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Treatment of Persistent Postpartum Bleeding Associated with Retained Placental Tissue with a Gonadotropin Releasing Hormone Agonist together with an Aromatase Inhibitor and Tranexamic Acid: Experience with 2 Cases and Review of the Literature

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Abstract

Objectives: To evaluate the efficacy of a gonadotropin releasing hormone agonist (GnRH-a) injection concomitantly with an aromatase inhibitor and tranexamic acid to treat postpartum hemorrhage associated with retained placenta increta or accreta.

Study Methods: Two women, who delivered at 16 weeks and 38 weeks gestation and presented with retained placental tissue were treated with a combination of Tranexamic acid 1 g TID for 5 days orally, an aromatase inhibitor (Letrozole 2.5 mg QD orally for five days) and Luprolide acetate IM injections for 3 and 5 months, respectively.

Results: In both women, the bleeding subsided within hours and the placental tissue disappeared within 3 to 5 months of treatment. Both women resumed normal menstruation; one nine months after breastfeeding.

Conclusion: A GnRH agonist in conjunction with a five-day course of an aromatase inhibitor and tranexamic acid may be an effective management strategy for retained placental tissue associated with abnormal uterine bleeding.

Keywords

Placenta accreta/increta, GnRH-a, Aromatase inhibitor, Tranexamic acid

Introduction

Three variants of abnormally invasive placentation include placenta accreta, where villi invade the surface of the myometrium, increta where villi extend into the myometrium, and percreta, where the villi penetrate through the myometrium and may invade adjacent organs, such as the bladder [1].

Any of the above abnormal placentations may be associated with major pregnancy complications, including life-threatening maternal haemorrhage, large-volume blood transfusion, and peripartum hysterectomy [2]. A study including all hospital deliveries in Canada (excluding Quebec) for the years 2009 and 2010 including 570,637 deliveries from the Canadian Institute for Health Information, showed that approximately 50% of the patients with placenta accreta experienced postpartum hemorrhage. Of these, 22.6% experienced a severe form of postpartum hemorrhage requiring blood transfusion (19.2%), undergoing hysterectomy (11.2%), or other procedures (5.2%) to control bleeding [3]. The risk of peripartum hysterectomy then in women with placenta accreta is quite significant and of utmost importance, especially in those women desiring future fertility or uterine conservation. Consequently, uterine sparing therapies have been explored and case reports and small series have indicated variable clinical outcomes [3-5].

Uterine sparing therapies for retained placenta include methotrexate injections, uterine artery embolization/occlusion (UAE/UAO) and hysteroscopic removal of retained placenta. Regarding the use of methotrexate, there are no standard dosing regimens or protocols for the treatment of retained placenta. Small case series have reported mixed results with little benefit in enhancing reabsorption of placental tissue and have questioned the benefit of methotrexate. Furthermore, although rare, life-threatening complications, including pancytopenia and nephrotoxicity, have been reported.

Since there are no convincing data on the risk-benefit ratio of the use of methotrexate [6] or uterine artery embolization (UAE) [7] for postpartum management of placenta accreta, we explored an alternative medical therapy using a combination of known medications which can be used by all health care providers. Herein, we report our experience with treating two women with persistent uterine bleeding associated with retained placental tissue using a combination of Tranexamic acid to initiate/maintain uterine blood clotting, a GnRH agonist to reduce uterine volume and blood flow, and a short-term aromatase inhibitor to eliminate the GnRH agonist induced estrogen surge.

Signed consent to publish both cases have been obtained and it is on file.

Case 1

A 25-year-old, P0G1 woman had a D & C following spontaneous abortion at 16 weeks gestation. She continued to bleed and two weeks later a transvaginal color Doppler ultrasound indicated a uterus measuring 15.3 x 7.2 x 7.8 cm containing a heterogeneous mass lesion with significant vascularity within the fundal endomyometrium. Following a second suction curettage, removing a moderate amount of retained products, the patient continued to experience moderate bleeding. Pathological findings were reported as placenta tissue with no significant pathologic changes. Two weeks after the second suction curettage, the bleeding became profuse and her hemoglobin dropped to 65 g/L. The beta HCG was 2000 IU/L. She was transfused 2 units of red blood cells and an emergency hysterectomy was contemplated although the patient wished to retain fertility.

Following a telephone consultation with our centre, the primary gynecologist was advised to initiate treatment with Tranexamic acid (1 g TID x 5 days orally), Luprolide acetate (3.75 mg IM, Saint-Laurent, Quebec, Canada), Letrozole (2.5 mg QD x 5 days orally; Novartis Oncology, East Hanover, New Jersey), and to consider intrauterine tamponade with a large Foley catheter if brisk bleeding persisted.

Following the above treatment, the heavy bleeding subsided within few hours. One week later, transvaginal ultrasound (TVS) was reported as "an irregular ill-defined vascular mass measuring 7.9 x 4.2 x 6.9 cm at the uterine fundus. The endometrium cannot be identified in the upper uterus and this may be because the mass involves both the endometrium and myometrium. The appearance may represent retained products and placenta accreta given the mass involves the fundal myometrium. A molar pregnancy is also a consideration". At this time, the hemoglobin was 107 g/L and the beta HCG 453 IU/L.

Five weeks from the initial injection of Luprolide acetate, the bleeding had completely subsided, and a transvaginal ultrasound measured the mass at 6.2 x 4.5 x 4.3 cm or 61 cc (previous 7.9 x 4.2 x 6.9 cm, 173 cc, 65% reduction) with internal vascularity. Consequently, a second injection of Luprolide acetate (11.25 mg) was given IM. Three months after the initial treatment, the hemoglobin was 130 g/L and the beta HCG < 5 IU/L.

Three months after the combined treatment, the retained placental tissue measured 4.0 x 3.4 x 4.5 cm (31 cc) and at five months, both TVS and Doppler US identified no residual tissue with a normal uterus and pelvic organs. The patient was not interested in pregnancy in the immediate future and she was started on an oral contraceptive pill.

Case 2

A 26-year-old, G1P1 woman was induced at 38 weeks gestation for new onset of moderate pre-eclampsia. Following an uneventful labor and normal vaginal delivery of a live male baby, the placenta was noted to be difficult to remove and it required manual removal under sedation in the operating room. There was difficulty with creating a retro placental plane and although the majority of the placenta was removed piecemeal, the gynecologist noted that there was adherent tissue remaining but since the patient was not actively bleeding, opted not to perform curettage. Pathological findings were reported as placenta tissue with no significant pathologic changes.

On postpartum day one, the patient experienced significant hemorrhage which required transfusion of 4 units of red blood cells and 2 units of fresh frozen plasma. The bleeding subsided, and post-transfusion hemoglobin was 87 g/L. Ultrasound showed retained products and possible placenta accreta as there was extension into the myometrium. An MRI on postpartum day 3, identified a mass measuring 6.5 x 7.9 x 13.5 cm (355 cc) and suggested that this may be a placenta increta. There was no active bleeding and no further treatment was offered at this time.

Approximately one month later, the patient developed endometritis requiring a 2-day hospital admission and intravenous antibiotic therapy (Clindamycin 600 mg and Gentamicin 80 mg every 8 hours). She continued to experience moderate bleeding and ultrasound indicated retained placenta. After a telephone consultation with our clinic, the patient was given tranexamic acid, 1 g TID orally for 5 days, Luprolide acetate 11.25 mg IM together with Letrozole 2.5 mg QD for 5 days.

The bleeding was markedly reduced and two weeks later an ultrasound measured the mass at 4.1 x 4.1 x 3.2 cm (28 cc) in size. The patient continued to pass "stringy tissue" which was likely necrotic placenta. A repeat ultrasound a month later measured the mass at 1.7 x 1.6 x 1.9 cm (2.6 cc) and two

months later at 1.7 x 1.3 x 0.7 cm (0.8 cc). Beta HCG levels are not available. At five months, the mass had disappeared, and the patient resumed normal menstrual periods after 9 months of breast feeding.

Discussion

Conservative, uterine-sparing approaches for the management of placenta accreta have been described to both reduce the morbidity and mortality of peripartum hysterectomy as well as to allow retention of fertility or the uterus. One uterine sparing measure is to leave the placenta in situ. Even in cases of placenta accreta/increta during Caesarian section, the placenta can be left in situ and the uterus is closed with or without additional hemostatic sutures. Immediate bleeding can be controlled with transient vasopressors and/or intrauterine balloon tamponade. Long-term measures for persistent bleeding and for the resolution of the retained placenta have included prolonged methotrexate therapy, uterine artery embolization and hysteroscopic removal of placental tissue with variable success [7].

The utility of methotrexate in the management of retained placenta remains controversial as discussed in the introduction.

The role of pelvic artery embolization to control hemorrhage in the immediate postpartum period and for persistent/prolonged uterine bleeding has been reported. After delivery, embolization can be performed either in the operating room or in an interventional radiology suite if the patient is stable and transferable. A review of 45 patients treated with pelvic artery embolization in the Netherlands noted that hysterectomy was required in only 18% of the embolized women, and 62% had resumption of normal menses [7]. However, fertility rates and pregnancy outcomes after pelvic artery embolization for retained placenta have not been reported. In general, studies examining pelvic artery embolization as a conservative management of placenta accreta have reported success rates of 85–95%.

Several case reports and case series have reported on hysteroscopic removal of retained placenta. One study reported on 12 consecutive patients with hysteroscopic resection of retained tissues after conservative management of placenta accreta. Complete resection of placenta accreta was achieved after the first procedure in 5 patients, after the second procedure in 2 patients, and after the third procedure in 4 patients; however, in 1 patient a delayed hysterectomy was necessary because of persistent bleeding and anemia after an incomplete first hysteroscopic resection [4].

Since treatment options for retained placenta are limited, and the clinical outcome after all conservative treatments appear to be unpredictable and variable, we have explored alternative therapies to treat abnormal uterine bleeding in general, and more specifically, associated with uterine arteriovenous malformation and post-partum hemorrhage associated with abnormal placentation.

The rationale for using the combination of antifibrinolytics, GnRH agonists and an aromatase inhibitor is derived from sound pharmacologic principles and our own personal experience provided below.

Antifibrinolytics

The efficacy of antifibrinolytics, particularly tranexamic acid, for the treatment of cyclical heavy menstrual bleeding in an otherwise normal uterus has been well established [8]. Tranexamic acid (Cyclokapron, Pfizer, New York, NY, USA), 1 g orally, three times daily for 5 to 7 days, has also been shown to be relatively effective when used to treat heavy menstrual bleeding in patients with uterine fibroids. Tranexamic acid can be administered intravenously, 1 g over 10 minutes or orally, or 1 g every 8 hours for the duration of bleeding. Tranexamic acid does not alter the coagulation profile of the patient and there is no evidence that it increases the incidence of thromboembolic events, even when used in women at high risk such as during pregnancy or in the immediate postpartum period [9].

Gonadotropin-Releasing Hormone Agonists (GnRH-a)

There are limited data evaluating the role of GnRH agonists in the management of women with postpartum bleeding. However, we have had considerable experience in treating successfully acute uterine bleeding associated with uterine fibroids and arteriovenous malformation (AVM) [10, 11] with the combined use of all three; tranexamic acid, a GnRH agonists and concomitant use of an aromatase inhibitor.

The mechanism by which GnRH-a affect acute uterine bleeding is unknown. GnRH agonists suppress gonadal steroidogenesis resulting in a profound hypoestrogenic state which shrinks the uterus and may cause mechanical compression/constriction and clotting of uterine and placental vascular tissue leading to its resolution. The shrinkage in uterine volume may also alter blood flow to the uterus and the residual placental tissue. 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 [12].

Aromatase inhibitors

It is well known that following administration of a GnRH agonist, there is an FSH flare effect which, in turn, causes a surge of ovarian estrogen. A study conducted in 13 women with endometriosis or uterine fibroids treated with leuprolide acetate, 3.75 mg monthly injections, (Lupron depot, Abbvie Pharmaceuticals, Mississauga, Ontario, Canada) concluded that adding an aromatase inhibitor, Letrozole 2.5 mg daily for 5 days (Femara, Novartis Pharmaceuticals Canada Inc., Dorval, Quebec) at the time of the first GnRH agonist administration can prevent the estrogen rise associated with the flare effect of gonadotropins in patients treated with GnRH agonists [13]. This observation leads us to the rationale of including an aromatase inhibitor for 5 to 7 days concomitantly with only the first injection of the GnRH agonist.

We have previously presented and reported our experience with treating 10 women with post pregnancy persistent uterine bleeding associated with uterine arteriovenous malformation (AVM) using either UAE (4 cases) or with a combination

of Tranexamic acid, a GnRH-agonist plus Letrozole (2.5mg orally daily x 5 days) with the initial injection of GnRH-agonist. All AVM resolved by 3 months post treatment with either UAE or GnRH-a therapy and all women who tried for pregnancy conceived spontaneously and had uneventful pregnancies and deliveries [10].

In addition, we have reported a case of a 35-year-old woman who presented with acute, profuse uterine bleeding associated with AVM, four months after discontinuing an oral contraceptive pill after she had been on it for 4 years. She wished to preserve her fertility and concomitantly with transfusion of 2 units of Red Blood Cells (RBC) for a hemoglobin of 70 g/L, she was treated with tranexamic acid (Cyclokapron, 1 g TID orally × 5 days), a GnRH-a (Gosarelin, 10.8 mg SC × 1) plus an aromatase inhibitor (Letrozole, 2.5 mg QD × 5 days). The heavy uterine bleeding subsided within hours and the AVM 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 [11].

To date, we have treated over 25 women with post pregnancy abnormal uterine bleeding and documented AVM with transvaginal ultrasound. The AUB and all AVM have resolved and all women who attempted pregnancy have conceived. The clinical and obstetrical outcomes of the first 20 women treated with this triple combination has been submitted for publication.

The advantages of this simple medical protocol include: efficacy (eliminated both uterine bleeding and retained placenta in both cases); safety (clinically available drugs with known minimal adverse effects); preservation of fertility and/or the uterus; and, universality (feasible/accessible to all patients by all health care providers). The limitations of this report are the inclusion of only two cases treated in a single center. Naturally, additional cases are required to be treated in other centers to determine the value of this uterine sparing medical therapy in women with post-delivery abnormal uterine bleeding with and without retained placental tissue.

Conclusion

In conclusion, our protocol including an antifibrinolytic drug to initiate blood clotting, a GnRH agonist to induce uterine shrinking and blood flow in conjunction with an aromatase inhibitor to eliminate the estrogen rise induced by the GnRH agonist FSH flare, was effective in the treatment of two women with persistent postpartum bleeding associated with retained placental tissue.

Conflict of Interest

All authors declare no conflict.

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