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-
ventional transarterial embolization have been report-
ed 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/m², was admitted
to the hospital department with dizziness and
heavy intermittent uterine bleeding of one month dura-
tion. 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 vi-
tals were normal with a blood pressure 120/80 mmHg
and pulse of 80 beats/min. Her hemoglobin on admis-
sion was 7 g/dL and her serum pregnancy test was neg-
ative. Transvaginal sonography with color Doppler re-
ported an inhomogeneous mass occupying the upper
endometrial cavity extending to the anterior and pos-
terior myometrium measuring 4.2 × 3.6 cm showing hy-
pervascularity 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 treat-
ment of her AVM, she was given a GnRH agonist (Go-
sarelin 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 bleed-
ing 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 small 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 nor-
mal blood flow (requiring no tampons) and transvaginal
ultrasound with color Doppler identified no residual hy-
pervascular lesion or evidence of AVM. Two years later,
the patient conceived spontaneously and had an un-
eventful pregnancy and normal vaginal delivery at term.
The placenta was expelled spontaneously and there was
normal blood loss and no requirement of excessive oxy-
tocics. 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 pa-
tient to publish her case.

Discussion

Uterine AVMs may present with acute heavy or chron-
ic irregular bleeding. Acute presentation may manifest as
torrential vaginal bleeding, suggesting arterial origin and
in such cases immediate intervention to prevent hemor-
raghic shock and even death is frequently required. In a
systematic review of 100 AVM, total abdominal hysterec-
tomy was performed in 29 patients (29%) while spontane-
enous 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 in-
trauterine 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 publica-
tions, uterine artery embolization was the most com-
mon treatment option performed in 59 patients (59%).
In 18 patients (18%), haemorrhage due to UAE recur-
ced after UAE, and in 17 patients (17%) recurrence of AVM
occurred after treatment with UAE [1]. But, in some re-
ports, 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 inva-
sive 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 ac-
quired 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, Pfiz-
er, 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 treat-
ment with a GnRH agonist, and the patient subse-
quently 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 leiomyomata [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.

References