Spontaneous Pregnancy Following Ulipristal Acetate Treatment in a Woman with a Symptomatic Uterine Fibroid

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Abstract

Background: Uterine fibroids (UFs) may impair fertility and promote miscarriage. The optimal treatment for women with UFs who wish to conceive is uncertain.

Case: A 35-year-old woman of African ancestry with a history of recurrent miscarriage (gravida 5, para 0) had a solitary submucosal UF (volume: 102.4 cm³) extending into the uterine cavity. Following a three-month course of ulipristal acetate (UPA) 5 mg daily, UF volume decreased to 72.1 cm³. The patient conceived approximately two months after discontinuing UPA. She had an uncomplicated pregnancy and underwent a planned induction of labour at 38 weeks’ gestation. The patient had a normal vaginal delivery of a healthy male infant weighing 3130 g. An ultrasound performed three months post-delivery revealed further reduction in UF volume to 14.5 cm³.

Conclusion: This report demonstrates the utility of UPA in the management of women with UFs who desire pregnancy but opt for non-surgical management.

INTRODUCTION

Uterine fibroids are benign tumours common among women of reproductive age.1-3 Although UFs may be asymptomatic and often remain undiagnosed, some can cause significant morbidity in the form of heavy and/or prolonged menstrual bleeding, pelvic pressure or pain, anemia, and reduced quality of life.4 Depending on anatomical location, UFs may also cause reduced fertility and an increased miscarriage rate.5 Specifically, UFs that distort or protrude into the uterine cavity may cause problems with sperm migration and embryo transport, due to dysfunctional uterine contractility, as well as implantation failure or miscarriage, due to localized endometrial vascular disturbance and inflammation.6

The ideal treatment for UFs should provide relief of symptoms, reduce fibroid size, and maintain or improve fertility.7 Unfortunately, UF treatment in Canada has often resulted in hysterectomy,8,9 which provides a definitive cure at the expense of future fertility. Given that women are increasingly deferring childbearing to the later reproductive years,10 when UF symptoms become most pronounced,11 demand has been growing for less invasive therapeutic options that preserve fertility.

Ulipristal acetate, a once-daily oral agent, recently became the first approved medical treatment for UFs in Canada.12

Key Words: uterine fibroids, pregnancy, fertility, ulipristal acetate, submucosal, medical treatment

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Specifically, UPA is indicated for the treatment of moderate to severe signs and symptoms of UF in adult women of reproductive age who are eligible for surgery. As a selective progesterone receptor modulator, UPA induces a number of favorable effects on fibroid tissue, including a suppression of neovascularization and cell proliferation, as well as induction of cell apoptosis. The efficacy of UPA in controlling heavy uterine bleeding and reducing fibroid volume among women with symptomatic UF has been demonstrated in a series of clinical trials. After three months of treatment with UPA (5 mg daily), UF volume was reduced by 21% to 36%, and uterine bleeding was controlled in most (>90%) patients. Importantly, the reduction in UF volume was maintained at six months after completion of UPA treatment. Most recently, the effectiveness of alternating three-month UPA treatment cycles with off-treatment periods was demonstrated, suggesting the potential for longer-term medical management of UF.

The effect of prior UPA treatment on fertility and pregnancy outcomes is not well established. Case studies in Poland and Spain and a case series of 21 participants in the pivotal phase III PEARL trials of UPA in Europe provide encouraging results. Of the combined 14 women with symptomatic fibroids who carried their pregnancies to term, 12 had undergone surgical removal of fibroids following UPA treatment, and one underwent in vitro fertilization. This report describes the first spontaneous pregnancy in North America following UPA treatment of a symptomatic UF, managed without surgery.

The Case
A 35-year-old woman of African ancestry with a history of five consecutive early pregnancy losses was referred for management of UF and fertility difficulties. Over a 13-year period, she had had five miscarriages at four to 16 weeks’ gestation. Her most recent pregnancy had miscarried at a gestational age of five weeks and had required dilation and curettage. No embryopathology assessment was carried out. The patient was seen approximately 12 months after this miscarriage, and at that time was found to have mild anemia (hemoglobin concentration 113 g/L), poorly controlled essential hypertension (159/99 mmHg), and a BMI of 33.7 kg/m². She had no history of surgery.

Transvaginal ultrasound examination showed an enlarged antverted uterus (16.5 × 8.1 × 7.1 cm), and a posterior submucosal uterine fibroid measuring 7.0 × 5.7 × 4.9 cm (volume: 102.4 cm³) (Figure 1). The patient reported no intermenstrual, postcoital, or heavy menstrual bleeding. She had recently completed a three-month course of a low-dose combined oral contraceptive.

The patient began a three-month course of UPA (5 mg daily) to reduce the size of the fibroid, in accordance with the Health Canada indication. During the three-month course, the patient experienced mild hot flashes and became amenorrheic for two months. Her blood pressure became well controlled on an increased dose of methyl-dopa 500 mg twice daily.

Three days after completing the course of UPA, the patient experienced five days of vaginal bleeding. She resumed unprotected intercourse 20 days after her first post-treatment bleed. As illustrated in Figure 2, an ultrasound assessment two months after the end of UPA treatment showed a reduction in fibroid size to 5.4 × 5.1 × 5.0 cm (volume: 72.1 cm³, a reduction of 29.6%).

Approximately four months after completion of UPA treatment, the patient reported amenorrhea and a positive home pregnancy test. Ultrasound showed a single live intrauterine gestation corresponding to 9 + 1 weeks’ gestation. Subsequent ultrasound assessment during the early second trimester showed normal fetal growth and a type 2 fibroid.

**ABBREVIATIONS**
- SPRM: selective progesterone receptor modulator
- UF: uterine fibroids
- UPA: ulipristal acetate

**Figure 1. Pre-treatment ultrasound imaging of the uterus showing a solitary fibroid measuring 7.0 × 5.7 × 4.9 cm**
Figure 2. Ultrasound imaging of the uterus after three months of UPA treatment, showing the fibroid reduced in size to 5.4 × 5.1 × 5.0 cm

submucosal fibroid (<50% extension into uterine cavity) measuring 9.8 × 9.6 × 7.8 cm (volume 384.2 cm³). Ultrasound assessment at 32 weeks showed a healthy fetus with appropriate growth.

Following an uncomplicated pregnancy, the patient underwent a planned induction of labour at 38 weeks. She had a normal vaginal delivery of a healthy male infant weighing 3130 g. Mother and baby were discharged from the hospital on the third postpartum day. The baby was breastfed beyond six months of age. An ultrasound performed at three months postpartum showed marked reduction in the size of the fibroid to 3.2 × 2.7 × 3.2 cm (volume 14.5 cm³).

DISCUSSION

This is the first North American report of a spontaneous pregnancy following UPA treatment aimed at reducing UF size. A patient with a history of five prior miscarriages and an otherwise asymptomatic solitary submucosal UF responded positively to UPA treatment, showing an approximately 30% reduction in UF volume. Soon after completion of UPA treatment, she became pregnant naturally, had an uncomplicated pregnancy, and delivered a healthy infant at 38 weeks’ gestation. This report adds to the previously published European cases¹⁷–¹⁹ and demonstrates the utility of UPA in the management of women with UFs who desire pregnancy but prefer non-surgical intervention.

Studies using ultrasound imaging indicate that by age 50 approximately 80% of women of African ancestry and 70% of women of Caucasian ancestry have developed UFs.²⁰ UF symptoms depend on the size, number, and location of tumours. While the detrimental effects of submucosal and intramural UFs on fertility are reasonably established,⁵ the role that subserosal fibroids may play in pregnancy loss or reduced fertility remains controversial.⁶,²¹,²² The patient described here presented with a solitary submucosal UF that protruded into the uterine cavity, providing a plausible cause for her repeated pregnancy losses. Indeed, UFs that extend into the uterine cavity may cause problems with sperm migration, embryo transport, and implantation.⁷

Various surgical and medical options are available for the management of symptomatic UFs, but the effect of these options on fertility is unclear, and the optimal treatment for patients with UFs and a desire to conceive remains unsettled.⁷ For instance, myomectomy is a common surgical alternative to hysterectomy among women with UFs who wish to maintain fertility.⁵ However, a recent Cochrane review concluded that evidence from randomized controlled trials is insufficient to establish the effect of myomectomy on fertility.²³ Of particular concern is the observation that intraoperative complications during myomectomy can sometimes result in an unplanned hysterectomy.²⁴ Additionally, patients are generally advised to wait a minimum of three months following myomectomy to attempt conception, and may require Caesarean sections for all future deliveries.⁵ In Canada, the gonadotropin-releasing hormone agonist leuprolide acetate has been widely used off-label in the medical management of UFs. During the course of three to six months of treatment, leuprolide acetate has been shown to reduce UF volume by 30% to 50% and to improve UF-related symptoms.¹⁴,²⁵–²⁷ However, in comparison with UPA treatment, the effect of leuprolide acetate on UF size is relatively short-lived.¹⁴ Indeed, UFs begin to enlarge by one month following the last dose of the GnRH agonist, whereas fibroid size continues to be reduced for at least six months following completion of UPA treatment.¹⁴ Additionally, GnRH agonist treatment has been associated with flaring of symptoms during the first weeks,²⁸ as well as subsequent menopausal symptoms such as hot flashes and reduced bone density that may necessitate concurrent hormonal
add-back therapy. Estrogen add-back is not generally thought to be necessary in patients on UPA, in contrast to those on GnRH agonist treatment.

In 2013, based on its demonstrated efficacy in controlling heavy uterine bleeding and reducing UF volume, UPA became the first approved medical treatment for UFs in Canada. Two prior clinical case studies and a case series in Europe have demonstrated successful pregnancies in women with symptomatic fibroids following UPA treatment. In Poland, a 35-year-old woman with a history of fertility difficulties became pregnant via intrauterine sperm injection after UPA treatment (5 mg/day for 3 months) was used to reduce the size of her two UFs. In Spain, a 37-year-old woman who had previously undergone multiple myomectomy by laparotomy conceived three months after completing 13 weeks of UPA treatment (5 mg/day). In the case series of patients previously participating in UPA clinical trials, 21 women with a desire to conceive received various combinations of UPA doses (5 mg or 10 mg daily) and treatment duration (range 3 to 12 months). In that series, 15 of 21 patients (71%) who attempted to conceive were successful, resulting in a total of 18 pregnancies. Of these, 12 resulted in live births, while six (33%) ended in early miscarriage. In all, of the combined 14 reported women with symptomatic UFs who carried their pregnancies to term, 12 had undergone myomectomy following UPA treatment, and one underwent in vitro fertilization. Thus, the present case study represents the second report of a patient who, without surgery, achieved a spontaneous pregnancy following UPA treatment of symptomatic UFs.

In addition to having a UF, the patient described here was obese and had poorly controlled hypertension. Since obesity and hypertension are both associated with poor pregnancy outcomes, the possibility that these factors had a role in the patient’s history of recurrent pregnancy losses cannot be excluded. Additionally, the improved control of blood pressure may have contributed to the success of this most recent pregnancy.

Changes in estrogen and progesterone levels during pregnancy and the postpartum period have a marked effect on the growth of UFs. Such hormonal changes in early pregnancy may explain the five-fold increase in fibroid volume (72.1 to 384.2 cm³) seen in this case between post-UPA treatment and the end of the first trimester. In a similar case study in Spain, the patient’s two UFs increased in maximal diameter from 1.5 to 2.7 cm and 2.1 to 4.5 cm (increases of 80% and 114%, respectively) between post-UPA treatment and the 28th week of pregnancy. Conversely, no change in UF size was reported during pregnancy in 15 women participating in the PEARL studies, even among the two women who did not undergo surgery following UPA treatment. The discrepancy in changes in UF size during pregnancy between women may be explained by differences in a number of patient variables, including age, pre-pregnancy BMI, and parity. Alternatively, the lack of UF regrowth in the case series of women from the PEARL studies may be a result of use of higher UPA doses (up to 10 mg/day), longer treatment duration (up to 12 months), or both. Conversely, various mechanical and cellular mechanisms related to giving birth and uterine involution may drive reduction in UF size. In a prior prospective analysis of 494 women with UFs, three of four women who gave birth experienced a volume reduction of over 50% in their UFs between early pregnancy and three to six months postpartum. The marked reduction in UF size from the first trimester to three months postpartum in the patient described here agrees with these observations.

Administration of SPRMs, such as UPA, is associated with the development of benign endometrial changes (progesterone receptor modulator-associated endometrial changes) in over half of treated patients. However, these endometrial changes do not appear to be influenced by the duration or cumulative dose of UPA treatment; endometrial histology returns to normal within six months of discontinuing treatment. That a growing number of patients, including the patient described here, are reported to have conceived shortly after UPA treatment indicates that any on-treatment endometrial changes are rapidly reversed and the endometrium retains sufficient quality to allow for implantation.

CONCLUSION

This case represents the first North American report of a spontaneous pregnancy following UPA treatment of a woman with a solitary UF and repeated pregnancy losses. As the patient became pregnant within two months of completing UPA treatment, surgical removal of the UF was not performed. This case demonstrates the utility of UPA in the management of women with UFs who desire pregnancy but opt for non-surgical management.

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