Creatine Kinase and Its Isoenzymes in the Serum of Women during Pregnancy and the Peripartum Period

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In serum obtained from 28 women before, during, and after normal labor and delivery, creatine kinase activity was seen to be distinctly elevated immediately after labor and 24 h later, but had returned to normal six weeks later. In most cases the increase was due to the MM isoenzyme and was attributed to skeletal-muscle damage associated with labor. In 15 cases, the BB isoenzyme was observed, and in three patients the MB isoenzyme. Cord blood, which contains all three isoenzymes, may be the source of the MB and BB isoenzymes. Uterine muscle contains exclusively BB isoenzyme, and therefore uterine muscle damage is a likely source of the serum BB isoenzyme. The relationship among these isoenzymes in serum after delivery must be recognized, to avoid misdiagnosing myocardial infarction at this critical time.

The recent introduction of practical methods for separating creatine kinase (CK; EC 2.7.3.2) isoenzymes is a notable advance in the diagnosis of myocardial damage. It is widely accepted that MB isoenzyme of CK in serum is a specific indicator of cardiac muscle damage. For this reason, the discovery of CK-MB in a clinical setting not associated with cardiac muscle damage is very important.

Maternal myocardial infarction is an unusual event at the time of delivery, but when it does occur, its diagnosis may be difficult. Maternal serum CK activity has been shown to increase after delivery (1–3), and myometrial CK increases during pregnancy (3). The purpose of the present study was to examine the nature of this peripartum change in activity, study the nature of the isoenzymes released, investigate the source of the liberated enzyme, and define the potential problem of diagnosing myocardial infarction in pregnancy.

Methods

Twenty-eight women in the third trimester of pregnancy were enlisted into the study, after informed consent. They received no medications other than vitamins and iron, and none had a prior history of chronic illness. All of the pregnancies were uncomplicated. Venous blood specimens were obtained at the following times: (1) during the third trimester, between 30 and 36 weeks gestation, (2) on admission to hospital in labor, (3) within 30 min after delivery, (4) between 0700 and 0900 h on the morning after delivery, (5) on the fifth day postpartum, and (6) at the time of the routine six-week check-up. Serum was separated within 1 h of venipuncture, stored at 4 °C, and analyzed on the first working day after collection. These conditions were selected because they represent usual laboratory procedure and because the enzymes under consideration are known to be minimally affected by the process. Three samples were missed in periods 1 and 2, two in period 3, and six in period 6.

Total CK activity was assayed at 30 °C by an automated, continuous spectrophotometric technique (4). CK isoenzymes were separated by electrophoresis on agarose gel (Corning aci, Palo Alto, Calif. 94306), and inspected visually under ultraviolet light. The gels were scanned with a Densicomp Model 445 (Clifford Instruments Inc., Natick, Mass. 01760). Exact quantitation of the isoenzyme fractions was not attempted. However, the existence of an isoenzyme fraction was not confirmed unless at least 10 U/liter activity was observed (as compared to a standard run in parallel). Using this approach on the sera of over 200 hospitalized patients, we have only observed MB fractions in association with myocardial infarction.

We investigated uterine muscle, using uterine tissue in two cases obtained during cesarian section and in two cases at the time of hysterectomy. About 200 mg of wet myometrium was homogenized in a Polytron homogenizer, with use of 5 ml of a pH 7.4 solution containing,
Table 1. Summary of CK Activity, U/liter

<table>
<thead>
<tr>
<th>Collection time no.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>25</td>
<td>25</td>
<td>26</td>
<td>28</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>Mean</td>
<td>29</td>
<td>45</td>
<td>109</td>
<td>132</td>
<td>49</td>
<td>35</td>
</tr>
<tr>
<td>Average deviation</td>
<td>-6</td>
<td>+7</td>
<td>+76</td>
<td>+104</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>Range of deviation</td>
<td>+63/+60</td>
<td>+71/-60</td>
<td>+199/-16</td>
<td>+343/-12</td>
<td>+104/-38</td>
<td></td>
</tr>
<tr>
<td>No. &gt; limit of normal</td>
<td>4</td>
<td>7</td>
<td>17</td>
<td>20</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

a: Usual adult female range, 10–55 U/liter.
b: The difference between this and the control group (specimen 6) is shown to be statistically significant at the 95% confidence level by Wilcoxon’s signed rank test (6).

n: data points available; Average deviation: the arithmetic mean of all deviations; Mean: the arithmetic mean of all points; Range of deviation: the largest positive deviation/the largest negative deviation; deviation: the value obtained on a sample minus the same patient’s result at 6 weeks postpartum; No. > limit of normal: number of values exceeding the accepted upper limit of normal for adult ambulant women.

per liter, 250 mmol of sucrose, 10 mmol of tris(hydroxymethyl)aminomethane, 1 mmol of ethylenediaminetetraacetic acid, and 1 mmol of mercaptoethanol (5). The homogenate was centrifuged at (0 °C, 10 min, 16,000 × g) in a Model J21B centrifuge (Beckman Instruments, Inc., Spincio Division, Palo Alto, Calif. 94304) and the supernatant fluid was analyzed for CK activity and isoenzyme composition by the techniques described above. The isoenzyme distribution of placental tissue is exceedingly difficult to assess because of the large amount of maternal and fetal blood that is present in this organ; CK was estimated after expressing as much blood as possible.

Results

Table 1 summarizes the results. The Wilcoxon signed rank test (6) was used to compare the values of the six-week postpartum “control” samples with those obtained at the other time intervals. The values for CK are significantly increased during the peripartum period. Most of the CK in the blood in each instance was the MM isoenzyme. However, as shown in Figure 1, 15 of the patients’ sera had a BB band present: first seen in one patient in the third trimester, in three early in labor, in 15 immediately after delivery, and in eight others the morning after delivery. In blood collected on discharge of the patients and at the six-week examination, no BB band was found. In two patients, immediately after delivery and on the following day, an MB as well as a BB band was seen in addition to MM. In one patient, MM and MB was seen the day after delivery.

Myometrium was found to contain 15 U of CK activity per gram of wet tissue (myocardium contains about 50 U/g). The myometrial CK consisted exclusively of the BB isoenzyme. The CK activity of the gravid uterus specimens was greater than that of the nongravid specimens. The total activity of CK in placenta was small, <5 U/g of wet tissue.

Discussion

During normal delivery, there is a marked increase in serum CK activity, up to sixfold the upper limit of normal. At least 90% of the increase is attributable to the MM component, which is known to increase after severe muscular exercise, intramuscular injections, or muscle trauma. These factors, all of which may be present during labor and delivery, probably account for the postpartum increase in the MM isoenzyme (2).

There are several possible sources for the BB band that is commonly seen. It is known that cord blood contains all three isoenzymes, and cord blood admixure with maternal blood may be the source of the BB band. However, most of the increase in BB occurs postpartum, and so this explanation appears unlikely. Another possible explanation is brain injury in the mother, but there was no clinical evidence of brain or central nervous system disorder in our subjects and BB isoenzyme does not increase in the blood unless brain injury is quite severe. Thus this would not account for the presence of BB in the blood of our patients. Because the placenta has only a low total CK activity, its contribution to

![Fig. 1. Creative kinase activity in serum at the blood-sample collection times described in the text.](image-url)
blood CK would be small. We think that the most probable cause of the BB isoenzyme rise is injury to the myometrium during delivery. We have shown that the CK in myometrium is exclusively BB, and the time sequence of the increase would be in harmony with such a hypothesis.

The presence of the MB band also may be explained in several ways. Cord blood admixture is again unlikely in view of its appearance postpartum. Traces of MB may be seen with very marked increases in MM but the increases seen in our cases were not high enough to account for this. It is well known that cardiomyopathy of pregnancy may occur in rare instances. Possibly the MB isoenzyme of CK seen in our three patients postpartum may represent a minimal myocardial damage that may occur in what appears to be a normal pregnancy. This concept requires further study and noninvasive cardiological investigation of normal pregnancies and correlation of any abnormal findings with MB elevations is under way.

In conclusion, we think that the increase in isoenzyme after delivery is due to skeletal muscle injury, the BB band is due to uterine muscle trauma, and the MB band may represent previously unsuspected minimal myocardial damage associated with normal pregnancy. The presence of abnormal CK isoenzymes postpartum severely limits their value in the diagnosis of postpartum myocardial complications.

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References