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Harnessing Technology to Revolutionize Personalized Therapies for Metrorrhagia

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Abstract

Background: Metrorrhagia is defined as irregular uterine bleeding occurring between normal menstrual cycles. Unlike normal menstruation, metrorrhagia is irregular in frequency, duration, and volume. Understanding the etiology of metrorrhagia requires reviewing the hormonal regulation of the normal menstrual cycle.

Purpose: This abstract provides an overview of metrorrhagia, including epidemiology, etiology, diagnostic evaluation, management approaches, and future directions.

Main Body: Metrorrhagia has a variable prevalence depending on age and underlying causes. Etiologies include hormonal dysfunction leading to anovulatory cycles, uterine structural abnormalities like fibroids or polyps, systemic conditions affecting coagulation or thyroid function, and iatrogenic causes such as intrauterine devices. Diagnostic evaluation aims to elucidate the cause through history, physical exam, laboratory studies, and imaging like pelvic ultrasound or endometrial biopsy. Treatment targets the underlying etiology, using hormonal therapy to regulate ovulation or procedural interventions for structural abnormalities unresponsive to medical management. Traditional herbal medicines provide another historical approach to managing metrorrhagia, though most lack standardization. Looking forward, advances in genomics, biologics, and artificial intelligence may enable more personalized, targeted therapies.

Conclusion: Metrorrhagia arises from diverse etiologies encompassing hormonal, structural, systemic, and iatrogenic causes. Diagnosis hinges on a thorough evaluation to direct appropriate treatment ranging from medications to surgery. Further research on individualized therapies promises progress in long-term management.

Keywords: Metrorrhagia, Abnormal uterine bleeding, Anovulation, Endometrium, Hormonal therapy, Hysteroscopy, Complementary medicine

Background

Metrorrhagia refers to uterine bleeding that occurs between normal menstrual cycles, in irregular frequencies and volumes. In contrast to normal cyclical menstruation, metrorrhagia occurs irregularly and with variable bleeding patterns. To understand metrorrhagia, it is important to first review the physiology of the normal menstrual cycle [1]. The menstrual cycle results from a complex interplay of hormones produced by the hypothalamus, pituitary gland, ovaries, and uterus. Each cycle is divided into three phases - the follicular phase, ovulation, and the luteal phase. During the follicular phase, follicle stimulating hormone (FSH) from the pituitary stimulates the maturation of follicles containing immature egg cells in the ovaries. Rising estrogen levels from the developing follicles exert negative feedback on FSH and stimulates the endometrial lining to proliferate. This proliferative endometrium prepares the uterus for implantation of a fertilized egg. Mid-cycle, a surge of luteinizing hormone (LH) triggers ovulation - release of a mature ovum. After ovulation,

the ruptured follicle transforms into a corpus luteum which produces progesterone in addition to estrogen. Progesterone converts the proliferative endometrium into a secretory lining and suppresses the hypothalamic-pituitary axis to prevent further ovulation. If fertilization does not occur, falling progesterone withdraws its support of the secretory endometrium, triggering menstruation and shedding of the lining. This cycle then repeats approximately every 21-35 days in reproductive aged women [2-6]. This review focuses exclusively on metrorrhagia to provide a comprehensive, up-to-date overview of this distinct entity. Our objective is to elucidate diagnostic approaches for underlying causes and appraise evidence for both conventional and complementary treatment options, in order to delineate clear management recommendations rooted in current literature. This focused synthesis will aid clinicians in achieving individualized care for metrorrhagia patients.

Epidemiology

Metrorrhagia can occur across the lifespan and has a variable prevalence depending on the underlying etiology. In adolescents, metrorrhagia is estimated to occur in 8-27% of menstruating girls and is often due to anovulatory cycles as hormonal regulation is established post-menarche. In reproductive-aged women, metrorrhagia from menstrual disorders has a prevalence of approximately 9-14%. Prevalence increases in perimenopause, affecting 24-37% of women in their forties as cycles become more anovulatory. Up to 20% of postmenopausal women also experience metrorrhagia, often due to structural causes like endometrial atrophy or polyps [7]. Risk factors for metrorrhagia are multifactorial. Polycystic ovarian syndrome (PCOS) is associated with irregular anovulatory bleeding. Coagulation disorders, hypothyroidism, diabetes, and chronic illness can contribute to metrorrhagia. Intrauterine devices (IUDs) are an iatrogenic cause. Uterine structural abnormalities like fibroids, polyps, and hyperplasia often underly metrorrhagia in premenopausal women. Endometrial cancer, though rare before menopause, has a peak incidence at 55-64 years old and should be ruled out in postmenopausal bleeding [8-11].

Etiology

The etiology of metrorrhagia can be classified into hormonal causes, structural uterine abnormalities, systemic conditions, and iatrogenic factors.

Hormonal causes

Anovulatory cycles are a common physiologic cause of metrorrhagia. In anovulatory cycles, follicles develop but fail to rupture and release an egg. Persistent estrogen stimulation of the endometrium without progesterone priming can lead to abnormal buildup and shedding of the lining. Anovulation underlies most adolescent metrorrhagia and much of perimenopausal abnormal bleeding as cycles become irregular [12]. Other hormonal causes include estrogen breakthrough bleeding and progestin-only contraceptives. Estrogen breakthrough bleeding can occur with low dose estrogen-containing contraceptives before the endometrium becomes stabilized on the medication. Progestin-only contraceptives like depot medroxyprogesterone acetate injections or etonogestrel implants work primarily by thinning the endometrial lining to prevent proliferation. However, this thin endometrium can be prone to irregular sloughing, manifesting as metrorrhagia [13,14].

Structural causes

Structural abnormalities of the uterine endometrium or myometrium can disrupt orderly sloughing of the endometrial lining during menses. Uterine fibroids, or leiomyomas, are benign smooth muscle tumors arising from myometrium. Up to 70% of reproductive aged women develop fibroids. Submucosal fibroids which distort the endometrial cavity are most likely to cause abnormal bleeding. The mechanism relates to altered vascularity and ulceration of the endometrium overlying the fibroid [15]. Endometrial polyps are focal overgrowths of endometrial glands and stroma attached to the uterine wall by a vascular pedicle. They are estrogen-dependent growths and up to 10% of women have endometrial polyps. Abnormal bleeding results from disruption of normal sloughing of endometrium over the polyp [16]. Adenomyosis occurs when endometrial glands and stroma from the endometrial lining become trapped within the myometrial wall. This ectopic endometrial tissue bleeds in response to hormonal cycles, causing metrorrhagia. Up to 20% of reproductive aged women have adenomyosis at hysterectomy [17-19]. Endometrial hyperplasia is a diffuse thickening of the endometrium due to unopposed estrogen stimulation. This predisposes to abnormal buildup and sloughing of endometrium. If left untreated, endometrial hyperplasia can progress to endometrial cancer. Endometrial cancer classically presents with postmenopausal bleeding, but up to 10% of cases occur before menopause. Abnormal metrorrhagia warrants endometrial sampling to rule out malignancy [20-24].

Systemic causes

Systemic conditions affecting liver function, the coagulation cascade, or thyroid hormone regulation can contribute to metrorrhagia. Liver dysfunction can cause metrorrhagia through multiple mechanisms. Estradiol metabolism occurs in the liver, so liver disease can increase circulating estrogen levels. Production of clotting factors and binding proteins is also impaired, which can worsen bleeding [25-34]. Coagulation disorders like von Willebrand disease inhibit normal platelet plug formation at the time of menses. This allows for prolonged or excessive menstrual bleeding. Up to

20% of women with bleeding disorders have metrorrhagia [35-37]. Hypothyroidism causes anovulatory cycles and sluggish endometrial development, predisposing to irregular shedding. Overt hypothyroidism doubles the risk of metrorrhagia, while subclinical hypothyroidism is also associated with heavier and prolonged menstrual bleeding [38].

Iatrogenic causes

Intrauterine devices (IUDs) are a well-known cause of abnormal uterine bleeding, especially in the first 3-6 months after placement. The mechanism relates to the endometrial inflammatory reaction and altered vasculature associated with a foreign body in the uterine cavity. Up to 12% of women using the levonorgestrel IUD and 2% with the copper IUD have metrorrhagia significant enough to warrant removal [39].

Many medications can alter menstrual cycle regularity. Antibiotics like rifampin induce liver enzymes that increase estrogen clearance from the body. Anticoagulants, especially warfarin, impair normal hemostasis. Chemotherapies and radiation disrupt the hypothalamic-pituitary-ovarian axis. Other drugs like anticonvulsants, antipsychotics, and antihypertensives have multiple mechanisms leading to breakthrough bleeding or metrorrhagia [40,41].

Diagnostic Evaluation

The initial evaluation of metrorrhagia involves a detailed history, physical exam, laboratory testing, and imaging to elucidate the underlying etiology as depicted in **Table 1**.

The patient's history explores onset, duration, frequency, volume, and symptoms associated with abnormal bleeding episodes. The quantity of bleeding can be assessed with the pictorial blood loss assessment chart. Sexual history, contraceptive use, medical conditions, medication list, and family history should be noted [42]. Pelvic exam evaluates for cervical lesions, uterine enlargement, and adnexal masses. Bimanual exam documents uterine size, shape, and tenderness.

Laboratory testing includes a pregnancy test, complete blood count, thyroid studies, and coagulation testing if warranted by history. Serum estradiol, FSH, and LH levels may clarify ovulation status. Pelvic ultrasonography helps identify uterine structural causes like fibroids and polyps. Thickened endometrium requires tissue sampling to exclude hyperplasia or cancer. Endometrial biopsy is the gold standard for evaluating the endometrial lining in metrorrhagia. This can be performed with office endometrial biopsy devices or formal dilation and curettage (D&C) in the operating room. Histology guides further management, especially in postmenopausal women [43-45].

Management

Treatment of metrorrhagia targets the underlying etiology. For anovulatory abnormal bleeding, combination oral contraceptives or cyclical progestins can regulate the endometrium as depicted in **Table 2**. Medical management of structural causes may focus on regulating menstrual cycles or directly reducing abnormal bleeding. When medical therapies fail, surgical resection can definitively treat sources of abnormal bleeding like polyps, fibroids, or diffuse endometrial pathology.

Hormonal therapies

Combination oral contraceptives containing estrogen and progestin provide cycle regulation and reduce heavy menstrual bleeding. Traditional 21/7 day cyclical regimens with a 7 day hormone free interval are less effective for metrorrhagia than extended or continuous regimens. Extended regimens have shortened (4 day) or eliminated hormone free intervals, conferring more endometrial stability. Continuous regimens eliminate the week of inactive pills, leading to amenorrhea in over 50% of women [46]. Cyclical progesterone therapy induces predictable shedding of the endometrium. Progestins like norethindrone acetate or

Table 1. Differential Diagnosis of Metrorrhagia.

Condition	Typical Age Group	Key Findings	Diagnostic Tests
Anovulatory cycles	Adolescents, perimenopausal	Irregular, heavy menses	Serum FSH, LH, estradiol
Uterine fibroids	Reproductive age	Enlarged or irregular uterus on exam	Pelvic ultrasound
Endometrial polyps	Premenopausal	Focal uterine tenderness	Hysteroscopy
Endometrial hyperplasia	Perimenopausal	Thickened endometrium on ultrasound	Endometrial biopsy
Endometrial cancer	Postmenopausal	Postmenopausal bleeding	Endometrial biopsy
Coagulopathy	Any age	Prolonged bleeding episodes	Coagulation studies
Hypothyroidism	Any age	Fatigue, weight gain, hair loss	TSH, free T4
Intrauterine device	Reproductive age	IUD in place	Pelvic exam

Table 2: Medical Management of Metrorrhagia by Etiology.		
Cause	**First Line Treatment**	**Second Line**
Anovulatory bleeding	Oral contraceptives, cyclical progestins	GnRH agonists
Uterine fibroids	NSAIDs, antifibrinolytics	Gonadotropin releasing hormone agonists
Endometrial polyps	NSAIDs, antifibrinolytics	Operative hysteroscopy
Endometrial hyperplasia	Progestins	Hysterectomy
Coagulopathy	Combined oral contraceptives	Antifibrinolytics
Hypothyroidism	Levothyroxine	Add oral contraceptive

micronized progesterone are given for 10-14 days per month to trigger monthly withdrawal bleeding. This provides stability without suppressing ovulation [47]. Gonadotropin releasing hormone (GnRH) agonists induce medical menopause by downregulating the hypothalamic-pituitary-ovarian axis. This stops estrogen stimulation of the endometrium and slows abnormal bleeding. Use is limited to short durations due to adverse effects like hot flashes and bone loss [48,49].

Non-hormonal therapies

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce menstrual blood loss by up to 50% by inhibiting uterine prostaglandin synthesis. High dose regimens are initiated just before and continued during menses [50]. Antifibrinolytics like tranexamic acid slow clot breakdown through inhibition of plasminogen. They reduce menstrual flow by 40-50% with minimal adverse effects [51].

Surgical therapies

Dilation and curettage (D&C) involve dilation of the cervix and scraping of the endometrial lining as depicted in **Table 3**. It provides both diagnostic and therapeutic benefits, as removal of the endometrium allows for new growth. D&C often provides temporary improvement, but metrorrhagia recurs in over 30% of cases [52]. Operative hysteroscopy allows direct visualization and surgical resection of focal pathology like polyps and some submucosal fibroids. Compared to blind D&C, it is more effective for selective removal of bleeding sources [53]. Myomectomy surgically removes fibroids while preserving the uterus. Submucosal fibroids, most contributory to abnormal bleeding, are best targeted. It may be done via open surgery or minimally invasive techniques [54,55]. Hysterectomy definitively stops abnormal uterine bleeding and may be indicated after failed medical and conservative surgical therapies. The approach (vaginal, laparoscopic, robotic) is tailored to the clinical scenario [56].

Traditional and Herbal Medicine to Metrorrhagia

Traditional and herbal medicine have a long history of use in managing abnormal uterine bleeding like metrorrhagia. Different healing traditions around the world have developed pharmacological treatments for regulating menstruation based on locally available medicinal plants. While the scientific basis for many traditional remedies is lacking, they represent an important cultural backdrop for understanding historical management of menstrual disorders [57-61]. In traditional Chinese medicine, metrorrhagia falls under the categories of "uterine bleeding" and "flooding and spotting." Herbal formulations containing ingredients like *Rehmannia* root, Asiatic cornflower, and notoginseng are used to nourish yin, invigorate blood, and restrain bleeding. Acupuncture protocols also aim to rectify imbalances in the chong and ren meridians associated with uterine bleeding [62]. Ayurvedic medicine describes metrorrhagia as raktapradara and associates it with vitiation of the pitta dosha. Herbs like ashoka, shatavari, and lotus seeds are renowned for their styptic properties. Dietary and lifestyle changes like fasting, oil massage, and meditation may supplement herbal therapies [63,64].

Unani medicine, practiced in South Asia and parts of the Middle East, classifies metrorrhagia as istihaza and recommends herbs like ginger, turmeric, cinnamon, and Indian gooseberry to normalize humoral imbalance. Dietary modification to avoid cold, wet foods is also employed [65].

Table 3. Surgical Approaches for Metrorrhagia		
Procedure	**Indications**	**Considerations**
Dilation and curettage	Diagnostic, temporary control	>30% recurrence rate
Operative hysteroscopy	Removal of focal pathology	Preserves uterus
Myomectomy	Fibroids unresponsive to medical treatment	Preserves uterus
Hysterectomy	Failed medical/surgical therapies	Definitive treatment

Multiple Native American tribes have used medicinal plants as emmenagogues, astringents, and uterine tonics in abnormal bleeding. Examples include bethroot, raspberry leaf, cramp bark, and shepherd's purse. Customized ceremonial practices may also supplement the use of medicinal herbs [66]. Though herbal remedies have shown some promise in clinical trials, lack of standardization limits their incorporation into conventional practice. Further research should explore purified compounds from traditionally used herbs like vitex agnus-castus and *Cinnamonum cassia* to elucidate mechanisms of action and establish safe, effective dosing. As complementary medicine gains prominence, clarifying the evidence base for traditionally used therapies can improve multidisciplinary care for metrorrhagia [67].

Future Directions

Advances in genomics and epigenetics offer promising avenues for elucidating the contributory mechanisms and risk factors for metrorrhagia. Genome-wide association studies can help identify genetic variants that predispose women to abnormal uterine bleeding or alter their drug responses. Evaluating epigenetic modifications and gene expression changes specifically in the endometrium may highlight new defective molecular pathways involved in metrorrhagia pathogenesis. Incorporating pharmacogenomic testing into clinical care could enable individualized drug and dosing selection based on a woman's genomic profile [68,69].

Emerging biologic therapies provide opportunities for more targeted medical management of metrorrhagia. Introducing anti-fibrinolytic factors, anti-inflammatory cytokines, or pro-angiogenic growth factors directly into the uterus could normalize aberrant endometrial healing responses underlying abnormal bleeding. High-throughput screening enables evaluating libraries of novel compounds to find new medications that regulate the endometrium without systemic effects. Investigational selective progesterone receptor modulators also show promise for heavy menstrual bleeding with an improved side effect profile [70,72].

Harnessing artificial intelligence and big data analytics creates new possibilities for elucidating metrorrhagia patterns and generating predictive models. Machine learning algorithms applied to diverse clinical, genetic, and imaging datasets could identify novel phenotypes or subtypes of metrorrhagia patients. Natural language processing of electronic records can rapidly analyze real-world data to clarify trends, outcomes, and treatment responses. Multivariate predictive models combining omics and clinical data may help determine which women are at highest risk of endometrial hyperplasia/cancer progression when metrorrhagia is the presenting symptom [73,75].

Conclusions

Metrorrhagia is a condition of abnormal uterine bleeding with diverse potential etiologies that must be clarified during diagnostic evaluation. Treatment encompasses medications, conservative procedures, and surgery tailored to address the specific underlying cause. Further research into personalized therapies guided by advanced technologies promises to improve targeted management of metrorrhagia arising from different mechanisms. A multifaceted approach incorporating the best available options for regulating ovulation, managing structural abnormalities, and supporting endogenous endometrial healing will provide the optimal strategy for long-term control of abnormal bleeding.

Recommendations

Further research is recommended to better characterize the genetic and epigenetic risk factors predisposing women to metrorrhagia. Advancing non-invasive diagnostic techniques to quickly triage patients and identify those requiring urgent intervention is also a priority. Additional clinical trials are needed to establish the efficacy and safety of promising biologic agents and natural compounds for normalizing aberrant endometrial bleeding. On a health systems level, improving access to comprehensive menstrual disorder care and coverage for required medications, procedures, and surgeries will enable optimal individualized treatment of metrorrhagia. A patient-centered, multidisciplinary approach incorporating both conventional and complementary therapies should be pursued to provide women the best chance of regulating abnormal uterine bleeding and improving quality of life.

List of Abbreviations

FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; PCOS: Polycystic Ovarian Syndrome; IUD: Intrauterine Device; NSAID - Non-Steroidal Anti-Inflammatory Drug; GnRH: Gonadotropin Releasing Hormone; D&C: Dilation and Curettage

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data is available, and sharing is available as well as publication.

Competing interests

The authors hereby declare that they have no competing interests.

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Authors' contributions

The corresponding author completed the study protocol and was the primary organizers of data collection and the manuscript's draft and revision process. Tamer A. Addissouky wrote the article and ensured its accuracy. Lastly, the author reviewed and confirmed the final version of the manuscript.

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