The missed vital sign

Every minute, somewhere in the US, a woman requires a blood transfusion because of her menstruation. Heavy menstrual bleeding (HMB) often involves blood loss so significant that if it was associated with an injury, it would result in a call for an ambulance or a trip to the emergency room. HMB is reported by 1 in 3 women and is more common than asthma or diabetes in reproductive aged women. It causes adverse health conditions like anemia, and it negatively impacts emotional and financial wellbeing. Girls don't go to school – women can't go to work. And yet, HMB is largely ignored by society, healthcare professionals and researchers. The result? Currently, women suffer for an average of 5 years before getting help.

We aim to make menstruation *The missed vital sign*. Doing so will require routinely recording and quantitatively measuring menstruation. Menstrual parameters provide a unique signal of overall health for women, generally, and are critical to identification, diagnosis and treatment of HMB, specifically. We need to close the gap in our biological understanding of the fundamental mechanisms that occur when the uterine lining (the endometrium) breaks down, sheds, and repairs at menstruation. In this program, we intend to demonstrate the advances in women's health that are possible when menstruation is treated as a vital sign – our goal is to reduce the time it takes a woman to get effective treatment for HMB more than tenfold – from 5 years to 5 months.

What is the problem?

Menstruation provides unique information about the health of half the population* – it indicates the presence or absence of gynecology conditions, such as leiomyoma (fibroids) or adenomyosis, as well as wider health issues like thyroid disease, bleeding disorders, and pituitary tumors.

Despite its importance as an indicator of overall health, current clinical practice in the UK is that menstruation is only routinely asked about and recorded by women's health specialists, estimated to be less than 10% of all healthcare consultations. The result is that significant health conditions go undiagnosed, untreated, and millions of reproductive-aged women are in health crisis before they are helped.

For example, HMB is reported by 1 in 3 reproductive-aged women when directly asked as part of research[1,2] – this rate is 10 times that of asthma or diabetes in the same population. Up to 50% of reproductive aged women are iron deficient, that is up to 950 million women globally, with chronic HMB expected to be a major contributor.[3] Iron deficiency causes fatigue,

shortness of breath, and difficulty concentrating. If HMB is left untreated, iron deficiency can progress to iron deficiency anemia, which at its most severe will necessitate blood transfusion. Across the globe, girls routinely miss school due to their menstruation, with an average of 9 days lost per girl per year in the UK; compared to 7.8 days for coughs and colds and 3.6 days due to truancy.[4] This equates to a loss of 11 academic weeks due to menstruation per girl across the formative teenage years and girls. In the US, it is estimated that there are more than 100M school absences per year due to menstruation. Girls with HMB are one third less likely to achieve the minimum grades needed for apprenticeships and further education than those without HMB.[5] Women with HMB miss work an average of 3.6 working weeks annually,[6] costing the US economy >$94 billion every year. Experiencing HMB is associated with rates of anxiety and depression that are three times the average of the broader female population.[7,8]

At best, HMB is life restricting, at worst, it can be life threatening. And it is a symptom that affects more women for longer than ever before. A few centuries ago, women experienced just over 100 menstrual cycles in their lifetimes. On average, they had 5 children and lactated for 12 months with each child. Today, women living in high resource settings can expect to menstruate over 400 times, due to a combination of extended reproductive lifespan and reduced pregnancy and lactation. Menstruation always was an important sign, but it is more relevant to women's lives today than ever before.

What are the limits of current practice?

Despite its frequency, prevalence, and negative physical, emotional and financial effects, women endure HMB for an average of 5 years before getting effective treatment.[9] This is due to delays in identification, diagnosis, and suitable treatment.

Taboos surrounding menstruation result in HMB being normalized by women and society. Further, not all menstrual loss is blood, meaning women cannot conveniently or accurately quantify the volume of their menstrual blood loss, compare it to population averages, or determine levels that put them at risk. Self-perception of menstrual blood loss has sensitivity and specificity values of only 60-70%.[10] This, combined with the insidious onset of adverse health effects such as iron deficiency, means that 50% of women with HMB have never sought help. Those who do take an average of 3 years to present.[7] And when they do present, healthcare providers lack the tools needed to identify HMB, meaning 84% of women who seek help feel dismissed.[11] The combined result is that only 8% of women who suffer with HMB are accessing the tests and treatments required to alleviate it.

Things don't get much better once HMB is identified. We know that structural conditions such as leiomyomas and adenomyosis are associated with HMB,[12] but a survey of women in the UK in 2020 revealed that 40% had required more than 10 appointments to diagnose leiomyoma.[7] Currently, there are no diagnostic tests that can be performed by women or their primary care

physicians. Service pressures slowing access to specialists have therefore added to diagnostic delays. For example, the number of women waiting for specialist gynecology input in the UK has doubled since the COVID pandemic.[13]

Perhaps more concerning, in approximately half of women with HMB, no underlying structural condition is identified. Indeed, we still do not understand the fundamental mechanisms that result in HMB when the endometrium breaks down, sheds, and repairs at menstruation. This lack of biological understanding means the mainstay of current treatment is fertility removing surgery or hormonal medication, which can completely override natural ovarian hormone production. Exogenous hormones have intolerable side effects for many women, meaning 50% change medical treatments within 1 year. And up to 60% eventually opt for surgery.[14]

The goal of *The Missed Vital Sign* program is to demonstrate that routine recording, quantifiable measurement, and better treatment options for menstruation can reduce the time a woman experiences heavy menstrual bleeding from 5 years to 5 months. We aim to do this without increasing unwanted surgical intervention or menstrual cycle suppression.

Why now?

Every month during the reproductive years, in response to declining ovarian hormones, the endometrium breaks down and repairs without scarring or loss of function. We know the endometrium becomes inflamed and hypoxic at menstruation and that activation of matrix metalloproteases causes the breakdown and shedding of the upper two thirds of the endometrium.[15] But, our understanding of the endometrial mechanisms that result in HMB is limited, regardless of the presence or absence of structural uterine conditions. Determining the underpinning biological causes is necessary to revolutionize the diagnosis and treatment of HMB.

Single-cell omics technologies have transformed our understanding of cellular function and the impact of tissue architecture in other complex human tissues in health and disease.[16] Single-cell profiling of the human endometrium to detect differences across the menstrual cycle (proliferative vs secretory endometrium) has been performed, revealing previously unreported cell types and the mechanisms determining cell fate and differentiation.[17] This means is it now possible to leverage these high resolution, unbiased techniques to compare the endometrium from women with and without HMB, in the presence or absence of associated conditions, from across the menstrual cycle. To date, human research using a candidate approach has identified that excessive inflammation, defective hypoxia and aberrant coagulation are displayed in the endometrium of women experiencing HMB.[15] The application of newer techniques now has the potential to reveal previously unidentified dysregulated endometrial pathways that result in HMB.

Genetic and environmental factors also influence a woman's menstrual blood loss. A GWAS study of women of European ancestry has revealed four regions associated with HMB[18] but association with underlying conditions (e.g., adenomyosis, coagulopathies) and confirmation across diverse populations remains to be determined. Environmental influences, such as endocrine disruptors, diet and exercise are known to affect the reproductive system[15,19] but we do not yet know how these factors differ in those with and without HMB. Furthermore, behavioural data, such as number of menstrual products purchased or activity levels during menstruation, may be a good indication of HMB that results in iron deficiency, but personal and cultural preferences could result in significant bias. Advances in wearable technologies and digital phenotyping may mean it is possible to measure diagnostically useful parameters with objectively measured HMB.

Gut microbiome dysbiosis is associated with human disease, including inflammatory bowel disease, cardiovascular disease and colorectal cancer, leading to gut microbiome and microbiota derived metabolites being proposed as diagnostic biomarkers.[20] The vaginal microbiome has been characterised across the menstrual cycle, showing Lactobacillus species dominance in healthy women.[21] Small studies indicate a distinct vaginal microbiome signature in women with adenomyosis and endometriosis, highlighting its potential as a diagnostic marker for reproductive disease.[22,23] Hypoxia and inflammation, processes known to be perturbed in the endometrium of women with HMB, are key regulators of the gut microbiome.[24] Therefore, the vaginal microbiome may provide novel prognostic and diagnostic markers for HMB.

Endometrial models are necessary to delineate the cause HMB and test novel therapeutics, particularly considering that women were excluded from clinical research for decades due to the reluctance to test new treatments on women in their reproductive years. Mice do not naturally menstruate, so menstrual simulation is achieved by removing their ovaries and administering sequential ovarian hormones. While this is a useful model, it is time consuming and expensive, blocking the path to scale and limiting scientific progress. Cell-based studies have provided insights into endometrial function but do not replicate the complexity of the multicellular endometrium, limiting translation of findings to clinical care.

Organ-on-a-chip systems are defining tissue function and the effects of therapeutics on other complex tissues such as the lung, liver, pancreas and heart. For example, in diabetes care 'pancreas on a chip' technology has made it possible for clinicians to test insulin-producing cells in real time before transplanting them into a patient to potentially remove the need for lifelong insulin treatment.[25] Previously, this was performed by culturing and treating cells in a lab and then performing ELISAs, a process so long that it was not of clinical use. In reproductive health, a microfluidic culture model of the whole human reproductive tract has reproduced a 28-day menstrual cycle *in vitro*.[26] More recent advances have replicated the

cellular complexity of the endometrium *in vitro*, incorporating immune and vascular systems as well as endometrial stromal and epithelial cells.[27] This means we are now primed to model endometrial breakdown and repair *in vitro* and define measurable outputs of HMB to significantly advance in our understanding of endometrial function at menstruation in health and disease.

A data driven *in silico* approach to model endometrial breakdown and repair in those with HMB is now also within reach. An ovarian cycle *in silico* model has simulated the hormonal regulation of the menstrual cycle to predict changes in ovarian function.[28] Endometrial *in silico* models are emerging that dynamically predict volume changes in the functional endometrium, including tissue shedding and spiral arteriole blood flow.[29] Refining and extending these *in silico* modelling and simulation techniques to better understand aberrations that cause HMB and their mitigation is now eminently possible.

Together, new representative *in vitro* and *in silico* models of endometrial breakdown and repair at menstruation that simulate HMB promise to enable high-throughput screening for non-hormonal HMB therapeutics, to assess efficacy and toxicity. Such treatments would allow women to reduce menstrual blood loss without suppressing the reproductive axis, maintaining fertility and enabling time specific treatment, e.g. limited to menstruation.

Finally, new, self-administered therapeutic strategies for HMB that are time specific could bypass waiting times for specialist input, increase uptake, reduce off-target effects and decrease time to effective treatment. The reproductive system is amenable to local delivery of therapeutics, with intrauterine delivery of hormonal medications for HMB currently available. Although effective in 60-80% of users,[30] insertion of these intrauterine devices requires specialist skills and may be painful for women. As a result, we estimate that <1% of women globally have ever tried intrauterine treatments for HMB.[31] Novel drug delivery systems are now addressing the limitations of conventional delivery, increasing bioavailability and limiting side effects. For example, nano-based drug delivery systems have been shown to better cross mucosal barriers, reduce side effects of anti-tumor therapies, and localize delivery to the placenta without crossing to the fetal compartment.[32,33] In addition, microneedle technologies with wearable and programmable capabilities allow controllable, accurate and painless delivery of drugs via skin patches. Transdermal administration of estradiol is known to reduce the risk of thromboembolism when compared to oral administration,[34] making such delivery methods an attractive option for HMB therapeutics.

It is clear that the breakthroughs needed to reduce the time to effective treatment for HMB tenfold are now possible – doing so will require advancing each step in the pathway from diagnosis to treatment. When implemented at scale, such advances could prevent more than 68 billion episodes of HMB in a single decade and would allow more women and girls to thrive.

To achieve the goals of the program, we seek advances in 3 thrust areas.

To ensure women get effective treatment within 5 months, we must optimize each part of the pathway. Firstly, methods to identify women with HMB must do so within 3 months of onset and be scalable across different ages, geographies, cultures, abilities and demographics to ensure reach. In parallel, we must define the underpinning endometrial causes of HMB sufficiently to conduct high-throughput screening to identify new non-hormonal treatment targets and validate them so that they can progress to clinical trials. In addition, for speed and personalization of treatment, new point-of-care diagnostics to determine the cause of HMB and presence of any associated conditions are required for effective treatment to be provided within 2 months of presentation. Whilst acknowledging the significant negative impact of HMB on social, emotional and material quality of life, this program focuses on the mitigation of physical harm, with the aim of catalyzing diagnostic and treatment breakthroughs for all women with HMB.

Thrust 1. A high-performance multivariate tool to identify women who have HMB at levels that would result in iron deficiency, ensuring they access help within 3 months not 3 years.

Iron deficiency is the first manifestation of physical harm from chronic heavy menstrual bleeding. Therefore, this tool should have an accuracy of >80%, as determined by the area under the curve (AUC) in a receiver operating characteristic (ROC) curve across diverse populations and ages. It should not require specialist training and be scalable to home and/or community healthcare settings such that screening can reach at least 60% of women globally. This would enable the identification of over 91M women with HMB at levels that lead to iron deficiency within 3 months. To achieve this, biomarkers of HMB that will result in iron deficiency must be developed, validated and combined with environmental, behavioral and demographic factors to predict and stratify women at risk of physical ill health from their menstruation.

A. **Identify biomarkers and/or lifestyle factors that can predict menstrual blood loss at levels leading to iron deficiency.** These should have a sensitivity and specificity of >80% when detecting HMB in real-world settings with the current gold standard alkaline hematin method of menstrual blood volume measurement as a reference. Pictorial-based assessment charts, or other methods, could be used as a substitute and are desirable when they are scalable and can be verified as accurate (see Thrust 1B). Alternatively, subjective HMB may be used to define study groups in larger cohorts, but only where it can be linked to iron deficiency.

We are particularly interested in the comparison of accessible biological samples (e.g., endometrial tissue, menstrual fluid, vaginal swabs, blood and urine) from women with and without objectively measured HMB. Assessment may include, but is not limited to, microbiome signatures, genetics, and analysis of menstrual fluid/blood/urine.

Assessment of lifestyle factors such as diet, consumer behavior, or physical activity levels that could be associated with HMB is also of interest, including data from wearable technologies or mobile technologies capable of assessing these factors in real world settings.

We are interested in studies that aim to identify HMB to inform Thrust 1C and those that will inform diagnosis of underlying conditions in Thrust 3B, e.g., presence of structural conditions (e.g., leiomyoma, adenomyosis, endometrial cancer) and non-structural conditions (e.g., coagulopathies). Therefore, imaging for structural pathology is desirable and should be defined by internationally agreed standards, e.g., FIGO classification system for uterine leiomyoma,[12] MUSA criteria for adenomyosis.[35] Assessment of causality in factors associated with HMB is also desirable, where possible, to inform Thrusts 2 & 3A.

Note: non-human studies for biomarker development are not of interest due to the lack of fidelity with human menstruation, given few species menstruate naturally. In addition, the program does not seek studies that compare samples without correlation to menstrual blood loss (e.g., fertile vs non-fertile) or those that would prove difficult to access in the community (e.g., comparison of leiomyoma tissue versus normal myometrium). Human biological samples should be carefully categorized for stage of menstrual cycle and studies should adjust for or exclude those using exogenous hormones or an intrauterine device. Diversity of age, race and ethnicity should be considered to ensure extrapolation of findings across the reproductive lifespan and the globe. At a minimum, findings should be validated in an external cohort with different geography, age, ethnicity and will be facilitated within the program. Therefore, data and biological samples must be accessible by relevant researchers within the program for analysis and a clear data management plan detailing how this can be achieved should be provided.

B. **Develop quantification methods for menstrual blood loss that can be deployed at scale.** These should have a sensitivity and specificity of >80% for HMB in real world settings with the current gold standard modified alkaline haematin method as a reference. Unlike the alkaline hematin method, these methods should not require specialist skills, should enable independent quantification and be convenient for women during menstrual management to prevent additional burden for women with HMB. Methods may include, but are not limited to, image-based technologies or wearable sensors. These technologies should have potential to be transferable across different menstrual products, including menstrual cups, pads, tampons, and underwear to accommodate women's preferences. Methods must be applicable across both high and low resource settings, therefore should be assessed for accuracy in at least two different populations with different cultures and geography.
C. **Develop a high-performance, multivariate, scalable tool that can predict which women are at risk of iron deficiency due to their menstrual bleeding**. Create models to identify women in whom their menstrual bleeding will result in iron deficiency. We seek teams that can leverage the latest computational techniques to develop and integrate models. These should include menstrual symptoms, demographics and factors identified as being associated with HMB in Thrust 1A. They should also consider factors known to alter predisposition to iron deficiency (e.g., intestinal infection rates, iron intake, body mass). These models should be tested, refined and validated using longitudinal cohorts, data from menstrual tracking apps or electronic patient records of reproductive aged women that contain menstrual parameters and hemoglobin or ferritin measurements. Examples include, but are not limited to, The Avon Longitudinal Study of Parents and Children (ALSPAC), The Australian Longitudinal Study on Women's Health (ALSWH), The Adolescent Brain Cognitive Development (ABCD). Tools that women can use independently or that can be easily deployed by non-specialists during routine clinical care are of interest.

Thrust 2: Identify causal factors for HMB to inform diagnostic development and identify new, precise, non-hormonal therapeutic targets, particularly those that could be self-administered.

Currently, we estimate that 316M women globally seek help for HMB. If 84% are dismissed, approximately 50M women currently access specialist investigations and treatment for HMB. If

identification of HMB causing iron deficiency is robust and accurate, the number of women requiring clinical management will almost double (91M). Without developing new diagnostics and treatments for HMB in parallel, large numbers of women will leave clinic undiagnosed, without effective treatment, and still at risk of iron deficiency. To ensure effective treatment within 2 months of presentation, we need to identify the factors that cause the endometrium to bleed heavily at menstruation to inform diagnostics and develop precise treatments that are tailored to women's needs.

A. **Develop and validate *in vitro* and *in silico* experimental models of endometrial breakdown and repair at menstruation**. These experimental models must reflect the complexity of the menstrual endometrium and consider the interplay between endocrine, immune, and vascular systems. These models may include, but are not limited to, human cell organoids/assembloids, organ-on-a-chip technologies, mathematical or *in silico* models. Models should be shown to recapitulate the human endometrial response to ovarian hormones and human menstruation. Methods to quantify menstrual breakdown and repair and/or menstrual bleeding must be developed to assess clinically relevant menstrual blood loss changes. Given that mice and most other animals do not naturally menstruate, we do not anticipate funding *in vitro* models that propose use of non-human cells.

B. **Determine causality of known and novel factors (identified in Thrust 1) that are associated with HMB**. Manipulate (e.g., increase, decrease and rescue) factors associated with HMB in models developed in 2A and existing pre-clinical models of menstruation to determine endometrial mechanisms that result in HMB and identify novel therapeutic targets. Studies should ensure an effect size of >0.2 in parameters that contribute to HMB to maximize translation. Studies using the animal model of simulated menstruation will be considered only if they provide an essential translational bridge to achieve program goals, but will ideally be informed by findings *in vivo* and *in silico* models to reduce and replace animal numbers. Studies should include relevant controls and sufficient biological and technical replicates.

C. **Identify at least two new non-hormonal therapeutic targets for HMB and ensure effect sizes of >0.2 or menstrual blood loss reduction of >50% in pre-clinical models.** Employ *in silico* screening of known and newly identified dysregulated pathways causing HMB against drug repurposing libraries to identify potential non-

hormonal therapeutics for HMB. Where possible, test candidate compounds in *in vitro* models with appropriate technical and biological replicates, quantifying endometrial breakdown and repair and toxicology. These *in vitro* studies will then inform proof-of-concept experiments of candidate drugs or other therapeutic interventions versus appropriate placebo/controls in pre-clinical *in vivo* models to assess impact on menstrual blood loss/endometrial repair and bioanalytics where required. Based on recent FDA approvals of a hormonal treatment for HMB in women with fibroids, menstrual blood loss reduction in pre-clinical models of HMB should be at least 50%.[36]

D. **Develop novel delivery methods for HMB therapeutics that decrease menstrual blood loss by more than 50% and ensure discontinuation rates are less than 20% at 1 year.** Optimize temporal, parenteral delivery of current non-hormonal treatments for HMB to increase effectiveness and acceptability of treatments. These novel delivery methods could include, but are not limited to, development of nanosuspensions to optimize vaginal mucosal penetration or transdermal administration. Endometrial tissue availability, effectiveness, off-target effects and persistence/clearance of therapeutics by the window of implantation should be assessed in pre-clinical models of HMB and be comparable or superior to standard administration. A reduction of menstrual blood loss by 50% would ensure that 80% of women with HMB are no longer at risk of iron deficiency. Treatment delivery should also limit side effects to prevent discontinuation (currently 40-50% of women discontinue hormonal treatments within 1 year[30]). Teams should be flexible and be able to rapidly develop such delivery systems for new therapeutics for HMB identified in Thrust 2C.

Thrust 3. Develop and validate patient stratification tools to personalize management when HMB is identified and ensure effective treatment. This would mean women get treatments that work for them within 2 months, not 2 years.

A. **Develop tools using known and newly identified causal factors for HMB identified in Thrust 2B to facilitate personalization of current and new treatments**. These should prevent current 'one size fits all' or 'trial and error' approaches. Such tools could include non-invasive point of care diagnostics (e.g., using menstrual fluid, swabs, urine or pinprick blood tests) for known and newly

identified causal factors for HMB (identified in 2B) alone or may involve integration with clinical history and examination to form clinical decision aids. Therefore, teams with expertise in assay design and proposals that validate these tests in women are of particular interest. In addition, we are seeking teams that can harness the latest computational techniques, e.g. unsupervised models that personalize treatment decisions. These personalization tools should be easily used by non-specialists to ensure time to effective treatment within 2 months, assessed by patient reported outcomes, continuation rates or measures of ferritin/menstrual blood loss.

B. **Develop predictive tools for the presence of underlying conditions associated with HMB that can be used by non-specialists.** These should identify, conditions that require or would benefit from referral for specialist input with >80% accuracy as defined by AUC in a ROC curve analysis. Common conditions in those with HMB causing iron deficiency include structural uterine conditions such as leiomyoma (fibroids near the endometrium or >3cm), adenomyosis (endometrial invasion into muscle layer of uterus), and von Willebrand disease (coagulation disorder).[12] Therefore, accurate, non-invasive methods of predicting these conditions should be developed, using factors identified in Thrust 1A. In addition, endometrial cancer is a rare cause of HMB in pre-menopausal women (<1.33%) but is life-threatening and essential to exclude in at-risk women. A non-invasive, low-cost predictive test for endometrial cancer in pre-menopausal women with a sensitivity of >90% and specificity of >80% would be comparable to current cervical screening test accuracy, ensuring rapid, appropriate specialist referral for invasive diagnostic endometrial sampling. These predictive tests may be used alone or in combination with features such as menstrual symptoms and demographics to increase accuracy.

Advances across the three thrusts should inform each other to improve and validate predictive markers for HMB, underlying conditions and endometrial cause to stratify women and personalize management. It is not necessary to form large consortiums or teams to do this - it will be facilitated by Wellcome Leap to make progress together towards the program goals.

*The program is intended to benefit and catalyse research for anyone suffering with heavy menstrual bleeding.

References

1 Fraser, I. S. *et al.* Prevalence of heavy menstrual bleeding and experiences of affected women in a European patient survey. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* **128**, 196-200, doi:10.1016/j.ijgo.2014.09.027 (2015).

2 Sinharoy, S. S. *et al.* Prevalence of heavy menstrual bleeding and associations with physical health and wellbeing in low-income and middle-income countries: a multinational cross-sectional study. *Lancet Glob Health* **11**, e1775-e1784, doi:10.1016/S2214-109X(23)00416-3 (2023).

3 Munro, M. G. *et al.* The relationship between heavy menstrual bleeding, iron deficiency, and iron deficiency anemia. *Am J Obstet Gynecol* **229**, 1-9, doi:10.1016/j.ajog.2023.01.017 (2023).

4 *Breaking the Cycle*, <https://www.phs.co.uk/media/l5idzgti/breaking-the-cycle.pdf> (2023).

5 Sawyer, G., Fraser, A., Lawlor, D. A., Sharp, G. C. & Howe, L. D. Associations of adolescent menstrual symptoms with school absences and educational attainment: analysis of a prospective cohort study. *medRxiv*, 2024.2004.2024.24306294, doi:10.1101/2024.04.24.24306294 (2024).

6 Cote, I., Jacobs, P. & Cumming, D. Work loss associated with increased menstrual loss in the United States. *Obstetrics and gynecology* **100**, 683-687 (2002).

7 *Heavy Menstrual Bleeding, breaking the silence and stigma*, <https://static1.squarespace.com/static/5ccc3b392727be60b3a02ec3/t/5e5e1c515406da1b393d470c/1583225943688/HMB_Report+02.03.20.pdf> (2020).

8 Weyand, A. C. *et al.* Depression in Female Adolescents with Heavy Menstrual Bleeding. *J Pediatr* **240**, 171-176, doi:10.1016/j.jpeds.2021.09.007 (2022).

9 Warner, P. *et al.* Low dose dexamethasone as treatment for women with heavy menstrual bleeding: A response-adaptive randomised placebo-controlled dose-finding parallel group trial (DexFEM). *EBioMedicine* **69**, 103434, doi:10.1016/j.ebiom.2021.103434 (2021).

10 Magnay, J. L., O'Brien, S., Gerlinger, C. & Seitz, C. A systematic review of methods to measure menstrual blood loss. *BMC Womens Health* **18**, 142, doi:10.1186/s12905-018-0627-8 (2018).

11 Women's health - 'Let's talk about it' survey. (2022).

12 Munro, M. G., Critchley, H. O. D., Fraser, I. S. & Committee, F. M. D. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* **143**, 393-408, doi:10.1002/ijgo.12666 (2018).

13 *Waiting for a way forward: Voices of women and healthcare professionals at the centre of the gynaecology care crisis*, <https://www.gov.uk/government/calls-for-evidence/womens-health-strategy-call-for-evidence/outcome/3fa4a313-f7a5-429a-b68d-0eb0be15e696> (2024).

14 RCOG. National Heavy Menstrual Bleeding Audit: Final Report. (2014).
15 Jain, V., Chodankar, R. R., Maybin, J. A. & Critchley, H. O. D. Uterine bleeding: how understanding endometrial physiology underpins menstrual health. *Nat Rev Endocrinol*, doi:10.1038/s41574-021-00629-4 (2022).
16 A focus on single-cell omics. *Nat Rev Genet* **24**, 485, doi:10.1038/s41576-023-00628-3 (2023).
17 Mareckova, M. *et al.* An integrated single-cell reference atlas of the human endometrium. *Nat Genet* **56**, 1925-1937, doi:10.1038/s41588-024-01873-w (2024).
18 Gallagher, C. S. *et al.* Genome-wide association and epidemiological analyses reveal common genetic origins between uterine leiomyomata and endometriosis. *Nature communications* **10**, 4857, doi:10.1038/s41467-019-12536-4 (2019).
19 *Impact of endocrine disrupting chemicals on reproductive systems*, <https://www.endocrine.org/topics/edc/what-edcs-are/common-edcs/reproduction> (
20 Hou, K. *et al.* Microbiota in health and diseases. *Signal Transduct Target Ther* **7**, 135, doi:10.1038/s41392-022-00974-4 (2022).
21 Ravel, J. *et al.* Vaginal microbiome of reproductive-age women. *Proc Natl Acad Sci U S A* **108 Suppl 1**, 4680-4687, doi:10.1073/pnas.1002611107 (2011).
22 Chen, C. *et al.* The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. *Nature communications* **8**, 875, doi:10.1038/s41467-017-00901-0 (2017).
23 MacSharry, J. *et al.* Endometriosis specific vaginal microbiota links to urine and serum N-glycome. *Scientific reports* **14**, 25372, doi:10.1038/s41598-024-76125-2 (2024).
24 Pral, L. P., Fachi, J. L., Correa, R. O., Colonna, M. & Vinolo, M. A. R. Hypoxia and HIF-1 as key regulators of gut microbiota and host interactions. *Trends Immunol* **42**, 604-621, doi:10.1016/j.it.2021.05.004 (2021).
25 Glieberman, A. L. *et al.* Synchronized stimulation and continuous insulin sensing in a microfluidic human Islet on a Chip designed for scalable manufacturing. *Lab Chip* **19**, 2993-3010, doi:10.1039/c9lc00253g (2019).
26 Xiao, S. *et al.* A microfluidic culture model of the human reproductive tract and 28-day menstrual cycle. *Nature communications* **8**, 14584, doi:10.1038/ncomms14584 (2017).
27 Gnecco, J. S. *et al.* Organoid co-culture model of the human endometrium in a fully synthetic extracellular matrix enables the study of epithelial-stromal crosstalk. *Med* **4**, 554-579 e559, doi:10.1016/j.medj.2023.07.004 (2023).
28 Margolskee, A. & Selgrade, J. F. Dynamics and bifurcation of a model for hormonal control of the menstrual cycle with inhibin delay. *Math Biosci* **234**, 95-107, doi:10.1016/j.mbs.2011.09.001 (2011).
29 Arbelaez-Gomez, D. *et al.* A phenomenological-based model of the endometrial growth and shedding during the menstrual cycle. *J Theor Biol* **532**, 110922, doi:10.1016/j.jtbi.2021.110922 (2022).

30 Beelen, P. *et al.* Predictive factors for failure of the levonorgestrel releasing intrauterine system in women with heavy menstrual bleeding. *BMC Womens Health* **21**, 57, doi:10.1186/s12905-021-01210-x (2021).
31 da Silva Filho, A. L., Caetano, C., Lahav, A., Grandi, G. & Lamaita, R. M. The difficult journey to treatment for women suffering from heavy menstrual bleeding: a multi-national survey. *Eur J Contracept Reprod Health Care* **26**, 390-398, doi:10.1080/13625187.2021.1925881 (2021).
32 Mitchell, M. J. *et al.* Engineering precision nanoparticles for drug delivery. *Nature reviews. Drug discovery* **20**, 101-124, doi:10.1038/s41573-020-0090-8 (2021).
33 Zierden, H. C. *et al.* Avoiding a Sticky Situation: Bypassing the Mucus Barrier for Improved Local Drug Delivery. *Trends Mol Med* **27**, 436-450, doi:10.1016/j.molmed.2020.12.001 (2021).
34 Canonico, M. *et al.* Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* **115**, 840-845, doi:10.1161/CIRCULATIONAHA.106.642280 (2007).
35 Harmsen, M. J. *et al.* Consensus on revised definitions of Morphological Uterus Sonographic Assessment (MUSA) features of adenomyosis: results of modified Delphi procedure. *Ultrasound Obstet Gynecol* **60**, 118-131, doi:10.1002/uog.24786 (2022).
36 Al-Hendy, A. *et al.* Treatment of Uterine Fibroid Symptoms with Relugolix Combination Therapy. *The New England journal of medicine* **384**, 630-642, doi:10.1056/NEJMoa2008283 (2021).