ISSN: 2474-1353

Vilos et al. Int J Womens Health Wellness 2017, 3:056
DOI: 10.23937/2474-1353/1510056
Volume 3 | Issue 3
Open Access

International Journal of
Women's Health and Wellness

CASE REPORT

Resolution of Uterine Arterio-Venous Malformation Followed by Uneventful Pregnancy after Administration of Gonadotropin Releasing Hormone Agonist Concomitantly with an Aromatase Inhibitor and Tranexamic Acid

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Abstract

Objectives: To evaluate the efficacy of a Gonadotropin Releasing Hormone Agonist (GnRH-a) concomitantly with an aromatase inhibitor and tranexamic acid to treat a uterine Arteriovenous Malformation (AVM) associated with Abnormal Uterine Bleeding (AUB).

Case and study methods: Doppler ultrasound demonstrated AVM in a 35-year-old woman who presented with acute, profuse uterine bleeding four months after discontinuing an oral contraceptive pill after she had been on it for 4 years. She wished to preserve her fertility. Concomitantly with transfusion of 2 units of Red Blood Cells (RBC) for a hemoglobin of 7 g/dL, she was treated with Tranexamic acid (Cyclokapron, 1 g TID orally × 5 days), a GnRH agonist (Gosarelin, 10.8 mg SC ×1) plus an aromatase inhibitor (Letrozole 2.5 mg OD × 5 days).

Results: The heavy uterine bleeding subsided within hours and the AVMs resolved within 3 months of treatment. At 6 months, the patient resumed normal menstruation, conceived spontaneously and had an uneventful pregnancy and term vaginal birth.

Conclusion: A GnRH agonist in combination with an aromatase inhibitor and tranexamic acid may be a candidate for uterine sparing management strategy for AVM associated with AUB.

Keywords

Arteriovenous malformation, Abnormal uterine bleeding, GnRH-a, Aromatase inhibitor, Tranexamic acid, Uterine artery embolization

Introduction

Uterine Arterio-Venous Malformations (AVM), also referred to as uterine vascular malformations, arteriovenous fistulae or shunts, consist of a cluster of abnormal interconnections between the arterial and venous system in an area of the endomyometrium. The vast majority of uterine AVMs are encountered in reproductive aged women following pregnancy, and they are thought to represent a delayed or failed resolution of the utero-placental bed and its vessels.

Uterine bleeding has been described as irregular, prolonged, unpredictable and/or heavy unresponsive to traditional conservative therapies. When the bleeding is acute and heavy, immediate intervention is required because of impending hemodynamic instability and hemorrhagic shock. These cases invariably require surgical interventions such as uterine artery occlusion or hysterectomy all of which may not be immediately available, possible to perform, desirable or appropriate, especially in women who wish to preserve their fertility.

To preserve the uterus and/or fertility, case reports of conservative medical therapies with oral contraceptives, danazol, methylergonovine, and Gonadotropin Releasing Hormone Agonist (GnRH-a), as well as inter-

Citation: Vilos GA, Vilos AG, Rafea BA, Ghadeer Al-Shaikh S, Sabr Y, et al. (2017) Resolution of Uterine Arterio-Venous Malformation Followed by Uneventful Pregnancy after Administration of Gonadotropin Releasing Hormone Agonist Concomitantly with an Aromatase Inhibitor and Tranexamic Acid. Int J Womens Health Wellness 3:056. doi.org/10.23937/2474-1353/1510056

Received: July 15, 2017: **Accepted:** August 08, 2017: **Published:** August 11, 2017

ventional transarterial embolization have been reported with varying degrees of success [1]. In the present manuscript we describe complete resolution of an AVM treated with a combination of tranexamic acid, a GnRH agonist and an aromatase inhibitor.

Case

A 35-year-old, G3P3A0, BMI 24 kg/m^2, was admitted through the emergency department with dizziness and heavy intermittent uterine bleeding of one month duration. She had 3 prior term vaginal deliveries and she was on an Oral Contraceptive Pill (OCP) for 4 years for cycle control and contraception until 3 months prior to her presentation. While on OCP, she had normal monthly bleeding.

On examination, she appeared quite pale but her vitals were normal with a blood pressure 120/80 mmHg and pulse of 80 beats/min. Her hemoglobin on admission was 7 g/dL and her serum pregnancy test was negative. Transvaginal sonography with color Doppler reported an inhomogeneous mass occupying the upper endometrial cavity extending to the anterior and posterior myometrium measuring 4.2 × 3.6 cm showing hypervascularity consistent with an AVM or hemangioma. The patient was transfused with 2 units of packed Red Blood Cells (RBC) and the post-transfusion hemoglobin was 10.2 g/dL.

To control her bleeding she was given 1 gram of tranexamic acid IV followed by 1 g orally every 8 hours for 5 days to initiate clotting of the AVM. For the treatment of her AVM, she was given a GnRH agonist (Gosarelin 10.8 mg, SC) concomitantly with an aromatase inhibitor (Letrozole 2.5 mg orally for 5 days) to avoid the FSH 'flare' and the subsequent induced estrogen surge associated with the GnRH-a injection. The bleeding subsided within the first day and the patient had no more acute episode of heavy vaginal bleeding but only irregular mild bleeding. Two months later, MRI showed normal myometrial signal intensity with a mall 1.1 × 1.8 × 1.9 cm low signal intensity lesion seen near the fundal region with enhancement of the lesion.

At 6 months of follow up, the patient experienced regular menses every 28 days, lasting 6 days with normal blood flow (requiring no tampons) and transvaginal ultrasound with color Doppler identified no residual hypervascular lesion or evidence of AVM. Two years later, the patient conceived spontaneously and had an uneventful pregnancy and normal vaginal delivery at term. The placenta was expelled spontaneously and there was normal blood loss and no requirement of excessive oxytocics. Currently, at 5 years post-AVM treatment, at 40 years of age, she has regular menses with normal flow using no contraception.

Signed consent (on file) has been provided by the patient to publish her case.

Discussion

Uterine AVMs may present with acute heavy or chronic irregular bleeding. Acute presentation may manifest as torrential vaginal bleeding, suggesting arterial origin and in such cases immediate intervention to prevent hemorrhagic shock and even death is frequently required. In a systematic review of 100 AVM, total abdominal hysterectomy was performed in 29 patients (29%) while spontaneous resolution of AVM occurred in six patients (6%) [1]. In addition, approximately 30% of patients with AVM require blood transfusion [2].

In the last 20 years conservative therapies have been introduced as alternatives to hysterectomy including intrauterine tamponade, a variety of medications and/or Uterine Artery Embolization (UAE) with varying degrees of resolution of the AVM [1].

In many centers, UAE for AVM has become the first choice treatment. In a 2011 systematic review of 100 uterine arteriovenous malformations from 85 publications, uterine artery embolization was the most common treatment option performed in 59 patients (59%). In 18 patients (18%), haemorrhage due to AVM recurred after UAE, and in 17 patients (17%) recurrence of AVM occurred after treatment with UAE [1]. But, in some reports, trans-arterial UAE was not successful as a result of technical difficulties or the risk of complications [3].

In our practice, during the last 6 years, we provided UAE in five women with AVM as previously described [4]. However, since the effect of UAE on fertility and pregnancy outcomes remains controversial and since there is unpredictable response of AVM to UAE with a recurrence rate of 17% [1], we explored other less invasive therapies to treat AVMs in women who wished to retain their fertility and/or their uterus. The rationale of using the combination of the three drugs described in the present case is based on clinical evidence and acquired experience as described below.

The efficacy of antifibrinolytics, particularly tranexamic acid, for the treatment of cyclical heavy menstrual bleeding in an otherwise normal uterus and in women with fibroids has been well established [5]. Tranexamic acid (Cyclokapron, Pfizer, New York, NY, USA) can be administered intravenously, 1 g over 10 minutes or orally, 1 g every 8 hours for the duration of bleeding, usually 5 days. It doesn't alter coagulation profile with < 1% risk of VTE. Time to peak is 3 hours and the half-time elimination is 2-11 hours.

There are limited data evaluating the role of GnRH agonists in the management of women with abnormal uterine bleeding associated with AVMs. In a previous case report, the uterine arteriovenous malformation lesion completely disappeared after 6 months of treatment with a GnRH agonist, and the patient subsequently had a successful pregnancy and delivery [6]. In two additional cases the AVM persisted after GnRH agonist therapy and they required UAE [7,8].

The mechanism by which GnRH-a effect acute uterine bleeding and AVMs is unknown. GnRH agonists suppress gonadal steroidogenesis by down regulating and desensitizing GnRH receptors, resulting in a profound hypoestrogenic state resulting in uterine atrophy and shrinking of the entire uterus [9]. This may cause mechanical compression/constriction and clotting of the AVM leading to its resolution. The shrinkage in uterine volume may alter blood flow to the uterus and the AVM. Doppler studies have demonstrated a reduction of uterine artery blood flow by approximately 25% after GnRH-a therapy and increased vascular resistance index of both the uterus and leimyomata [10].

Letrozole, an aromatase inhibitor, inhibits the conversion of androgen into estrogen and the estrogen rise induced by the FSH induced flare effect by the initial injection of the GnRH agonist. After 5 days, the pituitary is down regulated and the aromatase inhibitor can be stopped. Therefore, adding an aromatase inhibitor at the time of GnRH agonist administration can prevent the estrogen surge, allowing a flexible cycle start of the therapy [11].

We propose that the present case, likely, had her AVM following her last normal vaginal delivery, 4 years prior, and it was in a dormant state with bleeding controlled by the cyclic oral contraceptives. Oral contraceptives may control bleeding associated with AVM but not complete resolution.

In conclusion, a GnRH agonist to shrink the uterus and reduce its blood supply, in combination with an aromatase inhibitor to minimize the estrogen surge induced by the GnRH agonist FSH flare and tranexamic acid to initiate clotting, was effective in treating a case of AVM and resulted in spontaneous, uneventful pregnancy and normal term vaginal birth.

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