GLUCOSE CONTENT OF THE AMNIOTIC FLUID IN DIABETIC PREGNANCIES
CORRELATIONS WITH THE MATERNAL BLOOD SUGAR

By
Jørgen Pedersen

Not until the advent of modern micromethods during the second decade of this century, was it definitely established that liquor amnii normally contains glucose. From several investigations performed during the last 25 years it appears, that in normals the concentration of glucose varies considerably with a mean of about 30 mg.%, and a range from (0) 10 to 70 (90) mg.% (e. g. Mohs, 1931, Shrewsbury, 1933, Oakley & Peel, 1949, and Bevis, 1952). Mohs (1931) examined 100 normal women and found a mean of 27 mg.% and a range of 8 to 75 mg.% (Hagedorn-Jensen method). Bevis (1952) found 26 ± 8.1 mg.% (King’s method) and Oakley & Peel (1949) who examined 10 normals, give a mean of 32 mg.% with a range of 11 to 51 mg.% (method not stated). Thus the concentration of glucose is far below that of the blood.

Although sugar was demonstrated in the liquor amnii of diabetics before the century end (Ludwig, 1895, Offergeld, 1906) no comprehensive investigations seem to have been made until those of Oakley & Peel (1949), published in a short summary. The mean amniotic sugar in 53 diabetics was 100 mg.% with a range of 26 to 256 mg.% Thus there is a significant increase in the sugar content of the amniotic fluid in diabetic pregnancies.

The Rigshospital Lying-in-Department B 1945 programme of clinical research in diabetes and pregnancy included a study of the amniotic fluid and in the following our studies on the glucose concentration are reported. Previously a study on the amount of fluid was published (Pedersen & Jørgensen, 1954).

1. Aided by grants from Kong Christian den Tiendes fond, Landsforeningen for Sukkersyge and Statens almindelige Videnskabsfond.
MATERIAL AND PROCEDURE

Diabetics: In 34 cases, 42 values of the glucose content of the capillary blood of the mother and the amniotic fluid were determined simultaneously. In 17 cases there was hydramnios (more than 1000 ml. of amniotic fluid); 10 cases suffered from toxaemia. 19 were long-term treated (l.t.) and 15 short-term treated (sh.t.) cases. The difference between l.t. and sh.t. cases is that l.t. cases were treated for a much longer time at department B than the sh.t. cases. The present 19 l.t. cases were treated as in-patients for an average of the last 50 days before delivery. The blood sugar was kept down by a diet and plenty of insulin, and controlled by means of four blood sugar values taken daily. The mean blood sugar level of each mother during this last stay in hospital was computed (the maternal pregnancy level). The sh.t. patients were treated in the same way, but for a considerably shorter period, on an average 19 days, and no maternal pregnancy level was computed. (For a more detailed account see J. Pedersen, 1954). In all but one case the amount of amniotic fluid was measured.

Non-diabetics: In 27 cases 34 values of the glucose content were determined simultaneously in the capillary blood of the mother and in the amniotic fluid. In 2 cases there was a slight clinical hydramnios (the amniotic fluid was not measured), in 8 cases there was toxaemia, in 1 case eclampsia and in 1 lues. In 12 cases the volume of the amniotic liquor was measured.

In 4 patients varying amounts of glucose was given (3 times intravenously and once orally) to get a rise in the sugar content, before a total of 5 glucose values were determined simultaneously in blood and liquor amnii. These cases are labelled »glucose cases«.

Procedure: Specimens of the amniotic fluid were gained by a catheter by which the membranes were ruptured or by collecting at the moment of spontaneous rupture of the bags and/or at delivery. Specimens with visible blood were discarded, but in 2 cases both with a macerated foetus the dark-reddish fluid gave values that did not differ from others, and hence they were incorporated on account of their special interest.

Each value of the amniotic sugar is the average of 2–4 determinations. The capillary blood sugar values are likewise the average of 2–4 determinations made just before and/or after the sampling of the water.

In the diabetic mothers blood sugar values are available to a varying extent for the hours preceding delivery or rupture of the membranes and so the »six-hour level of the blood sugar« could be computed. This is the average of the available maternal blood sugar values obtained during the last six hours before the sampling of the amniotic fluid. In non-diabetic cases blood sugar values from the time preceding the sampling of the amniotic fluid were only obtained in the glucose cases, and in these cases the average value during the glucose intake was computed.
The Hagedorn-Jensen method (Hagedorn et al., 1946) was used for the determination of the glucose. This method gives »total reducing substance«, the normal values for the blood sugar of the fasting adult being 60 to 120 mg.%.

RESULTS

The material is set out in Tables 1, 2 and 3 and Figs. 1 A, 1 B and 2.

The statistical calculation shows that the variation about the regression lines for the correlation between the maternal blood sugar at the moment of sampling and the sugar concentration of the amniotic fluid is less, when the average values of the blood sugar in glucose cases, respectively, the six-hour level of the blood sugar, are used (Fig. 1 B as compared to Fig. 1 A). Hence, these values are given for the blood sugar in the Tables.

Table 1.
The concentration of glucose in the amniotic water as compared to the corresponding values for the capillary blood of diabetic and non-diabetic mothers.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of values</th>
<th>Glucose concentration (mg. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range</td>
</tr>
<tr>
<td>diabetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>l. t.</td>
<td>25</td>
<td>81-263</td>
</tr>
<tr>
<td>sh. t.</td>
<td>17</td>
<td>83-254</td>
</tr>
<tr>
<td>total diabetics</td>
<td>42</td>
<td>81-263</td>
</tr>
<tr>
<td>non-diabetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>glucose cases</td>
<td>5</td>
<td>130-205</td>
</tr>
<tr>
<td>non-glucose cases</td>
<td>29</td>
<td>70-161</td>
</tr>
<tr>
<td>total non-diabetics</td>
<td>34</td>
<td>70-205</td>
</tr>
</tbody>
</table>

For the meaning of l. t., sh. t., glucose cases: see text.

In non-diabetic cases which have not received glucose the mean value of the glucose concentration in the fluid is 32 mg.% with a range of 10 to 61 mg.% (Table 1), thus confirming the result of others (see above). In diabetic cases the glucose concentration is higher i.e. 61 mg.% with a range 23-139 mg.%, although not as high as in the diabetic material of Oakley & Peel (1949). In non-diabetic cases, receiving glucose just before the sampling of the amniotic fluid, the amniotic sugar level is significantly increased and in our 5 determinations, averaged 58 mg.%, i.e. as high as in the diabetic cases.
For explanation of the terms l.t., sh.t., six-hours level, glucose cases: see text.

Figs. 1 A and 1 B show a positive correlation between the maternal capillary blood sugar at the moment of sampling the amniotic fluid and the amniotic sugar.
Taking the maternal blood sugar as the independent and the amniotic sugar as the dependent variable the statistical calculation shows only minor – not statistically significant – differences between l. t. and sh. t. diabetic cases with regard to the variation about and the slope and level of the regression lines. The equation for the common regression line in diabetic cases may be reduced to: amniotic sugar (mg. °/o) = 0.523 maternal capillary blood sugar (mg.°/o) – 12.2 ± 16.8.

In non-diabetic cases the regression equation may be reduced to: amniotic sugar (mg.°/o) = 0.367 maternal blood sugar (mg.°/o) – 6.5 ± 11.9. Thus the variation about the regression line and its level differ in diabetic and non-diabetic cases.

The different levels are exemplified in Table 2, in which only cases with a maternal blood sugar of 100 to 160 mg.°/o at the moment of sampling are incorporated.

Table 2.
The relationship between the maternal capillary blood sugar within the range of 100 to 160 mg.°/o and the corresponding values for the glucose of the liquor.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of values</th>
<th>Glucose content (mg. °/o)</th>
<th></th>
<th>Amniotic fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Blood</td>
<td>Range</td>
<td>Average</td>
</tr>
<tr>
<td>l. t. diabetics</td>
<td>16</td>
<td>100–160</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>sh. t. diabetics</td>
<td>9</td>
<td>100–160</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>total diabetics</td>
<td>25</td>
<td>100–160</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>non-diabetics</td>
<td>22</td>
<td>100–160</td>
<td>121</td>
<td></td>
</tr>
</tbody>
</table>

Although the mean of the maternal blood sugar is the same in diabetics (124 mg.°/o) and non-diabetics (121 mg.°/o) there is a difference in the amniotic sugar level of 12 mg.°/o, since in diabetic cases the amniotic sugar is 51 mg.°/o, in non-diabetics 39 mg.°/o. This might be expressed by saying that the »amniotic sugar threshold« is lower in diabetics.

In l. t. diabetics we know the maternal pregnancy level of the blood sugar (see above) as well as the six-hour level at the moment of sampling the liquor. In Fig. 2 and Table 3 a negative correlation of the pregnancy level of the blood sugar with the amniotic sugar in l. t. diabetics is shown.

Comments to Fig. 2 and Table 3: The positive correlation of the maternal blood sugar at the moment of sampling the liquor with the amniotic sugar level has to be overcome. This is obtained by using values only from cases
AMNIOTIC SUGAR IN RELATION TO THE MATERNAL PREGNANCY BLOOD SUGAR

11 L.T. DIABETICS

SIX-HOUR LEVEL RANGE:
100-150 MG PER CENT

AMNIOTIC WATER SUGAR (MG PER CENT)

Fig. 2.

whose six-hour level is within the range of 100 to 150 mg.%. Besides, this is the range of the maternal pregnancy level in all but one case. This leaves 13 l.t. cases for examination. In cases with more than 1 pair of corresponding values within this range, the value pair with a six-hour level nearest to the mother's pregnancy level was chosen.

Table 3.
Relationship between the pregnancy level of the blood sugar and the glucose values of the amniotic fluid and its amount. 13 l.t. diabetics with a six-hour level of the blood sugar ranging from 100 to 150 mg.%.

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Glucose (mg. %)</th>
<th>Volume of amniotic fluid (ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Six hour level</td>
<td>Pregnancy level</td>
</tr>
<tr>
<td>7</td>
<td>Range</td>
<td>100-143</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>119</td>
</tr>
<tr>
<td>6</td>
<td>Range</td>
<td>102-149</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>120</td>
</tr>
</tbody>
</table>
The equation for the regression line corresponding to Fig. 2 was calculated. A reasonable fit is obtained by the line: amniotic sugar = \(-0.392\) maternal pregnancy level of blood sugar + 98.8 ± 8.6 (sugar in mg.%).

The negative correlation is exemplified in Table 3. It is seen that the average six-hour level happens to be the same in the two halves of Table 3 and thus the influence of this factor is absent. It should be noted that this negative correlation can be demonstrated only when the ranges of the six-hour and pregnancy levels are the same.

It should be stated that no correlation was found between the amount of amniotic fluid and its sugar content but for a very slight tendency to higher values, when the volume is small. This is also exemplified in Table 3. Oakley & Peel (1949), too, failed to find any direct relationship.

DISCUSSION

Our knowledge of the production and composition of the liquor amnii is limited, but it is now known that the liquor is not a static fluid. The composition and the amount varies considerably in different patients and in the same patient at different times. The water content is said to change hourly (Gellhorn & Flexner, 1942), other constituents remaining for a longer time. It seems probable that liquor is a mixture of active secretion, dialysate of the placenta and amnion, and excretion products of the foetus. It is evident that there is a blood-liquor barriere as with the spinal fluid.

From the present investigations it is clear that the sugar concentration of the liquor changes very rapidly, although not momentarily, and follows that of the mother very closely but at a lower level. This has also been shown directly by sampling the same patients several times at an interval of some hours.

We have come to the conclusion that the glucose concentration of the liquor actually follows that of the foetus, i.e. it is a real foetal product. The blood sugar of the foetus is positively correlated with that of the mother at the moment of delivery and during foetal life (see J. Pedersen, 1952). Moreover it is of interest that the blood sugar of the fasted infant of diabetic mothers during the first 24 hours of life was also positively correlated with the maternal blood sugar at the moment of delivery as well as negatively correlated with the maternal pregnancy level, the latter factor being decisive (J. Pedersen, 1952).

The finding in l.t. diabetics that the glucose concentration in liquor is negatively correlated with the maternal pregnancy level shows that the amniotic sugar concentration cannot be a direct maternal product, as in that case it would be expected that the sugar content would be positively correlated with
the maternal pregnancy level. As long as the foetus is in connection with the mother this factor can be demonstrated only during special circumstances viz: when the maternal blood sugar level at the moment of sampling has been in the range of the maternal pregnancy level for some time (steady state).

In the correlation of the blood sugar with the amniotic sugar we could not demonstrate any difference between l. t. and sh. t. diabetics in contrast to the findings in newborn infants. No doubt this is because the foetal blood sugar at the moment of sampling is the decisive factor, which is to be expected. In contrast to the examination of the newborn infants the examination of the liquor only gives an instantaneous picture.

It is not clear why the »amniotic sugar threshold« is lower in diabetics than in non-diabetics.

For a discussion of the possible rôle of the maternal pregnancy level of the blood sugar in the amount of amniotic fluid the reader is referred to Pedersen & Jørgensen (1954).

**SUMMARY AND CONCLUSIONS**

1) 29 values for the glucose concentration in the amniotic fluid were determined by the Hagedorn-Jensen method in 23-non-diabetic cases near term. The mean was 32 mg.% with a range of 10 to 61 mg.%. In 42 values from 34 diabetic cases the mean was 61 mg.% with a range of 23–139 mg.% and thus significantly increased.

2) The capillary blood sugar of the mother (and the foetus) at the moment of sampling the amniotic fluid has a positive correlation with the amniotic sugar in diabetic as well as in non-diabetic cases. No differences were found between long-term treated (l. t.) and short-term treated (sh. t.) cases. The reduced formula equation of the regression line in diabetics and non-diabetics is given.

3) The regression line in non-diabetics differs from that of diabetics especially in respect to the level of the line, indicating that the »amnion threshold of sugar« is lower in diabetic cases.

4) Under special conditions a negative correlation of the maternal pregnancy level of the blood sugar with the glucose concentration of the liquor could be demonstrated in l. t. diabetic cases.

5) The concentration of sugar in the amniotic fluid seems to be a direct product of foetal tissues.

6) No direct relationship was found between the concentration of sugar in the liquor and its amount.

The statistical calculations were carried out by Arne Nielsen, Actuary, of the firm Statistica.
REFERENCES

Mohs, H.: Arch. f. Gynäk. 147, 532, 1931.
Copenhagen 1952. Danish Science Press.