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VITAL: A Five-Domain Classification of Host-Tissue Regenerative Reserve in Regenerative Gynecology

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ABSTRACT

Background: Regenerative gynecology has been organised around technologies (laser, radiofrequency, platelet-rich plasma, autologous fat, exosomes) and, more recently, around clinical phenotype and evidence maturity. A variable that precedes both is missing: the biological capacity of the host tissue to respond to a regenerative stimulus. Energy-based and growth-factor interventions do not regenerate tissue by themselves; they ask the tissue to perform the regeneration. When that tissue is oestrogen-deprived, poorly perfused, fibrotic or inflamed, the same stimulus may be inert or harmful.

Purpose. To propose VITAL, to our knowledge the first classification designed to grade the regenerative reserve of vulvovaginal tissue and to link it to the mechanism of action of the intervention.

Development. VITAL was derived by conceptual reasoning from Paget's "seed and soil" principle, the oestrogen-dependent physiology of wound healing, the biology of radiation injury and pelvic senescence, and the inconsistencies observed in sham-controlled trials in regenerative gynecology. It was built to complement, not replace, the VAGINA-R phenotype model and the GRACE evidence classification previously proposed by the authors.

The framework. Five domains form the mnemonic VITAL: **V**ascular perfusion, **I**nflammatory activity, **T**rophic-hormonal status, **A**rchitecture of the extracellular matrix and **L**actobacillary ecology. The mnemonic is deliberate: it asks whether the tissue is still vital enough to regenerate. Each domain is scored from 0 (preserved) to 2 (exhausted), giving a total of 0–10 and four reserve grades: R0 preserved, R1 reduced, R2 compromised and R3 depleted, with a mandatory override rule for the ischaemic-fibrotic pattern. Three modifiers record iatrogenic exposure (x), senescence and duration of deprivation (s), and systemic metabolic-vascular load (m). In parallel, interventions are re-classified by their dependence on the host into four mechanistic classes: **C** (Condition the terrain), **T** (Trigger a host response), **S** (Signal) and **R** (Replenish cells and matrix). The terrain–mechanism compatibility principle predicts that the efficacy of classes T and S declines as reserve falls, and that R2–R3 terrains must be conditioned (class C) or replenished (class R) before any stimulus.

Application. Re-reading published trials through VITAL shows that null results of laser in breast cancer survivors receiving aromatase inhibitors, and of platelet-rich plasma in active lichen sclerosus, are compatible with terrain–mechanism mismatch — a hypothesis that cannot be confirmed retrospectively and requires prospective testing.

Conclusion. VITAL shifts the clinical question from "which technology should be used?" to "can this tissue respond to this technology now?". Four testable hypotheses and a four-phase validation programme are proposed before any routine clinical use.

Keywords: regenerative gynecology; regenerative reserve; genitourinary syndrome of menopause; vaginal laser; platelet-rich plasma; fat grafting; radiation injury; classification; precision medicine.

Abbreviations: BV, bacterial vaginosis; CST, community state type; FSFI, Female Sexual Function Index; GSM, genitourinary syndrome of menopause; GVHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; PRP, platelet-rich plasma; SASP, senescence-associated secretory phenotype; UTI, urinary tract infection; VHI, Vaginal Health Index; VMI, vaginal maturation index.

INTRODUCTION

Regenerative gynecology has grown faster than its conceptual architecture. Fractional CO_2 and Er:YAG lasers, radiofrequency, platelet-rich plasma (PRP), fat grafting, stromal vascular fraction, polynucleotides and extracellular-vesicle preparations are now offered for conditions as different as genitourinary syndrome of menopause (GSM), vulvar lichen sclerosus, stress urinary incontinence and the sequelae of pelvic radiotherapy. GSM was defined in 2014 as a collection of symptoms and signs associated with a decrease

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in oestrogen and other sex steroids, involving the labia majora and minora, clitoris, vestibule, vagina, urethra and bladder [1].

The clinical results of these interventions are strikingly inconsistent. For CO_2 laser in GSM, seven double-blind sham-controlled trials including 401 unique participants did not show a statistically significant advantage over sham [2]. The largest single trial, with 12 months of follow-up, found no difference in symptoms, quality of life or vaginal histology between laser and sham [3], and the 2025 AUA/SUFU/AUGS guideline concluded that the evidence does not demonstrate efficacy of energy-based therapies for any GSM symptom [4]. In breast cancer survivors receiving aromatase inhibitors, the LIGHT trial showed a 5.2-point improvement in the Female Sexual Function Index (FSFI) with laser versus 7.9 points with sham, with no significant difference [5]. In vulvar lichen sclerosus, the only double-blind placebo-controlled trial of PRP found histological improvement in 5 of 19 treated patients and in 5 of 10 controls ($p = 0.542$) [6].

At the same time, uncontrolled cohorts and smaller trials report meaningful improvement with the same technologies [7,8], and meta-analyses of laser versus vaginal oestrogen find similar results between arms [9]. The literature has tried to explain this heterogeneity through differences in device settings, product preparation or study design. In previous work we proposed two tools: VAGINA-R, a phenotype model based on the premise that women with GSM are not biologically homogeneous, and GRACE (Gynecologic Regenerative Axis Classification of Evidence), a five-axis classification coding anatomical compartment, clinical-biological phenotype, intervention, evidence maturity and anchor outcome [10].

These tools answer three questions: what the patient has, what is being applied and how solid the evidence is. They do not answer a fourth question that precedes the others: **is this patient's tissue capable, at this moment, of mounting the response that the intervention requires?** The search for predictors of response illustrates the gap. A review of laser for incontinence and GSM refers to the tissue's "collagen remodelling capacity" but records that predictive factors for the ideal CO_2 laser candidate were not identified [7]. In an Er:YAG study in breast cancer survivors, responders were younger at diagnosis (47.7 vs 59.7 years) and had a higher baseline Vaginal Health Index (VHI) (12.33 vs 9.33), without statistical significance in a small sample [11]. The signals exist, but there is no language to organise them.

This article proposes that language. VITAL grades the regenerative reserve of the vulvovaginal tissue terrain and crosses it with a re-classification of interventions according to how much they depend on the host. As far as we could determine from searches of the indexed literature and open sources, no published classification in regenerative gynecology addresses this object.

CONCEPTUAL BASIS: SEED, SOIL AND REGENERATION

Paget's analogy

In 1889, Stephen Paget proposed that the distribution of breast cancer metastases depended on both the "seed" (the tumour cell) and the "soil" (the receiving organ) [12]. The analogy became one of the most enduring concepts in oncology. We propose applying it, in an inverted and therapeutic sense, to regenerative gynecology: the intervention is the seed and the vulvovaginal tissue is the soil. An excellent seed sown in barren soil does not germinate; an average seed in fertile soil may succeed.

Every regenerative intervention asks something of the tissue

Fractional laser produces controlled thermal microinjuries and relies on the tissue to initiate orderly inflammation, angiogenesis, epithelial proliferation and collagen synthesis. A study of fractional CO_2 laser showed increased collagen, elastic fibres and hyaluronic acid in the lamina propria, and a correlation between collagen gain and telomere lengthening in epithelial cells ($r = 0.82$) [13], suggesting that the response tracks the proliferative capacity of the epithelium. PRP provides growth factors but not the cells that respond to them. A meta-analysis of vaginal wound healing showed that basic fibroblast growth factor stimulates proliferation in vitro, and its authors noted that postmenopausal status impairs vaginal healing, which complicates clinical translation [14].

Determinants of reserve

Five documented biological processes condition the response capacity of vulvovaginal tissue:

1. **Vascular perfusion (V).** In radiation injury, obliterative endarteritis leads to hypoxia, fragile neovessels and progressive fibrosis, and late injury inhibits the ability of irradiated tissue to repair itself [20,21]. In an animal model, vaginal blood flow fell after radiotherapy and epithelial thickness decreased by more than 50% at 9 weeks [22].
2. **Inflammation and senescence (I).** Markers of the senescence-associated secretory phenotype (SASP) can be quantified in vaginal secretions and are highest in postmenopausal women with prolapse [24]. Accumulated senescent fibroblasts reduce the homeostatic and regenerative capacity of pelvic tissue. Chronic inflammation, as in active lichen sclerosus or GVHD, disrupts vulvar architecture and creates a hostile milieu for repair [23].
3. **Trophic-hormonal status (T).** Oestrogen deprivation is a major determinant of age-related impaired tissue repair, and topical or systemic oestrogen reverses this defect in humans [15,16]. In skin, thickness falls by about 1.13% and collagen by

about 2% per postmenopausal year [16]. Oestrogen stimulates collagen type I and III synthesis in pelvic floor fibroblasts through the oestrogen receptor-α pathway and exerts anti-senescence effects on pelvic connective tissue [17].

4. **Architecture of the matrix (A).** Fibrosis, sclerosis and loss of elasticity physically alter the substrate in which regeneration should occur, as in cicatricial lichen sclerosus, graft-versus-host disease (GVHD) and post-radiation stenosis [20,23].

5. **Lactobacillary ecology (L).** The vaginal microbiome is organised into community state types (CSTs), four dominated by Lactobacillus and one (CST IV) with higher diversity and higher pH [18]. Vaginal ageing combines dysbiosis, epithelial thinning, fibroblast activation, matrix remodelling and chronic inflammation; in 913 women, epithelial thickness fell by 47.3% across age groups [19].

These determinants are already measured separately in clinical practice (pH, vaginal maturation index, VHI, vulvar examination, radiotherapy history), but they have never been combined into a single reserve scale or linked to the choice of therapeutic mechanism.

DEVELOPMENT METHODS

VITAL is a conceptual proposal by the authors, not a consensus. It was developed in four steps:

1. **Problem identification**, based on two prior syntheses by the authors (an umbrella review of regenerative and energy-based interventions in gynecology, and a comparative matrix of hormonal therapy versus regenerative interventions for GSM) and on the development of VAGINA-R and GRACE [10].

2. **Targeted narrative review** of five fields: oestrogen physiology of healing, the vaginal microbiome, pelvic radiation injury, cicatricial vulvar diseases (lichen sclerosus and GVHD), and sham- or placebo-controlled trials in regenerative gynecology.

3. **Domain selection** by three criteria: biological plausibility as a determinant of tissue response, measurability with office resources, and relative independence between domains.

4. **Preliminary operational definition** of each level (0, 1, 2), deliberately based on instruments already in use to facilitate adoption and future calibration by Delphi consensus.

No patient data were collected. All cut-off points are proposed for validation and should be regarded as provisional.

THE VITAL CLASSIFICATION

General structure

VITAL has two arms: **grading of the terrain** (five domains, total score, grade and modifiers) and **mechanistic classification of interventions** (four classes according to host dependence). Crossing the two arms produces a compatibility matrix.

Table 1. VITAL domains, proposed operational criteria and minimum assessment. Domains are listed in mnemonic order. Each domain is scored by the most severe criterion present.

Domain	0 — preserved	1 — reduced	2 — depleted	Minimum assessment
V — Vascular perfusion	Normal mucosal colour, no petechiae	Pallor, contact petechiae, loss of vascular turgor	Telangiectasia, spontaneous or light-contact bleeding, ulceration, or prior pelvic radiotherapy	Standardised speculum examination; photographic documentation; Doppler, thermography or Weber angioarchitecture score by handheld vital microscopy when available [27]
I — Inflammatory activity	No active inflammation	Controlled inflammatory dermatosis on maintenance; mild non-specific inflammation	Active lichen sclerosus or planus, active GVHD, erosive disease or uncontrolled autoimmunity	Clinical examination; biopsy when indicated; NIH genital GVHD scale [23]
T — Trophic-hormonal status	Premenopause or effective local/systemic hormone therapy; superficial cells present on VMI	Hypo-oestrogenism without pharmacological blockade; predominance of intermediate or parabasal cells	Active pharmacological deprivation (aromatase inhibitor, GnRH analogue) or hypo-oestrogenism with no option for replacement; parabasal predominance	Menopausal status and medications; vaginal maturation index
A — Architecture of the matrix	Preserved elasticity and calibre; rugae present	Reduced elasticity, loss of rugae, mild introital narrowing	Sclerosis, synechiae, fusion of vulvar structures, vaginal stenosis or shortening	Vulvovaginal examination with lesion map; introital calibre by dilator; high-frequency ultrasound when available
L — Lactobacillary ecology	pH ≤ 4.5; lactobacillary flora (Nugent 0–3 or CST I, II, III or V)	pH 4.6–5.9; Nugent 4–6 or asymptomatic CST IV	pH ≥ 6; recurrent BV or vaginitis (≥ 3/year), recurrent UTI (≥ 3/year) or epithelial erosions	pH; wet mount or Gram stain; CST when available

The five domains

The five domains were chosen first on biological grounds (Section 2.3) and then named so that their initials form an English word that carries the clinical question itself: is the tissue still **VITAL** enough to regenerate? Each initial corresponds to the standard English term already used in the literature for that determinant.

The separation between **V** and **A** is intentional. Perfusion and matrix deteriorate together in radiation injury, but they can dissociate: cicatricial lichen sclerosus may show a depleted matrix with relatively preserved perfusion, and advanced hypo-oestrogenism may reduce perfusion before architecture is altered.

Scoring and grades

The sum of the domains ranges from 0 to 10.

Table 2. Regenerative reserve grades.

Grade	Score	Label	Biological interpretation
R0	0–2	Preserved reserve	The tissue has full capacity to respond to a stimulus
R1	3–4	Reduced reserve	Response possible but attenuated; the terrain benefits from conditioning
R2	5–7	Compromised reserve	Response to a stimulus unlikely without prior conditioning
R3	8–10	Depleted reserve	The tissue does not regenerate on its own; a stimulus may cause harm

Mandatory override rule (ischaemic-fibrotic pattern). When V = 2 and A = 2 simultaneously, the terrain is classified as **R3** regardless of the total score. The rule exists because the combination of ischaemia and fibrosis is the setting in which an ablative stimulus is most likely to produce ulceration or necrosis rather than repair [20,21].

Modifiers

Modifiers do not change the score, but they are recorded because they change interpretation, risk and stratification in research.

- **x — iatrogenic exposure**, with type specified: xRT (pelvic radiotherapy or brachytherapy), xAI (aromatase inhibitor), xCT (gonadotoxic chemotherapy), xHSCT (haematopoietic stem cell transplantation), xSURG (prior vaginal surgery or mesh).
- **s — senescence and duration of deprivation:** age ≥ 65 years or more than 10 years since menopause without hormone therapy.
- **m — systemic metabolic-vascular load:** diabetes with HbA1c ≥ 8%, active smoking, vasculopathy, chronic immunosuppression.

Notation

The VITAL code records each domain, the sum, the grade and the modifiers:

VITAL [V·I·T·A·L] = sum → grade | modifiers

Example: a breast cancer survivor on an aromatase inhibitor, with pH 6.2, pallor and petechiae, loss of rugae and no active dermatosis is coded as **VITAL [1·0·2·1·2] = 6 → R2 | xAI**.

Domain scores are written as "V = 2" rather than "V2" to avoid confusion with the ESHRE/ESGE vaginal anomaly sub-classes V0–V4.

Dynamic reserve: ΔVITAL

Reserve is not a fixed trait. VITAL should be re-applied after each therapeutic phase. The difference between two assessments (**ΔVITAL**) measures the effect of terrain conditioning and defines the **regenerative window**: the point at which the tissue has sufficient reserve to receive a class T or S intervention. We propose as an operational target a reduction of at least 2 points or a shift to R1 or R0.

MECHANISTIC CLASSIFICATION OF INTERVENTIONS

Existing classifications group interventions by technology or product. VITAL regroups them by what each one demands of the tissue. Each class is named with a plain English verb describing what the intervention does to the terrain: it Conditions, Triggers, Signals or Replenishes (C–T–S–R).

Class S is deliberately separated from class R. Both are called "biologics" in practice, but PRP depends entirely on host cells to act, whereas a fat graft brings stromal cells and matrix with it. This distinction offers a hypothesis for why cicatricial tissue may respond to fat and not to platelets.

Table 3. Mechanistic classes according to host dependence.

Class	Principle	Examples	What it requires of the tissue
C — Condition	Conditions the terrain and raises reserve	Vaginal oestrogen, prasterone, ospemifene (where permitted); restoration of mucosal ecology; control of inflammation (topical corticosteroid in lichen sclerosus); dilators; pelvic floor physiotherapy; hyperbaric oxygen in radiation injury	Little; it acts precisely where reserve is low
T — Trigger	Produces a controlled injury or stimulus and depends on the tissue mounting a response	Fractional CO_2 and Er:YAG laser, radiofrequency, microneedling, photobiomodulation	Maximal: epithelial proliferation, angiogenesis, functional fibroblasts, orderly inflammation
S — Signal	Supplies signals but not effector cells	PRP and platelet derivatives, extracellular vesicles, conditioned media, polynucleotides	Intermediate: responsive cells and a vascular bed to distribute the signal
R — Replenish	Replenishes cells, matrix or vascularised tissue	Fat grafting, nanofat, stromal vascular fraction, cell therapies, flaps, scaffolds	Lower dependence on local cellularity; requires a minimally viable recipient bed for engraftment

6. The terrain–mechanism compatibility principle

The core of the proposal is a simple rule: **the lower the reserve, the less one should depend on the tissue and the more one should condition or replenish it.**

Table 4. Compatibility matrix (hypothesis to be tested). The matrix does not replace evidence maturity: a VITAL-"compatible" combination remains experimental if GRACE classifies it as such [10].

Grade	Class C	Class T	Class S	Class R
R0	Maintenance	Compatible, if indicated and within the evidence level	Compatible within research	Rarely needed
R1	First line; conditioning before or alongside the trigger	Conditional, after conditioning	Conditional, within research	For a specific structural defect
R2	Mandatory before any stimulus	Not recommended until ΔVITAL reaches R1	Research only	Consider if A ≥ 1
R3	Mandatory (including reperfusion therapies, where appropriate)	Contraindicated because of risk of injury	Response unlikely	First regenerative option, in a specialised centre and under protocol

Four clinical rules follow from the matrix:

1. **Grade before treating.** No class T, S or R intervention should be indicated without a recorded VITAL code.
2. **Condition before triggering.** In R1 and R2, phase C comes first, with reassessment at 8–12 weeks.
3. **Do not trigger a depleted terrain.** In R3, class T interventions are contraindicated.
4. **Replenish when the tissue cannot produce.** When A = 2, class R precedes class S.

RELATIONSHIP WITH VAGINA-R AND GRACE

The three tools answer different questions and are designed to be used together.

Table 5. Complementarity of the three classifications.

Tool	Central question	Unit classified	Main use
VAGINA-R	Which mechanism produces the symptom?	The patient's phenotype	Directing treatment to the dominant mechanism
GRACE	How solid is the evidence for this combination?	The compartment–phenotype–intervention triplet	Decision-making, trial registration and responsible communication
VITAL	Can the tissue respond now?	The tissue terrain and the intervention mechanism	Sequencing conditioning, triggering, signalling and replenishment; stratifying trials

There is apparent overlap between VITAL domains and VAGINA-R/GRACE phenotypes, for example in the hormonal and microbial components. The difference lies in function: in VAGINA-R, hypo-oestrogenism is a diagnostic target, the mechanism causing the symptom; in VITAL, it is a determinant of response, the condition limiting what the tissue can do. The same patient may have a dominant algesic phenotype in VAGINA-R and R2 reserve in VITAL. The first piece of information defines what to treat; the second defines in what order and with which type of mechanism.

In practice, a complete case record combines the three codes: phenotype (VAGINA-R / GRACE Axis P), terrain (VITAL), and intervention with its maturity level (GRACE).

ILLUSTRATIVE APPLICATIONS

The cases below are illustrative and do not represent real patients.

Case 1 — Natural GSM, salvageable terrain. A 56-year-old woman, four years postmenopausal, not on hormone therapy, with dryness and dyspareunia; pH 5.4, predominance of intermediate cells, mild pallor, reduced rugae, no dermatosis.

Code: **VITAL [1·0·1·1·1] = 4 → R1**.

Compatible management: phase C with vaginal oestrogen for 12 weeks, then reassessment; if the patient still wishes a class T intervention after partial response, consider it only under protocol, according to the GRACE level.

Case 2 — Breast cancer survivor on an aromatase inhibitor. A 49-year-old woman, pH 6.2, pale mucosa with petechiae, loss of rugae, no dermatosis.

Code: **VITAL [1·0·2·1·2] = 6 → R2 | xAI**.

Compatible management: non-hormonal phase C, or low-absorption local hormonal therapy subject to shared oncological decision; restoration of mucosal ecology; dilators and pelvic floor physiotherapy. Laser not recommended until ΔVITAL reaches R1. The LIGHT trial, conducted in exactly this population, found no benefit of laser over sham [5].

Case 3 — Sequelae of pelvic radiotherapy. A 52-year-old woman, five years after chemoradiation and brachytherapy for cervical cancer, with telangiectasia, contact bleeding, vaginal shortening and stenosis.

Code: **VITAL [2·0·2·2·1] = 7 → R3 (ischaemic-fibrotic override) | xRT, xCT**.

Compatible management: class T contraindicated; phase C with dilators and, when available and indicated, reperfusion therapy; class R (fat grafting) as the first regenerative option in a specialised centre. The use of lipoaspirate for radiation tissue damage has clinical precedent in plastic surgery [25].

Case 4 — Vulvar lichen sclerosus. A 61-year-old woman with biopsy-proven lichen sclerosus, active inflammation, partial fusion of the labia minora and clitoral burying.

Code in the active phase: **VITAL [1·2·1·2·0] = 6 → R2**.

Compatible management: phase C with topical corticosteroid until control (I falls to 1); then, if cicatricial sequelae persist with A = 2, consider class R under protocol. Class S in active disease is, according to the matrix, incompatible — consistent with the negative PRP trial [6] and with the favourable, still uncontrolled, signals of fat grafting for fibrosis in lichen sclerosus [8].

Table 6. Published studies read through VITAL.

Study	Population	Probable VITAL grade	Class	Result	VITAL reading
Li et al., 2021 [3]	Postmenopausal GSM	R1–R2, heterogeneous	T	Laser = sham at 12 months	Compatible with dilution of effect in a population mixed for reserve
Mension et al., 2023 (LIGHT) [5]	Breast cancer on aromatase inhibitors	R2 | xAI	T	Laser = sham	Compatible with terrain–mechanism mismatch
Quick et al., 2021 [26]	Gynecologic cancer survivors	R2–R3, heterogeneous	T	No difference on symptom scale; FSFI signal in a small sample	Inconclusive; V/A stratification not available
Ferreira et al., 2025 [11]	Breast cancer, Er:YAG, single arm	R1–R2	T	Responders younger and with higher VHI, non-significant	Direction consistent with hypothesis H1
Goldstein et al., 2019 [6]	Vulvar lichen sclerosus	R2 (I = 2 probable)	S	PRP = placebo	Compatible with a signal delivered to an inflamed terrain
Almadori et al., 2020 [8]	Fibrosis and scarring from lichen sclerosus	R2 (A = 2)	R	Improvement in symptoms and sexual function, no control group	Direction consistent with rule 4; requires a controlled trial

EXPLORATORY RE-READING OF THE LITERATURE

To test the internal coherence of the proposal, we approximately re-classified the populations of published studies based on their eligibility criteria and reported baseline characteristics. This is an interpretive exercise without individual patient data and is subject to hindsight bias; it does not constitute evidence in favour of VITAL.

The re-reading suggests that part of the heterogeneity attributed to device settings or products may reflect unmeasured heterogeneity of the terrain. It also exposes the risk of the proposal: any null result could be explained afterwards as a mismatch. For this reason, VITAL will only be of value if its predictions are specified before the data, as in the following section.

Testable hypotheses

- **H1 — Reserve × mechanism interaction.** In sham-controlled trials of class T interventions, the effect relative to sham will be greater in R0–R1 than in R2–R3 (significant interaction between VITAL grade and treatment arm).
- **H2 — Terrain conditioning.** Patients who achieve ΔVITAL ≥ 2 points after phase C will have a higher rate of clinically relevant response to a class T or S intervention than patients without conditioning.
- **H3 — Replenishment in a depleted matrix.** When A = 2, class R interventions will produce greater and more durable improvement in elasticity and calibre than class S interventions.
- **H4 — Safety.** The frequency of local adverse events after class T interventions will be higher in R3 than in R0–R2.

VALIDATION PROGRAMME

Phase 1 — Modified Delphi consensus. An international panel of gynecologists, urogynecologists, oncologists, radiation oncologists, vulvar dermatologists and methodologists, over at least two rounds, with $\geq$ 70% agreement required to retain each domain, criterion and cut-off point.

Phase 2 — Reliability. Independent assessment by two examiners blinded to each other, in a consecutive sample including all four grades; proposed targets of an intraclass correlation coefficient ≥ 0.75 for the total score and a weighted kappa ≥ 0.60 for each domain.

Phase 3 — Construct validity. Correlation of the VITAL score with independent measures of reserve: epithelial and lamina propria thickness by high-frequency ultrasound, microvascular and collagen density on biopsy, perfusion by Doppler and, in an exploratory sub-study, SASP markers in vaginal secretions [24].

Phase 4 — Predictive validity. (a) Secondary analysis, with individual patient data, of published sham-controlled trials, where baseline variables allow the domains to be reconstructed; (b) a prospective cohort with prior registration of hypotheses H1–H4 and stratification of randomisation by VITAL grade in trials of class T, S and C interventions. Because interaction tests require substantially larger samples than main-effect tests, a multicentre study or prospective meta-analysis is recommended.

Until Phases 1 and 2 are completed, VITAL should be used only as a research and reporting instrument.

DISCUSSION

The central contribution of VITAL is to make explicit an assumption that regenerative gynecology has left implicit: that the treated tissue is capable of responding. This assumption is reasonable in a 52-year-old woman in early menopause and doubtful in a cancer survivor under pharmacological oestrogen deprivation or in a patient after pelvic irradiation. Yet trials commonly pool these populations under the same diagnosis, and protocols commonly apply the same technology, with the same settings, to biologically opposite terrains.

The proposal has three practical implications. The first is sequential: the question is no longer “laser or PRP?” but “condition, trigger, signal or replenish?”. The second concerns safety: the ischaemic-fibrotic rule and the contraindication of triggering in R3 protect precisely the patients most vulnerable to injury from excessive stimulation. The third is methodological: stratification by VITAL grade allows future trials to distinguish absence of effect from a diluted effect.

VITAL also offers a different reading of the so-called sham gradient — the shrinkage of effect as the control becomes more rigorous — described in our umbrella review [10]. Part of this gradient is undoubtedly explained by placebo response, regression to the mean and measurement bias. VITAL adds a complementary and testable explanation: larger and more rigorous trials tend to include populations more heterogeneous in reserve, in which responders with preserved terrain are diluted by non-responders with compromised terrain.

It is important to state what VITAL does not do. It does not raise the evidence level of any intervention: a compatible combination remains experimental if GRACE classifies it as such. It does not authorise hormonal treatment in patients with an oncological contraindication; in such cases phase C should be non-hormonal or decided together with the oncology team. And it does not replace diagnosis: a patient with vestibular pain of neuromuscular origin does not benefit from a R0 terrain if the dominant problem is not tissue-related.

LIMITATIONS

VITAL was developed by a single author group without formal consensus. Cut-off points are provisional. Equal weighting of the five domains is a simplification: the V domain probably influences the response to class T interventions more than the L domain, and validation may lead to different weights. Some criteria depend on tests that are not universally available, such as CST determination and Doppler, which is why each domain has a minimum office-based version. The classification was designed for the vulvar and vaginal compartments; its extension to the endometrium and ovary, where the concept of reserve has different biological foundations, will require separate work. Finally, the literature re-reading is retrospective and approximate and cannot be used as evidence of validity.

CONCLUSION

VITAL proposes that, in regenerative gynecology, the tissue terrain be graded before the intervention is chosen, and that the intervention be chosen by what it demands of the tissue rather than by the technology it uses. Five domains (vascular perfusion, inflammatory activity, trophic-hormonal status, architecture of the matrix and lactobacillary ecology), four reserve grades and four mechanistic classes form a language that complements VAGINA-R and GRACE. The proposal generates falsifiable hypotheses and a validation programme; until that programme is completed, it should remain a research instrument.

DECLARATIONS

Author contributions. MAP: conceptualisation, coding rules and drafting. MAP and MHK: critical revision of the rules, checklist and manuscript. All authors approved the final version.

Conflicts of interest. None

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Ethics approval. Not applicable: conceptual proposal without collection of patient data. Clinical cases are fictitious.

Data availability. Not applicable.

Originality statement. VAGINA-R and GRACE are previous, not yet validated, proposals by the same authors. The VITAL mnemonic, its domains and the C–T–S–R intervention classes are original to this proposal; the "seed and soil" analogy is attributed to Paget [12].

Use of artificial intelligence. An AI-based writing assistant was used to support drafting and language editing. The authors verified all statements and references against the primary sources and accept full responsibility for the content.

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