A Perfect Storm: Polycystic Ovary Syndrome Masking Underlying Type 1 Von Willebrand Disease

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Abstract

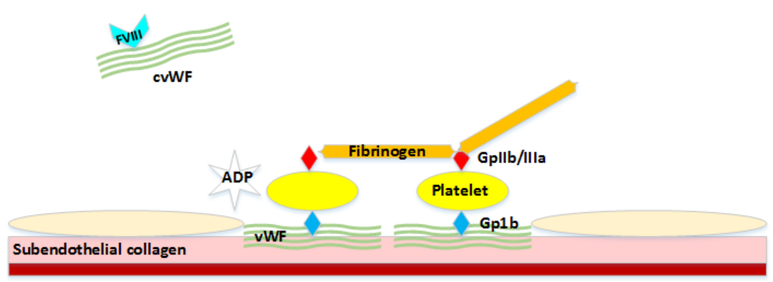
Von Willebrand Disease (vWD) is the most common inherited bleeding diathesis worldwide and results in defects in von Willebrand Factor (vWF), inducing a hypocoagulable state. Polycystic Ovary Syndrome (PCOS) is characterized by chronic inflammation and hyperestrogenism, both of which induce acute phase reactions and increase serum levels of vWF and Factor VIII, yielding a prothrombotic state. These laboratory elevations may obscure the diagnosis of underlying vWD in patients with both conditions.

We report a case of a 23 year-old female with PCOS and menorrhagia who presented prior to a surgical procedure for evaluation of bleeding risk. Evaluation for vWD was within normal limits. However, Factor IX assay was significantly elevated at 218% (60-150%), and thromboelastography (TEG) showed elevated MA and G, consistent with platelet hypercoagulability and increased clot strength. Subsequent review of remote external records determined that the patient had a previous evaluation for a bleeding disorder at age three and was diagnosed with type I vWD at that time. To the best of our knowledge, this is the first reported case of coexisting PCOS and vWD resulting in a false negative workup for underlying vWD. Management of such patients with superimposed hypercoagulable and hypocoagulable states, particularly perioperatively, may be complex.

Pathogenesis of vWD and PCOS

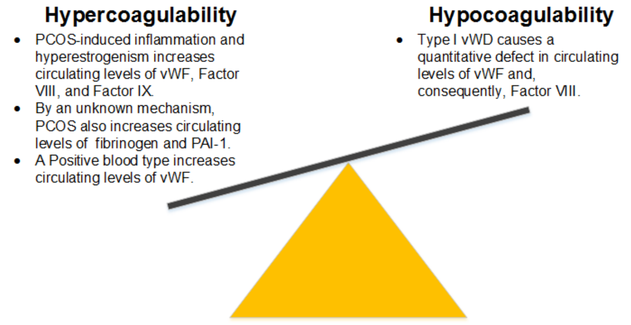
vWF normally serves to facilitate coagulation and to protect Factor VIII from peripheral degradation. vWD decreases vWF levels, causing a hypocoagulable state. However, levels of vWF and Factor VIII are susceptible to fluctuations. vWF and Factor VIII are acute phase reactants, and even mild stimulation of the acute-phase response can yield a falsely normal vWD workup.[1] Estrogen also increases levels of vWF, Factor VIII, and Factor IX. In PCOS, vWF and Factor VIII levels are increased due to inflammation and hyperestrogenism. PCOS also increases circulating levels of fibrinogen and PAI-1, yielding a prothrombotic state.

Figure 1. Normal physiology of primary hemostasis.



Adapted from *Robbins and Cotran Pathologic Basis of Disease, 9th edition.*

Figure 2. Schematic of patient's coagulation state.



Clinical History

A 23 year-old female with a BMI of 41 presented with a chief complaint of menorrhagia. She has 1-2 menstrual cycles per year, lasting 30-90 days each, during which she experiences heavy bleeding. Her medical history is significant for easy bruising, prolonged bleeding after surgical procedures, and PCOS. Her family history is significant for an unknown bleeding diathesis in her maternal grandmother. The patient was diagnosed with type I vWD at age three, following prolonged bleeding after tonsillectomy. However, multiple subsequent laboratory evaluations for vWD performed by different clinicians were within normal limits (WNL).

Laboratory Values

Age 3
Prolonged bleeding after tonsillectomy

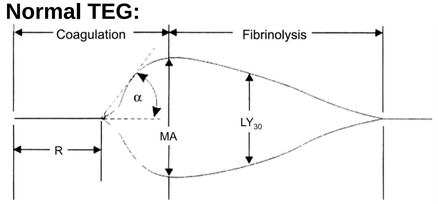
- **PTT 36.1 (21.0-31.0)**
- **Repeat PTT 35.2, corrected after mixing study (29.9)**
- **Factor VIII, IX, XI, and XII WNL**
- **Diagnosed with type I vWD**

Age 23
Self-referred to UMH

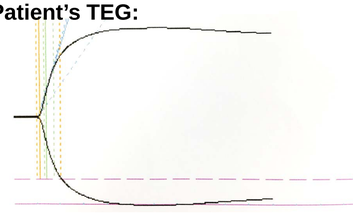
- **PT, PTT, vWF multimers WNL**
- **Factor IX 218% (60-150)**
- **vWF antigen 84% (55-200)**
- **vWF activity 68% (55-200)**
- **Factor VIII 75% (55-200)**
- **Blood type A Positive**

Thromboelastography

Normal TEG:



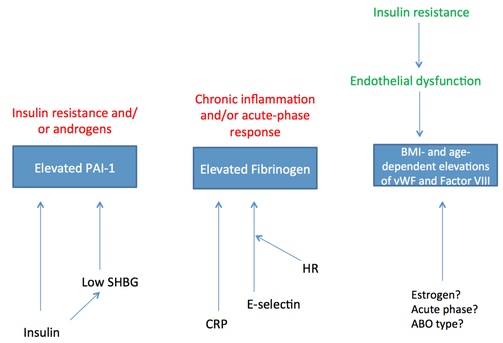
Patient's TEG:



Elevated MA indicates platelet hypercoagulability. Elevated G indicates increased clot strength. 38.8% inhibition with ADP (normal <20%).

DISCUSSION

PCOS induces a hypercoagulable state associated with hyperestrogenism and elevated vWF levels, which can result in a false negative workup for underlying vWD. We have proposed a model for PCOS-induced hypercoagulability, as follows:



Adapted from Manners-Holm[2] and Koiou[3].

CONCLUSIONS

In this case report, a patient with PCOS and a remote diagnosis of type I vWD had elevation of vWF levels into the normal range, and current laboratory workup did not reflect the underlying bleeding diathesis but rather was consistent with a hypercoagulable state.

Despite the high prevalence of vWD and the characteristic clinical picture, laboratory confirmation of vWD can be challenging, as both vWF and Factor VIII are elevated by inflammatory acute-phase reactions and hyperestrogenism.

References

[1]Laposata, M. *Coagulation Disorders.* Quality in Laboratory Diagnosis. 2011.

[2]Manners-Holm, et al. "Coagulation and fibrinolytic disturbances in women with polycystic ovary syndrome." J Clin Endocrinol Metab, April 2011, 96(4): 1068-1076.

[3]Koiou, et al. "Plasma von willebrand factor antigen levels are elevated in classic phenotypes of polycystic ovary syndrome." *Hormones*, 2012, 11(1): 77-85.