CASE REPORT

Abnormal excessive per vagina (PV) bleeding on Esmya—selective progesterone receptor modulator (SPRM) in a symptomatic patient with uterine fibroid

Lyubov Matytsina-Quinlan,¹ Laura Matytsina²¹ECCSH, MDGH, Macclesfield, Cheshire, UK²Nevill Hall Hospital, Aneurin Bevan Health Board, Abergavenny, UK**Correspondence to**

Dr Lyubov Matytsina-Quinlan, lyubov.matytsina@yahoo.com

Accepted 20 April 2015

SUMMARY

A woman in her late 40s presented with excessive per vagina (PV) bleeding and uterine fibroid. She reported excessive PV bleeding after starting Esmya; she was brought in by ambulance to the emergency department with profuse bleeding. Abnormal uterine bleeding (AUB) developed after selective progesterone receptor modulator (SPRM) administration in this symptomatic patient with uterine fibroid. The drug was withheld and surgical treatment considered. Progressive deterioration of PV bleeding after receiving SPRM led to an urgent *laparoscopic* total hysterectomy, which had to be postponed due to severe anaemia. Surgery took place regardless because the excessive bleeding continued. Histology revealed a 6 cm submucosal uterine fibroid (SMUF) and adenomyosis. Physicians prescribing SPRMs to stop PV bleeding should be aware of potential AUB, which could lead to urgent hysterectomy. The mechanism of action of SPRMs is not clearly understood. Awareness of the side effects of Esmya, such as AUB, must be kept in mind when administering SPRMs.

BACKGROUND

This rare case of an adverse effect of selective progesterone receptor modulator (SPRM)/Esmya for treatment of a symptomatic patient with uterine fibroid has valuable educational interest in clinical practice.

Ulipristal acetate (UPA) 5 mg daily/Esmya, is currently licensed for preoperative treatment of uterine fibroid. Approximately 90% of symptomatic patients with heavy menstrual bleeding (HMB) on 3-month preoperative therapy with Esmya become amenorrhoeic in the first 10 days of the start of Esmya; only 10% may have abnormal bleeding. There is no literature available regarding excessive per vagina (PV) bleeding leading to urgent hysterectomy, however, this ill-effect is mentioned in the Esmya product information leaflet.^{1 2} Furthermore, research has found an association between PV bleeding and presence of submucosal uterine fibroid (SMUF) in patients on 5 and 10 mg UPA.³

The mechanism of action of SPRMs is not clear. It is known that they act on the progesterone receptor, and exhibit agonist as well as antagonist effects.⁴

HMB and uterine fibroid are common. Uterine fibroid (uterine leiomyomata) is a benign disease, being non-cancerous smooth muscle tumour with fibroid elements that develop in the wall of the

uterus. Uterine fibroids occur in one in three women aged 30 years and over, more frequently as the women approach menopause.⁵ When the fibroids are small (less than 3 cm), patients may be asymptomatic (around 50%). Often the symptoms are associated with larger fibroids and include HMB, dysmenorrhoea, anaemia, lower abdominal pain and pressure effects, urinary urgency and subfertility.^{5 6} Moreover, fibroid location (subserosal, intramural or submucosal) is associated with particular symptoms. For example, HMB may occur with submucosal or intramural fibroids.⁷

The National Institute for Health and Care Excellence (NICE) and the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines recommend the use of ultrasound scan (USS) in combination with endometrial biopsy (pipelle) for HMB to identify structural uterine abnormalities.^{5 8}

CASE PRESENTATION

A 49-year-old woman presented with profuse PV bleeding and a history of uterine fibroid. She was known to have had a small intramural fibroid (approximately 3 cm) since the age of 30. However, a recent USS showed the fibroid growing inside the uterine cavity (up to 4–4.5 cm in diameter) and in the left lateral wall near the fundus; it was now found to be submucosal. The patient was symptomatic for HMB with iron deficiency anaemia for approximately 1 year.

The patient had two levonorgestrel intrauterine system (LNG-IUS) insertions to treat her HMB in the last 6 months, but they were not effective and the patient remained symptomatic for bleeding and pain. The first LNG-IUS had displaced after 2.5 months with further very HMB (VHMB), necessitating hospital admission. Haemoglobin (Hb) was 86 g/L (121–151 g/L in women) and ferritin level 5 ng/mL (18–160 ng/mL in women) at the time. The second LNG-IUS expelled spontaneously after 1 month following VHMB associated with abdominal pain and prolonged PV bleeding since LNG-IUS insertion.

The patient was on tranexamic acid 1 g three times per day and mefenamic acid 500 mg three times per day for just under a year, and norethisterone 5 mg three times per day for HMB, in the last 5 months.

The patient was in a monogamous relationship with low risk of pelvic inflammatory disease (PID). She had not been sexually active for a few months

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To cite: Matytsina-Quinlan L, Matytsina L. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-209015

due to the constant PV bleeding. A sexually transmitted infections (STIs) screen was negative prior to LNG-IUS insertion.

The patient had no history of endometriosis, dyspareunia or dysmenorrhoea.

Open appendectomy at the age of 12 was the only surgical history of note. The patient had one normal vaginal delivery complicated by retained products of conception, postpartum haemorrhage, endometritis and anaemia.

Medical history (MH) revealed hypothyroidism, for which the patient takes 100 µg of levothyroxine; there was nothing else to note.

The most recent US examination (trans-abdominal and trans-vaginal) revealed a SMUF approximately 5 cm in diameter.

The patient reported VHMB during the last 1.5 days, after having started Esmya medication 3 days previously. Esmya therapy 5 mg daily was started to stop PV bleeding, because of the anaemia and in preparation for surgical treatment of the uterine fibroid in 3 months' time, as per Esmya instructions. The patient developed more profuse bleeding on day 4 of taking Esmya, after having been advised to continue to take it, and then brought to the emergency department by ambulance with excessive bleeding and presyncopal episodes. Estimated blood loss was approximately 2 L. The patient had four blood transfusions for severe post-haemorrhagic anaemia. Esmya was stopped, as the profuse PV bleeding obviously developed as an adverse effect of Esmya administration, and surgical treatment was considered. The diagnosis of progressive deterioration with bleeding after receiving SPRM led to the decision to opt for urgent total hysterectomy, which had to be postponed for 4 weeks due to fully booked operating lists and the patient having anaemia.

To correct the anaemia preoperatively, the patient was advised to continue taking ferrous fumarate 5 mL two times per day, tranexamic acid 1 g three times per day, mefenamic acid 500 mg three times per day and norethisterone 10 mg three times per day for her bleeding, until the next available surgery, which was scheduled for 4 weeks later.

However, urgent total laparoscopic hysterectomy was undertaken in 3 weeks as PV bleeding recurred and conservative treatment was not effective to terminate the bleeding.

Four weeks postoperatively, the patient developed a painful left leg with swollen discoloured calf. She was admitted to hospital with deep vein thrombosis (DVT) of the left leg, as a D-dimer test was positive; low-molecular-weight heparin was administered. On USS, a Baker's cyst was found and was considered a possible cause of the sharp pain in the patient's left knee and swollen calf. The patient was further immobile for 3 weeks and partially mobile for a further 3 months.

INVESTIGATIONS

Full blood count (FBC) revealed post-haemorrhagic anaemia. Hb was 78 g/L (120–151 g/L) on admission. The patient had anaemia over the past 6 months, being symptomatic for HMB. Ferritin levels were 4–7 ng/L (normal range in women: 18–160 ng/L). The patient received oral iron replacement therapy for 9 months before surgery and for 6 months after surgery.

Haematocrit, mean cell volume and mean cell hb remained low for a few months as ferritin levels were significantly low, ranging from 4 to 7 ng/L (18–160 ng/L in women). Folate and vitamin B₁₂ levels were normal.

Urea and electrolytes were normal. Lipid profile showed total cholesterol 5.2 mmol/L (2.5–5.0 mmol/L), high-density lipoprotein (HDL) cholesterol 0.79 mmol/L (1.2–2.1 mmol/L) and

Figure 1 Submucosal uterine fibroid on pelvic transvaginal ultrasound scan, frontal view (D=52.8 mm).

total/HDL cholesterol ratio 6.6 (2.0–6.0). Coagulation screen results were normal.

Thyroid function test (TFT) was normal as the patient was on levothyroxine replacement therapy.

Tumour marker for ovarian and endometrial cancer was normal: CA-125–27 ku/L (0–34 ku/L).

To conclude, biochemical and haematological investigations were normal, except for persistently high levels of cholesterol and iron deficiency anaemia with depleted ferritin stores.

Pregnancy test was negative. The routine screen for STIs in the form of swabs for gonorrhoea and chlamydia, as well as serology for syphilis and HIV, which were taken as a part of pre-LNG-IUS insertion investigation, were negative.

USS confirmed a bulky retroverted uterus of 118 mm in length and round-shaped uterine fibroid, which was continuously growing, compared with the previous USS report. There was a heterogeneous mass measuring 52.8×45.3×48.1 mm in the centre of the uterus lying within the endometrial cavity, which was in keeping with the presence of a large submucosal fibroid (figures 1 and 2). Both ovaries had normal appearance.

The pipelle biopsy and histological investigations of endometrium before LNG-IUS insertion 6 months prior to surgery were unremarkable.

Histology revealed the following:

1. Fibroid—a large intraluminal nodule SMUF measuring 60 mm in diameter (figure 3);
2. Uterus 430 g, approximately 130×105×100 mm, endometrium up to 4 mm, myometrium up to 14 mm.

Figure 2 Submucosal uterine fibroid on pelvic transvaginal ultrasound scan, sagittal view (D=45.3 mm×48.1 mm).

Figure 3 Histology: submucosal uterine fibroid—a large intraluminal nodule (courtesy of Dr R Jenkins).

Descriptive histological diagnosis: the cervix shows some retention cysts, the endometrium is predominantly thin and there is some predecidual stromal reaction; the myometrium shows some nodularity and multiple foci of endometriosis. Features are those of adenomyosis uteri ([figure 4](#)). There is no evidence of malignancy.

D-dimer test was positive 280 ng/mL (normal range <250 ng/mL), when the patient developed DVT of the left calf 4 weeks postoperatively.

We suggest the following list of investigations that may be appropriate for symptomatic patients with uterine fibroid and PV bleeding, and where SMUF is suspected:

- ▶ FBC to check for anaemia; haematinics (ferritin, B₁₂, folate) and coagulation screen.
- ▶ Pelvic USS is indicated to confirm the presence, size and structure of a suspected uterine fibroid(s), distortion of uterine cavity, endometrial hyperplasia, etc. Transvaginal USS is usually more accurate.
- ▶ STI screening, swabs, cytology history, speculum and bimanual examination are recommended as routine.
- ▶ Endometrial sampling is important for histology assessment of abnormal uterine bleeding. In our case, pipelle biopsy histology was undertaken prior to the first LNG-IUS insertion, showing no evidence of malignancy. Therefore, hysteroscopy

with biopsy would be recommended where possible. In our case SMUF was occupying the whole uterine cavity.

DIFFERENTIAL DIAGNOSIS

NICE defines HMB as “excessive menstrual blood loss which interferes with a woman’s physical, social, emotional and/or maternal quality of life”. It can occur along or in combination with other symptoms.

The possible causes of HMB are:

- ▶ Uterine fibroid (subserosal, intramural or submucosal);
- ▶ Endometrial lesions (polyp, malignancy);
- ▶ Cervical lesions (polyp, cancer);
- ▶ Adenomyosis;
- ▶ Inflammatory response (from intrauterine device/IUS, PID);
- ▶ Coagulation defects (eg, Von Willebrand disease);
- ▶ Medical disorders (eg, hypothyroidism);
- ▶ Dysfunctional uterine bleeding, where no obvious abnormality is found.

Endometrial carcinoma was ruled out by histological investigation of the endometrium, that is, previous pipelle biopsy prior to LNG-IUS insertion.

The patient was treated for dyskaryosis 7 years previously with a large loop excision of transformation zone. Cervical malignancy was ruled out as she was on regular recall for cervical smears; the last smear was up-to-date and normal.

The patient had no family history of endometrial or other gynaecological cancers.

There was no MH of dysmenorrhoea, or dyspareunia or endometriosis.

PID was unlikely given the patient’s history as a low risk for STIs. She is married, that is, in a long-term stable relationship, and her recent and past STIs screening were normal. Furthermore, gynaecological examination was negative for PID findings.

The patient has hypothyroidism, which could be a medical cause of HMB, but she is on adequate replacement therapy with normal TFTs.

TREATMENT

HMB can be managed by medical treatment as per NICE, 2007, with LNG-IUS/mirena or other medical management

Figure 4 Histology: adenomyosis—the myometrium showing some nodularity and multiple foci of endometriosis (courtesy of Dr R Jenkins).

such as antifibrinolytics (tranexamic acid); prostaglandin synthesis inhibitors, non-steroid antiinflammatory (mefenamic acid); and combined oral contraception or long-cycle progestogens (norethisterone).⁵

Our patient was on tranexamic acid 1 g three times per day, mefenamic acid 500 mg three times per day and norethisterone 5 mg three times per day for her bleeding with an increased (doubled) dose of the latter, while awaiting urgent surgery in 3 weeks, and on ferrous fumarate for her iron-deficiency anaemia.

Urgent total laparoscopic hysterectomy was the ultimate treatment option in view of the adverse effects of SPRM/Esmya and ineffective conservative treatment. The patient remained symptomatic for PV bleeding with post-haemorrhagic anaemia up to and following the surgical treatment.

The option of treatment with gonadotrophin-releasing hormone analogues (GnRHa) was also discussed with the patient at, but she declined zoladex injection because of her experience of the adverse effect of Esmya medication. When hysterectomy was discussed with the patient, she opted for laparoscopic total hysterectomy and bilateral salpingectomy.

OUTCOME AND FOLLOW-UP

The patient was followed up in 3 months after total laparoscopic hysterectomy. The patient experienced no early complications after surgical treatment, but developed a DVT on her left calf 4 weeks postoperatively, which affected her mobility. Overall, she was unable to return to work for 6 months as she developed chest pain, palpitations and presyncopal episodes, as well as exertional dyspnoea; she is currently under investigation for cardiac pathology.

DISCUSSION

The NICE guideline on HMB is based on three studies looking into the use of USS in combination with endometrial biopsy (pipelle), and recommends it in the following cases: symptomatic women aged 45 years and over, treatment failure or ineffective treatment.⁵ RCOG is also in agreement with this.⁸ Imaging should be undertaken in the following circumstances: if the uterus is palpable abdominally, if vaginal examination reveals a pelvic mass of uncertain origin and in instances where pharmaceutical treatment fails. USS is therefore the first-line diagnostic tool for identifying structural uterine abnormalities.

Hysteroscopy, as a diagnostic tool, should only be used when ultrasound results are inconclusive.⁵

LNG-IUS is a first-line treatment for HBM.^{5 9 10} The guidelines advise on the need for a physical examination before LNG-IUS insertion and recommend investigations for structural and histological abnormalities. "Pharmaceutical treatment should be considered where no structural or histological abnormality is present, or for fibroids less than 3 cm in diameter which are causing no distortion of the uterine cavity".⁵ In our case, LNG-IUS were inserted inappropriately for symptomatic management of HMB, as the large (>3 cm) uterine fibroid was distorting the uterine cavity as SMUF. This intervention was harmful as it exacerbated the pain and bleeding.

UPA 5 mg daily/Esmya is currently licensed for preoperative treatment of uterine fibroids with treatment duration limited to 3 months. A recent randomised, parallel group, double blind, placebo controlled phase III trial (PEARL I), evaluated the efficacy and safety of oral UPA/Esmya versus placebo for treatment of symptomatic uterine fibroid prior to surgery.⁴

Recent research shows that patients with prolonged, frequent or irregular bleeding on 5 or 10 mg UPA are likely to have SMUF. This report of bleeding patterns provides clinicians with

a warning of potential responses in women with uterine fibroids using UPA.³ Despite the fact that a link has been demonstrated between PV bleeding on UPA and SMUF, there is no reliable evidence of whether UPA/SPRMs are beneficial for women with SMUF.

SPRMs induce amenorrhoea, so the majority of women would be symptom free for HMB, but the exact mechanism behind this is unknown. A recent study shows one possible mechanism of action of SPRM on uterine fibroid, which is that treatment with UPA induces apoptosis in uterine fibroid cells.¹¹ Apoptosis was present in a higher proportion of patients with uterine fibroid treated with 5 or 10 mg UPA compared with patients with GnRHa ($p=0.01$) treatment and with no hormonal treatment ($p=0.01$). The study concluded that this effect may contribute to a positive clinical outcome.¹¹

However, approximately 10% of symptomatic patients on Esmya will have abnormal PV bleeding.² Patients with HMB due to uterine fibroids are at risk of excessive bleeding that may require surgical intervention. A few cases have been reported during UPA treatment.^{1 2}

In patients with uterine fibroid on Esmya, a complication of abnormal bleeding is relatively rare uterine haemorrhage—common ($\geq 1/100$ – $<1/10$), metrorrhagia—uncommon ($\geq 1/1000$ – $<1/100$).¹ Complications are not well investigated as the mechanism of action of is uncertain.⁴

In our case, the patient continued to be symptomatic for PV bleeding even when Esmya was stopped owing to its adverse effect, and the dose of norethisterone was increased to 10 mg three times per day. The high dose of norethisterone (30 mg daily) was used as a last resort treatment before proceeding with urgent surgery. The patient continued experiencing PV bleeding up until surgery, despite the high dose of norethisterone in combination with tranexamic acid, mefenamic acid for 2 weeks while awaiting surgery.

Physicians prescribing SPRM to stop bleeding should be aware of potential abnormal uterine bleeding (AUB), which can be life-threatening (due to post-haemorrhagic anaemia, hypovolaemic shock) and lead to urgent hysterectomy. AUB in patients with uterine fibroid on Esmya is uncommon (1 in 100),^{1 2} and the mechanism of action of SPRMs is uncertain.^{4 6} Nevertheless, one ought to consider abnormal PV bleeding as a possible complication when prescribing Esmya for symptomatic patients with uterine fibroid, because nearly 1 in 10 of these patients will have AUB and not amenorrhoea, as per the Esmya user leaflet.

Furthermore, facility should be available for urgent hysterectomy if AUB occurs when starting SPRM/Esmya treatment. This highlights the need for easy and quick access to hospital and to urgent surgical treatment in the event of excessive bleeding.

Esmya and norethisterone compete for the same receptors. It is essential to stop norethisterone before starting a patient on Esmya.^{1 2 12}

NICE guidelines with regard to pharmaceutical treatment for HMB and uterine fibroids should be updated.

No recent relevant studies were identified to support the safety of SPRM in patients at risk of thromboembolism following a fact about DVT in this patient. Further studies would be useful to explore the association between SPRMs and the risk of thromboembolism.

Current surgical options for symptomatic patients with HMB and uterine fibroids are myomectomy (including trans-cervical resection), hysterectomy and uterine artery embolisation.^{4 7} Total or subtotal hysterectomy (laparoscopic or by laparotomy) can also be considered. Hysteroscopic myomectomy was not possible in our case because of the bigger size of the SMUF;

Patient's perspective

I went through terrifying experience and distressing time when I was waiting 3 weeks for urgent surgical treatment because of fully booked operating list. I had constant bleeding and multiple admissions. I spent 3 weeks' time in bed because of the bleeding and I was not able to walk and move as it was facilitating bleeding. The doses of given medications were exceeding normal BNF dose and duration. Back to normal activity after surgical treatment was significant delay and I was off sick from work for 6 months.

Learning points

- ▶ It is important to have a high index of suspicion for potential complications, such as abnormal or excessive per vagina (PV) bleeding, when prescribing Esmya for symptomatic patients with uterine fibroids, especially submucosal uterine fibroid (SMUF).
- ▶ Hysterectomy (laparoscopic or by laparotomy) is one surgical treatment option. Facilities should be available for urgent cases when a patient is started on Esmya in view of uncontrollable bleeding as a side effect.
- ▶ Esmya should not be prescribed with norethisterone, as they compete for the same receptors. It is essential to stop norethisterone prior to treatment with Esmya.
- ▶ Pharmaceutical treatment with levonorgestrel intrauterine system is contraindicated for SMUFs larger than 3 cm in size in symptomatic patients. The National Institute for Health and Care Excellence guidelines for heavy menstrual bleeding (HMB) should be reviewed with regard to use of pharmaceutical treatment with selective progesterone receptor modulator (SPRM)/Esmya for symptomatic female patients with uterine fibroid.
- ▶ Adenomyosis could be an accidental finding after hysterectomy in symptomatic patients with uterine fibroids. Further research in patients with SMUF, HMB and adenomyosis is needed for possible SPRM/Esmya adverse effects (eg, uncontrollable PV bleeding).

however, PV removal of small submucosal fibroids may be possible in some cases.

Adenomyosis might be found on histology, as it is the most common histopathological finding in hysterectomy specimens in

women with AUB, with a peak incidence in the perimenopausal age group (41–50 years).¹³ Transvaginal sonography can be helpful in differentiating between leiomyoma and adenomyosis. Despite this, adenomyosis still remains a clinical challenge as, being asymptomatic, it is usually not diagnosed clinically. However, clinicians should have a high suspicion index for this diagnosis in women with AUB.¹³

Adenomyosis could be an accidental finding after hysterectomy. Further research is needed regarding the risk of developing an adverse effect on Esmya administration in symptomatic patients with SMUFs alone and with suspected adenomyosis.

More investigations of possible side effects of SPRMs/Esmya and their mechanism of action are required, especially in women with SMUF and a history of post-haemorrhagic anaemia.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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