

DEVELOPMENT OF PERSONALIZED, NON-HORMONAL, AI-DRIVEN
TREATMENT PATHWAYS FOR HEAVY MENSTRUAL BLEEDING
BASED ON MENSTRUAL BLOOD BIOMARKERS AND UTERINE
MICROBIOME PROFILING

Dr. Asia Khan

MBBS, MRCOG, Consultant Obstetrician and Gynecologist, University Hospitals
Birmingham - UK

Author Details		
Keywords: Heavy menstrual bleeding; Personalized medicine; Menstrual blood biomarkers; Uterine microbiome; Non-hormonal treatment; Artificial intelligence; South Asia		
Received on 29 May 2025		
Accepted on 30 June 2025		
Published on 01 July 2025		
Corresponding Author*:	E-mail	&

Abstract

Heavy menstrual bleeding (HMB) is a prevalent gynecological issue that disproportionately affects women in South Asia, contributing to high rates of anemia and diminished quality of life 1 2. Conventional therapies, often hormone-based or surgical, are not universally acceptable and fail to account for individual etiological differences. Recent advances in menstrual blood biomarker discovery and uterine microbiome profiling offer opportunities for precision medicine approaches to HMB. This study presents a comprehensive overview of HMB in the South Asian context and proposes a novel framework for personalized, non-hormonal, AI-driven treatment pathways. We review real-time clinical trial data and current evidence on key menstrual blood biomarkers (e.g., prostaglandin E2, inflammatory cytokines, fibrinolytic factors) and uterine microbiome patterns (e.g., Lactobacillus deficiency, enriched anaerobic taxa) associated with HMB 3 4. An experimental methodology is outlined whereby patient-specific biomarker and microbiome profiles inform an artificial intelligence (AI) model to recommend tailored interventions – for example, antifibrinolytics for hyperfibrinolytic phenotypes or targeted antibiotics for microbiome dysbiosis – thereby avoiding blanket hormonal therapy. A proof-of- concept framework (Figure 1) illustrates integration of clinical data with machine learning to optimize treatment selection in real time. The clinical relevance of this personalized approach is emphasized, aiming to improve outcomes and patient satisfaction in low-resource settings. This manuscript underscores the novelty of combining “omics” data with AI in HMB management, and discusses the potential benefits and challenges of implementing such personalized, non-hormonal treatment pathways in South Asia.

INTRODUCTION

Heavy menstrual bleeding (HMB) – classically defined as menstrual blood loss exceeding 80 mL per cycle – is one of the most common gynecological complaints worldwide ⁵. It affects up to ~30% of women of reproductive age in the general population and nearly half of women in low- and middle-income countries ¹. A recent multinational study across South Asia and Africa found an average HMB prevalence of 48.6%, with South Asian sites like Nepal reporting rates as high as 77.6% ^{1 6}. In South Asia, HMB's impact is magnified by the high baseline prevalence of iron-deficiency anemia (over 50% of women) and cultural factors that may delay care-seeking ^{7 8}. Women suffering from chronic heavy periods often experience fatigue, dizziness, and reduced quality of life, and HMB can impose significant social and economic burdens on families and healthcare systems ^{9 10}. Despite these burdens, many South Asian women do not receive timely or appropriate treatment. Sociocultural beliefs can play a role – for instance, a qualitative study noted some South Asian women perceive heavy flow as “cleansing” and may refrain from seeking medical help, especially where female physicians are scarce ⁸. Management of HMB has traditionally relied on hormonal therapies (such as combined oral contraceptives or progestins) and invasive procedures (dilation and curettage, endometrial ablation, or hysterectomy) ^{11 12}.

While effective in many cases, these approaches are often empirical and not personalized to the underlying cause of bleeding. Hormonal treatments may be unsuitable for women desiring fertility or those with contraindications, and surgical options carry risks and resource constraints, particularly in low- resource settings ^{13 14}. Non-hormonal medical therapies for HMB, including antifibrinolytic agents (e.g. tranexamic acid) and nonsteroidal anti-inflammatory drugs (NSAIDs), are available alternatives that can reduce bleeding by 30–50% in selected patients ^{15 16}. However, without precise diagnostic insight, choosing the optimal therapy for an individual

patient remains challenging. A “one-size-fits-all” strategy often leads to suboptimal control of HMB or unnecessary side effects.

There is a clear need for personalized treatment pathways that target the specific pathophysiological drivers of HMB in each patient. The Federation Internationale de Gynecologie et d’Obstetrique (FIGO) classification (PALM-COEIN) provides a structured approach to identify causes of abnormal uterine bleeding (AUB) – including structural causes like Polyp, Adenomyosis, Leiomyoma (fibroids), Malignancy, and non- structural causes like Coagulopathy, Ovulatory dysfunction, Endometrial disorders, Iatrogenic, or Not yet classified 17 18 . Notably, many HMB cases fall under AUB-E (endometrial dysfunction) where no distinct structural lesion is found 19 . These cases point to underlying biochemical and micro-environmental disturbances in the endometrium as drivers of heavy bleeding. Emerging research has begun to identify measurable differences in menstrual blood composition – such as inflammatory mediators, local hemostatic factors, and tissue remodeling enzymes – between women with HMB and those with normal flow 3 20 . Similarly, the once-assumed sterile uterine environment is now known to harbor a uterine microbiome , and dysbiosis (microbial imbalance) has been implicated in gynecologic conditions that often present with heavy bleeding (e.g. fibroids, endometritis) 21 4 .

Concurrently, innovations in health technology have opened the door for artificial intelligence (AI) to aid clinical decision-making in women’s health. Machine learning algorithms can integrate complex biomedical data (“big data”), recognize patterns, and generate predictive models – potentially enabling clinicians to tailor treatments to an individual’s unique profile 22 . In HMB management, AI-driven tools could synthesize a patient’s symptoms, lab results, omics (biomarker and microbiome) data, and past responses to treatments, in order to recommend the most effective non-hormonal intervention. Such personalized, data- driven approaches align with the

broader trend of precision medicine, which has already transformed oncology and is beginning to influence benign disease management 23 .

This article focuses on the development of personalized, non-hormonal, AI-driven treatment pathways for HMB based on menstrual blood biomarkers and uterine microbiome profiling. We review current evidence on the pathophysiology of HMB with an emphasis on biomarkers and microbiota, highlight real-time clinical trial findings that inform non-hormonal therapies, and propose a novel experimental framework for implementing personalized treatment in the South Asian context. By leveraging menstrual blood – an easily obtainable, information-rich sample – and advanced analytics, this approach aims to move HMB care from a trial-and-error paradigm to one of targeted therapy. The goal is improved efficacy and safety of treatments, with particular relevance for South Asian women who may benefit from non-hormonal options and resource-appropriate innovations.

Literature Review

Heavy Menstrual Bleeding: Prevalence and Impact in South Asia

HMB is both a medical condition and a socio-cultural challenge in South Asia. Recent epidemiological data underscore its high prevalence in the region. For example, in a cross-sectional study spanning India, Bangladesh, and Nepal, nearly half of menstruating women reported heavy bleeding, with the highest rates in Nepal (over 75% of women surveyed) 16 . Such findings confirm that HMB is not only a Western clinical concept but a pervasive health issue in low-resource settings as well. The health consequences are profound: HMB is a leading cause of iron deficiency anemia in South Asian women 24 25 . National health surveys have consistently found anemia rates above 50% in South Asian women, and HMB contributes significantly to this burden by causing chronic blood loss 26 . The interrelationship between anemia and HMB creates a vicious cycle of fatigue and reduced productivity, impacting women's ability to work or care for their families 27 28 . Additionally, the

stigma and misconceptions around menstruation in some South Asian communities can lead to HMB being underreported. Cultural beliefs may normalize heavy bleeding as a purging of “impure blood,” and women may delay seeking care due to shame or lack of access to female providers 25 29 . These factors highlight that any medical innovation in HMB must also address awareness and acceptability in the local context.

From a healthcare perspective, South Asian countries face challenges in providing specialized gynecological care, especially in rural areas. HMB cases often present late, sometimes only when severe anemia or life- disrupting symptoms occur. By this stage, women may require blood transfusions or emergency surgery. Strengthening early diagnosis of HMB causes is thus crucial. However, standard diagnostic tools (ultrasound for fibroids, coagulation testing for bleeding disorders, etc.) may not be readily accessible to all populations. This gap sets the stage for alternative strategies – such as menstrual blood testing and point-of-care biomarker assays – that could be deployed even in resource-limited settings to guide therapy. Indeed, global health initiatives are now prioritizing research into cost-effective diagnostics for HMB that can distinguish among causes and inform treatment without extensive infrastructure 30 31 .

Pathophysiology of HMB: Insights from Menstrual Blood Biomarkers
Heavy menstrual bleeding can result from a spectrum of underlying mechanisms. In many women with HMB (particularly those without obvious structural pathology), the endometrium fails to achieve efficient hemostasis during menstruation. Normal menstrual regulation involves a complex interplay of vasoconstriction, clot formation, clot breakdown, inflammation, and tissue repair. Deviations in any of these processes can tip the balance toward excessive bleeding 32 20 . Table 1 summarizes key menstrual blood biomarkers that have been associated with HMB and their pathophysiological significance, based on current studies.

Table 1. Key menstrual blood biomarkers in heavy menstrual bleeding and their pathophysiological implications

Biomarker (Type)	Change in HMB (vs. normal)	Clinical/Pathophysiological Implication
Prostaglandin E2 (PGE2) – Eicosanoid (vasoactive)	Increased	Excess PGE2 causes vasodilation of spiral arterioles, contributing to heavier bleeding [31]. NSAIDs help by reducing prostaglandin synthesis.
Tumor Necrosis Factor-α (TNF-α) – Inflammatory cytokine	Increased	Elevated TNF- α indicates an inflammatory endometrial environment, which can impair normal hemostasis and endometrial repair [30].
Vascular Endothelial Growth Factor (VEGF-A) – Angiogenic factor	Decreased	Reduced VEGF-A expression in the endometrium may impair angiogenesis and vascular regeneration, leading to fragile vasculature during menstruation [30].
Matrix Metalloproteinases (MMP-2, MMP-9) – Tissue remodeling enzymes	Decreased activity	Lower MMP-2 and MMP-9 activity in menstrual effluent of HMB patients suggests altered extracellular matrix breakdown. Paradoxically, while MMPs drive endometrial breakdown, abnormally low activity could reflect dysregulated repair mechanisms [30].
Tissue Plasminogen Activator (tPA) – Fibrinolytic enzyme	Increased	High tPA levels promote plasmin generation and premature fibrin clot dissolution, leading to faster breakdown of menstrual clots and increased bleeding [33].
Plasminogen Activator Inhibitor-1 (PAI-1) – Fibrinolysis inhibitor	Decreased	Low PAI-1 fails to adequately counteract tPA, resulting in unabated fibrinolysis and excessive bleeding [33].

Note: HMB = heavy menstrual bleeding; normal = women with normal menstrual blood loss. Changes are as observed in studies comparing women with idiopathic HMB to healthy controls.

These biomarkers highlight that HMB often involves an exaggerated inflammatory and fibrinolytic milieu in the uterus. For instance, prostaglandin E2 (PGE2) is significantly elevated in women with unexplained HMB, which is thought to enhance vasodilatation and prevent adequate uterine artery constriction at the time of menses [3]. This aligns with clinical use of NSAIDs (which inhibit cyclooxygenase and prostaglandin synthesis) to reduce menstrual bleeding by 10–50% in women with HMB [34]. Likewise, the endometrial cytokine profile in HMB is tilted toward pro-inflammatory

mediators like TNF- α 20 . Elevated TNF- α and related cytokines can disrupt endothelial function and platelet aggregation locally, exacerbating bleeding. A landmark study by Malik et al. (2006) first demonstrated this inflammatory pattern, finding higher TNF- α and lower VEGF in the menstrual endometrium of HMB patients 20 35 . The reduction in VEGF-A and angiogenic MMPs suggests that endometrial repair (which normally starts during menses to halt bleeding) may be delayed or insufficient in HMB cases endometrial vessels open for longer, increasing blood loss.

Another well-documented contributor to HMB is hyperfibrinolysis. In normal menstruation, a transient increase in fibrinolysis helps disintegrate clots as the bleeding tapers. However, many women with HMB have been shown to have abnormally high endometrial fibrinolytic activity from the onset of bleeding. Specifically, tPA is elevated and its inhibitor PAI-1 is reduced in the endometrium of HMB patients This leads to rapid clot dissolution, so bleeding continues unopposed. Clinically, this mechanism is 33 . supported by the effectiveness of antifibrinolytic drugs (e.g., tranexamic acid, which blocks plasmin binding) in reducing HMB. Tranexamic acid has been shown to reduce menstrual blood loss by ~40–60% and is recommended as a first-line non-hormonal therapy for HMB, particularly in women with signs of bleeding diathesis or those who prefer to avoid hormones 37 . The recognition of hyperfibrinolysis in HMB underscores the value of biomarker-driven therapy : women with evidence of high fibrinolytic markers might especially benefit from antifibrinolytic treatment.

Beyond these, other biomarkers under investigation include endocrine factors (e.g., local progesterone or glucocorticoid receptor function) and growth factors . One novel hypothesis is that some cases of HMB reflect a localized endometrial glucocorticoid (cortisol) deficiency leading to impaired vasoconstriction 38 . The DexFEM clinical trial recently provided proof-of-concept for this idea by showing that a short course of low-dose

dexamethasone in the luteal phase significantly reduced menstrual blood loss in women with HMB (25 mL reduction vs. placebo, $p \sim 0.02$) 39 . Dexamethasone likely works by enhancing endometrial vasoconstriction and modulating inflammatory responses 38 . This trial's success (Warner et al., 2021) demonstrates how understanding a patient's biochemical milieu (in this case, steroid signaling in endometrial tissue) can open up new, non-hormonal treatment avenues (glucocorticoid therapy) 40 .

In summary, HMB frequently involves a combination of inflammatory, vascular, and hemostatic disturbances in the endometrium. Menstrual blood – which contains local secretions, cell fragments, and molecules reflective of the endometrial environment – is an emerging non-invasive diagnostic fluid to assess these disturbances. Studies have shown that menstrual blood can closely mirror endometrial tissue status and may harbor biomarkers for conditions like endometriosis and HMB 41 23 . The ability to collect menstrual effluent easily (for example, using a menstrual cup or an absorptive diagnostic tampon) and analyze it for biomarkers holds promise for real-time, personalized diagnosis . Indeed, researchers are now referring to the comprehensive analysis of menstrual fluid as the “menstrualome,” envisioning it as a tool for precise diagnostics and treatment selection in reproductive health 23 . For HMB, integrating menstrual biomarker data into clinical decisions could mean, for example, identifying women whose heavy bleeding is driven by excessive fibrinolysis versus those driven by inflammation, and tailoring therapy accordingly (antifibrinolytic vs. anti-inflammatory strategies). This level of personalization has not yet been fully realized in practice, but the scientific groundwork is rapidly being laid.

The Uterine Microbiome and Heavy Bleeding Parallel to biochemical factors, there is growing interest in how the uterine microbiome might influence heavy menstrual bleeding. Historically, the uterus was considered a sterile environment except during infections. However, advanced genomic

sequencing has revealed that even the healthy endometrium contains a low-biomass microbiota, often dominated by species of *Lactobacillus* (similar to the vaginal microbiome) 42 . Changes in this microbial community – termed dysbiosis – have been linked to various gynecologic pathologies. Table 2 summarizes observed uterine or vaginal microbiome profiles relevant to HMB and related conditions.

Table 2. Uterine/vaginal microbiome profiles associated with heavy menstrual bleeding (HMB) or related gynecological conditions

Microbiome profile or taxa	Relevance to HMB or abnormal uterine bleeding (AUB)
Lactobacillus-dominated flora (normal microbiota)	In healthy women, the uterine/vaginal microbiome is often dominated by <i>Lactobacilli</i> which produce lactic acid and maintain a low pH. A <i>Lactobacillus</i> -prevalent microbiome is associated with an anti-inflammatory milieu. In HMB patients with fibroids, <i>Lactobacillus</i> species are notably reduced in the uterine cavity , suggesting a loss of protective flora 21.
Diverse, BV-associated flora (dysbiosis) – e.g. <i>Gardnerella</i> , <i>Atopobium</i> , <i>Fannyhessea</i> , <i>Sneathia</i> , <i>Anaerococcus</i>	Women with conditions like fibroids or chronic pelvic pain often show an increased diversity of vaginal microbiota and enrichment of bacterial vaginosis (BV)-associated anaerobes. One study found that patients with fibroids and abnormal bleeding (including HMB) had higher abundance of BV-related bacteria such as <i>Bifidobacterium</i> (<i>Gardnerella</i>) <i>vaginalis</i> , <i>Megasphaera</i> , <i>Anaerococcus</i> , <i>Fannyhessea</i> (<i>Atopobium</i>), <i>Sneathia</i> , and <i>Mobiluncus</i> 43. These microbes are known to trigger inflammation; their presence in women with HMB suggests dysbiosis might contribute to endometrial inflammation and heavy bleeding.
Increased uterine microbial diversity (low <i>Lactobacilli</i> , high colonizers)	Fibroid-associated HMB: Pilot studies using sequencing of endometrial samples from fibroid patients (who often have HMB) show a greater diversity of bacteria in the uterus compared to controls 21. For example, <i>Acinetobacter</i> , <i>Pseudomonas</i> , and other commensals have been found dominating the endometrial microbiome in fibroid uteri, whereas <i>Lactobacillus</i> was scarce 21. Such shifts could affect local immune responses and angiogenesis in the endometrium.
Chronic endometritis pathogens – e.g. <i>Streptococcus</i> , <i>Escherichia coli</i> , <i>Mycoplasma</i>	Chronic low-grade endometritis (CLE) is characterized by plasma cells in the endometrium, often due to persistent bacterial presence. CLE can present with prolonged or heavy bleeding. Studies have identified common vaginal organisms (like <i>Streptococcus anginosus</i>) reaching the upper tract in women with pelvic pain and possibly AUB 43–44. Successful treatment of CLE with antibiotics has been shown to restore normal menstrual patterns in some cases, underscoring that an occult infection/inflammation can underlie HMB in a subset of patients.

Early research suggests a two-way relationship between the microbiome and menstrual health. On one hand, an abnormal uterine environment (such as in fibroids or polyps) might promote microbial changes;

on the other hand, microbial imbalance might itself incite endometrial inflammation that leads to heavy bleeding. For instance, the presence of BV-associated bacteria in the vagina is linked to increased production of inflammatory cytokines and metalloproteinases in the cervicovaginal fluid 4 45 . If these bacteria ascend into the uterine cavity (even intermittently), they could conceivably disrupt endometrial hemostasis during menstruation. A recent study of women with chronic pelvic pain and endometriosis noted that those with co-occurring abnormal uterine bleeding or fibroids had distinct vaginal microbiome signatures enriched with anaerobes, independent of menstrual blood contamination 4 46 . Importantly, the bacteria identified (like *Sneathia* and *Mobiluncus*) are known to activate immune cells and induce cytokine release. This supports the theory that microbial dysbiosis can create a pro-inflammatory endometrial environment, lowering the threshold for heavy bleeding.

Fibroids (uterine leiomyomas), one of the leading structural causes of HMB, provide an illustrative example of microbiome interaction. Fibroids themselves are benign tumors arising from the myometrium, but they commonly cause heavy bleeding by distorting the endometrium and its vascular supply 47 . Intriguingly, microbiome studies in fibroid patients show subtle but consistent differences: fibroid uteri tend to have fewer *Lactobacilli* and more diverse bacteria, as noted above 21 . Although causality is not established, it raises the possibility that a disrupted microbiome might exacerbate fibroid-related bleeding. For example, a *Lactobacillus*-deficient uterine environment might be less capable of suppressing inflammation, leading to more robust bleeding when fibroid-associated vessels shear during menstruation 48 . Moreover, the gut microbiome (estrogen-metabolizing bacteria, or “estrobolome”) has been implicated in fibroid pathogenesis by influencing systemic estrogen levels 49 50 . Given that high estrogen can worsen HMB by stimulating endometrial growth, women with fibroids and

concurrent gut dysbiosis might experience heavier bleeding due to elevated estrogenic stimulation alongside local uterine microbiome effects 51 .

From a clinical standpoint, profiling the uterine or vaginal microbiome in HMB patients could help identify those who might benefit from microbiome-targeted therapies. For example, if a patient with HMB shows evidence of chronic endometritis (detected via endometrial biopsy or markers like elevated IL-6 in menstrual fluid) and testing reveals pathogenic bacteria, a course of broad-spectrum antibiotics might resolve the inflammation and reduce bleeding. This approach is analogous to treating *Helicobacter pylori* in ulcer disease – address the underlying microbial cause to relieve the symptom. There is precedent: treating subclinical chronic endometritis has improved menstrual regularity and fertility outcomes in some studies 52 53 . Probiotics or vaginal microbiome transplants are other future strategies if a causal link between dysbiosis and HMB is firmly established.

In summary, while research on the uterine microbiome in HMB is still emerging, early findings suggest that “the bugs may influence the bleed.” An unhealthy microbial profile (similar to BV) is observed in a subset of women with heavy bleeding and may drive endometrial inflammation or vascular changes that exacerbate HMB 4 21 . The uterine microbiome thus represents both a biomarker source (to identify inflammatory vs. non-inflammatory HMB) and a therapeutic target (such as antibiotic or probiotic interventions). Particularly in South Asia, where genital tract infections (e.g., tuberculosis or reproductive tract infections) can present with menstrual disturbances, investigating and modulating the microbiome could have high clinical relevance.

Current and Emerging Treatments for HMB: Toward Personalization
Traditional management of heavy menstrual bleeding has largely been symptom-driven with a tiered approach. First-line medical therapy often includes tranexamic acid (an antifibrinolytic) for use during menses, or NSAIDs

if dysmenorrhea coexists 32 34 . Hormonal therapies, such as combined oral contraceptives or the levonorgestrel intrauterine system (LNG-IUS), are highly effective at reducing menstrual blood loss by regulating endometrial proliferation and enhancing stability 11 54 . The LNG-IUS in particular can reduce bleeding by 70–95% and often induces amenorrhea, making it a gold-standard treatment for HMB in many guidelines. However, hormonal treatments are not suitable for all women – some have contraindications or prefer to avoid systemic hormones due to side effects or personal reasons (including cultural or religious considerations in South Asia). Non-hormonal options like tranexamic acid are well-tolerated but only address the symptom (bleeding) without treating underlying causes like fibroids or endometrial pathology.

In refractory cases or when structural lesions are present, surgical interventions are pursued. These range from minimally invasive approaches like hysteroscopic polypectomy or endometrial ablation (which cauterizes the endometrial lining to reduce bleeding) to more major surgeries like myomectomy (removal of fibroids) or hysterectomy (removal of the uterus) 55 56 . Surgery guarantees resolution of bleeding but is associated with higher cost and potential complications; notably, hysterectomy, while curative, is a last resort given its impact on fertility and surgical risks 57 . In low-resource settings, access to skilled surgeons and operating facilities may be limited, making medical management the mainstay for most women. Personalized therapy for HMB is a relatively new concept, as historically the condition was treated in a uniform way (often starting with hormones). However, there is increasing recognition that different etiologies of HMB respond differently to treatments. For example, HMB due to a bleeding disorder (like von Willebrand disease) requires hemostatic therapies (desmopressin, coagulation factors) rather than hormones; HMB due to hypothyroidism resolves with thyroxine replacement 58 59 . The PALM-COEIN framework implicitly encourages

tailored treatment: address polyps or fibroids surgically, correct coagulopathies medically, etc. But even within the “endometrial dysfunction” category (AUB-E), personalization is possible and needed. This is where biomarkers and microbiome data can stratify patients. For instance, an HMB patient with evidence of high prostaglandins and inflammation might benefit most from NSAIDs or perhaps steroid therapy (as the DexFEM trial suggests) 40 , whereas another patient with high fibrinolysis markers should receive tranexamic acid. If a patient’s menstrual blood analysis indicates infection or dysbiosis, a course of antibiotics might reduce the inflammation and bleeding.

Emerging therapies are also expanding the non-hormonal arsenal. The low-dose dexamethasone trial (DexFEM) by Warner et al. (2021) demonstrated a novel use of a glucocorticoid in reducing HMB 40 . Though dexamethasone is a steroid, it is not a sex hormone; its short-term, luteal phase use is a targeted approach to correct a presumed endometrial defect (glucocorticoid receptor deficiency leading to poor vessel contractility) 38 . The positive result of DexFEM (with 1.8 mg/day dexamethasone for 5 days yielding a clinically significant reduction in bleeding) is a proof-of-principle that “personalized pharmacology” – treating the specific biochemical pathology – can work in HMB 39 . Another class of emerging treatments are Selective Progesterone Receptor Modulators (SPRMs) , such as ulipristal acetate, which have been shown to reduce fibroid size and bleeding without the systemic effects of estrogen/progesterone alterations. SPRMs act on progesterone receptors in the fibroid and endometrium to induce amenorrhea in many cases of fibroid-related HMB, and have an improved side effect profile compared to gonadotropin- releasing hormone agonists 60 . However, SPRMs are hormonal modulators (though not traditional “hormone therapy”), and their use has been limited by regulatory issues (e.g., liver toxicity concerns with ulipristal).

AI and digital health tools are also making inroads in HMB management. Smartphone apps for menstrual tracking are ubiquitous, and their data can be harnessed to identify abnormal bleeding patterns. For example, Flo Health, a popular period-tracking app, in partnership with a biopharmaceutical company, launched a digital screening tool for HMB that uses AI to help women quantify their bleeding and recognize when it is excessive ^{61 62} . Such tools, while not providing treatment, improve the accuracy of HMB detection and encourage timely clinical consultations. On the back end, the aggregated data from millions of users can feed machine learning models to discover new “digital biomarkers” of HMB ⁶³ . These might include patterns of bleeding intensity, cycle regularity, and symptoms that predict underlying causes (for instance, an algorithm might learn that women reporting severe cramps and heavy flow are more likely to have endometriosis-related HMB, and thus should be evaluated for that specifically).

In sum, the landscape of HMB treatment is moving toward multimodal management , combining symptom control with cause-specific interventions. The South Asian context calls for additional considerations: treatments must be affordable, acceptable, and accessible. The LNG-IUS (Mirena) is highly effective but uptake in South Asia has been slow due to cost and misperceptions about intrauterine devices. Oral tranexamic acid is cheap and widely used, but only effective if taken consistently each cycle and if the underlying fibrinolysis is a major factor. Iron supplementation is essential to address anemia but does not treat bleeding. Therefore, a personalized approach that accurately diagnoses the cause of HMB and directs the appropriate therapy could vastly improve outcomes and reduce unnecessary treatments. The next section outlines a proposed framework leveraging biomarkers and AI to achieve this precision medicine approach for HMB.

Methodology

To develop personalized, non-hormonal treatment pathways for HMB, we propose a multi-step methodology that integrates clinical evaluation with advanced laboratory and computational analysis. This methodology can be implemented as a prospective clinical study or as a care protocol in specialized centers. The key components are: patient profiling, sample analysis, AI-driven prediction, and personalized treatment selection. The process is illustrated in Figure 1 and detailed below.

Patient Selection and Profiling: We begin with enrolling women who meet clinical criteria for HMB (e.g., patient-reported heavy flow with a validated questionnaire or measured >80 mL loss per cycle) ⁵. In the South Asian context, recruitment would involve both urban tertiary hospitals and rural health centers to capture a representative cohort. Baseline clinical data are collected, including age, reproductive history, menstrual pattern, and known causes of HMB (fibroids, etc.). Standard investigations are performed: pelvic exam and ultrasound to identify structural causes (PALM), and blood tests (complete blood count, ferritin, coagulation screen, thyroid function) to detect systemic causes or effects (e.g., anemia, coagulopathy, hypothyroidism) ^{64 65}. This establishes each patient's initial profile.

Menstrual Blood and Microbiome Sampling: Each participant provides a menstrual blood sample during her period, preferably on the heaviest day. We employ a sterile menstrual collection method (such as a menstrual cup or a hygienic pad collection system) to gather the menstrual effluent. Patients can be instructed to insert a menstrual cup for a few hours to collect fluid, ensuring minimal discomfort and preserving sample integrity. Concurrently, a vaginal/cervical swab or a small endometrial biopsy (pipelle) is obtained for microbiome analysis, if feasible. Non-invasive approaches are prioritized; studies have shown that tampon-collected samples can yield endometrial cells and microbiota, even allowing detection of cells from the fallopian tubes and

ovaries when worn mid-cycle 66 67 . This means a simple tampon or swab can capture a snapshot of the upper reproductive tract environment.

Laboratory Analysis of Samples: The menstrual blood is processed to measure key biomarkers identified from the literature. For each sample, we conduct: - Immunoassays (e.g., ELISA) for cytokines and growth factors (TNF- α , IL-6, VEGF-A, etc.). - Enzyme assays for fibrinolysis markers (tPA activity, PAI-1 levels) and coagulation factors. - Mass spectrometry or multiplex assays for prostaglandins (PGE2, PGF2 α) and other lipid mediators. - Molecular tests for any specific markers (e.g., PCR for common endometrial pathogens if infection is suspected). In parallel, the microbiome sample is subjected to DNA extraction and 16S rRNA gene sequencing to characterize the bacterial composition 68 4 . Sequencing data are processed with bioinformatics pipelines (QIIME 2, etc.) to determine the relative abundance of *Lactobacillus* species versus other genera. We also assess vaginal pH and perform microscopy on vaginal fluid (Nugent score) to correlate with the molecular findings of dysbiosis.

Data Integration and AI Model Development: All collected data – clinical features, imaging results, lab tests, biomarker levels, and microbiome profiles – are integrated into a structured database. Given the high dimensionality of this dataset, we employ machine learning techniques to derive meaningful patterns. The approach could involve: - **Unsupervised Learning** : Use clustering algorithms (e.g., k-means, hierarchical clustering) on the biomarker/microbiome data to see if patients naturally group into distinct phenotypes (for example, an “inflammatory HMB” cluster with high cytokines, or a “fibrinolytic HMB” cluster with high tPA, etc.). This exploratory step can reveal subgroups that correspond to different underlying mechanisms. - **Supervised learning:** Train classification models to predict the most effective treatment for a given patient profile. This requires labeled outcomes – in a clinical study, each patient would receive a trial of a certain therapy and we

observe response (reduction in blood loss). Over time, we accumulate outcome data for various treatments (tranexamic acid, NSAIDs, LNG-IUS, etc.) in various patient types. Using this, we train a model (e.g., a Random Forest or XGBoost algorithm) where input features are the patient's biomarkers and microbiome composition, and the target is a binary outcome of response to a given treatment (responder vs. non-responder). Separate models could be developed for each treatment option. - **Predictive Analytics:** Alternatively, use regression models to predict the magnitude of menstrual blood loss reduction expected from each therapy for the individual. This way, the model can rank treatments by predicted efficacy for that patient.

To avoid overfitting and improve generalizability, we utilize cross-validation and, if the dataset is large enough, deep learning methods that can handle complex interactions (e.g., a neural network that takes biomarker levels as input and outputs recommended treatment). We also incorporate natural language processing (NLP) to parse any unstructured patient data, such as symptom descriptions or prior medical records, to extract additional features (for example, identifying terms suggesting severe dysmenorrhea, which might hint at endometriosis) 22 69 .

AI-Driven Treatment Recommendation: The end product is an AI-based decision support tool that can propose a personalized treatment plan. Practically, this could be a software interface where the clinician inputs a patient's key data (including biomarker panel results and microbiome findings). The AI model (trained as above) processes these inputs and provides ranked recommendations – for instance: “High likelihood of response to tranexamic acid and NSAIDs; low predicted benefit from LNG-IUS; consider antibiotic therapy due to microbiome dysbiosis.” Such recommendations would be accompanied by a rationale in terms of the patient's profile (e.g., “patient has elevated tPA and low PAI-1, suggesting hyperfibrinolysis – antifibrinolytic therapy advised”).

Throughout this methodology, clinical judgment remains vital. The AI is a support tool, not a replacement for physician decision-making. Any serious structural cause identified (like a large fibroid or malignancy) would still be addressed per standard of care (surgery or oncology referral), as our framework primarily refines medical therapy choices. Patients are counseled on the options presented and their preferences are taken into account, ensuring shared decision-making.

Validation: This methodology would be validated in a clinical trial setting. For example, after initial profiling, patients could be randomized to either standard care (physician's choice of therapy based on conventional evaluation) or AI-guided care (where the AI recommendation is followed, if deemed reasonable by the physician). Outcomes (reduction in bleeding measured by objective methods like pictorial blood loss assessment charts or alkaline hematin method, improvement in quality of life, etc.) would be compared between arms. We would also monitor safety (ensuring, for instance, that an AI suggestion of antibiotics does not lead to overuse or that NSAIDs are not given when contraindicated).

By iteratively improving the AI model with more data and recalibrating based on outcomes, this methodology aims to continuously learn and enhance the precision of HMB treatment. Over time, as the model becomes more robust, it could be implemented widely, including via telemedicine platforms. In low-resource areas, one could envision a scenario where a health worker collects a woman's menstrual blood on a treated card or portable device, some key colorimetric assays (for, say, fibrinolysis or inflammation markers) are performed on the spot, data is entered into a mobile app, and an AI algorithm instantly provides guidance on management (e.g., suggesting referral for possible fibroids or initiating tranexamic acid). This would greatly extend specialized care into the community.

Figure 1 provides a schematic overview of the proposed framework, from patient data collection to AI integration and personalized treatment recommendation.

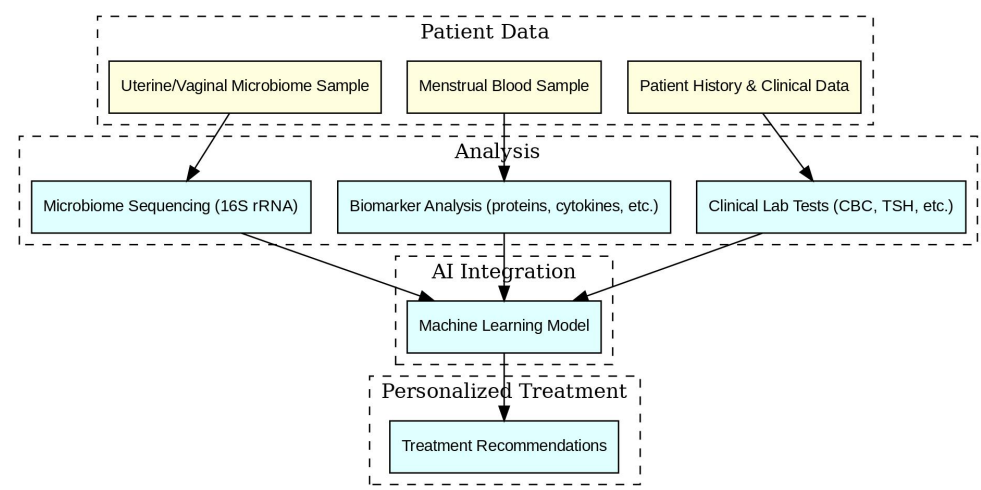


Figure 1: Proposed AI-driven personalized treatment framework for heavy menstrual bleeding. Patients undergo comprehensive profiling, including clinical evaluation, menstrual blood biomarker analysis, and uterine/vaginal microbiome sequencing. Integrated data are processed by a machine learning model which identifies underlying HMB phenotypes and predicts the optimal non-hormonal treatment. The output is a personalized treatment recommendation for each patient, which clinicians can use to guide therapy decisions.

Proposed Framework and Experimental Implementation

Building on the methodology above, we propose an experimental framework that can be implemented as a pilot program in a tertiary care center in South Asia (with capabilities for advanced lab tests) in collaboration with community clinics (for patient outreach). The framework has the following phases:

- **Phase 1:** Pilot Study and Model Training. Enroll ~100 women with HMB. Perform the full spectrum of analyses (as per methodology) and also record the outcomes of any treatments given over 6 months. Use this dataset to train the initial AI model. In this phase, we also refine practical aspects: Which biomarker assays are most feasible and informative? How can we streamline sample collection and processing in a busy clinic or peripheral setting? The data from Phase 1 will allow selection of a subset of biomarkers that are most predictive of treatment response, possibly enabling

development of a simplified point-of-care test kit for those markers in the future.

- **Phase 2: Prospective Validation.** Enroll another cohort of women and prospectively apply the AI model's recommendations. For example, if the model identifies a patient as an "inflammatory HMB" phenotype, we might prioritize an NSAID or a short course corticosteroid treatment and observe the outcome. Compare these outcomes with a matched group receiving standard empirical therapy. Metrics for success include reduction in menstrual blood loss (measured quantitatively), improvement in hemoglobin levels (for anemic patients), and patient-reported outcome measures (e.g., a validated Menorrhagia Questionnaire score).

- **Phase 3: Iteration and Community Extension.** Refine the model with Phase 2 data. Develop educational materials and simple diagnostic kits that can be used at community health centers – for instance, dipstick tests for elevated fibrinolysis (presence of excessive D-dimer in menstrual fluid) or inflammation (elevated CRP or IL-6). These could serve as surrogates when full lab work is not available, feeding into a pared-down algorithm on a mobile app. Train healthcare providers (including midwives and general practitioners) in the use of these tools.

- **Phase 4: Scale-up and Health Outcomes Evaluation.** Implement the personalized treatment protocol across multiple centers, urban and rural, and evaluate long-term outcomes such as the rate of anemia, need for blood transfusions, or progression to surgery in HMB patients before and after introduction of the personalized approach. We would also gather feedback on patient satisfaction, adherence to treatments, and any barriers faced.

This framework emphasizes clinical relevance and adaptability. The focus is on non-hormonal treatments as per the prompt; however, it does not exclude recommending hormonal therapy if truly indicated (e.g., the AI might still suggest an LNG-IUS if a patient's profile shows likely high benefit and she has no contraindications). But the novelty lies in systematically exploring the neglected non-hormonal avenues and matching them to patient biology. For instance, if our profiling finds a subset of women with HMB have subclinical endometritis, that subgroup could be treated with antibiotics – a strategy not typically part of HMB management today. If another subset has primarily hyperfibrinolytic endometrium, those women could be

managed long-term with tranexamic acid each cycle (or possibly newer antifibrinolytics in development) rather than cycling through hormones or having an unnecessary hysterectomy.

Another pillar of this framework is patient engagement and education. By personalizing therapy, we can better explain to patients why a particular treatment is chosen, which may improve their adherence. For example, telling a woman “Your menstrual blood analysis shows very high clot breakdown activity, so we are giving you a medicine to help stabilize clots and reduce bleeding” provides a logical rationale that she can understand, rather than a generic “try this pill and see if it helps.” This transparency and involvement can empower women in managing their menstrual health, a particularly important aspect in South Asia where menstrual issues are often taboo. Moreover, as indicated by Chapple (1998), some South Asian women have misconceptions about heavy bleeding ²⁵; a personalized approach offers an opportunity to debunk myths (e.g., explaining that extremely heavy periods are not beneficial but rather a medical problem that can be treated effectively).

From a health systems perspective, our framework could optimize resource utilization. Instead of every HMB patient being put on a trial of expensive hormonal therapy or undergoing surgical referral, the targeted approach might identify those who can be managed with inexpensive generics (like NSAIDs or TXA) and those who truly need advanced intervention. This stratification has economic benefits. A cost-effectiveness analysis would likely form part of Phase 4, comparing the upfront cost of biomarker testing versus savings from avoided surgeries or hospitalizations.

Discussion

The proposed development of personalized, AI-driven treatment pathways for heavy menstrual bleeding represents a paradigm shift from empirical management to evidence-based individualized care. In this discussion, we examine the potential benefits, challenges, and broader implications of this approach, particularly in the South Asian context.

Clinical Benefits: The foremost benefit of personalization is improved clinical outcomes. By aligning therapy with the underlying cause of HMB, one can expect higher efficacy. For instance, in a patient whose heavy bleeding is largely due to local hyperfibrinolysis, tranexamic acid is likely to dramatically reduce blood loss (as predicted by her biomarker profile) ³³. Conversely, a patient with significant endometrial inflammation might get limited relief from TXA alone but would benefit

from an anti-inflammatory regimen (be it NSAIDs or a short course of corticosteroids) 3 20 . Current practice often fails to make these distinctions, leading to trial-and-error – some women try multiple therapies over years before finding adequate relief or resorting to surgery. An AI-guided approach could shorten this therapeutic odyssey by recommending the right treatment first. This is especially valuable in South Asia, where access to follow-up and multiple consultations may be limited; getting it right the first time can prevent loss to follow-up and deterioration of anemia.

Another benefit is reducing unnecessary exposure to hormones and surgeries. Many women endure side effects from hormonal treatments (mood changes, weight gain, thrombotic risks, etc.) when perhaps a non- hormonal option could have sufficed if the cause was correctly identified. Similarly, some women might undergo invasive procedures that carry risks and fertility consequences, whereas a medical solution targeted to their condition might have controlled the bleeding. By providing a rationale for non-hormonal therapies, our approach could increase physician and patient confidence in using them as legitimate first- line options rather than as afterthoughts.

Relevance to South Asia: The framework aligns well with needs in South Asia. Countries like India, Pakistan, Bangladesh, and Nepal have heterogeneous healthcare landscapes – advanced hospitals in cities and basic clinics in villages. The idea of using something as accessible as menstrual blood for diagnostics means even women in remote areas could potentially have their condition assessed without needing immediate ultrasound or referral. It democratizes the diagnostic process. Moreover, focusing on non- hormonal treatments resonates with many South Asian women’s preferences. Qualitative studies indicate some women are hesitant to use hormonal contraception for bleeding due to fears of infertility or cultural disapproval 70 . Non-hormonal options like tranexamic acid or NSAIDs do not carry the same stigma and can be more acceptable. Even antibiotic treatment, if indicated by microbiome findings, might be readily accepted as treating an “infection” which is a concept people understand.

One cannot overstate the potential impact on anemia reduction. Timely and effective treatment of HMB will directly reduce chronic blood loss. Over months, this should translate to improved hemoglobin levels, better energy and work capacity, and fewer transfusions. The Lancet Global Health study showed HMB is significantly associated with feeling tired/breathless and poor self-rated health 6 71 –

improvements in HMB management could therefore have cascading benefits on women's overall health and socio-economic participation.

Role of AI: The integration of AI is a novel aspect and warrants discussion of its reliability and acceptance. AI in healthcare is still met with some skepticism due to concerns about accuracy, transparency, and ethical considerations. However, our use-case is well-suited for AI: it involves multi-dimensional data and complex pattern recognition (something AI excels at) and aims to support, not replace, clinician decisions. Early applications of AI in gynecology, such as predicting endometriosis from symptoms or AUB after vaccination, have shown promising accuracy ⁷². Our model's performance would need to be rigorously validated. Importantly, clinicians must be trained to interpret and trust the AI's recommendations. One way to build trust is to use explainable AI techniques – for example, the system can highlight which factors most influenced its suggestion (“high tPA was a key factor in recommending tranexamic acid”). Such transparency helps the provider and patient understand the logic, making it easier to accept.

Another challenge is the cost and sustainability of genomic microbiome sequencing. While costs are declining, routine 16S sequencing for every patient is unrealistic in general practice. Instead, future work could develop simpler proxies for microbiome status – for example, a PCR panel for a few key bacteria (dysbiosis markers like *Gardnerella* or *Sneathia*). Alternatively, vaginal pH and Nugent scoring, while crude, could be part of an algorithm to flag likely dysbiosis. We acknowledge that our framework in its fullest form is technologically intensive; thus, part of the research agenda is simplifying it without losing predictive power.

Data privacy and ethical considerations also arise when using AI and sensitive health data. Menstrual and genetic data must be handled with confidentiality. AI algorithms should be monitored for biases – for instance, if our training data mostly comes from one region or ethnic group, the model might not generalize elsewhere. It will be important to continuously update the model with diverse data, including representation from various South Asian subpopulations, to ensure equity.

Patient acceptability is another consideration. Will women be willing to undergo these extra tests (menstrual blood collection, swabs, etc.)? Preliminary evidence is encouraging: studies report that women are generally open to using menstrual cups or sending menstrual samples by mail for research, especially if it could yield health insights ^{73 74}. Education and proper counseling can address any

apprehensions. The inconvenience of an extra clinic visit for testing might be offset by the benefit of not having multiple trial- and-error treatment cycles.

Future Directions: If successful, this personalized approach to HMB could serve as a model for other menstrual or gynecological disorders. Endometriosis, for example, could similarly benefit from menstrual fluid biomarkers and AI, as research is already exploring (e.g., presence of certain immune cells in menstrual blood as an endometriosis indicator) 75 . The concept of an “AI-driven menstrual health platform” could emerge, where women can regularly monitor their menstrual health through smart devices and apps, and get alerts or suggestions if patterns deviate towards pathology (like HMB or irregular bleeding). On a research front, the data collected through this framework can also deepen understanding of HMB pathogenesis – by correlating certain microbiome profiles with biomarker patterns and clinical outcomes, we might discover new subtypes of HMB and perhaps new drug targets. For example, if a subgroup with high inflammation consistently responds to a short steroid course, larger trials could be done to formally establish that as a therapy. If another subgroup with dysbiosis improves with probiotics, that could open a new, simple treatment avenue.

Potential Challenges: One risk is over-reliance on technology in settings where basic needs are not met. Our approach must not inadvertently widen gaps in care – it should supplement, not replace, fundamentals like iron supplementation, basic ultrasound, and patient education. Also, health providers need training to interpret biomarker results; without proper knowledge, there’s a risk of misusing the information (e.g., over-treating a transient lab abnormality). Therefore, capacity building is integral to this framework: laboratory technicians, clinicians, and even community health workers would receive training modules as part of the program.

Policy Implications: If our personalized approach proves more effective, guidelines for HMB management might evolve to incorporate biomarker assessment. Professional societies in obstetrics and gynecology could recommend a panel of tests (much like how checking TSH is routine in AUB workup, perhaps checking a fibrinolysis marker could become routine in HMB workup). In South Asia, public health policymakers could integrate such screening into women’s health programs. For example, national programs that tackle anemia could include HMB evaluation and personalized management as a component, acknowledging that treating HMB is critical to preventing anemia.

In conclusion, the personalized, non-hormonal, AI-supported framework for HMB has the potential to significantly improve patient-centered care. It leverages modern science (biomarkers, microbiomics, AI) to solve an age-old problem in a tailored way. While challenges exist, they are surmountable with interdisciplinary collaboration – involving gynecologists, biochemists, microbiologists, data scientists, and public health experts. The South Asian focus of this study highlights that such innovations are not just for high-resource settings; in fact, they may be most transformative where resources are limited and smart allocation is needed. By treating “the right patient with the right therapy at the right time,” we can reduce the burden of heavy menstrual bleeding and empower women to lead healthier lives.

Conclusion

Heavy menstrual bleeding is a multifactorial condition that demands a multifaceted solution. This research article presented a comprehensive analysis of HMB in the South Asian context and outlined a novel approach to its management, centered on personalized, non-hormonal treatment pathways informed by menstrual blood biomarkers and uterine microbiome profiling. Our key insights can be summarized as follows:

- **Prevalence and Impact:** HMB is extremely common in South Asia and is closely linked to adverse health outcomes like anemia and reduced quality of life [1, 71]. Addressing HMB effectively is therefore a public health priority in the region. Cultural factors influencing health-seeking behavior must be recognized and incorporated into care strategies [25].
- **Biological Underpinnings:** We identified and reviewed critical biomarkers involved in HMB pathophysiology – notably, an imbalance in vasoconstrictive and vasodilatory mediators (excess PGE₂, deficient vasoconstrictors), a hyperfibrinolytic state (high tPA, low PAI-1) leading to clot instability, and an inflammatory milieu (elevated TNF- α , etc.) impairing normal endometrial repair [3, 20]. These findings underscore that HMB is not a singular entity but has identifiable sub-mechanisms that can be targeted.
- **Uterine Microbiome:** Emerging evidence of altered uterine/vaginal microbiota in HMB patients, such as reduced Lactobacilli and increased BV-associated bacteria, suggests that microbial dysbiosis may play a contributory role in heavy bleeding [4, 21]. This opens new diagnostic and therapeutic avenues (for example,

screening for chronic endometritis in refractory HMB and treating with antibiotics).

- **AI-Driven Personalization:** We proposed an experimental framework wherein comprehensive patient data (clinical, biomarker, microbiome) are integrated via machine learning to generate personalized treatment recommendations. This approach capitalizes on AI's ability to handle complex data and provide decision support 22 . In practice, it could mean shifting from a uniform treatment algorithm to a tailored one – treating the cause, not just the symptom.
- **Non-Hormonal Therapeutic Focus:** While not dismissing the value of hormonal therapies, we emphasized non-hormonal treatments in our personalized pathways. These include anti-fibrinolytics, NSAIDs, glucocorticoids (short-term), antibiotics/probiotics, and emerging agents like SPRMs or other modulators, chosen based on individual profiles. The recent DexFEM trial's success with luteal- phase dexamethasone exemplifies how identifying a specific defect (glucocorticoid deficiency in endometrium) and correcting it can ameliorate HMB interventions.
- **Feasibility and Scalability:** We discussed how this model could be implemented in South Asia, highlighting the need for developing simplified biomarker tests and ensuring acceptability. While challenges exist, they are addressable with interdisciplinary efforts and technology adaptation. Importantly, the cost-benefit equation appears favorable – better HMB control leads to fewer complications and interventions, likely offsetting the costs of testing.

In conclusion, the development of personalized, non-hormonal, AI-driven treatment pathways for HMB is not merely a theoretical exercise, but a plausible and promising advancement in women's healthcare. It brings the vision of precision medicine to a condition that affects millions silently. By focusing on menstrual blood as a diagnostic “liquid biopsy” and harnessing modern analytical tools, we can transform HMB management from generalized protocols to individualized care plans. For South Asian women, who have long suffered the consequences of heavy periods often in silence, this approach offers hope for more effective relief that is tailored to their bodies and respectful of their preferences. The framework outlined in this article now requires prospective validation, but if proven effective, it could be scaled up, leading to new standard-of-care practices. Ultimately, success in this endeavor would mean fewer women debilitated by heavy menstrual bleeding, fewer women

forced to choose between unsafe surgery or enduring misery, and more women empowered by understanding and controlling their menstrual health.

References

1. Addissouky, T. A. (2024). Harnessing technology to revolutionize personalized therapies for metrorrhagia . *Archives of Obstetrics and Gynecology*, 5(1), 40–47.
2. Chapple, A. (1998). Iron deficiency anaemia in women of South Asian descent: a qualitative study. *Ethnicity & Health*, 3(3), 199–212.
3. DeMarco, S. (2022, August). Menstrual blood holds the key to better diagnostics *Drug Discovery News*.
- 23 74
4. Flo Health & Myovant Sciences. (2018, October 8). Myovant Sciences and Flo Health partner to develop digital tool to screen women for heavy menstrual bleeding [Press release]
- 61 .
5. Jimenez, N., Norton, T., Diadala, G., Bell, E., Valenti, M., Farland, L. V., & Herbst-Kralovetz, M. M. (2024). Vaginal and rectal microbiome contribute to genital inflammation in chronic pelvic pain. *BMC Medicine*, 22(1), 283–4 .
6. Malik, S., Day, K., Perrault, I., Charnock-Jones, D. S., & Smith, S. K. (2006). Reduced levels of VEGF-A and MMP-2 and MMP-9 activity and increased TNF- α in menstrual endometrium and effluent in women with menorrhagia. *Human Reproduction*, 21(8), 2158–2166 20 .
7. Sinharoy, S. S., Chery, L., Patrick, M., Conrad, A., Ramaswamy, A., Stephen, A., ... & Caruso, B. A. (2023). Prevalence of heavy menstrual bleeding and associations with physical health and wellbeing in low-income and middle-income countries: a multinational cross-sectional study. *The Lancet Global Health*, 11(11), e1775–e1784
- 1 6
8. Sriprasert, I., Pakrashi, T., Kimble, T., & Archer, D. F. (2017). Heavy menstrual bleeding: diagnosis and medical management. *Contraception and Reproductive Medicine*, 2(1), 20
- 3 20 .
9. Warner, P., Whitaker, L. H. R., Parker, R. A., Weir, C. J., Douglas, A., Hansen, C. H., ... & Critchley, H. O.

(2021). Low-dose dexamethasone as a treatment for women with heavy menstrual bleeding: a response-adaptive randomised placebo-controlled trial (DexFEM). EBioMedicine, 66, 103434

39 40 .

10. Grand Challenges (Bill & Melinda Gates Foundation). (2023). Accelerating innovations to address heavy menstrual bleeding in women in low-resource settings (Request for Proposals)

30 31 .

1 Prevalence of heavy menstrual bleeding and associations with physical health and wellbeing 6 in low-income and middle-income countries: a multinational cross-sectional study - PubMed

7 <https://pubmed.ncbi.nlm.nih.gov/37802092/>

71

2 Prevalence and correlates of anemia among women in the ...
<https://pmc.ncbi.nlm.nih.gov/articles/PMC8552273/>

3 9

10 13

14 15

Heavy menstrual bleeding diagnosis and medical management | Contraception and Reproductive Medicine | Full Text
<https://contraceptionmedicine.biomedcentral.com/articles/10.1186/s40834-017-0047-4>

16 17

18 19

20 26

27 28

32 33

34 35

56 57

4 43

44 45

46 68

5 30

31

8 24 25

29 70

11 12 22

54 55 58

59 60 64

Vaginal and rectal microbiome contribute to genital inflammation in chronic pelvic pain | BMC Medicine | Full Text
<https://bmcmmedicine.biomedcentral.com/articles/10.1186/s12916-024-03500-1>

Accelerating Innovations to Address Heavy Menstrual Bleeding
<https://gcgh.grandchallenges.org/challenge/accelerating-innovations-address-heavy-menstrual-bleeding-women-low-resource-settings>

Iron deficiency anaemia in women of South Asian descent: a qualitative study - PubMed <https://pubmed.ncbi.nlm.nih.gov/9798118/>

Harnessing Technology to Revolutionize Personalized Therapies for Metrorrhagia
<https://www.scientificarchives.com/article/harnessing-technology-to-revolutionize-personalized-therapies-for-metrorrhagia>

65 69

21 42 47

48 49 50

51

23 41 66

67 73 74

The role of microbiota in the pathophysiology of uterine fibroids – a systematic review - PMC <https://pmc.ncbi.nlm.nih.gov/articles/PMC10250666/>

Menstrual blood holds the key to better diagnostics | Drug Discovery News
<https://www.drugdiscoverynews.com/menstrual-blood-holds-the-key-to-better-diagnostics-15454>

75

36 The composition of menstrual fluid, its applications, and recent .<https://www.sciencedirect.com/science/article/pii/S266657192400032X>

37 Heavy menstrual bleeding: work-up and management - PMC
<https://pmc.ncbi.nlm.nih.gov/articles/PMC6142441/>

38 Low dose dexamethasone as treatment for women with heavy menstrual bleeding: A response- 39 adaptive randomised placebo-controlled dose-finding parallel

- group trial (DexFEM) - PubMed 40
<https://pubmed.ncbi.nlm.nih.gov/34218053/>
- 52 Impact of antibiotic treatment for chronic endometritis on pregnancy ...
<https://pmc.ncbi.nlm.nih.gov/articles/PMC9669752/>
- 53 The effectiveness of intrauterine antibiotic infusion versus oral ...
<https://bmcmwomenshealth.biomedcentral.com/articles/10.1186/s12905-022-02128-8>
- 61 62
- 63
- Myovant Sciences and Flo Health Partner to Develop Digital Tool to Screen Women
 for Heavy Menstrual Bleeding
<https://flo.health/collaborations/innovations/myovant-sciences-and-flo-will-develop-tool-to-screen-heavy-menstrual-bleeding>
- 72 Artificial intelligence models predicting abnormal uterine
 bleeding ...
<https://www.nature.com/articles/s41598-025-91882-4>