Bleeding problems in late reproductive and perimenopausal years

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Background: Menstruation is the genital sign of systemic endocrine and immunitary events. Data indicate that the heterogeneity of perimenstrual symptoms is associated with levels of inflammation, triggered by the fluctuation and fall of estrogens and progesterone, at genital, systemic and brain level. Abnormal uterine bleeding refers to any change in the regularity, frequency, heaviness or length of menstruation. There are several potential causes for bleeding disturbances, the two most common being primary endometrial dysfunction and fibroids. Management of abnormal uterine bleeding involves both medical and surgical options and will largely depend on a patient's fertility plans and "meaning" of the uterus for her sexuality and inner self-perception.

Aims: to concisely analyze the evidence on:

1. genital and systemic endocrine and inflammatory events associated with periods and perimenstrual symptoms, focusing on bleeding problems;

2. rationale of intervention to reduce their intensity and impact on women's lives, with focus on the still too neglected Iron Deficient Anemia (IDA) and associated comorbidities

Method: concised review of the pertinent literature with a clinical perspective, useful in the physician's daily practice

Results: evidence supports the inflammatory basis of the menstrual event, triggered by the estrogens' and progesterone' fall. It is modulated by the degranulation of mastcells at the basal level of the endometrium, in the blood, in all the organs where mast-cell are already activated from local/genetic pathologies, and within the brain.

Menstrual inflammation is physiologic, when:

- it is finalized («resolving») to renovate the endometrium when conception did not happen
- it is limited in its intensity, just to accomplish the renovation goal
- it is strict in its timing as it synchronously involves the basal layer of the endometrium.

Menstrual inflammation becomes increasingly **pathologic** when:

- its intensity and duration increase menstrual and systemic pain
- systemic mastc-cells degranulation increases symptoms related to inflammation of remote organs
- when its timing anticipates and follows the menstrual sign itself
- when hormonal dysfunctions and/or organic factors (such as submucosal myomas, endometrial hyperplasia, endometrial polyps..) contribute to heavy menstrual bleeding, iron deficient anemia (IDA) and associated comorbidities

The presentation analyzes the endocrine and inflammatory basis of perimenstrual symptoms such as: menstrual pain, menstrual irregularities and heavy bleeding, premenstrual syndrome, gastrointestinal symptoms, catamenial headache and depression.

Attention is focused on heavy menstrual bleeding, associated iron deficient anemia (IDA), brain and behavioural conseguences.

Key point: all perimenstrual symptoms persist, although attenuated, during the contraceptive hormone free interval (HFI). Evidence suggest that by reducing the HFI in hormonal contraception from seven to four, two days - or none - may significantly improve the perimenstrual genital and systemic symptoms, also in perimenopausal years.

Specifically, the estradiol valerate + dienogest pill is the only contraceptive pill approved (also) for the dysfunctional heavy menstrual bleeding. It has been studied and approved until 50 years of age, with excellent safety profile recently confirmed. Thanks to the continuous estradiol plasmatic levels, and the positive synergy with dienogest, this pill may reduce as well the majority of premenopausal symptoms, offering women (who do not have contraindications to this treatment) a user-friendly contraceptive and therapeutic option to smooth the perimenopausal transition from the bleeding, behavioural, systemic and psychosexual point of view.

Finally, other medical therapies to address heavy menstrual bleeding in perimenopausal years will be briefly addressed. The use of levonorgestrel-releasing intrauterine devices for heavy menstrual bleeding is increasingly considered first-line medical management for women who desire a “fit and forget” approach. Tranexamic acid, non-steroidal anti-inflammatory drugs, and oral progestins offer alternatives. Hysterectomy offers a definitive surgical approach to abnormal uterine bleeding and is associated with high levels of patient satisfaction. Women wishing to preserve their fertility, or avoid hysterectomy, may be offered myomectomy. Submucosal fibroids should be removed via hysteroscopy in symptomatic or infertile patients. Intramural and subserosal fibroids may be removed via an open or laparoscopic approach. There are several minimally invasive options, including uterine artery embolisation, magnetic resonance-guided high intensity focused ultrasound (HIFU) and endometrial ablation.

Conclusion

Menstruation is the genital sign of systemic endocrine and inflammatory events.

The shift of inflammation from physiological to a pathologic intensity increases the severity of perimenstrual symptoms, more so in the perimenopausal years when uterine factors my further contribute the bleeding problems up to heavy menstrual bleeding.

Menstrual inflammation and associated symptoms persist, although attenuated, during the HFI in contraception. Shortening the HFI may constitute a first line intervention to modulate the bleeding problems, perimenstrual symptoms and associated comorbidities also in perimenopausal women (who currently do not desire getting pregnant, with a last minute baby).

Different options should be well discussed and pros-and-cons carefully considered, to offer the individual woman the tailored choice that best addresses her bleeding problems and associated comorbidities.

Attention to cultural variations in the "meaning" of the uterus for the woman' (and partner') sexuality and inner self-perception should be considered in the evaluation of treatment options.

KEY REFERENCES:

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• *Spencer JC1, Louie M2, Moulder JK2, Ellis V2, Schiff LD2, Toubia T3, Siedhoff MT4, Wheeler SB5.Cost-effectiveness of treatments for heavy menstrual bleeding. Am J Obstet Gynecol. 2017 Nov;217(5):574..*
• *Graziottin A. The shorter, the better: A review of the evidence for a shorter contraceptive hormone-free interval. Eur J Contracept Reprod Health Care. 2016;21(2):93-105*

CASE 1

Dysfunctional heavy bleeding

35 years, married, 2 children, part-time employeed, white **Consultation complaint:** polymenorrhea (22-24 days), heavy bleeding (7 days), worsened in the last year. **Symptoms comorbidities include:** worsening PMS with premenstrual depression, worsening fatigue, cramps, poor sleep quality with 2-3 night awakenings, light hot flushes and tachycardia during periods, difficulties in concentration at work; loss of sexual desire, unwanted increase in body weight (+ 4 kg in the last year), Father hypertension, mother, type 2 diabetes recently diagnosed Autoimmune thyroiditis diagnosed 4 years ago, celiachia diagnosed 2 years ago **Exams:** Iron Deficient Anemia (IDA) (Hb 8.5 gr/dl, ferritin 5ng/dl, iron 12 mcg/dl), FSH (in the 3rd day of periods) 15 mUI/ml **TV eco:** normal uterus, ovaries "within the normal range" **Pap-smear:** normal **HPV test:** negative

CASE 2

Myomata and heavy bleeding

42 years, common-law, 1 child, nurse, shift worker, white. **Consultation complaint:** heavier menstrual bleeding in the last two years, with menstrual cramps worsened in the last 3 month **Symptom comorbidities include:** Fatigue, pollachiuria, nicturia (x2), deep dyspareunia, weight gain (+6 kg in the last year) Parents in good health. **Exams:** Iron Deficient Anemia (IDA) (Hb 9.5 gr/dl, ferritin 8ng/dl, iron 18 mcg/dl), FSH (in the 3rd day of periods) 10 mUI/ml. **TC eco:** Uterine myomata: submucosal (1 cm), 2 intramural (3 and 4 mean diameter), 1 intramural/subserosal anterior (5,8 cm); 1 uterine polyp, of 1 cm dm, with increased thickness of the endometrium. Pap-smear and HPV =negative

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