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# VAGINA-R: A Clinical-Biological Phenotype Classification for the Genitourinary Syndrome of Menopause, With a Protocol for Phenotype-Guided Regenerative Care (The REGEN-VAG Study)

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## ABSTRACT

**Background:** The genitourinary syndrome of menopause (GSM) is defined as a single syndrome, but women who meet the definition differ in the mechanism that drives their symptoms. Some have predominantly hypoestrogenic epithelial atrophy; others have provoked pain, pelvic-floor dysfunction, recurrent urinary infection, persistent dysbiosis, or a cancer history that limits hormonal options. Trials of regenerative and energy-based interventions — platelet-rich plasma (PRP), fractional $CO_2$ and Er:YAG lasers and radiofrequency — have mostly enrolled women with GSM as an undifferentiated group, and the sham-controlled results have been largely null.

**Objective.** To propose VAGINA-R, a clinical-biological classification of GSM into seven phenotypes, and to describe REGEN-VAG, a two-phase study to validate the classification and test whether phenotype-guided care improves outcomes compared with standard care.

**Classification.** VAGINA-R defines seven phenotypes: V, vulvovaginal atrophic; $A_1$, algesic/inflammatory; G, genitourinary (urinary); I, tissue-integrity compromised; N, neuromuscular/sexual; $A_2$, altered microbiome; and R, risk and hormonal-reserve. Each phenotype has proposed operational criteria based on history, examination and simple tests. A woman may carry more than one phenotype; one is designated dominant. R is treated as a modifier that changes which treatment pathways are permitted rather than as a mechanism.

**Protocol.** Phase 1 is a modified Delphi consensus followed by an inter-rater reliability study. Phase 2 is a pragmatic randomised trial comparing phenotype-guided care with standard guideline-based care, with the primary outcome a clinically important improvement in the most bothersome symptom at 6 months, and follow-up to 12 months. A nested, sham-controlled pilot tests a fully characterised PRP product as an adjunct in women with V or I phenotypes that are refractory to first-line therapy. A biological sub-study explores the vaginal microbiome (16S rRNA sequencing), cytokines and matrix metalloproteinases.

**Conclusions.** VAGINA-R is a hypothesis-generating proposal and has not been validated. If phenotypes prove reliable and predictive, they could explain part of the inconsistency in the regenerative GSM literature and support more precise trial enrolment. Regenerative interventions remain research-only in this protocol.

**Keywords:** genitourinary syndrome of menopause; phenotype; classification; precision medicine; platelet-rich plasma; vaginal laser; vaginal microbiome; Delphi; study protocol.

## INTRODUCTION

The genitourinary syndrome of menopause (GSM) was introduced in 2014 as a more accurate and acceptable term than vulvovaginal atrophy. It is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids, involving the labia, clitoris, vestibule, introitus, vagina, urethra and bladder, and including genital, sexual and urinary symptoms that must be bothersome and not better explained by another diagnosis [1]. GSM affects approximately 27% to 84% of postmenopausal women, depending on the population, and is underdiagnosed and undertreated [2].

The definition is deliberately broad. It joins under one name a woman with dryness and a raised vaginal pH, a woman

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whose main complaint is provoked pain at the vestibule with an overactive pelvic floor, a woman with recurrent cystitis, and a breast cancer survivor on an aromatase inhibitor whose symptoms are severe and whose hormonal options are restricted.

In a survey of women with breast cancer, 69% reported at least one genitourinary symptom and 47% at least one moderate or severe symptom [3]; aromatase inhibitors are associated with more severe symptoms than tamoxifen [4].

Treatment guidelines respond to this breadth with a stepwise logic: non-hormonal lubricants and moisturisers, then low-dose vaginal estrogen, vaginal DHEA or ospemifene [2,5]. The 2025 AUA/SUFU/AUGS guideline recommends offering low-dose vaginal estrogen (strong recommendation) and advises that the evidence does not support $CO_2$ laser, Er:YAG laser or radiofrequency for GSM symptoms; $CO_2$ laser may be considered only within shared decision-making and with disclosure that it is experimental outside clinical trials [5]. In our own analysis of conventional hormonal therapy versus emerging regenerative interventions for GSM, we proposed a three-tier model that places hormonal therapy in Tier 1, energy-based devices in Tier 2 (conditional, after documented failure of or contraindication to Tier 1) and PRP in Tier 3 (research only) [6]; the GRACE classification later carried these tiers forward as evidence-maturity levels M1 to M3 and added a preclinical level, M4 [15]. In the PRP evidence base for GSM, we found only four sham- or placebo-controlled trials, with 187 participants in total, three of which were null [6].

One explanation for null sham-controlled results is that the interventions do not work. Another, not mutually exclusive, is that they have been tested in populations in which only a minority has the mechanism the intervention targets. A treatment intended to restore epithelium and lamina propria would not be expected to help a woman whose dominant problem is pelvic-floor overactivity, and its effect in the minority who could benefit would be diluted in an unselected trial. This second explanation is a hypothesis, not a finding. It can only be tested if GSM phenotypes are defined, measured reliably and used to stratify patients. VAGINA-R is a proposal to do that.

## THE VAGINA-R CLASSIFICATION

### Principles

VAGINA-R rests on four principles.

1. **Mechanism over label.** The classification describes the dominant biological or functional mechanism, not the presenting word (“dryness”, “pain”, “laxity”).
2. **Multi-label by design.** A woman can carry more than one phenotype. One phenotype is designated dominant — the one most responsible for the most bothersome symptom — and the others are recorded as secondary.
3. **Measurable with simple tools.** Each phenotype should be assignable in an ordinary gynecology clinic with history, examination, pH, a wet mount or Gram stain and validated questionnaires. Advanced tests (for example, 16S sequencing) support research but are not required for classification.
4. **Context modifies options.** The R phenotype describes a context — cancer history, endocrine therapy, premature ovarian insufficiency — that changes which pathways are permitted. It is recorded as a modifier (R+) alongside the dominant mechanism.

### The seven phenotypes

The thresholds in **Table 1** are working proposals, drawn from common clinical practice and the cited consensus documents. They are expected to change during Phase 1. In particular, the 2020 NAMS position statement notes that vaginal pH and the maturation index are not essential components of GSM diagnosis, which rests on symptoms and examination [2,11]; VAGINA-R uses these tests to separate phenotypes, not to diagnose GSM.

### Writing a VAGINA-R profile

A profile lists the dominant phenotype first, secondary phenotypes in parentheses and the R modifier last. For example:

- **V(I)** — atrophic GSM with tissue fragility, no restricting context.
- **$A_1$(N)** — pain-dominant presentation with pelvic-floor overactivity.
- **G(V)·R+** — recurrent urinary infection with atrophy in a woman on an aromatase inhibitor.
- **$A_2$(V)** — persistent dysbiosis despite estrogenisation.

The profile is recorded at baseline and repeated at each scheduled visit, because phenotypes can change with treatment. A V phenotype that resolves on vaginal estrogen may leave a residual N or $A_1$ phenotype that was previously masked.

### Why the microbial phenotype matters

The vaginal microbiome changes with menopause. Ravel and colleagues described five community state types in reproductive-age women, four dominated by *Lactobacillus* species and one (CST IV) with fewer lactic-acid bacteria, more strict anaerobes and a higher pH [9]. In a cohort of pre-, peri- and postmenopausal women, women with signs of vulvovaginal atrophy had markedly higher odds of a CST IV-A community than of an *L. crispatus*-dominated one [10].

Estrogen therapy increases *Lactobacillus* abundance in postmenopausal women [12]. The $A_2$ phenotype is defined not by dysbiosis alone — which is common and partly physiological after menopause — but by dysbiosis that persists *after* adequate estrogenisation, because that is the subgroup in which an atrophic explanation is no longer sufficient.

**Table 1.** VAGINA-R phenotypes and proposed operational criteria.

| Code | Phenotype | Core features | Proposed operational criteria (to be refined by Delphi) |
|---|---|---|---|
| **V** | Vulvovaginal atrophic | Dryness, burning, irritation; thin pale epithelium; loss of rugae | Bothersome genital symptom plus at least two of: vaginal pH > 5.0 without infection; low superficial-cell fraction on maturation index; vaginal health index ≤ 15 |
| **$A_1$** | Algesic/inflammatory | Burning, dyspareunia, provoked vestibular pain, hypersensitivity | Pain as most bothersome symptom; provoked pain on cotton-swab test at the vestibule; vulvar pain described with the 2015 ISSVD/ISSWSH/IPPS descriptors [7]; dermatoses (for example, lichen sclerosus) identified and recorded |
| **G** | Genitourinary (urinary) | Urgency, frequency, dysuria, recurrent urinary infection, mild incontinence | Urinary symptom as most bothersome; recurrent UTI defined as two culture-confirmed episodes in 6 months or three in 12 months [8]; validated urinary questionnaire |
| **I** | Tissue-integrity compromised | Fissures, friability, petechiae, contact bleeding, introital narrowing, reduced elasticity | At least two examination signs of fragility or loss of elasticity; vaginal health index elasticity and integrity sub-scores at the lowest levels |
| **N** | Neuromuscular/sexual | Tense or weak pelvic floor, myofascial pain, arousal or orgasm dysfunction | Pelvic-floor tone or strength abnormality on digital examination; myofascial trigger points; sexual-function questionnaire below its validated threshold |
| **$A_2$** | Altered microbiome | Recurrent discharge, odour, persistent high pH, recurrent bacterial vaginosis or candidiasis | pH persistently > 4.5 after at least 12 weeks of adequate local estrogen, or Nugent score ≥ 7, or recurrent culture- or microscopy-confirmed vaginitis; research option: low-*Lactobacillus* community state type IV on 16S sequencing [9,10] |
| **R** | Risk and hormonal reserve (modifier) | Hormone-dependent cancer, endocrine therapy, premature ovarian insufficiency, contraindication to estrogen | History of estrogen-dependent cancer; current aromatase inhibitor or tamoxifen; POI; risk-reducing bilateral salpingo-oophorectomy; pelvic radiotherapy; other contraindication to estrogen |

## Why R is a modifier

Women with a history of estrogen-dependent breast cancer are a distinct clinical group. ACOG recommends non-hormonal methods as first line; if they fail, low-dose vaginal estrogen may be used after discussion of risks and benefits, including in women taking tamoxifen, and in women taking aromatase inhibitors after shared decision-making between the patient, gynecologist and oncologist; vaginal DHEA or testosterone may be considered if estrogen is not an option [13]. Premature ovarian insufficiency carries its own pathway: hormone therapy is recommended until the usual age of menopause, with vaginal estrogen added if genitourinary symptoms are not relieved by systemic therapy [14]. These contexts do not describe a mechanism of

symptoms; they change the permissible treatments. Recording R as a modifier keeps the mechanism and the context separate.

## PHENOTYPE-GUIDED PATHWAYS

Table 2 links each phenotype to evidence-based first-line care and to the role, if any, of regenerative or energy-based interventions. Maturity labels (M1 to M4) follow the GRACE classification [15], which extends our three-tier GSM model [6].

**Table 2.** VAGINA-R phenotypes and treatment pathways.

| Phenotype | Evidence-based first line | Regenerative or energy-based role | Level |
|---|---|---|---|
| V | Moisturisers and lubricants; low-dose vaginal estrogen; vaginal DHEA; ospemifene [2,5] | $CO_2$ laser only after documented failure of or contraindication to Tier 1, with written disclosure; PRP only in registered research | Hormonal M1; laser M2; PRP M3 |
| $A_1$ | Pain management; pelvic-floor physiotherapy; treatment of any identified dermatosis; local estrogen if atrophy co-exists [7] | None outside research | M3 |
| G | Vaginal estrogen for recurrent UTI in peri- and postmenopausal women without contraindication [8]; urogynecologic assessment; pelvic-floor training for incontinence [16] | Periurethral PRP or energy devices only in research | M3 |
| I | Local estrogen to restore epithelium; dilators where narrowing is present | Adjuncts targeting extracellular matrix and vascularity (laser, PRP) only after Tier 1 failure and within protocol | Laser M2; PRP M3 |
| N | Pelvic-floor physiotherapy; sexual therapy; treatment of co-existing atrophy | None outside research | M3 |
| $A_2$ | Diagnosis and treatment of infection; confirmation of adequate estrogenisation [12] | None; microbiome-directed therapies remain investigational | M3–M4 |
| R+ | Non-hormonal first; vaginal estrogen, DHEA or ospemifene after shared decision-making with oncology [13]; POI pathway per ESHRE [14] | Energy-based and PRP options are attractive in this group but have no stronger evidence here than in other groups; research only | M3 |

Two rules apply across the table. First, every pathway begins with Tier 1 care where it is permitted; failure of Tier 1 is declared only after at least 12 weeks of documented adherence with repeat pH and cytology [6]. Second, no regenerative intervention is offered as established therapy for any phenotype.

## THE REGEN-VAG STUDY PROTOCOL

### Aims

1. To reach international consensus on the VAGINA-R phenotypes, their operational criteria and the profile notation (Phase 1a).
2. To estimate inter-rater reliability of VAGINA-R phenotype assignment (Phase 1b).
3. To test whether phenotype-guided care improves the proportion of women with a clinically important improvement in their most bothersome symptom at 6 months, compared with standard guideline-based care (Phase 2, main trial).
4. To estimate the feasibility and effect size of a fully characterised PRP adjunct, against sham, in women with V or I phenotypes refractory to Tier 1 care (Phase 2, nested pilot).
5. To explore biological correlates of phenotype and response (biological sub-study).

### Phase 1a — Modified Delphi consensus

**Panel.** Gynecologists, urogynecologists, menopause specialists, sexual-medicine specialists, pelvic-floor physiotherapists, oncologists with survivorship practice, microbiologists, methodologists and women with lived experience of GSM. The panel will be international, with a target of at least 40 panellists across at least three continents.

**Process.** Two to three online rounds. Items will cover the phenotype list, each operational criterion and threshold, the dominant/secondary rule, the treatment of R as a modifier and the notation. Items will be rated on a nine-point scale. Consensus will be defined in advance (for example, at least 70% of ratings in the 7–9 range and no more than 15% in the 1–3 range), following published recommendations on defining consensus in Delphi studies [17]. A final virtual meeting will resolve items without consensus. The process will be reported according to the ACCORD guideline [18].

**Phase 1b — Inter-rater reliability**

**Design.** Cross-sectional reliability study in at least two centres.

**Participants.** Consecutive postmenopausal women, or women with iatrogenic or premature hypoestrogenism, presenting with bothersome genitourinary symptoms.

**Procedure.** Two trained clinicians will assess each woman independently, on the same day and blinded to each other's results, using the consensus criteria. Each clinician will assign a dominant phenotype, secondary phenotypes and the R modifier.

**Analysis.** Agreement on the dominant phenotype will be estimated with Cohen's kappa; agreement on each phenotype as present or absent with kappa per phenotype; and multi-rater agreement, if more than two raters are used, with Fleiss' kappa. Interpretation will use conventional thresholds [19]. A kappa of at least 0.61 for the dominant phenotype will be required before Phase 2 begins; phenotypes below that threshold will be revised or merged. The sample size (planning estimate approximately 100–150 women) will be calculated by the study statistician for the target and null kappa values and the expected phenotype prevalence.

**Phase 2 — Main trial**

**Design.** Multicentre, pragmatic, parallel-group randomised controlled trial with blinded outcome assessment. Randomisation 1:1, stratified by centre and by R status, using concealed computer-generated allocation.

**Participants.** *Inclusion:* women aged 40 years or older who are postmenopausal, or women of any adult age with iatrogenic or premature hypoestrogenism; at least one bothersome genitourinary symptom for at least 3 months; ability to complete questionnaires. *Exclusion:* active genital infection at baseline (until treated); undiagnosed genital bleeding; current pregnancy; pelvic malignancy under active treatment; pelvic surgery within the previous 6 months; inability to consent.

**Interventions.**

- *Standard care (control):* management according to current guidelines [2,5,13], without phenotype assessment, delivered by the usual clinician.
- *Phenotype-guided care (intervention):* VAGINA-R profiling at baseline and at each visit, with treatment selected according to the pathways in Table 2. Regenerative or energy-based interventions are *not* part of the main trial intervention; they are tested only in the nested pilot (Section 4.5). This keeps the main comparison focused on whether phenotyping itself improves care.

**Visits.** Baseline, 3, 6 and 12 months.

**Primary outcome.** Proportion of women with a clinically important improvement in the most bothersome symptom at 6 months, measured on a validated 0–10 or ordinal severity scale, with the threshold for clinically important improvement pre-specified in the statistical analysis plan.

**Secondary outcomes.** The eight COMMA core outcomes for genitourinary symptoms: pain with sex, vulvovaginal dryness, vulvovaginal discomfort or irritation, discomfort or pain on urination, change in most bothersome symptom, distress or interference, satisfaction with treatment, and side effects [20]; vaginal health index; vaginal maturation index; vaginal pH; Female Sexual Function Index; ICIQ-SF; number of culture-confirmed UTIs; all outcomes at 3, 6 and 12 months; adverse events throughout.

**Sample size (planning assumptions).** If 45% of women in standard care and 60% in phenotype-guided care achieve the primary outcome, 173 women per group are needed for 80% power at a two-sided α of 0.05. Allowing for 15% attrition, the planning target is approximately 205 women per group (about 410 in total). These assumptions are illustrative and will be revised using response proportions observed in Phase 1b and published trials before the protocol is finalised.

**Statistical analysis.** Intention-to-treat analysis with logistic regression adjusted for stratification factors. Pre-specified subgroup analyses by dominant phenotype and R status, with interaction tests, will address the central hypothesis that the benefit of phenotype-guided care differs by phenotype. Missing data will be handled by multiple imputation under a missing-at-random assumption, with sensitivity analyses.

**Nested sham-controlled pilot — characterised PRP adjunct**

**Rationale.** PRP is a Tier 3 (GRACE M3) intervention for GSM [6]. The most plausible target, on biological grounds, is a woman whose dominant mechanism is epithelial and stromal (V or I) and who has not responded to adequate Tier 1 care. Testing PRP in this enriched group, against sham, is the most direct way to see whether phenotype selection reveals an effect that unselected trials have missed.

**Participants.** Women in either trial arm with a V or I dominant phenotype whose symptoms persist after at least 12 weeks of documented adherence to Tier 1 therapy, and who give separate research consent.

**Intervention.** Autologous PRP, prepared with a single standardised protocol and characterised for each participant with the PAW and MARSPILL descriptors (platelet concentration, leukocyte content, red-cell content, activation, spins, method) [21,22], with fixed volume, injection sites and schedule. Tier 1 therapy continues.

**Comparator.** Sham procedure with blood draw and injection of sterile saline at the same sites and schedule, so that participants and outcome assessors remain blinded.

**Outcomes.** Feasibility (recruitment, retention, blinding success); change in the most bothersome symptom and vaginal health index at 6 and 12 months; adverse events.

**Sample size.** Approximately 30 women per group, as a pilot to estimate variability and effect size for a definitive trial, not to test efficacy.

### Biological sub-study

In consenting participants at selected centres, vaginal swabs will be collected at baseline, 6 and 12 months for 16S rRNA gene sequencing (community state type assignment) [9,10], and vaginal fluid for cytokine panels and matrix metalloproteinases. These analyses are exploratory: they will test whether biological profiles differ between phenotypes and whether baseline profiles predict response.

### Ethics, safety and registration

The protocol will be approved by the relevant research ethics committees before enrolment and registered in a public trial registry. All participants will give written informed consent; the nested PRP pilot will require separate consent stating that PRP is an experimental intervention for GSM and that participants will not be charged for it. Adverse events will be recorded and graded; serious adverse events will be reported according to local regulations. An independent data monitoring committee will review safety data for the nested pilot. The trial will be reported according to CONSORT, and the protocol according to SPIRIT.

## DISCUSSION

### What VAGINA-R adds

VAGINA-R does not replace the GSM definition [1]; it works inside it. Its contribution is to give clinicians and researchers a shared vocabulary for the differences between women who meet the same definition. In clinical practice, that vocabulary helps explain why a treatment that works for one patient fails for another and points to the next step — for example, pelvic-floor physiotherapy for a residual N phenotype after estrogen has corrected a V phenotype. In research, it allows trials to enrol the phenotype that an intervention targets, to stratify randomisation and to test whether effects differ by phenotype.

### Relationship to GRACE

VAGINA-R is condition-specific. The GRACE classification is a separate, broader framework that describes any regenerative or energy-based gynecologic intervention along five axes — compartment, phenotype, intervention, evidence maturity and anchor outcome [15]. Within GSM, a VAGINA-R profile can be written in the GRACE phenotype position. The two systems are reported separately so that each can be validated on its own terms.

### What VAGINA-R does not claim

VAGINA-R does not claim that regenerative interventions work in any phenotype. It claims only that, if they work, they are more likely to show it in a well-defined target group than in an undifferentiated population, and that this can be tested. The protocol keeps regenerative interventions research-only and compares them against sham.

## LIMITATIONS

First, the classification is author-generated and its criteria are provisional; Phase 1 exists to test and revise them. Second, the phenotypes overlap, and some women will be difficult to classify; the multi-label rule reduces but does not remove this problem. Third, several criteria depend on examination, which varies between clinicians; the reliability study is designed to measure this, and phenotypes that cannot be assigned reliably will be revised or merged. Fourth, the sample size assumptions for Phase 2 are illustrative. Fifth, the biological sub-study is exploratory and is not powered for formal hypothesis testing. Finally, a pragmatic trial of a classification-based strategy cannot separate the effect of phenotyping from the effect of more structured follow-up; the visit schedule is the same in both arms to limit this.

## CONCLUSION

GSM is one syndrome with several mechanisms. VAGINA-R proposes seven phenotypes, a multi-label notation and an explicit modifier for the clinical contexts that restrict treatment. REGEN-VAG proposes to validate the classification, test whether phenotype-guided care improves outcomes, and give regenerative interventions a fair test in the patients most likely to benefit — against sham, and within research.

## DECLARATIONS

**Ethics approval and consent to participate.** This article describes a proposed study. Ethics approval will be obtained before enrolment; see Section 4.7.

**Consent for publication.** Not applicable.

**Availability of data and materials.** Not applicable; no data have yet been collected.

**Competing interests.** The authors have no relationship with manufacturers of vaginal energy-based devices, platelet-rich plasma systems, cell-based or exosome products, or menopausal hormone therapy products.

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