smooth,

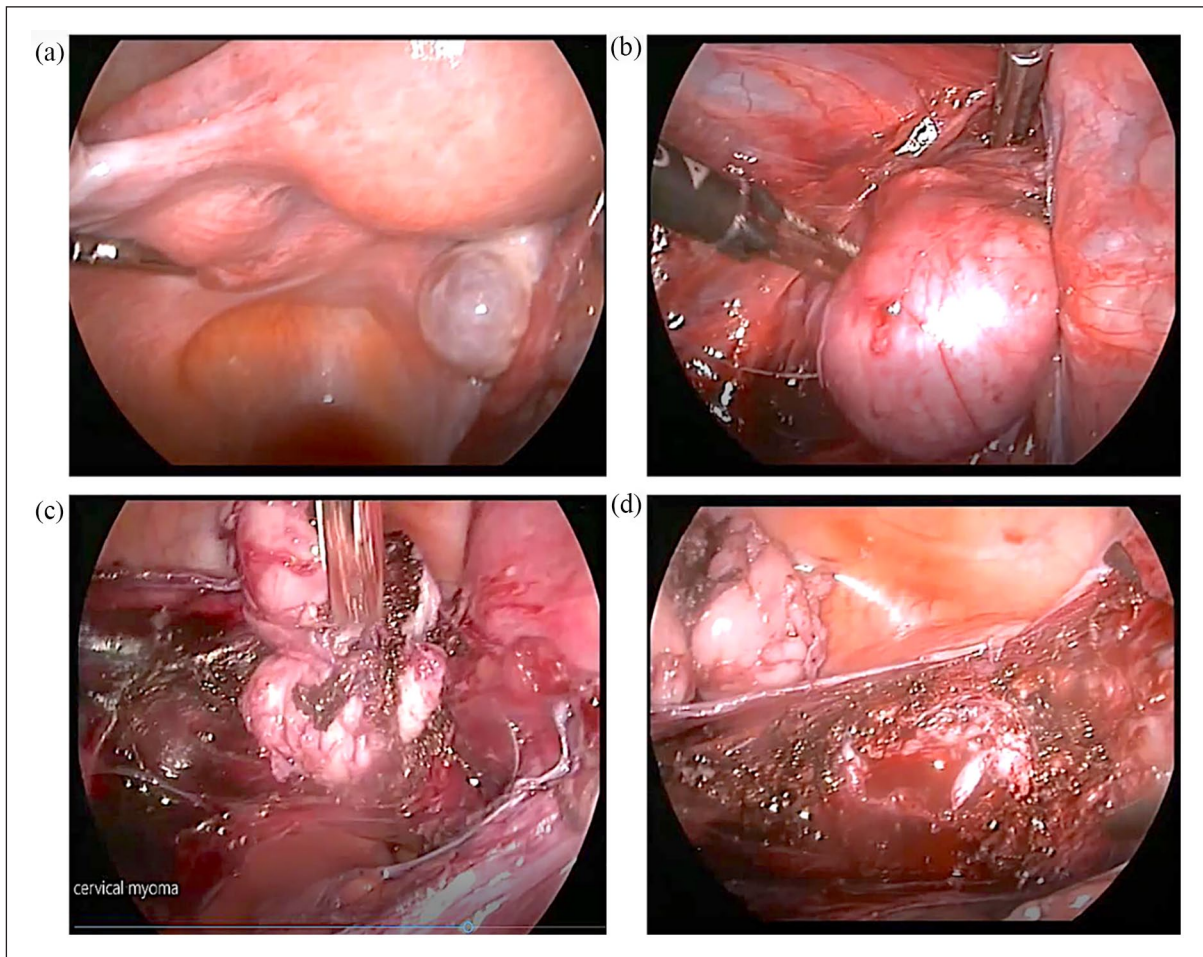


Figure 2. Laparoscopic images depicting the stages of STUMP morcellation: (a) the presence of a smooth well-defined 5 cm mass attached to the left side of the cervix, (b) STUMP after opening the broad ligament, (c) solid adhesions of STUMP to adjacent tissues and (d) the bed of STUMP after its removal.

well-defined mass attached to the left side of the cervix which was removed. Considering the young of patient's age, the lesion size and the MRI report, the lesion was removed by power morcellation (Figure 2). Frozen sections were negative for malignancy (Figure 3). The final histological examination revealed a smooth muscle neoplasm with epithelioid morphology (Figure 3(a)) with low to moderate nuclear atypia (Figure 3(b) and (c)) without necrotic areas or mitotic activity (p53 (-) Caldesmon (+) p16 (-) compatible with STUMP (Figure 3(d)). The case was reviewed by the oncology board of our institution which deemed that no further surgical treatment was required. One year after surgery the patient remained recurrence-free of disease.

Discussion

As previously mentioned, diagnosis, surgical management, and follow-up of STUMP remains controversial, especially in pre-menopausal women who desire fertility, while the optimal management of the infertility in STUMP patients remains

obscure. For such patients, a multidisciplinary approach should be pursued to assess tumour characteristics and the patient's wishes for future pregnancy. While fertility preservation remains a significant factor of consideration in patients of child-bearing age, standardised protocols and guidelines of STUMP management in this patient group, have not been developed. Nonetheless, a number of studies have demonstrated that fertility-sparing approaches such as myomectomy or initial treatment with GnRH agonists remain feasible within this population.^{6,7} Current management strategies involve mainly surgical interventions including myomectomy by hysteroscopy, myomectomy by laparotomy or laparoscopy. Of note, warning have been raised regarding the use of electro-mechanical power morcellation.⁶ It is important to mention that the technique of power morcellation in a bag is suggested to minimise the risk of inadvertent tissue spread and should be performed especially in cases where the fast-growing mass is presented, even in young patients.

The GnRH agonists have been used to decrease the size of fibroids, especially in symptomatic women to resolve anaemia.⁷

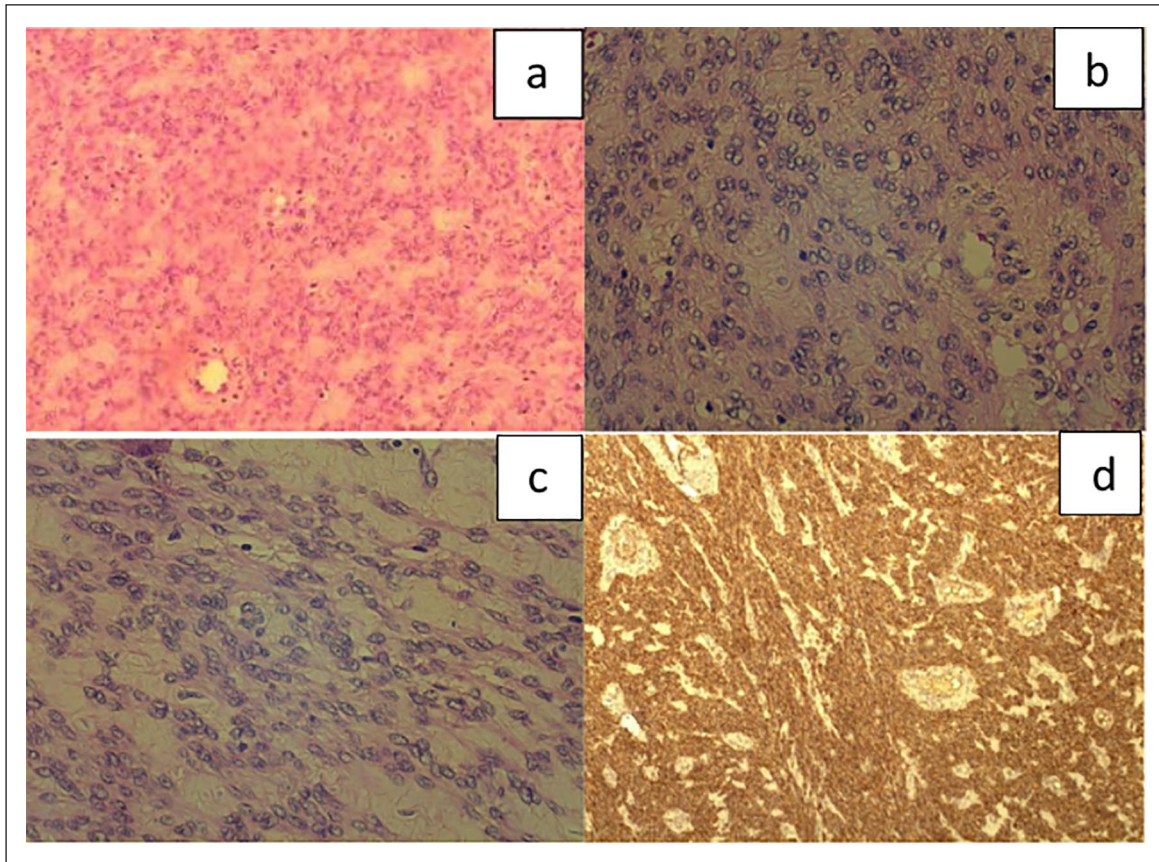


Figure 3. Histological examination of section. Smooth muscle neoplasm identified with epithelioid morphology (a) (H-E $\times 100$) and diffuse low to moderate nuclear atypia throughout the tumour (b) and (c), (H-E $\times 400$). The mitotic count was low with less than five mitoses or 10 HPF. Areas of necrosis were not observed. Immunohistochemically, the neoplastic cells stained positive for calponin (d) ($\times 40$) and were negative for p16 and p53.

Goserelin (GnRH agonist) has been shown to quantifiably decrease the size of STUMP prior surgical removal and consequently decrease the extend of the necessary myomectomy, albeit this approach has been used in a small number of studies.^{6,7} GnRH agonists may function through activation of Pten, Tp53, Myocd and Rb1, proteins which have been previously identified as deregulated in STUMP development (Figure 4).⁸ Nonetheless, GnRH agonists cannot be used for long time because of their side effects and the risk of osteoporosis. However, it is well known that the removal of myomas after GnRH treatment is difficult, taking into account that the diagnosis of STUMP cannot be suspected prior the surgical removal. The preoperative use of GnRH agonists seems to be beneficial in patients with only submucous fibroids.⁷ Benefits also include a resolution of preoperative anaemia.

By inducing a state of hyperestrogenism during ovarian stimulation for IVF, COS theoretically may increase the size of leiomyomas. Surprisingly, it seems that COS does not modify the dimension of subserosal and intramural leiomyomas. Moreover, previous literature does not confirm any relationship between COS and the magnitude of the ovarian responsiveness. In 2003, a big follow-up study of 8714

women showed that IVF treatment did not affect the occurrence of uterine leiomyomas neither influenced the leiomyoma's size.¹⁰ According to these data, we can consider that even, in our case, the treatment with gonadotropins for infertility had not affected the occurrence of STUMP. A recent retrospective study by Şahin et al.,¹¹ which explored fertility and oncological outcomes in 57 patients with a STUMP diagnosis, identified similar recurrence rates (14%) for patients undergoing either hysterectomy or myomectomy for STUMP management, in agreement with a previous retrospective study by Guntupalli et al.⁹ A 37% (N 10 out of 27) of patients that underwent myomectomy, achieved pregnancy within the study follow-up period [57 (Min: 16 to Max: 125) months].¹¹

In our case, we presented the infertile women with poor ovarian reserve. Her infertility treatment after surgery remains questionable as data in the literature regarding STUMP and the ovarian stimulation remain unclear. STUMP recurrence should be monitored and evaluated; ideally in a multidisciplinary approach, prior attempts for pregnancy have taken place.^{1,5,12} Even after conception, obstetric outcomes and prognosis remain stratified among patients with STUMP consequently great care should be given in monitoring these

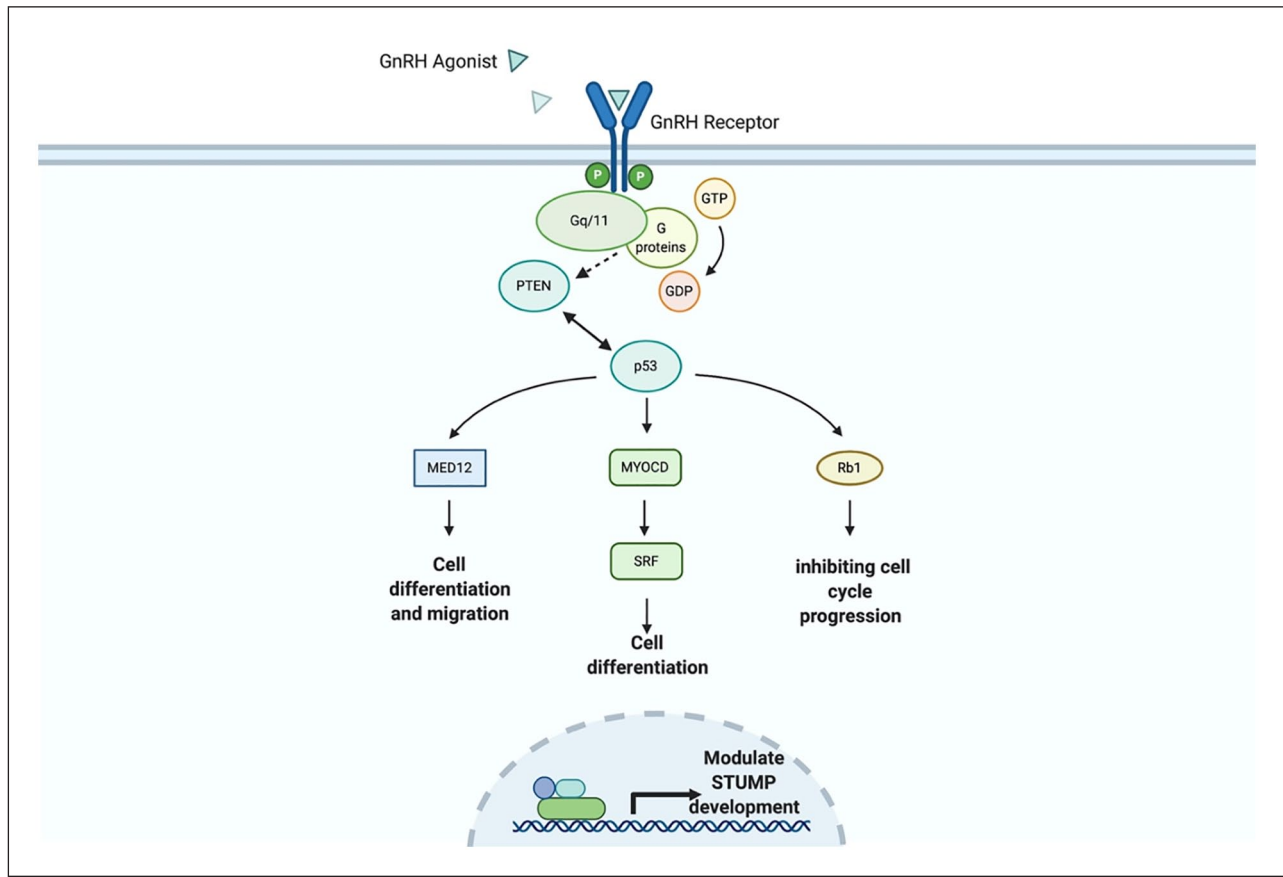


Figure 4. Putative mechanism of STUMP size modulation through GnRH agonists.

Putative pathway: GnRH agonist activates GnRH receptor which through currently unidentified, Gq/11 G-protein family members, activating Pten phosphatase which in turn activates Med12, Myocd and Rb1 leading to cell development and cell-cycle regulation potentially regulating and decreasing STUMP growth.⁹ Protein associations were mined and generated through the STRING V. 11 (<https://string-db.org/>), Cytoscape freeware platform and Agilent Literature plugin (V. 3.8) and the National Library of Medicine (US), Bethesda (MD): The Library; (15 July 2020). Available from: <https://ghr.nlm.nih.gov/>. Pathway was reconstructed through BioRender online design platform.

patients' prior conception and throughout gestation to ensure the best possible outcomes. Annual surveillance with pelvic imaging (transvaginal ultrasound and MRI with gadolinium) potentially every 6 months depending on STUMP histologic features may be necessary in fertility-preserving patients to ensure timely management of potential recurrence.

Conclusion

There is no data in the literature regarding the influence of COS with gonadotropins on the development of STUMP in infertile women. Consequently, the risk uncertainty of malignancy and the lack of standardised management still complicate the decision process, especially for women who may require additional fertility treatments.

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Author contributions

T.O., K.S.L., and M.P. contributed to concept, analysis, format, revision, literature search, and manuscript drafting. T.O. and V.N. conducted the operation. K.S.L. and G.K. contributed to editing. T.O. and V.N. gave expert opinion.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The authors state that the manuscript is original; all the authors were active participants, and take full responsibility for this article, which they have read and approved, and that it is not simultaneously under consideration by other publication. The authors report no conflicts of interest. Contribution to the paper of each author is indicated.

Ethical approval

Case report was approved by the Leto Hospital IRB ethics committee and the patient with patient identifiers removed for data protection purposes (Protocol number: 125Δ796EZ/2020).

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Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

IRB approval

Patient informed consent was obtained for image use for education and academic purposes. Case report was approved by the Leto Hospital IRB ethics committee and the patient with patient identifiers removed for data protection purposes.

ORCID iD

Kastora Stavroula Lila  <https://orcid.org/0000-0003-4470-5267>

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