

Variations of Factor XII Level During Pregnancy in a Woman with Hageman Factor Deficiency

Dear Sir,

The plasma level of Hageman factor (factor XII) varies under the influence of different hormones. This variation, demonstrated in animals (1), has been found in woman taking oral progestins besides any initial factor XII deficiency (2, 3, 4). We noted the persistence of identical modifications in a woman with homozygous factor XII deficiency.

Here we report the case of a 24-year old patient. The diagnosis of factor XII deficiency was established when she was 22, during a family investigation following the discovery of a homozygous deficiency in her sister during a preoperative evaluation. Our patient did not present any thrombotic or hemorrhagic clinical features. Her APTT was 43" (control: 30"), PT 13" (control: 12"8), fibrinogen 2.5 g/l, factor XII:C 0.08 I.U./ml (plasma depleted of factor XII OSDG 12/13 from Behring) and factor XII:Ag 0.08 I.U./ml (antiserum anti factor XII from Nordica Immunological Laboratories). A new evaluation was performed at the 20th week of her first pregnancy (Fig. 1), at 30 weeks, 35 weeks, 40 weeks (just before delivery), and 1 week after delivery when the patient began to breast-feed her baby. The levels remained unchanged during the 3 months of breast-feeding. Oral contraception with progestogen-estrogen combination was then undertaken: norethisterone acetate 1 mg + ethinyl estradiol 0.03 mg from D 1 to D 11, norethisterone 2 mg + ethinyl estradiol 0.04 mg from D 12 to D 21. The factor XII levels remained high and constant; the oral contraception was stopped 6 months later: the control performed 2 months after the end of oral progestogen-estrogen combination indicated the basic levels (factor XII:C 0.08 I.U./ml).

In this patient with a homozygous factor XII deficiency, we note a marked increase of factor XII during pregnancy, breast-feeding and oral progestogen-estrogen intake (Fig. 1). These data allow us to evoke a regulation of factor XII synthesis subject to natural or synthesized progestogen-estrogen combinations in patients with such a deficiency.

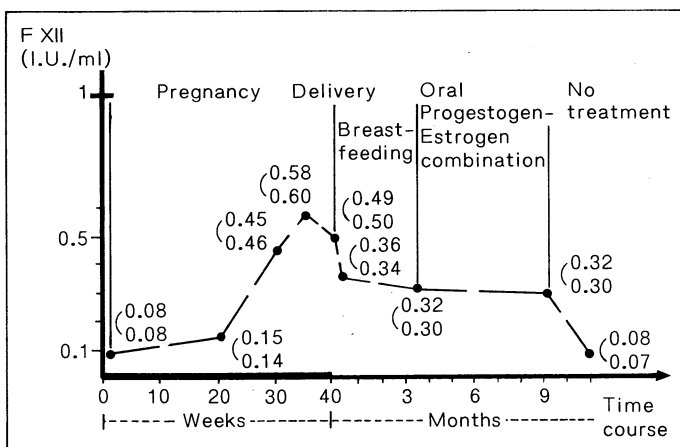


Fig. 1 Variation of factor XII plasma levels according to the patient's clinical history.

for each bracket: F XII:C value
F XII:Ag value

These observations can be compared to experimental data established in animals: increase in factor XII induced by estrogens and prolactin in ovariectomized and hypophysectomized female rats (1). Increases in factor XII have also been noted in woman without deficiency but given oral progestogen-estrogen combinations: Jespersen and Klufft (4) found a mean increase of 30% in factor XII:C during the intake of a combination of ethinyl estradiol 30 µg, levonorgestrel 150 µg. Gordon et al. (3) note a factor XII:C level of 0.92 ± 0.31 I.U./ml in a normal population and 2.09 ± 0.68 I.U./ml in patients taking diverse types of progestogen-estrogen combinations: 0.5 to 1 mg progestonic compounds (norethindrone, ethynodiol acetate, or norgestrel) and 0.035 to 0.08 mg estrogenic compounds (ethinyl estradiol or mestranol); there has not been found to be any correlation between the respective levels of estrogens and progestogens and the increase in factor XII. This finding is consistent with Gevers Leuven's work (2), which compares two low dose progestogen-estrogen combinations: 750 µg lynestrenol + 37.5 µg ethinyl estradiol on the one hand, and 150 µg levonorgestrel + 30 µg ethinyl estradiol on the other. After a 3-month treatment, factor XII:C increases in both treated groups as compared to a control: 47% in the first group, 34% in the second. The authors conclude to a dose-dependent effect of estrogens on factor XII plasma concentration. The problem of pregnancy is more complicated as the hormonal influences are multiple. Gore et al. (5) find an increase in factor XII in the normal woman's follow-up during pregnancy.

In our patient the proportional increase in factor XII during pregnancy is greater than in normal persons. The basic level of factor XII:C = 0.75 I.U./ml; and the data found in the family (both parents: factor XII:C = 0.75 I.U./ml; known consanguinity; one sister with XII:C = 0.02 I.U./ml and another with XII:C = 0.75 I.U./ml; one brother, with normal factor XII:C = 1 I.U./ml) confirm the homozygous deficiency. However, the patient preserves a residual factor XII:C activity. In such a case, a modulation of factor XII genomic transcription, namely its regulation by female sexual steroid hormones, could be persistent and inducible by high hormonal levels. This might be impossible in patients with no factor XII residual activity: as previously described for C1 esterase inhibitor deficiency, may be not all Hageman trait patients respond similarly to hormonal stimulation.

If abnormal manifestations were definitively correlated to the factor XII deficiency (6), it would be worth while to consider the progestogen-estrogen combinations as preventive treatment in women.

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References

- 1 Gordon E, Douglas J G, Ratnoff O D, Arafah B U M. The influence of estrogen and prolactin on Hageman factor (factor XII) titer in ovariectomized and hypophysectomized rats. *Blood* 1985; 66: 602-5.
- 2 Gevers Leuven J A, Kluff C, Bertina R M, Wessel L W. Effects of two low-dose oral contraceptives on circulating components of the coagulation and fibrinolytic systems. *J Lab Clin Med* 1987; 109: 631-6.
- 3 Gordon E, Ratnoff O D, Saito H, Donalson V H, Pensky J, Jones P K. Rapid fibrinolysis, augmented Hageman factor (factor XII) titers, and decreased C1 esterase inhibitor titers in woman taking oral contraceptives. *J Lab Clin Med* 1980; 96: 762-9.
- 4 Jespersen J, Kluff G. Increased euglobulin fibrinolytic potential in woman on oral contraceptives low in estrogen - levels of extrinsic and intrinsic plasminogen activators, prekallikrein, factor XII, and C1-inactivator. *Thromb Haemostas* 1985; 54: 454-9.
- 5 Gore M, Eldon S, Trofatter K F, Soong S J, Pizzo S V. Pregnancy induced changes in the fibrinolytic balance: evidence for defective release of tissue plasminogen activator and increased levels of the fast-acting tissue plasminogen activator inhibitor. *Am J Obstet Gynecol* 1987; 156: 674-80.
- 6 Mannhalter C, Fisscher M, Hopmeier P, Deutsche E. Factor XII activity and antigen concentrations in patients suffering from recurrent thrombosis. *Fibrinolysis* 1987; 1: 259-63.

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