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Case Report

Use of GnRH Analog Combined with Parenteral Progesterone Following Intravenous Estrogen Administration in the Treatment of Life-Threatening Dysfunctional Uterine Bleeding: A Case Report

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- Medroxyprogesterone Acetate
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Abstract

Objective: To report a case of life-threatening anovulatory dysfunctional uterine bleeding (DUB) successfully treated without the use of oral contraceptives.

Design: Case report

Setting: Academic center

Patient: A 15-year-old female with autism presented with confusion, severe anovulatory vaginal bleeding and inability to tolerate oral contraceptives.

Intervention: Parenteral hormone induction of amenorrhea

Main Outcome Measures: Control of life-threatening anovulatory DUB

Result: High-dose intravenous estradiol therapy was started immediately and followed by three-months of gonadotropin-releasing hormone (GnRH) analog therapy (leuprolide acetate, 3.75 mg intramuscular, monthly) rather than oral contraceptive administration. With the onset of pituitary desensitization to GnRH, GnRH analog therapy was replaced with medroxyprogesterone acetate (medroxyprogesterone acetate, 150 mg intramuscularly every 3 months) to provide longer control of abnormal menstrual bleeding.

Conclusion: The use of GnRH analog in combination with parenteral progestin administration may be a reasonable first-line alternative to oral contraceptives following intravenous estrogen administration to treat life-threatening DUB in women unable to use oral steroid hormones.

INTRODUCTION

Dysfunctional uterine bleeding (DUB) refers to irregular menstrual bleeding of an abnormal quantity or duration without a known etiology in young reproductive-aged women [1]. Commonly due to anovulatory menstrual cycles in adolescent girls with, it can develop after menarche as an immature hypothalamo-pituitary-ovarian axis exposes the endometrium to chronic estrogen stimulation unopposed by progesterone [1]. Under these circumstances, anovulatory DUB is usually managed with oral progestins or oral contraceptives. In life-threatening conditions, however, treatment of anovulatory DUB requires immediate delivery of high-dose intravenous (IV) estrogen to induce rapid regrowth of the endometrium and inhibit bleeding. With the cessation of vaginal bleeding, IV estradiol therapy is usually replaced by high-dose oral contraceptive therapy, in which an oral contraceptive is initially started three times daily and then decreased to once daily over the next few weeks to gradually induce an atrophic endometrium [1]. Unfortunately, such high-dose oral contraceptive therapy has several side effects, including nausea/vomiting, inconsistent patient compliance, and gastrointestinal malabsorption, which may require a parenteral hormonal strategy to accomplish the same goal.

Gonadotropin-releasing hormone (GnRH) analog provides such a parenteral approach to treating severe anovulatory DUB through the ability of pituitary desensitization to GnRH to induce endometrial atrophy over time [2]. Limitations of pituitary desensitization to GnRH include hot flashes, bone demineralization, and cost [3], so a change to another parenteral

hormonal therapy is required for longer control of menstrual bleeding in an individual unable to use oral steroid hormones. The present report describes the use of IV estrogen combined with GnRH analog followed by parenteral progestin therapy to successfully treat life-threatening anovulatory DUB in an adolescent girl unable to use oral steroid hormones. Informed consent was obtained from the patient's guardian for this case report.

CASE PRESENTATION

A 15-year-old nulliparous female with anovulatory menstrual cycles presented to the emergency room with dizziness, confusion and heavy vaginal bleeding of one-week duration. Her mother reported that her daughter's menarche occurred at 13 years of age and was followed by acne and irregular menses unassociated with hirsutism, hair loss, or galactorrhea. A recent 10-day course of prometrium 200 mg orally daily was unsuccessful in controlling vaginal bleeding.

Past medical history was significant for autism, traumatic brain injury, postural orthostatic tachycardia syndrome (POTS), Tolchin-Le Caignec syndrome due to SOX6 mutation and gastroparesis. Medications included tretinoin 0.025% cream and albuterol inhaler. The patient could not take oral steroid hormones, metformin, or semaglutide due to severe nausea and vomiting.

Laboratory testing three months before presentation to the emergency room showed normal serum androgen, prolactin, thyroid-stimulating hormone, hemoglobin A1c and lipid levels, except for a reduced fasting serum high-density lipoprotein level of 32 mg/dL (normal, 33-70 mg/dL). A dexamethasone suppression test was also normal. A hemoglobin of 9.8 g/dL was accompanied by a reduced serum iron level of 24 mcg/dL (normal, 34-173 mcg/dL), with normal iron binding capacity and 6% saturation.

At hospital admission, she was weak and had heavy vaginal bleeding. Vital signs were: temperature 98.6 degrees Fahrenheit, BP 100/65 supine, pulse 124 beats per minute, respirations 16 per minute, body mass index (BMI), 46.7 kg/m^2. General physical examination was unremarkable and pelvic examination was deferred due to limited compliance. Laboratory evaluation showed blood type O positive, hemoglobin 5.8 g/dL, and normal coagulation studies as well as Von Willebrand Factor activity. Serum follicle-stimulating hormone (FSH) was 4.8 mIU/mL, estradiol 43 pg/mL, and progesterone 0.4 ng/mL (luteal phase > 3.0 ng/mL). Trans-abdominal sonography showed normal post-pubertal pelvic organs and a 5 mm endometrial thickness.

The patient immediately received estrogen 25 mg IV every 6 hours with hydration, along with 4 units of packed red blood cells. Within 24 hours, vaginal bleeding had ceased, but severe nausea prevented the patient from starting oral contraceptives as IV estrogen was discontinued. Therefore, GnRH analog (leuprolide acetate, 3.75 mg intramuscular, monthly) was administered to induce pituitary desensitization to GnRH. Two days later, vaginal bleeding had ceased, and the patient was discharged from the hospital on an iron-rich diet.

Over the next 3 months, she continued to receive leuprolide 3.75 mg intramuscularly monthly, and to experience amenorrhea with occasional hot flashes. Her hemoglobin was 10.8 g/dL and laboratory evaluation showed serum FSH 3.5 mIU/mL, LH 0.5 mIU/mL, estradiol <12 pg/mL, progesterone 0.2 ng/mL, total testosterone 9 ng/dL (normal 6-52 ng/dL), and free testosterone 1.7 pg/mL (normal 1.2-7.5 pg/mL). A discussion was held with family members regarding various long-acting reversible contraceptives that could replace GnRH analog on a long-term basis. Parenteral medroxyprogesterone acetate was chosen rather than a progesterone implant or IUD, which in this patient would likely require placement under anesthesia and might be traumatic during insertion or removal. Therefore, medroxyprogesterone acetate (150 mg intramuscularly, every 3 months) was administered following GnRH analog therapy and was continued every 3 months. The patient is doing well and continues to have amenorrhea to date.

DISCUSSION

The present case report describes the use of GnRH analog in combination with parenteral medroxyprogesterone acetate as an alternative to oral contraceptives following IV estrogen treatment of life-threatening anovulatory DUB in an adolescent girl unable to use oral steroid hormones.

Although considered a second- or third-line treatment for DUB [4], intramuscular GnRH analog administration to our patient receiving IV estrogen provided several benefits compared to high-dose oral contraceptives. Upon binding to pituitary GnRH receptors, GnRH analog induces a transient rise in circulating pituitary gonadotropins and ovarian estradiol production followed by suppression of the hypothalamo-pituitary-gonadal axis [2]. Consequently, GnRH analog administration would be expected to initially increase circulating estradiol levels to promote IV estrogen action on endometrial regrowth without worsening nausea/vomiting, but later to induce pituitary desensitization to GnRH to cause endometrial atrophy [2]. Moreover, unlike oral contraceptives, GnRH analog action does not worsen adiposity-dependent dyslipidemia, increase the risk for thromboembolic events [5], nor require gastrointestinal absorption or first-pass hepatic metabolism [6]. Nevertheless, that long-term GnRH analog use eventually induces significant side effects, including hot flashes and bone demineralization [3] called for its replacement by some form of parenteral progesterone for longer control of this patient's abnormal menstrual bleeding.

Several long-acting reversible contraceptives, including the progestin-containing IUD and progesterone implant, were discussed with the family as longer effective management of anovulatory DUB. Although not user-dependent, the use of long-acting reversible contraceptives calls for an invasive procedure, which for this patient would require anesthesia, has risks of complications with insertion, and may not be well tolerated

[7]. Alternatively, parenteral medroxyprogesterone acetate administration (150 mg intramuscularly, every 3 months) is cost-effective for treatment of gynecological disorders [3], is unaffected by BMI, and avoids first-pass hepatic metabolism [6]. Moreover, as a safe, effective hormonal strategy, parenteral medroxyprogesterone acetate administration offers several long-term advantages for this patient. During the first year of use, it limits outpatient doctor visits, although continued surveillance for possible bone demineralization, lipid abnormalities and irregular menstrual bleeding is important [8]. It also simplifies care by promoting future self-administration of SC depot medroxyprogesterone acetate by family members in the care of their child with autism [9].

Regarding the family perspective about the treatment they received:

Our child was in great spirits the moment she arrived at the Emergency Room because she had such faith in the care she would be provided. We are forever grateful to the entire medical team for saving the life of our child.

CONCLUSION

The use of GnRH analog in combination with parenteral progestin administration may be a reasonable first-line alternative to oral contraceptives following IV estrogen administration to treat life-threatening anovulatory DUB in women unable to use oral steroid hormones.

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DISCLOSURE STATEMENT

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