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Role of Antimicrobials in management of Dysfunctional Uterine Bleeding in Premenopausal Women

Abd Elsamie A. Abd Elsamie¹, Sahar M. Elbaradie¹, Haitham M. Badran¹, Mohammed G. Hassan^{1*}

¹ Department of obstetrics and gynecology, Faculty of Medicine, Fayoum University, Fayoum, Egypt.

* Correspondence Mohammed G. Hassan, aldrwsymhmd443@gmail.com; Tel: (002) 01006326247.

Abstract

Introduction: Abnormal uterine bleeding (a term that refers to menstrual bleeding of abnormal quantity and/or duration) is a common gynecologic complaint accounting for one-third of out-patient visits to gynecologists.

Aim of the study: to evaluate infection as an etiological factor of dysfunction in bleeding women.

Subjects and Methods: 200 patients from the outpatient Gynecological Clinic were treated with doxycycline 100 mg twice daily for two weeks, then evaluated for the change in bleeding.

Results: the duration of menses change after administration of doxycycline with a significant P-value. Less than half of cases with irregular menses became regular.

Conclusion: Doxycycline is a broad-spectrum antibiotic. In recent years, Dox has also been studied extensively in humans that are characterized by high levels of pro-inflammatory mediators and protease activities.

Keywords: Bleeding; doxycycline; infection dysfunctional bleeding.

1. Introduction

Vaginal bleeding occurs in approximately 4 to 11 percent of premenopausal women. The incidence of bleeding appears to correlate with time since menopause, with the likelihood of bleeding decreasing over time. For example, in a study that asked 271 premenopausal women to complete a daily record, the estimated incidence of bleeding has fallen from 409/1000 women-years immediately after the first 12 months of amenorrhea following menopause to 42/1000 women-years more than three years after menopause [1-2].

The common etiology includes endometrial hyperplasia and polyps: Endometrial hyperplasia may manifest clinically as uterine bleeding. Since premenopausal women should be estrogen deficient, endometrial hyperplasia at this time is abnormal and requires an explanation [3], Leiomyomata uteri: The prevalence in premenopausal women is one-tenth that of premenopausal women [4], Adenomyosis [5] (it can cause pain and menorrhagia during the reproductive years, Infection [6] (endometritis is an uncommon cause of premenopausal bleeding, in the developing

world endometrial tuberculosis may present as premenopausal bleeding, Cancer [7] (the incidence of cancer as a cause of uterine bleeding increases with increasing age and adeno-carcinoma of the endometrium is the most common genital cancer in women over 45 years of age), and finally the anticoagulant therapy [8].

In recent years, doxycycline has been studied at sub-antimicrobial concentrations in human and animal diseases, which are characterized by high levels of pro-inflammatory mediators and protease activities. Osteoarthritis, rheumatoid arthritis, adult periodontitis, and pelvic inflammatory disorder are common [9].

Alteration in endometrial microvasculature and inflammatory reaction, coinciding with infiltrating leukocytes,

2. Subjects and methods

2.1. Subjects

This study includes 200 patients from the outpatient Gynecological Clinic, Fayoum General Hospital. All cases suffered from premenopausal bleeding. Ages were between 40 to 47 years. Complaining of premenopausal dysfunctional bleeding were included.

2.2. Exclusion criteria

Structural causes of premenopausal bleeding and medical disorders such as Thyroid disease, Hypertension, and Coagulopathies were excluded.

2.3. Methods:

monocytes, and mast cells, is among the key events occurring during normal menstruation and irregular uterine bleeding [9].

Many cytokines act as key regulators of leukocyte differentiation, activation, and local tissue inflammatory response. Dox therapy may alter the endometrial production of these cytokines, resulting in the stabilization of the inflammatory response during menses and women experiencing irregular bleeding [9].

We, therefore, hypothesized that infection is an etiological factor of dysfunctional bleeding in women and the role of antimicrobial treatments.

The present study aimed to assess the role of antimicrobial in the treatment of abnormal bleeding.

All patients were subjected to the following:

- Reporting of history of bleeding including onset, course, duration, criteria of bleeding, recent hormonal contraception, and history of bleeding tendency.
- Local examination of the external genitalia, Bimanual examination to detect the uterine size, mobility, tenderness, and adnexal masses, and Speculum examination for cervical masses, erosions, hypertrophy, ulcers, or vaginal lesions.
- Laboratory Investigations as Complete blood count, bleeding time, Coagulation profile, Fasting,

postprandial blood sugar, and Liver and kidney functions.

treated with doxycycline 100 mg twice daily for two weeks. After that, these cases were evaluated for the change in the pattern of bleeding.

After exclusion of organic causes of abnormal uterine bleeding, all cases were

3. Results

Table 1: Demographic characteristics among the studied cases.

Variables	Mean±SD	Range
Age (years)	43.6±2.4	40.0–47.0
BMI (kg/m ²)	26.5±1.3	23.2–30.1
Parity	3.3±1.5	1.0–7.0

Total=200. BMI: Body mass index. Values are presented as mean ± SD, range.

The duration of menses changes after administration of doxycycline with significant P-value. Less than half of cases

with irregular menses became regular. The differences were statistically significant (Table 2 & Figure 1).

Table 2: Menses duration (days) among the studied cases.

Variables	Mean±SD	Range	P-value
Before	5.1±1.6	3.0–10.0	<0.001*
After	4.6±1.5	3.0–9.0	
Change#	-0.5±1.1	-5.0–2.0	

Total=200. #Change=after-before, negative values indicate reduction. *Significant.

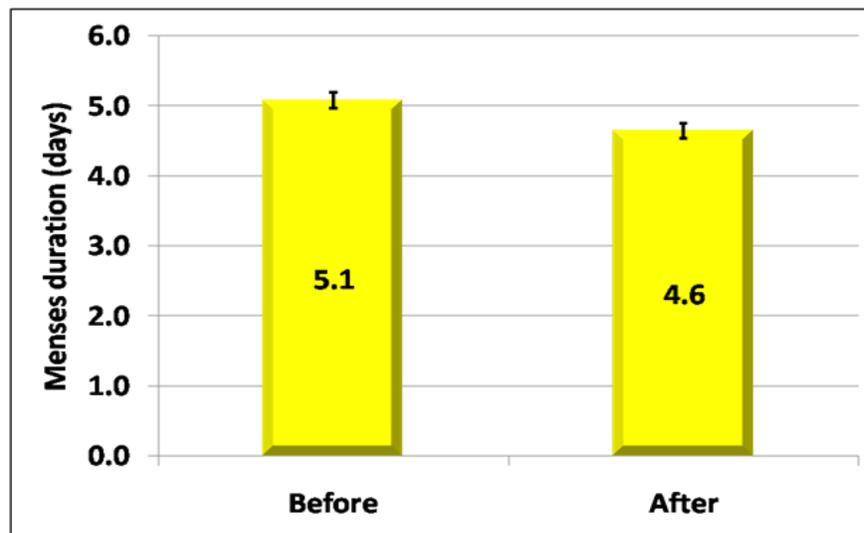


Figure 1: Menses duration (days) among the studied cases.

Less than half of cases with intermenstrual spotting became negative.

The differences were statistically significant (Table 3 & Figure 2).

Table 3:
spotting among the

Time	Status	N	%
Before	Spotting	21	10.5
	No spotting	179	89.5
After	Spotting	13	6.5
	No spotting	187	93.5

Intermenstrual studied cases.

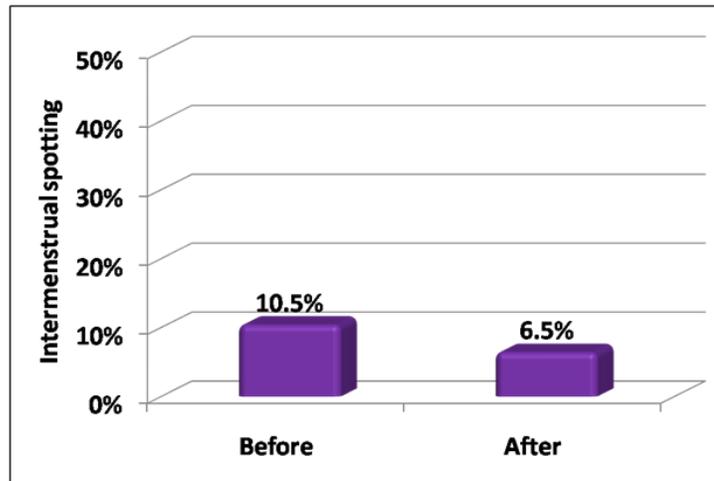


Figure 2: Intermenstrual spotting among the studied cases.

4. Discussion

Dysfunctional uterine bleeding is abnormal uterine bleeding patterns in the absence of a medical illness or pelvic pathology. It is a diagnosis of exclusion. Menstrual history and physical examination are the mainstays of evaluation of cases [10].

Nowadays, medical therapy is the first-line therapy for dysfunctional uterine bleeding. Cyclic progestogens are the most

commonly prescribed drugs for dysfunctional uterine bleeding. Combined oral contraceptives and levonorgestrel intrauterine system provide the additional contraceptive effect. Nonsteroidal anti-inflammatory drugs and tranexamic acid offer a simple therapy during menses. Hysterectomy was the most commonly performed treatment for menorrhagia in the past. 80% of the women treated for

menorrhagia had no uterine abnormality, while over a third of the women undergoing hysterectomies for heavy menstrual bleeding had a normal uterus removed [11].

The endometrial environment during normal menstrual and irregular uterine bleeding has been characterized by increased infiltration of the number of leukocytes and mast cells and alterations in endometrial tissue integrity with apparent matrix degradation [12].

Doxycycline (Dox), a member of the tetracycline family, is a broad-spectrum antibiotic effective against a wide range of gram-positive and gram-negative organisms. In recent years, Dox has also been studied extensively in human and animal diseases that are characterized by high levels of pro-inflammatory mediators and protease activities. The beneficial effects of Dox or other tetracycline analogs are not due to their antimicrobial effects, but because of their efficacy in inhibiting pro-inflammatory and protease activity [13].

A recent pilot study examining the efficacy of two treatment strategies revealed that Dox, at 100 mg twice daily for five days, is equally effective as mifepristone and mifepristone plus Ethinyl estradiol (EE) in reducing the number of days of uterine bleeding/spotting in women using a progesterone-only contraceptives [13].

Interestingly, Dox at 250 mg four times daily for four days is routinely used in women undergoing IVF starting a day before embryo transfer. No reason has been given for the beneficial use of Dox in these women under this protocol; however, Dox therapy is considered to act through antimicrobial properties under this and other

protocols such as pelvic inflammatory disease and premenstrual syndrome [14].

It was observed that few incidences of endometritis in Norplant users with abnormal uterine bleeding, and doxycycline therapy acting through both antimicrobial and anti-inflammatory properties may be beneficial, although bleeding patterns return to normal following removal of the implants. Doxycycline either directly or through modulation of these cytokines and chemokines may also alter the expression of matrix metalloproteinases (MMPs), proteases known to regulate tissue remodeling, which is a critical event in endometrial tissue repair following menses and patients with irregular uterine bleeding [15-16].

In our study, we observed that the duration of menses changes after administration of doxycycline with a significant P-value. Less than half of cases with irregular menses became regular. Only one regular case turned irregular after treatment. The differences were statistically significant. Less than half of cases with intermenstrual spotting became negative. Only two cases that had no intermenstrual spotting turned positive after treatment. The differences were statistically significant.

5. Conclusion

In conclusion, Dysfunctional uterine bleeding might be treated either medical by hormones, antifibrinolytic, or by surgery by endometrial ablation or hysterectomy. Antibiotics have a role in treating abnormal intermenstrual, postcoital, and menorrhagia bleedings associated with cervicitis and endometritis associated with pelvic inflammatory disease.

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Ethical Approval Statement: The protocol was approved by the Ethical Committee of Fayoum Faculty of Medicine, Fayoum, Egypt. The researcher informed the participants about the objectives of the study, the examination, investigations that were done, the confidentiality of their

information, and their right not to participate in the study.

Informed Consent Statement: Written informed consents were obtained from all patients.

Conflicts of Interest: All authors declare no conflict of interest.

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