Unusual Bleeding During Pregnancy: Report of a Case Due to Hypoprothrombiminemia and Hypoproconvertinemia

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It is well known that deficiencies of prothrombin and proconvertin can be the cause of serious bleeding.1-5 In addition to recognized causes of these deficiencies, such as inadequate intake, absorption or utilization of vitamin K, cases of unrecognized cause may be encountered.6 To date, an acquired idiopathic deficiency of these two substances in pregnancy has been reported in only one patient.7 It is our purpose to present the second.

Case Report: O. S., 1016-54, C. M. 4759: A forty year old caucasian female, the wife of a physician, was admitted to the Salt Lake County General Hospital for the first time on February 8, 1954, with a chief complaint of bleeding for the previous five days.

The patient had been in excellent health until late November, 1953, when she developed "flu." At that time she was some seven or eight weeks pregnant (last menstrual period September 28, 1953). Treatment consisted of penicillin and streptomycin. Erythema nodosum developed, and she was given cortisone. This was effective, but was discontinued after one week because of ankle edema. The erythema nodosum returned. From the middle of December until January 11, 1954, she was given ACTH intermittently as the lesions waxed and waned. About the sixteenth of January, a red maculopapular pruritic skin eruption appeared, extending from her neck to her knees. Partial subsidence of the rash followed a single injection of ACTH. Caladryl Lotion and Quontane Cream were applied locally.

By February 1, the rash had disappeared, leaving a slight brownish discoloration of the skin of her legs.

During the months of December and January, she confined herself to bed. Besides the drugs previously mentioned, she took Benadryl, rutin, ascorbic acid, Natabec Capsules, and an occasional aspirin.

On February 1, 1954, she complained of pain in the lower part of the back and legs, and of abdominal "gas pains" for which she took Anexia tablets. At this time, epistaxis occurred but lasted only "three to four minutes." On February 4 hematuria and gingival bleeding began. She received injections of water soluble vitamin K and vitamin C. The next day, when large superficial ecchymoses appeared on her arms, she was hospitalized in Price, Utah. Her hemoglobin was reported as 11 Gm. per cent, the platelet count and clot retraction as normal. The clotting time was prolonged and the Quick one stage prothrombin time was 2 minutes, 46 seconds, with a control of 12.5 seconds. She received large doses of vitamin K and vitamin C intravenously plus 1000 cc. of banked blood. On February 6, her prothrombin time was 48 seconds with a control of 11.5 seconds. On February 8, it had increased to 1 minute, 45 seconds. Accordingly, she was transferred to our care, some eighteen weeks pregnant.

This was her sixth pregnancy, four having resulted in normal issue. The second terminated in a spontaneous abortion after two months and was preceded by ten days of vaginal bleeding. There had been no abnormal vaginal bleeding during the present pregnancy. Her diet had been adequate, and she denied access to coumarin-like drugs. There was no personal or family history of easy bruising or bleeding.

On admission, she appeared slightly pallid and moderately ill. Temperature was 99.4 F. by mouth, pulse 110, respirations 20, blood pressure 120/70, weight 1211/2 pounds and height 60 inches.

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64 inches. There were many large ecchymotic areas over her arms and legs. A few petechiae were present on the extremities and palate. Blood was oozing from her gums. The heart and lungs were normal. The uterus was palpable 23 cm. above the symphysis pubis; fetal movements and heart sounds were not detected. Varicosities of the lower extremities were present. The urine was turbid, grayish black, grossly and microscopically bloody. There was a trace of reducing substance as well as 1+ albuminuria, pH 6 and specific gravity 1.023. The hemoglobin was 11.8 Gm. per cent, volume of packed red cells 34.5 ml. per 100 ml. blood, red blood cells 3,230,000 per cu. mm., white blood cells 7,400 per cu. mm. and the differential normal. Reticulocytes were 0.8 per cent and the icterus index was less than 5 units.

Although the platelet count (Rees-Ecker) was recorded as 100,000 (normal 200-400,000), they appeared to be quantitatively and qualitatively normal on examination of the blood smear, where they were present in numerous small clumps. The clot was firm and retraction was good, being complete in three hours. Bleeding time (Ivy) on two occasions was 1½ and 4 minutes, respectively. Capillary fragility (Rumpel Leede) was normal. The coagulation time (Lee-White) was 25 minutes (our upper limit of normal is 16 minutes). The one stage prothrombin time (Quick) was 13.2 seconds with a control of 15.5 seconds. Specific determinations of prothrombin and proconvertin by the method of Owren and Aas* revealed less than 10 per cent prothrombin and less than 20 per cent proconvertin. Thromboplastin generation,* using the patient's plasma, was normal. Recalcification times of the patient's plasma were slightly prolonged. Circulating anticoagulants could not be demonstrated immediately or after incubation. Antiprothrombin and antiproconvertin were looked for specifically and not found. Increased fibrinolysis was not observed. Fibrinogen, determined by a modification of the method of Morrison,10 was 331 mg. per cent (normal 180-300 mg. per cent). Stools were brown and Guaiac negative.

* Equal volumes of the patient's plasma were added to normal plasma. Prothrombin and proconvertin levels of the mixture were determined immediately and after incubation for 1 hour at 37°C by the method of Owren and Aas. Antiprothrombin or antiproconvertin would have increased the clotting time of the mixtures over and above the factor of dilution.

Fig. 1. Course of patient O. S. following admission to Salt Lake General Hospital.
UNUSUAL BLEEDING DURING PREGNANCY

A 72 hour stool specimen was examined for fecal fat. The average daily fat intake during the collection period was 99 Gm. and the average daily fecal fat output was 0.56 Gm. Blood urea nitrogen was 10 mg. per cent and the fasting blood sugar 75 mg. per cent. At this time, total plasma proteins were 5.2 Gm. per cent with 3.4 Gm. of albumin and 1.8 Gm. of globulin; direct reacting bilirubin was 0.2 mg. per cent and total 0.8 mg. per cent. The thymol turbidity was 8 units (normal 0 to 4), alkaline phosphatase 5.5 units (normal 1.5 to 10) and cephalin flocculation 4+ (normal 0 to 2+). A week later the cephalin flocculation was 1+, thymol turbidity 7 units, and the bromsulphalein retention 1.5 per cent (normal 0 to 5 per cent).

It was concluded that the bleeding was due to prothrombin and proconvertin deficiency, the cause of which was not obvious. Because of the urgency of the situation, she was treated immediately with vitamin K₃ (Mephyton), given intravenously. Her response to this and subsequent therapy is indicated in figure 1 and table 1.

On February 12, two days after treatment was initiated, the patient stated that she had not "felt life" for several days. However, at this time normal fetal heart sounds were present in the right umbilical region and fetal movements were palpable. The pregnancy was considered to be nineteen weeks old by history and normal by examination.

**Table 1.**—Course of patient O. S. following admission to Salt Lake General Hospital

<table>
<thead>
<tr>
<th>Date</th>
<th>Hours from Beginning Therapy</th>
<th>Quick One Stage Prothrombin Times (Sec.)</th>
<th>Pre thrombin (Owen) Per Cent</th>
<th>Proconvertin (Owen) Per Cent</th>
<th>Coagulation Time (Lee and White) Minutes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/9/54</td>
<td>0</td>
<td>132.4</td>
<td>15.5</td>
<td>&lt;10</td>
<td>&lt;20</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ecchymoses, Hematuria, Gingival Hemorrhage</td>
</tr>
<tr>
<td>2/10</td>
<td>4</td>
<td>15.4</td>
<td>17.3</td>
<td>17</td>
<td>50</td>
<td>Vitamin K₃, 350 mg. I. V.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.5</td>
<td>17.3</td>
<td>23.5</td>
<td>72</td>
<td>All bleeding ceased</td>
</tr>
<tr>
<td>2/11</td>
<td>33</td>
<td>14.5</td>
<td>17.3</td>
<td>45</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>2/12</td>
<td>59</td>
<td>13.1</td>
<td>18.1</td>
<td>55</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2/13</td>
<td>83</td>
<td>16.5</td>
<td>16</td>
<td>45</td>
<td>37</td>
<td>13</td>
</tr>
<tr>
<td>2/14</td>
<td>106</td>
<td>29.3</td>
<td>18</td>
<td>15.5</td>
<td>&lt;20</td>
<td>14.5</td>
</tr>
<tr>
<td>2/15</td>
<td>135</td>
<td>21.1</td>
<td>17.6</td>
<td>29.5</td>
<td>27</td>
<td>Vitamin K₃, 50 mg. I. V.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No further bleeding</td>
</tr>
<tr>
<td>2/16</td>
<td>159</td>
<td>15.6</td>
<td>17.6</td>
<td>35.5</td>
<td>70</td>
<td>Ecchymoses fading</td>
</tr>
<tr>
<td>2/17</td>
<td>167</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vitamin K (water soluble) 216 mg. I. V.</td>
</tr>
<tr>
<td>2/18</td>
<td>188</td>
<td>26.6</td>
<td>19.4</td>
<td>21</td>
<td>&lt;20</td>
<td>Vitamin K (water soluble) 360 mg. I. V.</td>
</tr>
<tr>
<td>2/19</td>
<td>212</td>
<td>28.9</td>
<td>16.7</td>
<td>18.5</td>
<td>&lt;20</td>
<td>Vitamin K₃, 100 mg. I. V.</td>
</tr>
<tr>
<td>2/20</td>
<td>236</td>
<td>17.8</td>
<td>15.4</td>
<td>55</td>
<td>78</td>
<td>Ecchymoses about gone, discharged</td>
</tr>
<tr>
<td>2/21</td>
<td>260</td>
<td>15.7</td>
<td>15.9</td>
<td>59.5</td>
<td>98</td>
<td>Hgb. 9.5 Gm. % 500 cc. blood</td>
</tr>
<tr>
<td>2/22</td>
<td>284</td>
<td>14.3</td>
<td>15.5</td>
<td>55</td>
<td>100</td>
<td>No further bleeding; no visible hemorrhage</td>
</tr>
<tr>
<td>2/24</td>
<td>11</td>
<td>11.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/26</td>
<td>11.5</td>
<td>13.45</td>
<td></td>
<td>Determinations in Price, Utah</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/1</td>
<td>11</td>
<td>10.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/3</td>
<td>11</td>
<td>10.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/4</td>
<td>15.2</td>
<td>15.3</td>
<td>94</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Following the first injection of $K_1$, two additional injections were required. It is notable that 100 mg. produced the same effect as 350 mg., whereas 50 mg. had somewhat less effect. There was no response to the intravenous administration of water soluble preparations of vitamin $K$.

On February 21, the patient was discharged. Measurements of one stage prothrombin times were made every other day. No additional therapy was required. Eleven days later the prothrombin was 94 per cent and the proconvertin 100 per cent of normal. There had been no further bleeding. She had received a transfusion of one pint of whole blood because her physician regarded the hemoglobin of 9.5 Gm. per cent as being too low. The remainder of her pregnancy was uneventful until May 12, the eighth month of pregnancy, when premature labor took place and twins were born. The first was a stillborn measuring 18 cm. in length (compatible with a gestation of eighteen weeks). The second was a viable infant with webbing of the second and third toes bilaterally (a familial defect), microcephaly and muscular spasticity. Abnormal post-partum icterus was not noted. The placenta were fused, but the membranes and cords were separate. The placenta of the stillborn was completely infarcted and felt firm and fibrous; the second placenta appeared normal. The stillborn fetus was not macerated. No unusual bleeding occurred during or after delivery.

When last seen, May 20, 1955, the patient had not suffered any recurrences of hemorrhagic manifestations; both the prothrombin and proconvertin levels were 100 per cent. Aspirin and penicillin had been administered to her since delivery without ill effect. Studies done at this time to determine if parental blood group incompatibility, leading to an erythroblastic state in the fetus, had existed were negative. One stage prothrombin times of the four oldest children were normal.

**DISCUSSION**

The patient's most striking laboratory abnormality was the markedly prolonged one stage prothrombin time. This was shown to be due to deficiency of both prothrombin and proconvertin. Proaccelerin and AHG deficiency were ruled out by the normal plasma thromboplastin generation.

The most common hematologic causes of abnormal bleeding during pregnancy are thrombocytopenia and afibrinogenemia. Afibrinogenemia occurs following abruptio placentae or as the result of intrauterine retention of a dead fetus, often the consequence of Rh incompatibility. Under these circumstances, it is postulated that thromboplastin-like material enters the maternal circulation and causes rapid intravascular utilization of fibrinogen. During this process, decreases in prothrombin activity (prothrombin, proconvertin, proaccelerin) have been reported but never to ranges usually associated with hemorrhage.

It seems reasonably certain that neither significant thrombocytopenia nor afibrinogenemia was present in our case. Intrauterine death due to blood group incompatibility was reasonably excluded. It was suggested that fibrinogen, prothrombin and proconvertin all may have been reduced below normal, but that fibrinogen had been restored more rapidly than the other factors. Thus, when we studied the patient, the fibrinogenopenic phase would have passed. However, during active bleeding, the clots that formed were all of appropriate bulk and consistency. One would have expected that, if the bleeding had been due to hypo- or afibrinogenemia, the clots, if any, would have been of poor quality.

One can only speculate concerning the cause of the changes observed in our patient. Recognized causes of hypoprothrombinemia and hypoproconvertinemia, such as the presence of obstructive jaundice, the administration of antibiotics to reduce the growth of bacteria in the bowel, failure of absorption due to a
sprue-like state or a familial defect, can be ruled out. Sensitivity to aspirin can also be excluded. Surreptitious ingestion of a vitamin K antagonist was suspected. We were unable to substantiate this, but Dicumarol blood levels were not obtained. Gross liver disease seems unlikely for the only demonstrable abnormalities were a slight elevation of the thymol turbidity and a cephalin flocculation which rapidly returned to normal.

The evidence suggests that there must have been a severe, even though temporary, abnormality of prothrombin and proconvertin metabolism, either of production or utilization which resulted in their deficiency. In the syndrome associated with pregnancy where bleeding is known to follow the increased intravascular utilization and subsequent depletion of a substance vital to coagulation, fibrinogen, there is evidence of decreased concentration of other substances involved in coagulation.\(^{13,15,16}\) Therefore, one would expect that, if utilization of prothrombin and proconvertin were responsible for their deficiency, activation of other substances would occur and decreases in proaccelerin and fibrinogen would be noted. As this was not found, increased utilization is an unlikely explanation. It would appear more probable then that decreased production was the cause, and it seems likely that this originated at the hepatocellular enzyme level. The occurrence of such malfunction was temporally coincident with placental infarction and fetal death. One wonders whether this accident of pregnancy adversely influenced the liver cell.

In the report of Hill et al.,\(^7\) no mention was made of the placenta, and the infant was said to be healthy. The onset of bleeding in their patient was also during the fifth month of pregnancy. These authors suggested that a period of slight hepatic dysfunction was the cause of the coagulation defect.

**Summary**

A case of transient hypoprothrombinemia and hypoproconvertinemia associated with bleeding and occurring during the eighteenth and nineteenth weeks of a twin pregnancy has been described. The coagulation defect responded to intravenous K\(_2\) therapy but not to water soluble K. Death of one fetus and complete infarction of its placenta occurred during the eighteenth week. It is suggested that these events, or their cause, may have adversely influenced liver cell function and precipitated the severe deficiencies of prothrombin and proconvertin.

**Summario in Interlingua**

Es describite un caso de transiente hypoprothrombinemia e hypoproconvertinemia asociate con sanguination e occurrente durante le 18ve e 19ne septimanas de un pregnantia a geminios. Le defecto de coagulation respondeva al administracion intravenose de K\(_2\), sed non de K solubile in aqua. Le morte de un del fetos e le complete infarcimento de su placenta occurreva durante le 18ve septimana. Es formulate le interpretation que iste evenimentos (o lor causa) habeva exercite un influentia adverse super le function del cellulas hepatic e assi precipitava le sever carentias de prothrombina e proconvertina.
REFERENCES


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