

Recovery from endometrial thinning and successful pregnancy following vitamin E and C supplementation in infertile woman undergoing myomectomy for diffuse leiomyomatosis of the uterus: a case report

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Summary

The authors here report a case of an infertile woman with diffuse leiomyomatosis of the uterus, which is a rare benign pathological condition in which the myometrium is occupied by innumerable small fibroid nodules. Due to the progressive abdominal distension of the patient and the desire for pregnancy of the couple, myomectomy was performed as a primary treatment. Urgent relaparotomy was required for hematoma debridement on the following day. Despite the evidence of the follicular growth and cyclic ovarian steroid secretion, the patient had postoperative endometrial thinning that was unresponsive to hormone replacement therapy. Supplementation of oral tocopherol nicotinate/vitamin E and ascorbic acid/vitamin C was effective for immediate recovery of withdrawal bleeding and gradual gain of endometrial thickness. The patient had a successful pregnancy in an *in vitro* fertilization-embryo transfer program and gave a birth to a healthy baby.

Key words: Ascorbic acid; Diffuse leiomyomatosis; Endometrial thinning; Tocopherol nicotinate.

Introduction

Diffuse leiomyomatosis of the uterus (DLU) is a rare benign pathological condition where the myometrium is occupied by innumerable, confluent, unencapsulated, small fibroid nodules, which is distinct from common uterine leiomyoma [1]. The cause and etiology of DLU remain yet undetermined, although the clonality analysis for random X chromosome inactivation patterns suggests the polyclonal origins of the leiomyoma cells [2].

DLU often involves young women of reproductive ages in menorrhagia, menorrhagia, and infertility. Early reports reviewed the cases that were found patho-anatomically in the hysterectomized uterus, but recent advances in medical imaging techniques such as ultrasound and magnetic resonance imaging facilitated its non-invasive diagnosis. Literature introduced a variety of fertility-sparing strategy including surgery, pharmacotherapy, and conservative follow-up for women with DLU and desire for pregnancy [3-5]. However, there is no consensus or guideline on the clinical management for fertility preservation in DLU.

The authors here report a case of an infertile woman with DLU. Due to progressive abdominal distension and wish for a baby, myomectomy was chosen as a primary treatment. On the following day, urgent relaparotomy was required for hematoma debridement. Despite the evidence of the follicular growth and cyclic ovarian steroid secretion,

the patient had postoperative endometrial thinning that was unresponsive to hormone replacement therapy using estrogens and progestogens. Supplementation of tocopherol nicotinate/vitamin E and ascorbic acid/vitamin C was effective for immediate recovery of withdrawal bleeding and gradual gain of endometrial thickness. The patient was able to conceive in an *in vitro* fertilization-embryo transfer program and give a birth to a healthy baby.

Case Report

A 29-year-old nulliparous infertile woman suffering from abdominal distension and menorrhagia presented to the outpatient clinic. Physical examination revealed a bulging abdominal wall with a palpable, solid, fixed mass. Ultrasound tomography demonstrated the presence of innumerable hypoechoic nodular lesions throughout the myometrium. The maximal diameters of the nodules ranged from five to 80 mm, which were confirmed by magnetic resonance imaging and thus diagnosed with DLU. The patient had iron-deficiency anemia (hemoglobin concentration 7.8 g/dl, serum iron concentration < 20 mg/dl), which was treated with sodium ferrous citrate. Due to narrowness and sharp bend of cervical canal, the authors were unable to evaluate the degree of the uterine cavity deformation with office hysteroscopy or hysterosalpingography. They opted for myomectomy under a written informed consent, as the patient had progressive abdominal distension and desire for pregnancy. Prior to the operation, a total of 1,200 g venous blood were collected for autologous blood transfusion.

Under general anesthesia, cervical canal was dilated using Hegar dilators and a double lumen catheter was installed in the uterine cavity. Following the peritoneal incision, indigo carmine dye injection through the catheter revealed bilateral tubal occlu-

Revised manuscript accepted for publication June 24, 2013

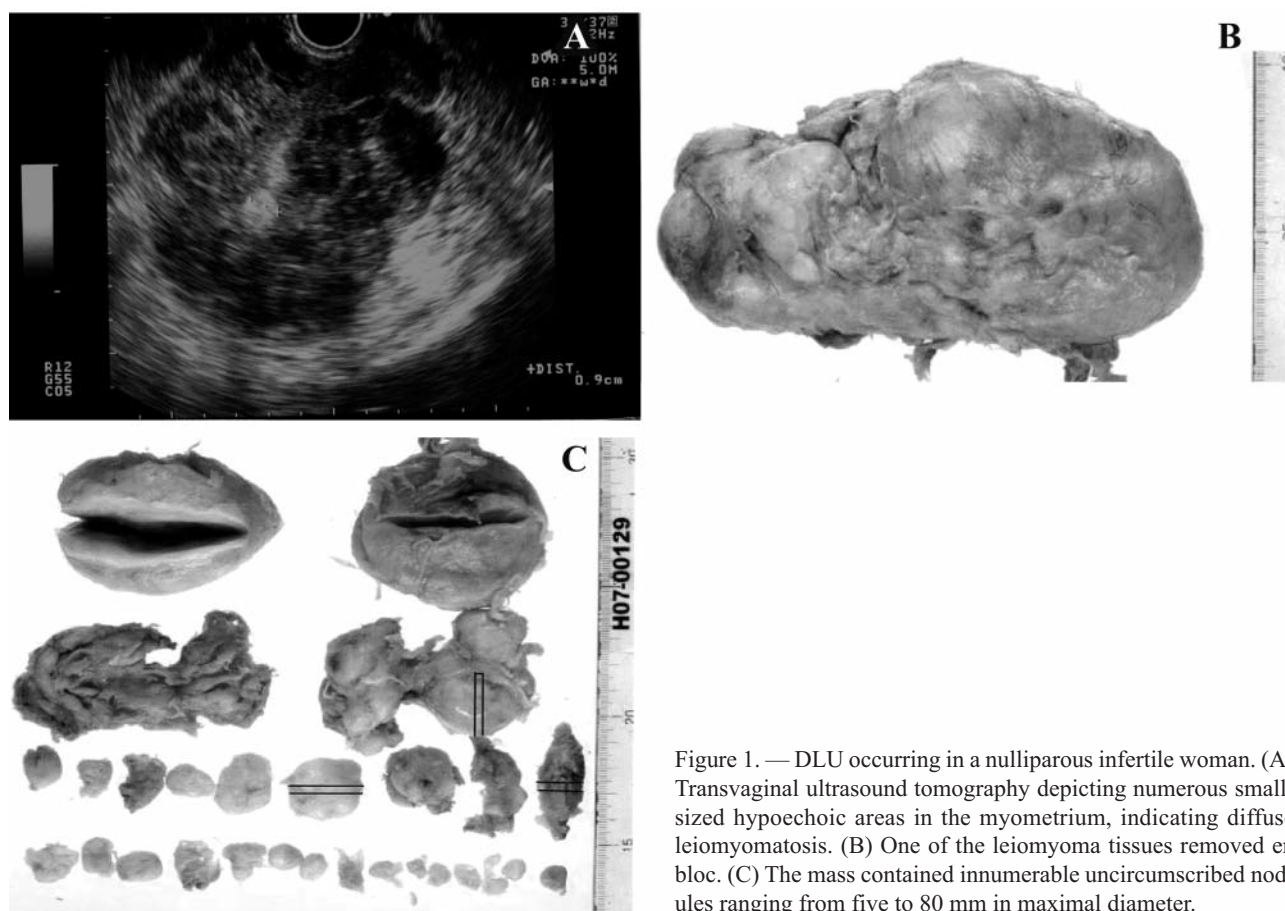


Figure 1. — DLU occurring in a nulliparous infertile woman. (A) Transvaginal ultrasound tomography depicting numerous small-sized hypoechoic areas in the myometrium, indicating diffuse leiomyomatosis. (B) One of the leiomyoma tissues removed en bloc. (C) The mass contained innumerable uncircumscribed nodules ranging from five to 80 mm in maximal diameter.

sion. Twenty IU arginine vasopressin (diluted in 50 ml saline) was injected into the fibroid nodules prior to incision. More than 80 subserosal and intramural nodules were surgically removed with an estimated blood loss of 3,300 g (Figure 1). On the following day, the patient complained of uncontrolled abdominal pain. Venous blood hemoglobin concentration measured low (8.2 g/dl) despite full transfusion of autologous blood and additional homologous red blood cells (2,000 g) and frozen fresh plasma (six units). A hyperechoic lesion was detected in the mid-to-low section of the uterine corpus on ultrasound, implicating hematoma formation. Urgent relaparotomy was performed under general anesthesia. Hematoma debridement and surgical suture were added to the bleeding points. Histopathologic diagnosis was leiomyoma except the largest nodule with atypical leiomyoma.

Residual fibroid nodules were treated with intramuscular injection of gonadotropin releasing hormone agonist leuprolide acetate depot (3.75 mg, every four weeks) for three times. Over the next three months, the patient had a secondary amenorrhea with endometrial thinning measured between 3.2 mm and 4.6 mm thickness, despite the evidence of the follicular growth and fluctuating serum estradiol (61–312 pg/ml) and progesterone (0.8–11 ng/ml) concentration. Withdrawal bleeding did not occur even following three cycles of hormone replacement therapy with conjugated equine estrogens (0.625 mg, twice a day, for 21 days) and progestogens (two mg, twice a day, for ten days). Vaginal bleeding was first noted following oral supplementation of tocopherol nicotinate (600 mg/day) and ascorbic acid (2,000 mg/day) along with hormone replacement therapy. After four years of continuous medication, the

endometrial thickness gradually increased to seven mm or more. During these periods, the size of two major fibroid nodules (the maximal diameter 22 mm and 18 mm) remained unchanged on ultrasound. The patient underwent conventional *in vitro* fertilization, conceived in the first fresh embryo transfer cycle, and delivered a healthy baby weighing 1,720 g at 34 weeks of gestation by elective cesarean section in a maternal care unit.

Discussion

It is difficult to determine the best therapeutic path to preserve fertility for infertile women with DLU. Previous reports presented the successful cases that were managed with myomectomy, gonadotropin releasing hormone agonist, or a combination of these treatments [3-5]. Considering the progressive abdominal distension of the patient and the desire for pregnancy of the couple, the authors chose myomectomy as a primary treatment. They removed as many nodules as possible, but had to perform urgent relaparotomy for hematoma debridement.

Following two consecutive surgeries and three months of gonadotropin releasing hormone agonist treatment, the patient had a secondary amenorrhea for a total of six months. Despite the evidence of the follicular growth and cyclic estradiol and progesterone secretion, endometrial thickness

was always less than five mm. Hormone replacement therapy was not effective for induction of withdrawal bleeding, suggesting postoperative endometrial thinning.

Vitamin E is capable of improving microvascular blood flow by inhibiting lipid peroxidation in erythrocyte membranes [6] or protecting endothelial cells from oxidative stress [7]. Vitamin E was demonstrated to increase the endometrial thickness and the clinical pregnancy rates in infertile women with thin endometrium [8]. In addition, vitamin C was shown to stimulate *in vitro* proliferation of human endometrial epithelial cells [9]. The authors thus attempted tocopherol nicotinate and ascorbic acid, along with conventional hormone replacement. Menstruation immediately recovered following the supplementation of these agents, while the endometrium remained unresponsive and thin.

It is generally accepted that endometrial thickness with less than six to seven mm in the proliferative phase is closely associated with low pregnancy rate in the cycle [10]. Following four years of continuous medication, the patient was able to gain the endometrial thickness and eventually had a successful pregnancy in an *in vitro* fertilization-fresh embryo transfer program. Recently, infertile women with endometrial thinning were found to have high blood flow impedance of uterine radial arteries and low endometrial vascular endothelial growth factor expression, which was improved by vitamin E administration [11]. Vitamin C was also shown to support endometrial epithelial cell proliferation via nitric oxide-mediated signalling [9]. Thus, vitamin E and C are likely to contribute to endometrial growth via the pathways distinct from estrogens.

Conclusion

The authors presented a case report of endometrial thinning following myomectomy for DLU and its recovery with a long-term combination therapy of tocopherol nicotinate, ascorbic acid, and hormone replacement. Continuous vitamin E and C administration may be a therapeutic option for women with postoperative endometrial thinning.

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