the observations of Martin and Olson.\(^1\) Other reports of radiation-induced thyroid cancer have dealt with the consequences of therapeutic irradiation. The history of past irradiation in our first patient was not obtained until his brother also developed a cancer, when

Thromboxane \(A_2\) in pregnancy and puerperium

A recent report presented evidence that despite the rise in the anti-aggregatory agent prostacyclin during late pregnancy the aggregation of platelets was enhanced.\(^1\) An increase in the proaggregatory agent thromboxane \(A_2\) (\(TxA_2\)) could explain this discrepancy.\(^2\) To study the production of the proaggregatory and vasoconstricting agent thromboxane \(A_2\) during human pregnancy and puerperium we measured the concentrations of its stable metabolite thromboxane \(B_2\) (\(TxB_2\)) in plasma and serum from 45 women at 11-41 weeks of normal pregnancy, 11 puerperal women 53-60 days postpartum, and 22 healthy non-pregnant control women.

**Subjects, methods, and results**

Seventy-eight healthy women aged 17-39 volunteered for the study. None had taken drugs known to interfere with the synthesis of prosta-glandins within 10 days of starting the study. We determined their \(TxA_2\) production by measuring plasma and serum concentrations of its stable metabolite thromboxane \(B_2\) (\(TxB_2\)) by radioimmunoassay. The rationale of this approach was to measure the circulating \(TxB_2\) in vivo and the capacity of the platelet to produce \(TxB_2\) during spontaneous clotting. The amount of \(TxB_2\) produced during spontaneous clotting correlates closely \((r>0.90)\) with the amount of \(TxB_2\) released from platelets during induced aggregation in platelet-rich plasma. Thus two blood samples were collected with the same venepuncture. To obtain plasma blood was taken into ice-cold heparinised tubes containing acetic acid at a final concentration of 0.02 mol/l (1.3 mg/100 ml) and centrifuged immediately at 4°C. For the sera, blood samples were taken into dry tubes and allowed to clot at 37°C for exactly 60 min before centrifugation. Both plasma and sera were stored frozen at -20°C until assayed. The samples from pregnant, puerperal, and non-pregnant women were equally distributed in different radioimmunoassay batches.

The results were subjected to the two-tailed Student's \(t\) test and regression analysis. \(TxB_2\) concentrations in plasma were higher in the pregnant and puerperal women than in the controls, but no significant changes could be seen with advancing gestational age (table). Similarly, \(TxB_2\) production during spontaneous clotting was greater during pregnancy and the puerperium than in the non-pregnant women. The \(TxB_2\) concentrations in plasma and serum correlated significantly with each other \((r=0.515, n=78, p<0.001)\).

**Mean (±SE) concentrations of thromboxane \(B_2\) in plasma and production of thromboxane \(B_2\) during clotting of blood samples at 37°C for 60 min in pregnant and puerperal women compared with those in healthy, non-pregnant women**

<table>
<thead>
<tr>
<th>Population</th>
<th>No of women</th>
<th>(TxB_2) in plasma (pg/ml)</th>
<th>(TxB_2) in serum (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women:</td>
<td>45</td>
<td>260±44 ±38±6(^*)</td>
<td>255±20 ±14±6(^*)</td>
</tr>
<tr>
<td>2nd trimester week 11-28</td>
<td>21</td>
<td>200±57 ±47±11</td>
<td>261±10 ±19±4</td>
</tr>
<tr>
<td>Pregnancy week 32-41</td>
<td>24</td>
<td>323±60 ±50±6</td>
<td>249±20 ±20±7</td>
</tr>
<tr>
<td>Puerperal women (53-60 days postpartum)</td>
<td>11</td>
<td>196±30 ±23±7</td>
<td>162±17 ±27±7</td>
</tr>
<tr>
<td>Non-pregnant controls</td>
<td>22</td>
<td>99±3 ±11±5</td>
<td>183±4 ±14±5</td>
</tr>
</tbody>
</table>

\(^*p<0.001, \text{tp}<0.01, \text{tp}<0.05\) compared with concentrations in non-pregnant controls.

**Comment**

Our results show that both plasma \(TxB_2\) concentrations and \(TxB_2\) release in response to thrombin-induced platelet aggregation during spontaneous clotting rise during pregnancy and the puerperium. This rise in proaggregatory \(TxA_2\) production could explain the increased platelet reactivity\(^3\) and the common occurrence of thromboembolic complications\(^4\) at these times. Our results could also explain why the capacity of platelets to aggregate was increased despite the enhanced production of the antiaggregatory agent prostacyclin in late pregnancy.\(^1\) Conceivably the balance between \(TxA_2\) and prostacyclin shifts to the side of \(TxA_2\) dominance during pregnancy and puerperium.

The actual source of high plasma \(TxB_2\) concentrations throughout normal pregnancy, as observed in this study, and at term is not known. Several pregnancy-associated tissues such as amnion, chorion, decidua, and placenta are capable of producing \(TxB_2\) in vitro\(^5\); and they may contribute to the high plasma concentrations of \(TxB_2\) during pregnancy but not during puerperium. Possibly the raised plasma \(TxB_2\) concentrations reflect a greater incidence of microthrombi in the circulation at these times. But we must emphasise that despite the use of adequate anticoagulants and prostaglandin synthesis...
Acute folate deficiency during peritoneal dialysis

Acute megaloblastic arrest of haemopoiesis in patients receiving parenteral nutrition after extensive surgery or trauma is well recognised.1 Rapidly developing life-threatening pancytopenia in pregnancy complicated by severe bacterial infection has also been described.2 Both have been attributed to acute folate deficiency. Less well recognised is the occurrence of acute folate deficiency in other conditions needing critical care.2 We report a case of severe rapid-onset pancytopenia resulting from acute folate depletion during the course of peritoneal dialysis.

Case report

A 64-year-old man was referred with acute tubular necrosis that developed after intravenous anti hypertensive treatment. The results of initial haematological investigations (figure) were: haemoglobin concentration 13·7 g/dl, mean corpuscular volume 84 fL, white cell count 10·2 × 10⁹/l (10 200/mm³) with a normal differential count. The reticulocyte count was <1%. His platelet count was 280 × 10⁹ (280 000/mm³), prothrombin time 12 s (control 12 s), partial thromboplastin time 40 s (control 38 s), fibrin degradation products, <10 mg/l. His urine to serum osmolarity ratio was <1.0, and urinary sodium concentration was 40 mmol (mEq/l). Sediment microscopy showed red and white cells but no casts. Blood and urine cultures were sterile. Renal tomography showed large swollen kidneys. He required three courses of peritoneal dialysis, each consisting of 40 exchanges, during the oliguric phase of 16 days. During peritoneal dialysis he suddenly had generalised bleeding and blood staining of the dialysate. Repeat investigations showed that his white cell count had fallen to 1·2 × 10⁹/l (1200/mm³) and the platelets to 12 × 10⁹/l (12 000/mm³). The haemoglobin was 8·4 g/dl mean corpuscular volume 87 fl, mean corpuscular haemoglobin concentration 32·4 g/dl, and mean corpuscular haemoglobin 28·0 pg. The reticulocyte count was <1%. Occasional macrocytes and hypersegmentation of polymorphs were noted on the peripheral blood film. Bone marrow aspirate showed severe megaloblastic change particularly affecting the white cell series. Megakaryocytes were present and the myeloid-erythroid ratio was 11:1. Folate concentrations measured at the time of the pancytopenia later showed a much diminished serum folate concentration of 0·5 μg/l (normal 2–7–20 μg/l) and a normal red cell folate concentration of 224 μg/l (normal 150–1000 μg/l). His vitamin B₁₂ concentration was 230 ng/l (normal 150–1000 ng/l).

Intravenous folate 10 mg/day was given and his platelet and white cell counts returned to normal levels within four to five days. Associated with this was a mild reticulocyte response of 3%. He was given a further two-week course of folate 5 mg/day by mouth. He made a satisfactory recovery and when discharged his full blood count and peripheral film were normal and his renal function mildly impaired. His renal function has since improved further and there has been no recurrence of any haematological abnormalities.

Comment

Apart from ethanol, which may interfere with the intermediary metabolism of folate, other factors may contribute to the development of acute folate deficiency in severely ill patients.3 In normal subjects taking a diet deficient in folate it may be 18 to 20 weeks before megaloblastic changes appear within the bone marrow although serum folate concentrations may become subnormal within two to three weeks. Therefore anorexia probably had only a minor role in our patient. Systemic infection appreciably interferes with jeunal absorption of folate and may also adversely affect folate metabolism.4 Our patient showed no evidence of local or systemic infection at any time. Folate is loosely bound to protein in serum and is thus lost from the body during haemodilutions—about 50 μg in each exchange. Similarly, serum folate is lost during peritoneal dialysis, although how much is lost is uncertain. In the absence of any of the recognised precipitating factors we are tempted to speculate that the recurrent peritoneal dialysis, by rapidly removing folate, played a predominant part in causing our patient’s pancytopenia.

The diagnosis depends on being aware of the condition and of the implication of a rapidly developing pancytopenia in a severely ill patient. It is confirmed by examination of a bone marrow aspirate. Because of the delay in recovery of white cell and platelet counts, even after early diagnosis and treatment, we suggest that prophylactic folinic acid supplements should be given to patients having repeated peritoneal dialysis. At a minimum white cell and platelet counts should be closely monitored.


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