

Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema

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Background: Two genetic forms of hereditary angioedema (HAE) are currently recognized. Both are transmitted in an autosomal dominant manner and are characterized by recurrent episodes of localized angioedema. Involvement of the gut leads to episodes of severe abdominal pain, and laryngeal involvement can lead to airway obstruction and even death. One type results from heterozygosity for a nonexpressed C1 inhibitor allele, and the other results from heterozygosity for a nonfunctional C1 inhibitor allele.

Objective: This report identifies a third type of HAE, with a unique estrogen-dependent phenotype.

Methods: Detailed medical histories were obtained from family members, and a pedigree was constructed to ascertain the mode of inheritance. Determination of serum complement factors, C1 inhibitor protein, C1 inhibitor function, coagulation factor XII, plasma prekallikrein, high molecular weight kininogen, and selected DNA sequences were performed in affected members by using standard assays.

Results: Episodes of angioedema were clinically indistinguishable from those associated with previously described forms of HAE; however, these occurred only during pregnancy or the use of exogenous estrogens. Patients were otherwise asymptomatic, except for one patient who had acetyl salicylic acid/non-steroidal anti-inflammatory drug-related angioedema later in life. History was available for members spanning 4 generations, and affected individuals were identified in 3 generations. Of 46 family members, phenotype could be determined in 13 members. Seven were affected, and 6 were not. One male of undetermined phenotype was an obligate carrier. The unique estrogen-dependent nature of the phenotype means that the status of several members in the third and fourth generation remains unknown. The disorder appears to be transmitted in an autosomal dominant fashion, although other modes of inheritance cannot be excluded entirely. C1 inhibitor protein,

C1 inhibitor function, C2, C4, C1q, coagulation factor XII, prekallikrein, and high molecular kininogen were normal in 3 affected family members during asymptomatic periods. DNA sequencing revealed no abnormality in 3 patients in the coding region of the gene encoding C1 inhibitor or in the 5' flanking regions of the genes encoding C1 inhibitor and factor XII.

Conclusions: This family appears to have a novel form of inherited angioedema that does not result from C1 inhibitor deficiency or dysfunction. The phenotype is uniquely estrogen dependent. Implications for diagnosis and treatment are discussed. Further studies are required to define the exact nature of the genetic abnormality involved. (*J Allergy Clin Immunol* 2000;106:546-50.)

Key words: Hereditary angioedema, estrogen, C1 inhibitor

Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by recurrent episodes of gross localized angioedema that may involve the larynx and lead to upper airway obstruction.^{1,2} Involvement of the gut leads to recurrent episodes of severe abdominal pain.¹⁻³ Two genetic forms are recognized. In the usual form (type I) there is reduced production of C1 inhibitor. In the variant form (type II) measured levels of the inhibitor are normal, but it is functionally inactive.⁴ In both forms of the disease, absence of C1 inhibitor function leads to continuous unopposed activation of both C1 (with subsequent activation and consumption of early complement components) and kallikrein (with consequent bradykinin generation), leading to angioedema.⁵ Affected individuals are heterozygous, with one normal and one abnormal copy of the gene encoding the C1 inhibitor. The amount of functional protein produced by the one normal gene is insufficient for appropriate homeostasis. Treatment with danazol or other attenuated androgens increases the level of functional inhibitor.⁶ It has been assumed that the androgen mechanism of action is through enhanced C1 inhibitor transcription, but this remains unproven.⁷⁻⁹

In this report a unique estrogen-dependent variant of inherited angioedema with normal C1 inhibitor level and function is described. Clinical manifestations are identical to the two previously recognized forms of HAE, except that in this pedigree symptoms are dependent on relatively high estrogen levels, whether endogenous (pregnancy) or exogenous (oral contraceptives, hormone replacement therapy, or both) in origin. This unique feature has important clinical implications for diagnosis and management.

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Abbreviation used

HAE: Hereditary angioedema

METHODS

Case histories of affected individuals

The family originated from Southern Italy (Calabria). There was no known consanguinity. Several family members and their descendants now reside in Canada, and part of the family has remained in Italy. In all affected patients descriptions of nonerythematous, nonpruritic, nontender swelling were consistent with angioedema. No afflicted individual reported urticarial symptoms. Episodes of angioedema typically involved the face or extremities, but possible laryngeal edema with airway compromise (throat swelling with difficulty talking, swallowing, and breathing) and episodes of severe abdominal pain with vomiting were also reported in several individuals. In affected individuals symptoms would typically begin 14 to 21 days after conception and continue regularly throughout the pregnancy. An episode of angioedema was considered by family members to be diagnostic and was often the first sign of pregnancy. One patient stated, "My period was just a day or two late, but the one side of my face swelled up and I knew I must be pregnant, because it was just like what happened to my mother and sisters when they were pregnant." No episodes occurred in the immediate postpartum period. With hormone replacement therapy given for menopausal symptoms, angioedema would most commonly occur after 12 to 14 days but did occur as early as 5 days after initiation of therapy. Symptoms of angioedema typically occurred 1 to 2 weeks after initiation of oral contraceptives. Episodes of swelling would persist for 48 to 72 hours and occasionally longer. There have been no reported fatalities to date.

Patient I-1. This patient was deceased when her daughters presented to the investigator. The daughters relate that their mother was gravida 12, para 8, aborta 4. Episodes of painless, nonerythematous, nonpruritic swelling occurred throughout all 12 of her pregnancies. Various parts of the body, including the face, hands, and feet were affected. It is unclear whether there were episodes of abdominal pain or vomiting during the pregnancies. The patient's eldest daughter (patient II-2) recalled that her mother had repeated episodes of swelling of her throat, with trouble swallowing and breathing during several pregnancies. She received treatment with adrenalin at these times. Patient I-1 never took birth control pills or received hormone replacement therapy. Episodes of swelling occurred at no other time during her life.

Patient II-2. This patient presented with episodes of painless, nonpruritic, nonerythematous swelling after being started on estrogen replacement for menopausal symptoms. On two separate occasions, she had severe abdominal pain and vomiting while receiving estrogen replacement, and at no time was the patient able to tolerate estrogen therapy without symptoms. These symptoms began approximately 7 to 10 days after initiation of therapy.

The patient was gravida 4, para 4. Each pregnancy was associated with episodes of swelling, starting 14 to 21 days after conception. Various areas of the body, including the hands, face, and feet were involved; several involved the oropharynx and were accompanied by difficulty swallowing. The patient did not recall any episodes of abdominal pain or vomiting during the pregnancies. She has never taken oral contraceptives. The swelling has occurred at no other time in her life.

Patient II-4. This patient was gravida 2, para 2. Characteristic angioedema occurred during both pregnancies, typically starting 14 to 21 days after conception. The patient did not recall episodes of throat swelling, abdominal pain, or severe vomiting associated with these pregnancies. She has never taken oral contraceptives or received hormone replacement therapy.

Patient II-7. This patient was gravida 4, para 4. She had episodes of typical swelling involving her face, hands, and feet during each of her 4 pregnancies. Again, the first episode would usually occur approximately 2 weeks after conception. No episodes ever occurred postpartum.

The patient received hormone replacement therapy on 2 occasions. In 1988, she was started on a combination of Premarin and Provera. After 13 days of therapy, she had an episode of characteristic swelling and stopped the medication. Premarin and Provera were reintroduced in 1995. An episode of facial swelling occurred after 12 days, and the medication was stopped.

The patient received an Estraderm 50 patch in 1993. She used this for 1 week without difficulty before discontinuing the patch for other reasons. She had received short courses of Provera numerous times, which she took during dysfunctional uterine bleeding; unfortunately, specifics about the duration of therapy are not available. No difficulties were encountered with this preparation.

The patient has never taken oral contraceptives. Episodes of swelling have occurred at no other time in her life.

Patient II-8. This patient was gravida 6, para 4, aborta 2. Typical episodes of swelling occurred during all 6 pregnancies within 2 and 2½ weeks of conception and were particularly severe. Involvement of the feet was so marked as to completely prevent walking, and the patient frequently had to be carried to antenatal visits by her husband. There were several episodes of throat swelling, with difficulty swallowing. The patient did not recall whether she had episodes of abdominal pain, vomiting during pregnancy, or both.

This patient has never used oral contraceptives. On a single occasion, she was given estrogen skin patches for menopausal symptoms and had typical swelling after several weeks. She is unique in that she is the only family member to experience episodes of swelling unrelated to high-estrogen states. She presented at 43 years of age when episodes of swelling began after a hysterectomy (but not oophorectomy). These incidents related to ingestion of acetyl salicylic acid/nonsteroidal anti-inflammatory drugs and have not recurred since acetyl salicylic acid and nonsteroidal anti-inflammatory drugs have been avoided. There was no evidence of nasal polyposis or asthma.

Patient III-4. This affected patient is a nonidentical twin of unaffected patient III-3. On one occasion, this patient had angioedema while taking oral contraceptives. There was no laryngeal or abdominal involvement.

Patient III-9. This 21-year-old gravida 0, para 0 patient was given a 28-day course of oral contraceptives to "regulate her menstrual periods." She had severe episodes of swelling, requiring hospitalization after 20 days. There was severe nausea but no abdominal pain. Swelling has not occurred at any other time in her life.

Case reports of unaffected individuals

Patient III-1. This patient is gravida 2, para 2. She did not experience episodes of swelling in either pregnancy.

Patient III-3. This patient is the nonidentical twin of affected patient III-4. She has tolerated oral contraceptives without difficulty.

Patient III-7. This patient has tolerated oral contraceptives without difficulty.

Patient III-10. This patient has had one normal pregnancy without episodes of swelling.

Patient III-12. This patient has had one normal pregnancy without episodes of swelling.

Patient III-23. This patient has had two normal pregnancies without episodes of swelling.

Other individuals

At present, the status of individuals in this pedigree who have never been pregnant or taken estrogen cannot be determined. None of these individuals has ever had angioedema. This includes all

male members of the family, except for patient II-1 who, by virtue of his daughter's (III-4) phenotype, is an obligate carrier.

Study design

C2 and C1 inhibitor antigen levels were determined by using radial immunodiffusion, and C4 antigen levels were determined by using automated immunonephelometry (Beckman). Functional C1 inhibitor assays were performed by using the ImmunoChrom C1-INH kit (ImmunoAG). This assay measures the ability of C1 inhibitor to inhibit the esterolytic activity of activated C1s. Coagulation factor XII, plasma prekallikrein, and high molecular weight kininogen activities were determined by the ability to restore kaolin-induced coagulation to the respective deficient plasmas (obtained from George Krug Bio Medical, Inc).^{10,11}

DNA was isolated from peripheral blood leukocytes, as previously described.¹² Southern blots were performed after digestion of genomic DNA with *Bcl*II and were probed with a phosphorous 32-labeled 1227-bp C1 inhibitor complementary DNA probe.¹³ The DNA sequence of each exon of the gene encoding C1 inhibitor and the 5' flanking region was determined, as described previously.¹³

RESULTS

A summary of the clinical presentation of female patients with known status are presented in Table I.

The family's pedigree is shown in Fig 1. It includes 4 generations, with known affected members in 3 generations. In generation II the phenotype of 4 of 8 of the individuals can be directly determined. All 4 of these female patients (patients II-2, II-4, II-7, and II-8) are affected. The status of one of the male patients can be inferred (II-1 is an obligate carrier); it is not possible to determine the status of the other 3 male patients (II-3, II-5, and II-6). Thus 5 of 8 represents the minimum number of individuals in generation II carrying the trait.

The observed pattern of inheritance is most consistent with an autosomal dominant modes of inheritance, the same pattern associated with both usual and variant forms of HAE previously described. However, autosomal recessive and X-linked inheritance cannot be completely excluded. Patient I-1, her spouse, and the spouses of all the members of generation II (except the spouses of II-6 and II-8) come from the same small area of Italy. It remains possible, although unlikely, that the spouses all carried one copy of an abnormal autosomal recessive mutation enriched in this population, even without known consanguinity (*founder effect*).

Male patients and many members of generations III and IV have not had the opportunity to declare clinical manifestations, and their status remains, as yet, undetermined. Results of determinations of levels of complement and C1 inhibitor antigenic and functional assays obtained at baseline (ie, not during pregnancy or exogenous estrogen therapy) are shown in Table II. In all cases the patients were asymptomatic at the time of these determinations. C4 levels were all normal, as were other complement determinations. C1 inhibitor protein levels and C1 inhibitor function were also normal. Similarly, coagulation assays for factor XII, prekallikrein, and high molecular weight kininogen in each of the 3 tested individuals (patients II-2, II-7, and II-8) revealed normal clotting times. A single set of determi-

nations performed at another laboratory of a single sample obtained from patient II-2 (data not illustrated) during exogenous estrogen therapy of approximately 6 days' duration that resulted in an episode of angioedema were as follows: C4, 0.31 (0.13-0.52) g/L; C3, 1.03 (0.73-1.73) g/L; and C1 inhibitor, 0.24 (0.12-0.45) g/L. A quantitative functional C1 inhibitor assay was not available.

DNA sequence analysis confirmed that the C1 inhibitor coding sequences and the 5' flanking region (375 bp) were normal in patients II-2, II-7, and II-8 (data not shown). This was expected on the basis of their C1 inhibitor functional levels during asymptomatic periods and normal C1 inhibitor and C4 antigenic levels during one episode of angioedema (patient II-2). In addition, the 5' flanking region of the gene encoding factor XII, which contains an estrogen response element,¹⁴ was also normal.

DISCUSSION

Affected members of this kindred experience symptoms, including angioedema of the face and extremities, airway compromise, and episodes of abdominal pain and vomiting (presumably caused by angioedema of the gut), that are identical in every way to those found in currently recognized forms of HAE, except for their dependence on high estrogen levels. This condition is clearly distinct from a previously reported familial urticaria and angioedema seen in late pregnancy¹⁵ because our patients never experienced urticaria (only angioedema, as with classic HAE). In addition, our patients have symptoms throughout pregnancy, as well as early during therapy with exogenous estrogens. The unique estrogen-dependent nature of the phenotype has considerable implications for diagnosis and treatment.

Affected individuals appear entirely normal both clinically and biochemically when asymptomatic, so that, at present, an individual's phenotypic status can be determined only by inducing states of relatively higher than normal circulating estrogen levels, either through pregnancy or administration of exogenous estrogen. In addition to obvious discomfort, such an approach would put the individual in question at risk for episodes of laryngeal edema. Although there have been no reported fatalities in this kindred, the striking similarity to previously recognized forms of angioedema indicates that this risk must be considered. Avoidance of exogenous estrogen sources by substituting alternative methods of birth control for oral contraceptives and other pharmacologic and nonpharmacologic methods for hormone replacement therapy is theoretically possible, but female patients of undetermined status would also have to avoid pregnancy completely.

Treatment of these patients is also problematic. Traditional forms of HAE are treated with attenuated androgens to prevent attacks. For the women reported here, angioedema occurs only during pregnancy, when androgen therapy is contraindicated.

Recently, C1 inhibitor concentrate for the treatment of acute angioedema has been developed¹⁶ and is available in Canada on a compassionate release basis. Despite the striking clinical similarity to known forms of HAE, there

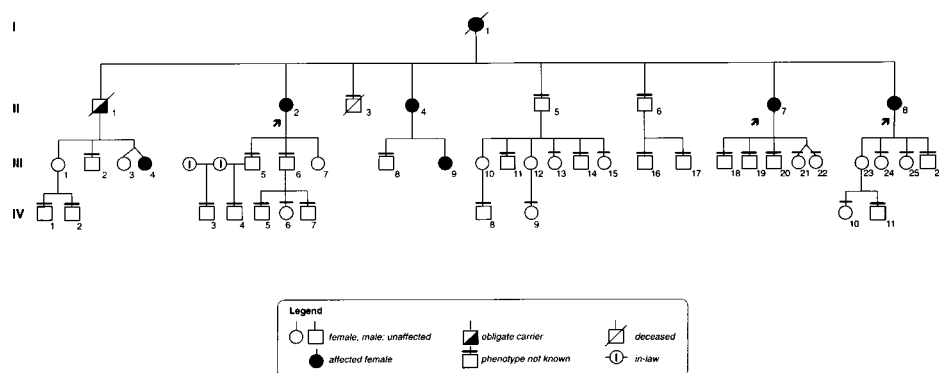


FIG 1. Pedigree of the affected family.

TABLE I. Clinical characteristics of affected and unaffected individuals

Patient	Pregnancy	OC	HRT	GI	A/W
Affected patients					
I-1	12/12	0	0	?	+
II-2	4/4	0	3/3	+	+
II-3	2/2	0	0	—	—
II-7	4/4	0	3/3	—	—
II-8	6/6	0	0	—	+
III-4	0/0	1/1	0	+	—
III-9	0/0	1/1	0	—	—
Unaffected patients					
III-1	0/2	0	0	NA	NA
III-3	0/0	0/1*	0	NA	NA
III-7	0/0	0/1*	0	NA	NA
III-10	0/1	0	0	NA	NA
III-12	0/1	0	0	NA	NA
III-13	0/2	0	0	NA	NA

Pregnancy, Number of pregnancies associated with angioedema/total pregnancies; OC, number of courses of oral contraceptive therapy associated with symptoms; HRT, number of courses of hormone replacement therapy associated with symptoms; GI, gastrointestinal symptoms suggestive of angioedema (present or absent/not recalled); A/W, upper airway swelling (present or absent); NA, not applicable.

*Prolonged use.

TABLE II. Normal complement, C1 esterase inhibitor levels, and function in 3 asymptomatic patients

Patient	C4 (g/L)	C2 (g/L)	C1q (g/L)	C1 inhibitor (g/L)	C1 inhibitor function (%)
II-2	0.35	0.03	0.07	0.16	103
II-7	0.35	0.03	0.06	0.17	108
II-8	0.31	0.02	0.07	0.15	102

Reference range: C4, 0.16-0.47 g/L; C2, 0.02-0.04 g/L; C1q, 0.05-0.08 g/L; C1 inhibitor, 0.12-0.20 g/L; C1 inhibitor function, 70%-130%.

is no documented evidence of C1 inhibitor deficiency or dysfunction in this family, and therefore the rationale for the use of C1 inhibitor concentrate is not established.

For now, affected female patients and female patients of unknown status have been advised to avoid exogenous estrogens and postpone pregnancy while efforts are made to clarify the nature of their condition and possible treatments. Although there have been no reported fatalities in this kindred, it appears to be possible, given the presence of laryngeal edema with airway obstruction reported by at least some of our patients. Historically, fatality from laryngeal edema in HAE approached 25%. Although multiple members are affected in this kindred, they are at risk for episodes

of angioedema only while pregnant or receiving exogenous estrogens and therefore have only expressed the condition for a small portion of their lives up to a maximum of about 10 years in patient I-1. This short period of disease expression may explain why fatalities have not been reported but could still occur. Every effort is being made to identify a means to identify the defect, so that (1) unaffected women could begin their families and (2) a strategy to treat affected women who wished to become pregnant could be devised.

The molecular basis of this family's condition is unknown. One might have predicted that C1 inhibitor levels in these patients would fall in response to the high estrogen levels analogous to, but more pronounced than,

the fall in C1 inhibitor levels in normal women during pregnancy¹⁷⁻¹⁹ and oral contraceptive use²⁰ and opposite to the increased levels of C1 inhibitor in patients with HAE during androgen therapy.⁶⁻⁹ One might speculate that abnormal mutation-associated downregulation of C1 inhibitor synthesis could then result in clinical symptoms from direct or indirect effects of high estrogen levels. For example, a mutation in the purported androgen-response element in the promoter region of the gene encoding C1 inhibitor that reduced androgen-mediated increases in C1 inhibitor levels could account for the observed phenotype. High estrogen levels would increase sex-hormone binding protein and reduce the amount of free androgen available to bind at the mutated, now lower affinity, androgen response element, thereby decreasing androgen-driven C1 inhibitor synthesis. Although attractive, this model is not supported by the observation that C1 inhibitor level was normal in the one sample obtained from a symptomatic individual receiving estrogen therapy. It also is not supported by *in vitro* studies that indicate that this putative androgen-response element is not functional.²¹ In addition, although estrogens may worsen angioedema in patients with C1 inhibitor, the decrease in attack frequency in patients with classic HAE in late pregnancy when estrogen levels are high and the increased frequency of attacks during menstrual periods when estrogen levels are low² suggest that the hormonal influences on angioedema formation are more complex.

Kinin and coagulation cascades are important in the genesis of angioedema, and measurements of their components in the reported patients during symptomatic periods would obviously be of great interest. However, we believe that it would be unethical to expose our patients to the risk of laryngeal edema by starting them on estrogen therapy to obtain such measurements. As described, baseline measurements of complement and contact system proteins and C1 inhibitor during asymptomatic periods have been normal.

For the above reasons, we have chosen a genetic approach, initially through DNA sequencing of candidate genes. The promoter regions of the genes encoding C1 inhibitor and factor XII were of particular initial interest. Factor XII is the contact system protease that activates prekallikrein, which in turn generates bradykinin from high molecular weight kininogen. Bradykinin is a key mediator of angioedema. In normal women factor XII levels increase in response to oral contraceptive or estrogen replacement therapy.^{20,22,23} The promoter of the gene encoding factor XII has been shown to contain a functional estrogen-response element.¹⁴ A gain of function mutation in this response element could cause increased factor XII levels in response to high estrogen levels. We have shown that this also is not the case in this family. Obviously, mutations outside the immediate 5' flanking region also could influence estrogen responsiveness. To test such possibilities, linkage analysis to identify the chromosomal location of the affected gene is being undertaken.

The eventual identification of the molecular defect carried by this family will enhance our understanding of

angioedema genesis in a variety of pathologic conditions, including classic HAE, and may suggest more rational treatments for patients with these conditions, as well as for the patients in this report.

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REFERENCES

1. Donaldson VH, Rosen FS. Hereditary angioneurotic edema: a clinical survey. *Pediatrics* 1966;37:1017-27.
2. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med* 1976;84:580-93.
3. Pearson KD, Buchignani JS, Shimkin PM, Frank MM. Hereditary angioneurotic edema of the gastrointestinal tract. *Am J Roentgenol Radiol* 1972;116:256-61.
4. Rosen FS, Alper CA, Pensky J, et al. Genetically determined heterogeneity of the C1 esterase inhibitor in patients with hereditary angioneurotic edema. *J Clin Invest* 1971;50:2143-9.
5. Davis AE III. C1 inhibitor and hereditary angioneurotic edema. *Annu Rev Immunol* 1988;6:595-628.
6. Gelfand J, Sherins R, Ailing D, Frank M. Treatment of hereditary angioedema with danazol: reversal of clinical and biochemical abnormalities. *N Engl J Med* 1976;295:1444-84.
7. Falus A, Feher K, Walcz E, et al. Hormonal regulation of complement biosynthesis in human cell lines. I. Androgens and gamma-interferon stimulate biosynthesis and gene expression of C1 inhibitor in human cell lines U937 and HepG2. *Mol Immunol* 1990;27:101-5.
8. Alabdullah IH, Sim RB, Sheil J, Greally JF. The effect of danazol on the production of C1 inhibitor in the guinea pig. *Complement* 1984;1:27-35.
9. Lappin D, McPhaden A, Yap P, et al. Monocyte C1-inhibitor synthesis in patients with C1-inhibitor deficiency. *Eur J Clin Invest* 1989;19:45-52.
10. Ratnoff OD, Davie EW. The purification of activated Hageman factor activated factor XII. *Biochemistry* 1962;1:967-75.
11. Breckenridge RT, Ratnoff OD. Studies on the nature of the circulating anticoagulant directed against antihemophilic factor: with notes on an assay for antihemophilic factor. *Blood* 1962;20:137-49.
12. Gross BM, Oudet P, Chambon P. Isolation of high molecular-weight DNA from mammalian cells. *Eur J Biochem* 1973;35:32-8.
13. Bissler JJ, Aulak KS, Donaldson VH, et al. Molecular defects in hereditary angioneurotic edema. *Proc Assoc Am Physicians* 1997;109:164-73.
14. Farsetti A, Misiti S, Citarella F, et al. Molecular basis of estrogen regulation of Hageman factor XII gene expression. *Endocrinology* 1995;136:5076-83.
15. Warin RP, Cuncliffe WJ, Greaves MW, Wallington TB. Recurrent angioedema: familial and oestrogen-induced. *Br J Dermatol* 1986;115:731-4.
16. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C I inhibitor concentrate. *N Engl J Med* 1996;334:1630-4.
17. Ogston D, Walker J, Campbell DM. C1 inactivator level in pregnancy. *Thromb Res* 1981;23:454-5.
18. Halbmayer WM, Hopmeier P, Mannhalter C, et al. C1-esterase inhibitor in uncomplicated pregnancy and mild and moderate preeclampsia. *Thromb Haemost* 1991;2:134-8.
19. Cohen AJ, Laskin C, Tarlo S. C1 esterase inhibitor in pregnancy. *J Allergy Clin Immunol* 1992;90:412-3.
20. Gordon EM, Ratnoff OD, Saito H, Donaldson VH, Pensky J, Jones PK. Rapid fibrinolysis, augmented Hageman factor (factor XII) titres and decreased C1 esterase inhibitor titres in women taking oral contraceptives. *J Lab Clin Med* 1980;96:762-9.
21. Prada AE, Zahedi K, Davis AE III. Regulation of C1 inhibitor synthesis. *Immunobiology* 1998;199:377-88.
22. Gordon EM, Williams SR, Frenchcheck B, Mazur CA, Speroff I. Dose dependent effects of postmenopausal oestrogen and progestin on antithrombin III and factor XII. *J Lab Clin Med* 1988;111:52-6.
23. Jespersen J, Kluft C. Increased englobulin fibrinolytic potential in women on oral contraceptives low in oestrogen levels of extrinsic and intrinsic plasminogen activators, prekallikrein, factor XII and C1 inactivator. *Thromb Haemost* 1985;54:454-9.