SOMATOMEDIN A AND B IN SERUM FROM NEONATES, THEIR MOTHERS AND CORD BLOOD

By
H. Svan, K. Hall, M. Ritzén, K. Takano and A. Skottner

ABSTRACT

Somatomedin A by radioreceptor assay and somatomedin B by radio-immunoassay were measured in serum from women immediately after parturition and from their newborns. The mean levels of somatomedin A in both mothers (0.54 U/ml) and infants (0.50 U/ml) were significantly decreased compared to a reference group consisting of 21 non-pregnant women (0.91 U/ml). There was no difference between the mothers and their children.

The mean somatomedin B value in serum from the mothers (63.9 μg/ml) was above that found in non-pregnant women (19.2 μg/ml) and the mean value in cord blood and serum from the infants (7.1 μg/ml) was below it. A positive correlation was noted between somatomedin A and B in cord blood; r = 0.78. The combined somatomedin A and B values in cord blood were positively correlated to birth weight (r = 0.51, P < 0.05).

Somatomedin activity has previously been measured in serum from pregnant women, newborns and cord blood using bioassay methods. Low somatomedin values have usually been found in cord blood, newborns and children under two years of age (Kogut et al. 1963; Van den Brande & du Caju 1974; Hintz et al. 1974; Tato et al. 1975; Giordano et al. 1976). Daughaday et al. (1959) reported normal levels in pregnant women, when using a rat cartilage bioassay. This was later confirmed by Giordano et al. (1976). On the other hand, Hintz et al. (1974) and Tato et al. (1975), using porcine cartilage assays, found significantly reduced somatomedin activity in comparison with normal adults.

All bioassays measure both stimulatory and inhibitory factors, and cartilage from various species may respond differently to these factors. Recently several somatomedins have been purified from human plasma (Hall 1972; Uthne 1973;
van Wyk et al. 1974; Fryklund et al. 1974a,b). The availability of pure somatomedin A, B and C has led to the development of radioligand methods, which are more specific and precise than the bioassays (Hall et al. 1974; Marshall et al. 1974; Takano et al. 1975; Underwood & Van Wyk 1975; Yalow et al. 1975).

The aim of the present study was to determine somatomedin A and B in serum from a group of newborns and their mothers utilizing radioligand methods.

**Material and Methods**

**Material**

Eighteen women and their newborn babies (8 girls, and 10 boys) compiled the total group studied. Twelve of the 18 infants were followed with blood sampling for 4–5 days. Six infants (3 boys and 3 girls) had been born by normal delivery (ND) and 6 infants (3 boys and 3 girls) had been delivered by Caesarian section (CS). In the following these will be referred to as the ND and CS groups.

All the women, who were between 23 and 36 years of age had a full term uneventful pregnancy. Eight of the deliveries were Caesarian sections in epidural anaesthesia (Marcain®) without pre-medication. The indication was mainly narrow pelvis. Ten women had a normal delivery, without any pharmaceutical stimulation. The birth weights ranged between 2800 and 4830 g, with a mean of 3515 g. There was no significant difference in birth weight between the two groups. As a reference, 21 non-pregnant women from a twin material 20 to 29 years of age, were used. One of each pair was selected by chance.

Maternal venous blood and mixed cord blood was obtained at delivery. In the infants capillary blood was taken from the heel at 24 h and four to five days of age. The individual blood samples were centrifuged and the serum was stored at -20°C until used.

**Methods**

Pure somatomedin A (Fryklund et al. 1974b) was labelled with $^{125}$I to a specific activity of 80–140 μCi/μg according to a peroxidase method (Takano et al. 1975). A particulate membrane fraction from human placenta was prepared by stepwise ultracentrifugation, and the assay performed as previously described by Takano et al. (1975). Pooled serum from blood donors was used as an arbitrary reference.

One unit (U) of somatomedin A is defined as the activity of 1 ml of this serum in chick cartilage bioassay. A symmetrical 4-point design was used with two volumes of the reference and the unknown serum, respectively. The volumes were chosen so that the same ratio (4) between the two doses was obtained for both the reference and the unknown serum. Each dose was determined by triplicates. Paralllism, precision (standard error) and 95% of fiducial limits of the measured somatomedin A were calculated as previously described by Hall (1970).

Somatomedin B was determined by radioimmunoassay (Yalow et al. 1975). Somatomedin B used for labelling and as standard was pure according to N-terminal analysis (Fryklund et al. 1974a). A linear standard curve was obtained between the ratio bound/free and the logarithm of dose between 0.5 and 40 ng/ml, when the antiserum was used at a dilution of 1/1500. No cross-reaction occurred with somatomedin A, human growth hormone or insulin.

The results are given as mean ± sem. Significance was calculated by Student’s t-test.
Fig. 1.
Levels of somatomedin A and B in serum from 12 mothers and their infants. M = mother, C = cord, 1D = one day of age, 4D = four days of age. The lines are drawn to connect the values of each child with that of respective mother.

RESULTS

Serum levels of somatomedin A and B in cord blood and in newborns

Consecutive capillary blood samples were obtained from 12 out of 18 infants, 6 from each group, at one and four to five days of age. The levels of somatomedin A and B of these samples as well as those of the mothers are shown in Fig. 1 and Table 1.

The range of somatomedin A levels in samples from cord blood and newborns (ND and CS groups) was 0.21 to 1.00 U/ml with a mean of 0.50 ± 0.05 U/ml. There was a slightly positive correlation between somatomedin A levels in cord blood and the individual mean value of somatomedin A at 24 h and at four days (r = 0.58; P < 0.05). No significant difference was found between the level in cord blood and serum from the infants or between the CS and ND groups (Fig. 1).
Table 1.
Somatomedin A and B in serum from non-pregnant women and from 12 newborns and their mothers. Mean ± sem is given.

<table>
<thead>
<tr>
<th></th>
<th>Normal delivery (ND) group</th>
<th>Caesarian section (CS) group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Somatomedin A U/ml</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-pregnant women</td>
<td></td>
<td></td>
<td>0.91 ± 0.06</td>
</tr>
<tr>
<td>mother</td>
<td>0.70 ± 0.08</td>
<td>0.39 ± 0.06</td>
<td>0.54 ± 0.07</td>
</tr>
<tr>
<td>cord</td>
<td>0.55 ± 0.05</td>
<td>0.46 ± 0.08</td>
<td>0.50 ± 0.05</td>
</tr>
<tr>
<td>child, 1D</td>
<td>0.53 ± 0.06</td>
<td>0.53 ± 0.11</td>
<td>0.53 ± 0.06</td>
</tr>
<tr>
<td>child, 4–5D</td>
<td>0.43 ± 0.07</td>
<td>0.49 ± 0.10</td>
<td>0.46 ± 0.06</td>
</tr>
<tr>
<td>mean of cord and child</td>
<td>0.50 ± 0.04</td>
<td>0.49 ± 0.10</td>
<td>0.50 ± 0.05</td>
</tr>
<tr>
<td><strong>Somatomedin B µg/ml</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-pregnant women</td>
<td></td>
<td></td>
<td>19.2 ± 1.5</td>
</tr>
<tr>
<td>mother</td>
<td>92.3 ± 21.8</td>
<td>35.4 ± 5.4</td>
<td>63.9 ± 13.7</td>
</tr>
<tr>
<td>cord</td>
<td>7.8 ± 1.0</td>
<td>7.2 ± 1.1</td>
<td>7.5 ± 0.7</td>
</tr>
<tr>
<td>child, 1D</td>
<td>5.4 ± 0.6</td>
<td>6.6 ± 0.6</td>
<td>6.0 ± 0.5</td>
</tr>
<tr>
<td>child, 4–5D</td>
<td>7.4 ± 0.7</td>
<td>7.8 ± 1.1</td>
<td>7.6 ± 0.6</td>
</tr>
<tr>
<td>mean of cord and child</td>
<td>6.9 ± 0.5</td>
<td>7.2 ± 0.5</td>
<td>7.1 ± 0.4</td>
</tr>
<tr>
<td><strong>Birth weight, infant g</strong></td>
<td>3636 ± 172</td>
<td>3376 ± 219</td>
<td>3505 ± 138</td>
</tr>
</tbody>
</table>

Immunoreactive somatomedin B levels in cord blood and in infant serum ranged from 3.8 to 11.7 µg/ml with a mean of 7.1 ± 0.4 µg/ml. There was no difference between the two groups. A positive correlation was found between somatomedin A and B in cord blood ($r = 0.78$) as seen from Fig. 2.

**Somatomedin A and B in serum from mothers**

The range and mean of somatomedin A in serum from the 12 mothers were 0.21 to 0.88 U/ml and 0.54 ± 0.07 U/ml, respectively. The same mean level was obtained in the total group of 18 mothers and was significantly lower than that found in the reference group consisting of 21 non-pregnant women (0.91 ± 0.06 U/ml) ($P < 0.001$). The mean somatomedin A level was significantly lower in the CS than in the ND group of women ($P < 0.01$). Comparing the mean of somatomedin A values found in each child and its
The relationship between somatomedin A and B in cord blood. The equation of the regression line is $y = 18.3x + 1.6$ and the correlation coefficient is 0.78 ($P < 0.005$).
DISCUSSION

As shown in the present study the serum level of somatomedin A, determined by radioreceptor assay, was low in cord blood and blood from newborns. The level was similar to that previously found in children between 0.8 and 1.9 years of age (Takano et al. 1976). This finding is in accordance with results obtained in the studies where somatomedin activity was determined by rat or porcine bioassays (Hintz et al. 1974; Kastrup & Andersen 1974; Tato et al. 1975; Gior¬dano et al. 1976; Gluckman & Brinsmead 1976). However, Tato et al. (1975) also reported normal adult levels at the age of four to five days in contrast to the low levels at birth and at one month of age. The present study does not confirm their findings at the age of four days.

The low somatomedin A level found in cord blood and infants is surprising, considering the rapid growth during this period of life. Normal growth is a complex interaction between hormonal factors and the responsiveness of their target organs. Therefore, an increased sensitivity of the target cells may compensate for the lower somatomedin A levels. It remains to be proven that the response and number of receptors of human tissues decrease with increasing age. It is well known that cartilage tissue from young animals is more sensitive to serum growth factors than cartilage from old ones (Heins et al. 1970). However, unknown growth-promoting factors may also be of importance and it has not yet been proven that exogenous somatomedins promote growth in vivo.

In spite of decreasing levels of growth hormone during the first days of life the somatomedin A levels were unchanged. This finding raises the question, at what age somatomedin generation starts to be growth hormone dependent. Studies performed in rats indicate that the liver is a source of growth hormone dependent somatomedin activity (Daughaday et al. 1976). The number of binding sites for growth hormone on liver cell membranes is lower in the foetal than in the adult rabbit (Kelly et al. 1974). In addition, the nearly normal size at birth of the anencephalic foetus and of infants, who later develop signs of pituitary dwarfism, supports the hypothesis that growth and somato¬medin generation during foetal life are not regulated by growth hormone (Job & Rappaport 1974).

The serum levels of somatomedin A in the women at delivery were decreased in comparison with non-pregnant adult women. Furthermore, the group delivered by Caesarian section had the lowest levels. This might be accounted for by different oestrogen levels. Etinyl-oestradiol administration to patients with acro¬megaly or Turner's syndrome reduced somatomedin activity in plasma, whereas it had no direct effect in vitro on the cartilage used in the assay (Almqvist et al. 1961; Wiederman & Schwartz 1972). Serum somatomedin A, measured by radioreceptor assay was found to decrease in tall girls during oestrogen treatment (not published).
The somatomedin B concentration, determined by radioimmunoassay, was high in serum from the mothers. At present, it is not known whether all of the somatomedin B measured represents biological activity or if factors present during pregnancy cross-react with somatomedin B in the radioimmunoassay. Preliminary studies indicate that increased levels of oestrogens may, at least partly, be responsible for the high somatomedin B levels.

The somatomedin values in cord blood represent the levels of somatomedin in the foeto-placental unit at birth. Since there was no correlation between the somatomedin A levels in cord and maternal blood it is probable that somatomedin A is produced also in the foeto-placental unit. The high level of somatomedin A in amniotic fluid also supports this assumption (Hall et al. 1976; Moberg et al. 1976). The placenta may be one source of somatomedin A since the content of somatomedin A in placental extract was higher than could be accounted for by its blood content and somatomedin A binding capacity (Hall, unpublished data). The great difference in somatomedin B values between serum from the mother and cord blood indicates that little, if any, transplacental passage of immunoreactive somatomedin B occurs.

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REFERENCES


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