antibody or a mixture of monoclonal antibodies that recognize the light and heavy chains of FVIIa was similar to that determined by immunoelectrophoresis. However, the level of the FVII:ag, using the monoclonal antibody recognizing the specific epitope located in the threedimensional structure near position 79, was remarkably low compared with QIEP or ELISA using a polyclonal antibody or a mixture of monoclonal antibodies that recognize the light and heavy chains of FVIIa. The levels of FVII:ag of the father and sister revealed a similar pattern to that of the propositus, although they were not as low. These findings strongly suggested that the mutation in the abnormal FVII of the propositus, her father, and her sister was in the structure near position 79 in the first EGF-like domain of human FVII. DNA sequencing revealed a G-to-A point mutation that was found at nucleotide position 6055 in exon 4 of the FVII gene. This produces a substitution in the CGG codon for Arg 79 in the first EGF-like domain such that it is changed to CAG. The mutation in the propositus, her father, and her sister was confirmed by restriction endonuclease digestion.

Clark et al. (18) reported that the first EGF-like domain of FVII is essential for binding TF, as analyzed by the reaction of monoclonal antibodies with amino acid residues 51–88 of the first EGF-like domain of human FVII, which was mapped with fusion protein fragments. Interaction between FVIIa and TF involves direct contact between TF, the first EGF-like domain of FVIIa, and the catalytic domain (19). O’Brien et al. (20) showed that the first EGF-like domain of FVII plays a key role in FVII complex formation with TF, as analyzed by surface plasmon resonance of the interaction between TF and recombinant FVII-R79Q. We reported (7) that the loss of charge associated with the substitution of Arg by Glu at position 79 in FVII Shinjo has a direct effect on the TF-binding site in this part of the first EGF-like domain of FVII. Recently, Banner et al. (21) determined the x-ray crystal structure of the complex of active site-inhibited FVIIa with subtilisin-treated soluble TF and showed that Arg 79 was close to Glu 24 and Glu 56 in the N-terminal domain of TF. The amino acid residues close to Arg 79 of FVIIa in the complex are conserved in human, rabbit, and bovine TFs. Why FVII with the substitution of Arg by Glu at position 79 gives different procoagulant activities using TF from various species is still unknown and will require additional studies. Our ELISA system can be used to check the abnormal FVII molecules that give different procoagulant activities using TF from various sources.

References

Serum Carcinoembryonic Antigen, Cancer Antigen 125, Cancer Antigen 15-3, Squamous Cell Carcinoma, and Tumor-associated Trypsin Inhibitor Concentrations during Healthy Pregnancy, Marie-Hélène Schlageret, Jérôme Larghero, Bruno Cassaint, Marie-Elisabeth Toubert, Caroline Borschneck, and Jean-Didier Rain (Service de Mé- decine Nucléaire, Hôpital Saint-Louis, 75475 Paris Cedex 10, France; * author for correspondence: fax 33 (0)1 42 49 94 05, e-mail schlageret@chu-stlouis.fr)

In the management of cancer patients, tumor-associated antigens are measured in serum as noninvasive tests for relapse detection [reviewed in Ref. (1)]. The tests have limited specificity because the serum concentrations of the
Table 1. Tumor marker concentrations in pregnancy.

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</thead>
<tbody>
<tr>
<td>n&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>5</td>
<td>13</td>
<td>14</td>
<td>10</td>
<td>12</td>
<td>20</td>
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<tr>
<td>CEA</td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>1.9 ± 0.7</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.8</td>
<td>1.4 ± 0.8</td>
<td>1.2 ± 0.7</td>
<td>1.4 ± 1.0</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>Range</td>
<td>1.4–2.4</td>
<td>0.8–1.6</td>
<td>0.6–3.5</td>
<td>0.6–2.8</td>
<td>0.4–2.8</td>
<td>0.5–3.4</td>
<td>0.7–3.3</td>
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<tr>
<td>SCC</td>
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<tr>
<td>Mean ± SD</td>
<td>1.6 ± 1.8</td>
<td>0.5 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.7 ± 0.5</td>
<td>1.0 ± 0.4</td>
<td>1.4 ± 1.1</td>
<td>1.2 ± 0.5</td>
</tr>
<tr>
<td>Range</td>
<td>0.3–2.9</td>
<td>0.3–0.9</td>
<td>0.2–1.0</td>
<td>0.1–2.2</td>
<td>0.6–1.5</td>
<td>0.6–4.3</td>
<td>0.5–2.2</td>
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<tr>
<td>CA 125</td>
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<tr>
<td>Mean ± SD</td>
<td>12.8 ± 6.9</td>
<td>18.7 ± 14.0</td>
<td>21.4 ± 15.9</td>
<td>19.9 ± 12.5</td>
<td>19.1 ± 7.8</td>
<td>22.3 ± 13.1</td>
<td>22.1 ± 12.3</td>
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<tr>
<td>Range</td>
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<td>6.1–41.5</td>
<td>4.4–63.5</td>
<td>6.5–54.3</td>
<td>7.6–38.0</td>
<td>6.1–51.3</td>
<td>6.2–49.3</td>
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<td>CA 15-3</td>
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<tr>
<td>Mean ± SD</td>
<td>12.3 ± 1.5</td>
<td>9.3 ± 4.0</td>
<td>12.9 ± 4.2</td>
<td>14.1 ± 4.1</td>
<td>17.1 ± 4.7</td>
<td>16.5 ± 4.1</td>
<td>16.9 ± 5.3</td>
</tr>
<tr>
<td>Range</td>
<td>12.2–14.3</td>
<td>5.0–15.0</td>
<td>9.2–20.5</td>
<td>10.0–22.8</td>
<td>8.9–24.8</td>
<td>8.8–24.2</td>
<td>5.1–27.0</td>
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<tr>
<td>TATI</td>
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<tr>
<td>Mean ± SD</td>
<td>12.0 ± 1.4</td>
<td>11.8 ± 5.4</td>
<td>14.4 ± 7.2</td>
<td>16.9 ± 7.7</td>
<td>18.3 ± 11.0</td>
<td>20.6 ± 10.8</td>
<td>26.8 ± 18.5</td>
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<tr>
<td>Range</td>
<td>11.0–13.0</td>
<td>5.0–18.0</td>
<td>6.0–33.0</td>
<td>7.0–35.0</td>
<td>9.0–44.0</td>
<td>7.0–44.0</td>
<td>9.0–65.0</td>
</tr>
</tbody>
</table>

<sup>a</sup>n is the number of samples. Mean ± SD, expressed in µg/L for CEA, SCC, and TATI and in kIU/L for CA 125 and CA 15-3.
could be fitted by a linear regression model, and the slope \( \beta_1 \) could be calculated. Except for TATI, the value of the slope \( \beta_1 \) was very small, which means that, although the evolution of tumor marker with time was linear, the concentration did not rise markedly during pregnancy.

CEA was slightly increased in four of nine samples from one woman (range, 3.2–3.5 \( \mu \)g/L). A linear evolution of CEA was found in one patient (slope \( \beta_1, 0.071 \)). CA 125 concentration was higher than 40 kIU/L in four samples, three from one woman and one from a second one (5.3% of all samples; range, 49–63 kIU/L). A linear evolution of CA 125 was found in three patients (slope \( \beta_1, 0.36 \pm 0.2 \)).

CA 125 is the most studied tumor marker in pregnancy. In the first trimester of pregnancy, CA 125 was increased in very different percentages of cases according to several authors: 16% (11), 55% (2), 12.5% (3), and 60% (12). Taken during the course of the pregnancy, a high CA 125 was found in 11 of 46 pregnant women (12) (with one extreme value of 143 kIU/L) or in 8 of 100 pregnant women (3). Furthermore, increased CA 125 concentration was correlated with a higher pregnancy rate in women undergoing an in vitro fertilization program (13).

In our study, all CA15-3 values were within the reference interval (<30 kIU/L), although in five patients, a linear temporal evolution of this marker was seen: slope \( \beta_1, 0.21 \pm 0.08 \). By a statistical analysis, Touitou and Bogdan (2) also showed increasing CA 15-3 but with concentrations in the usual range of values.

SCC concentrations increased over the cutoff value of 1.6 \( \mu \)g/L in eight samples coming from seven different women (10.5% of all samples; range, 1.7–4.3 \( \mu \)g/L). Except in one case, an increase occurred after 23 weeks of amenorrhea. Mean SCC concentration was higher after 30 weeks of amenorrhea than before 30 weeks. In two patients, a linear evolution of SCC was found with a slope \( \beta_1 = 0.05 \pm 0.01 \). In previous studies, high concentrations of SCC were found in amniotic fluid until a mean concentration of 670 \( \mu \)g/L in the third trimester of pregnancy, but in maternal serum, SCC was within the reference interval (14).

In our study, TATI concentrations increased >25 \( \mu \)g/L in 13 samples from six different women, mainly in the third trimester of pregnancy (17.1% of samples; range, 27–65 \( \mu \)g/L). TATI can be particularly high in some patients, up to 65 \( \mu \)g/L, i.e., 2.6 times the cutoff value. Furthermore, we found a marked linear increase of TATI in four patients. The values for the slope \( \beta_1 \) were much higher than for the other markers: 1.15 ± 0.66. A slope higher than 1 (and a sharp increase in patient 8) was found in three women (1.23, 1.43, and 1.73; Fig. 1). TATI increased above the cutoff value of 25 \( \mu \)g/L relatively late but began to rise from the beginning of pregnancy, staying in the reference interval until 20 weeks of amenorrhea. To our knowledge, no other publication reports TATI concentrations in pregnancy.

CA 19-9 (a marker of gastrointestinal tract), tissue polypeptide antigen (TPA), and neurone-specific enolase (NSE; a marker of small cell lung carcinoma) have been studied in pregnancy. Increased CA 19-9 (>37 kIU/L)
was reported in 4.8% of 21 patients (2) and in 10% of 100 patients (range, 38–117 kIU/L) (3). In another study, serum CA 19-9 and NSE were not increased in 87 pregnant women (15).

TPA (a marker of cell proliferation) (1) was studied as a possible marker of pathological pregnancy as eclampsia. TPA was higher in hypertensive pregnant women than in nonhypertensive ones (16), and TPA concentration was correlated with the severity of the disease.

Our results thus show and confirm that during pregnancy, tumor markers are rarely higher than the cutoff value but can increase markedly, staying under the cutoff value as for CA 15-3 or rising above it as for TATI or SCC. Increases of TATI and SCC occurred more frequently and mostly in the last months of pregnancy.

References