Time is Part of the Phenotype

Understanding von Willebrand Disease as a dynamic hemostatic vulnerability across the human lifespan.

Based on the clinical framework by William Aird

The underlying genetic abnormality may persist, but the bleeding phenotype does not remain fixed.

The Traditional Lens

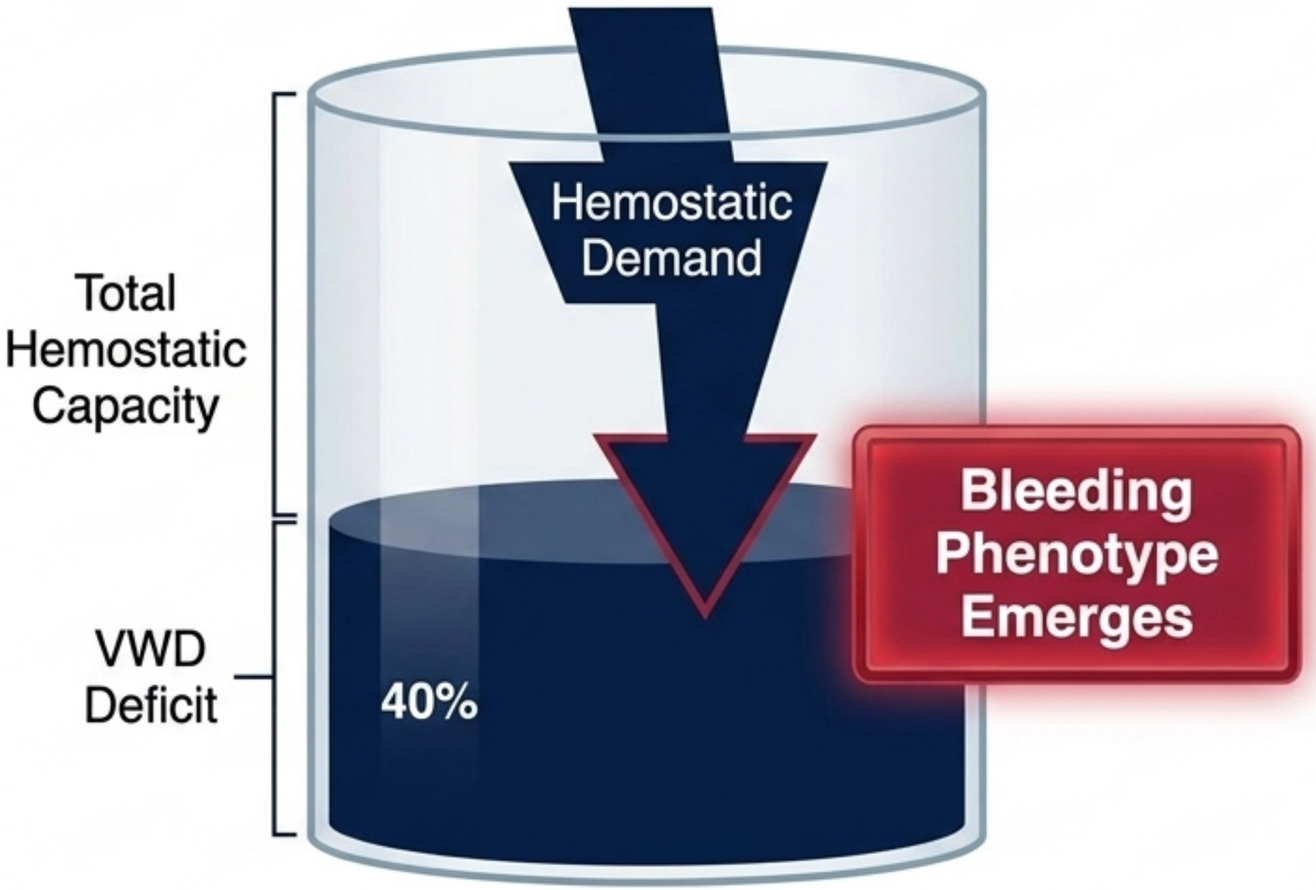
- Treats VWD as a lifelong, fixed symptom list.
- Relies on single laboratory values or isolated bleeding episodes to define the disease.
- Assumes a mild childhood guarantees lifelong mild disease.

The Lifespan Lens

- Treats VWD as a dynamic hemostatic vulnerability.
- Recognizes that disease visibility depends on hemostatic demand, physiologic state, and age.
- Understands that time modifies how the disease appears.

Bleeding emerges when demand eclipses a compromised hemostatic reserve.

Hemostatic Reserve Model



Core Concept

Hemostatic reserve is the capacity of the body's systems to maintain effective hemostasis when challenged.

The Clinical Shift

The central diagnostic question is no longer simply "Does this patient have VWD?" It must become:

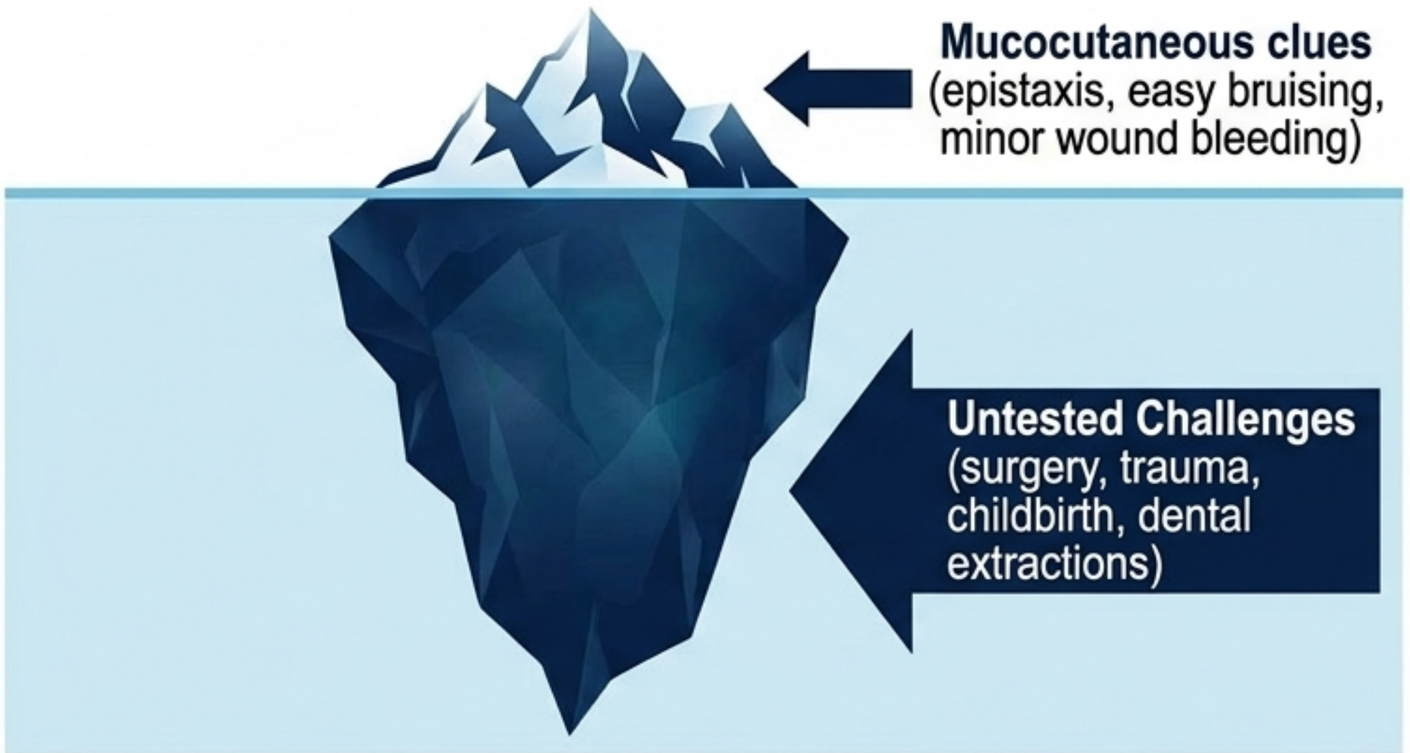
"What life stage is testing the patient's hemostatic reserve now?"

Three forces shape the clinical expression of VWD at every life stage

1	2	3
Biologic Modulation (Changes the measured hemostatic system)	**Exposure Risk** (Changes what the patient encounters)	**Interpretive Context** (Changes how bleeding is recognized)
• Includes: Age, ABO blood group, pregnancy, inflammation, hormonal state, and comorbid illness	• Includes: Tooth loss, menarche, dental extraction, surgery, childbirth, trauma, and anticoagulants	• Includes: What the patient considers normal, what clinicians ask, and whether meaningful prior hemostatic challenges have even occurred

Childhood history is often an emerging pattern, not a definitive test of reserve.

Childhood Exposure Iceberg



The Trap: A low bleeding score in a young child is less reassuring than in an adult. Why? The test may not yet have occurred.

The Reality: Children bruise and get nosebleeds regardless of bleeding disorders. But they lack exposure to major hemostatic challenges.

Bleeding Assessment Tools (BATs) can organize history, but they cannot create exposure where none has happened.

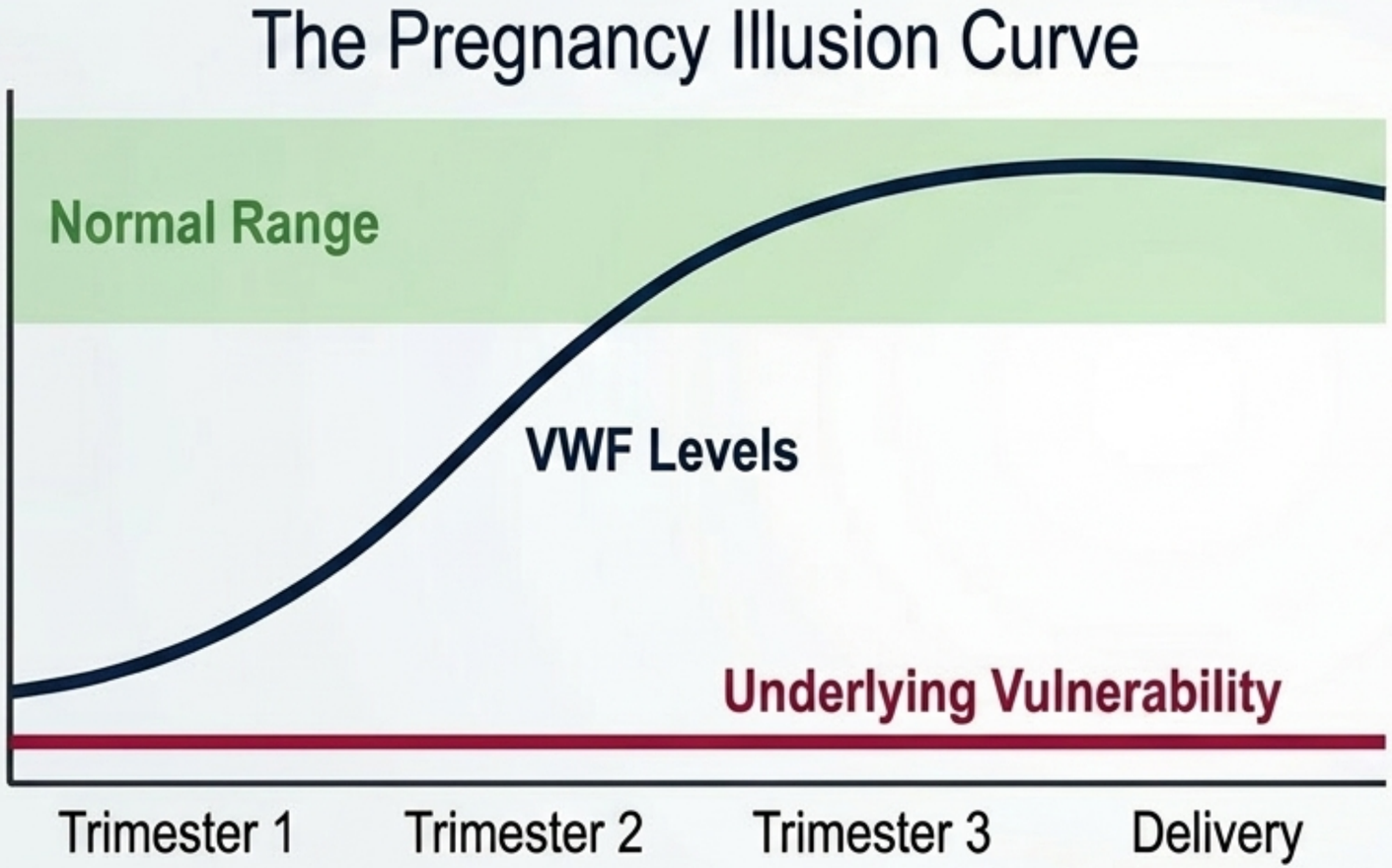
[Childhood] → Adolescence → Reproductive → Pregnancy → Aging

Menarche acts as the first repeated, physiologic, high-demand stress test.

1	2	3
The Hematologic Event	**Clinical Imperative**	**The Ferritin Rule**
• Heavy menstrual bleeding (HMB) should not be dismissed as “normal for her” or treated solely as a gynecologic symptom. In the right context, it is hematologic evidence of limited reserve.	• This challenge explains why VWD is diagnosed more often in females despite autosomal inheritance.	• A normal hemoglobin does not exclude clinically important menstrual blood loss. Ferritin matters in assessing chronic mucosal bleeding.

[Childhood] **[Adolescence]** Reproductive Pregnancy Aging

Pregnancy creates a temporary laboratory illusion, not a cure.

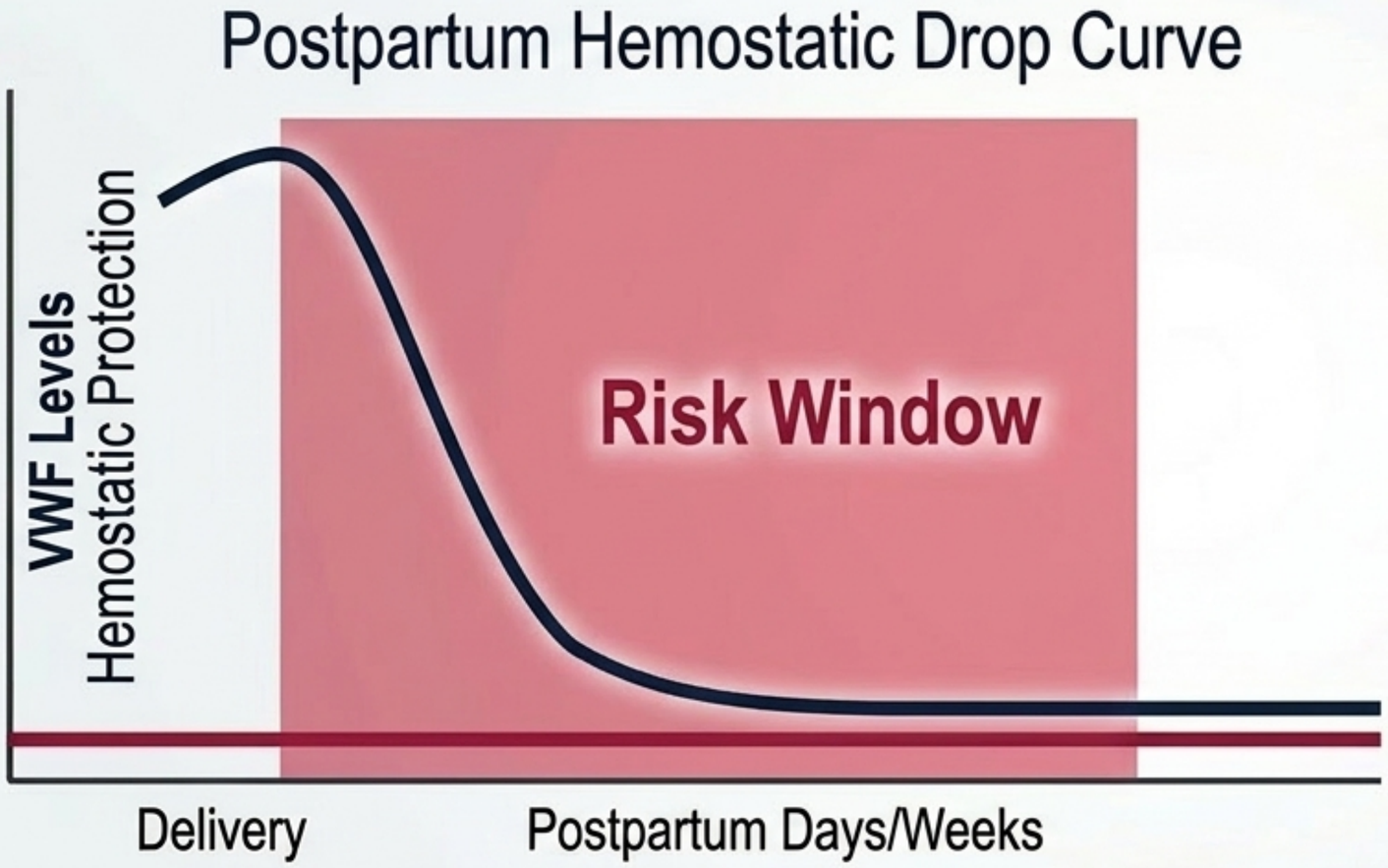


The Physiologic Rise: In many patients (especially Type 1 VWD), VWF and Factor VIII levels rise substantially, reaching reassuring ranges by the third trimester.

The Diagnostic Ambiguity: Testing performed for the first time during pregnancy obscures baseline VWF deficiency. The underlying susceptibility persists despite the improved laboratory environment.

[Childhood] Adolescence **[Reproductive & Pregnancy]** Aging

The postpartum period strips away the physiologic rise, revealing the baseline.

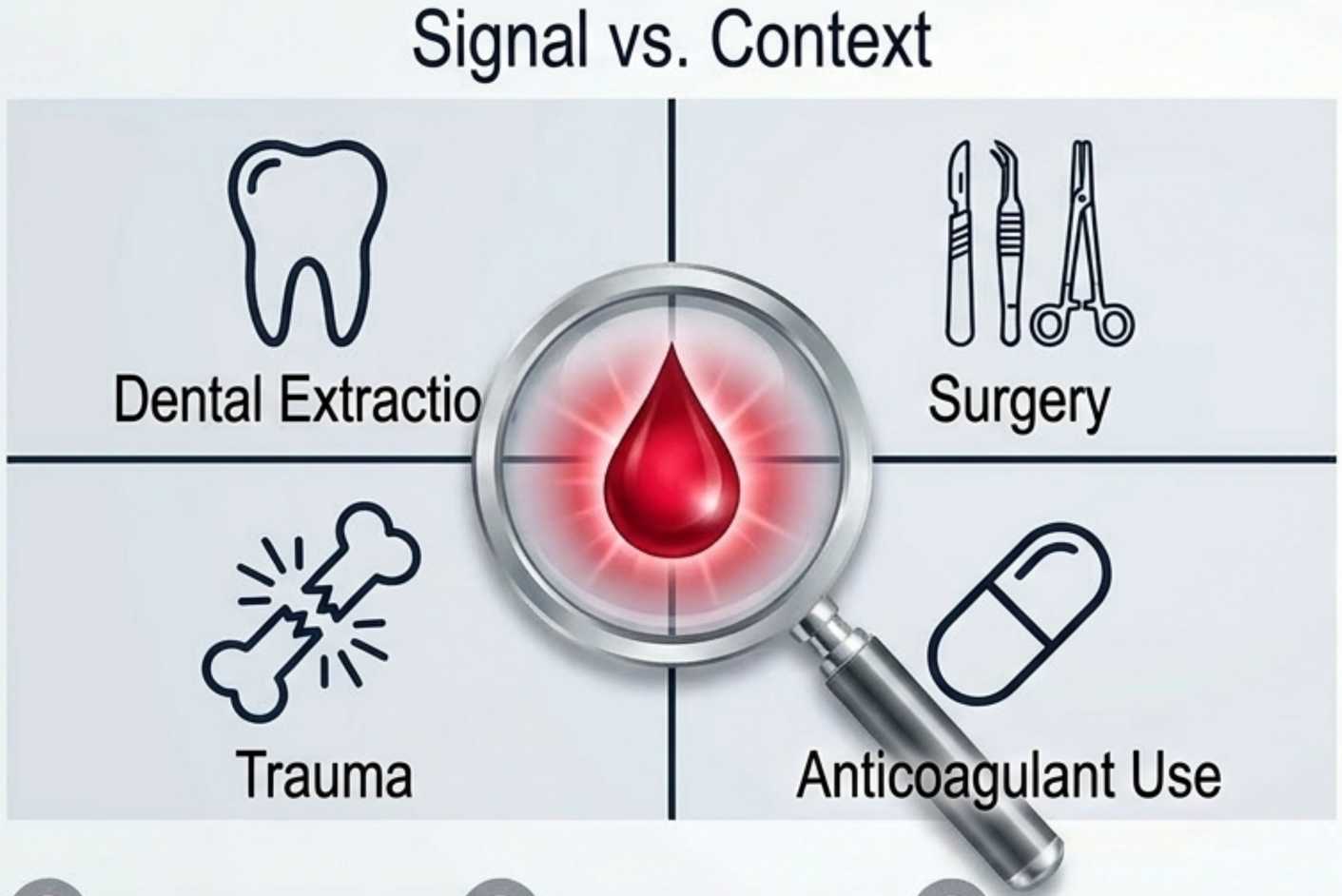


The Return to Vulnerability: After delivery, VWF and Factor VIII levels fall back toward baseline, removing the pregnancy-associated hemostatic protection.

Clinical Presentation: VWD may manifest as primary or secondary postpartum hemorrhage, prolonged lochia, or sudden iron deficiency.

The Lesson: Bleeding risk is not determined solely by genotype or a single antepartum lab value—it is shaped by timing.

In adulthood, VWD functions as a situational bleeding disorder.

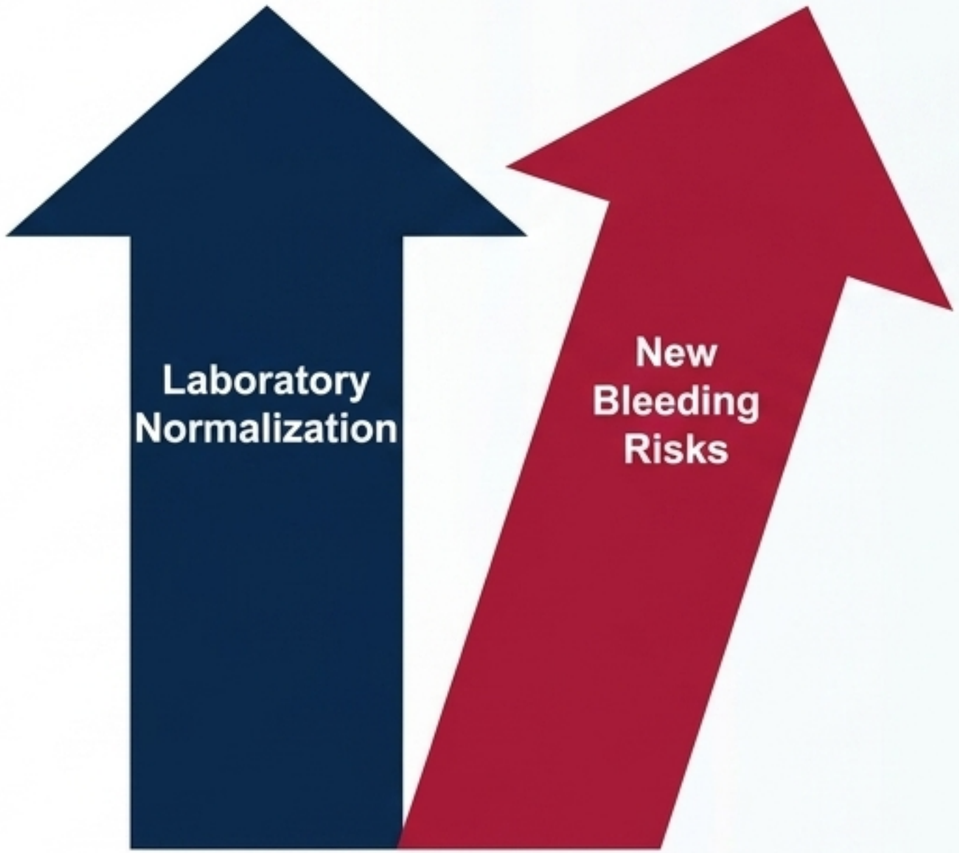


The Diagnostic Confusion: Many adults do not bleed spontaneously in daily life. A patient may claim “I do not really bleed,” yet report severe oozing after wisdom teeth removal or unexpected surgical complications.

Redefining the History: The adult bleeding history must be read as a history of exposures. The phenotype is not just what occurs spontaneously; it is what happens when the system is deliberately stressed.

[Childhood] Adolescence Reproductive & Pregnancy [Postpartum] **[Adulthood]** Aging

Aging forces clinicians to reconsider the diagnosis in two different directions.



VWF levels often rise with age. Prior Type 1 diagnoses may now show normal range levels.

Guideline note: Reconsider, but do not automatically erase prior diagnoses.

Aging introduces gastrointestinal angiodysplasia, severe aortic stenosis, LVAD support, or myeloproliferative neoplasms. These high-shear cardiovascular states and comorbidities can trigger Acquired von Willebrand Syndrome (AVWS).

[Childhood] — Adolescence — Reproductive & Pregnancy — [Postpartum] — **[Aging]**

Severe VWD maintains a higher baseline of visibility across all life stages.

	Type 1 / Low VWF (Situational Expression)	Type 3 / Severe (Spontaneous Visibility)
Baseline	VWF reduced.	VWF nearly absent; Factor VIII markedly reduced.
Phenotype	Highly dependent on situational triggers and biologic modifiers.	Visible from early life regardless of physiologic stress.
Bleeding Style	Primarily mucocutaneous and challenge-driven.	Mucocutaneous PLUS deep tissue, muscle hematomas, hemarthroses. Often requires long-term prophylaxis.

The Lifespan Diagnostic Matrix

Life Stage	Primary Challenge	Interpretive Trap	Clinical Imperative
Childhood	Untested reserve	Minimizing common bruises / False reassurance	Ask what has not happened yet.
Adolescence	Menarche	Dismissing heavy menses as strictly gynecologic	Treat heavy menses as a diagnostic hematologic event; check ferritin.
Pregnancy	Childbirth	Confusing physiologic rise with a cure	Anticipate the postpartum baseline drop.
Aging	Acquired comorbidities	Assuming normal labs erase past history	Evaluate for high-shear acquired VWS and vascular lesions.

Separating clinical signal from developmental and situational noise

The Clinical Signal (What presents)	The Confounding Noise (The limitation)	The Reality (Synthesis)
Pediatric BAT Scores Low score	**Pediatric BAT Scores** Lack of surgical/trauma exposure	**Pediatric BAT Scores** Scores underrepresent risk before meaningful challenges
Normal 3rd Trimester Labs VWF levels in normal range	**Normal 3rd Trimester Labs** Pregnancy artificially improves lab environment	**Normal 3rd Trimester Labs** Values obscure the true baseline vulnerability
Late-Life Normalization Rising VWF levels in seniors	**Late-Life Normalization** New high-shear cardiovascular lesions (LVAD, AS)	**Late-Life Normalization** Lab improvement does not necessarily equal bleeding improvement

Clinical Imperatives for the Dynamic Phenotype

DO:

- Read the adult bleeding history as an exposure history.
- Anticipate secondary postpartum hemorrhage even if antepartum labs are reassuring.
- Reconsider—rather than automatically erase—prior Type 1 diagnoses if levels normalize with age.

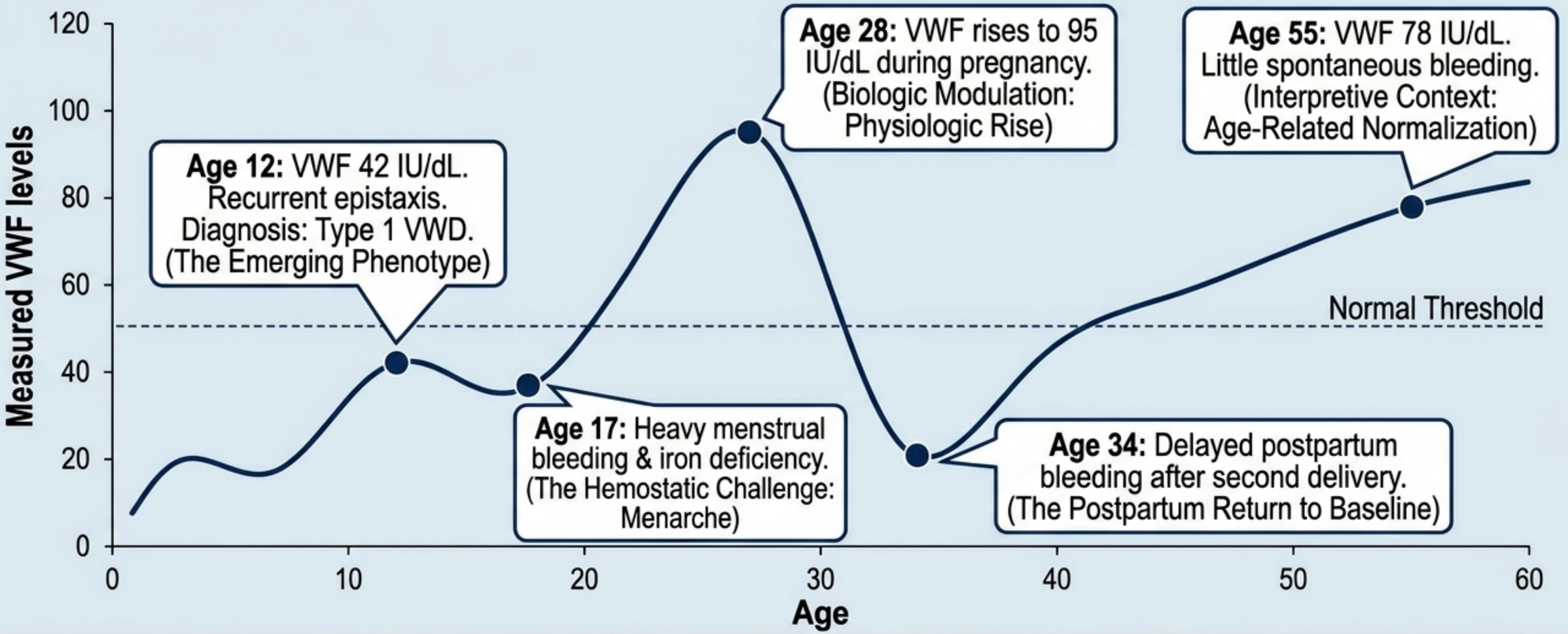
DON'T:

- Assume a mild childhood phenotype guarantees lifelong mild disease.
- Treat heavy menstrual bleeding solely as a gynecologic issue without checking ferritin and hemostatic context.
- Confuse the physiologic VWF rise during pregnancy with a cure.

ASK:

- In children: "What major hemostatic challenges have they NOT yet faced?"

A Lifetime in Focus: One Genetic Defect, Multiple Phenotypes



She does not have four different diseases.
She has a single hemostatic vulnerability shaped by time.