SERUM IONIC CALCIUM LEVELS DURING PREGNANCY

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Summary

Serum ionic calcium levels during pregnancy were investigated with a calcium flow-through electrode. It was found that the ionic calcium levels decreased with the progress of pregnancy. The possible reasons for this decrease have been discussed in the light of other studies on serum calcium changes during pregnancy.

Previous studies have shown the existence of maternal hypocalcaemia in the late months of pregnancy (Nicholas et al., 1934; Newman, 1953; Hardy, 1956) but the reason for this is uncertain. According to Mull and Bill (1934) the hypocalcaemia is due to diversion of large amounts of maternal calcium to the growing fetus. On the other hand, Hutchin and Kessner (1964) accept that it is due to hypoprotinaemia occurring during pregnancy.

Calcium exists in serum in three forms—an ionized fraction, a protein-bound fraction, and a fraction complexed with organic anions such as citrate, phosphate, bicarbonate, and lactate. Although all these forms are in physiochemical equilibrium with one another, it is the ionized fraction that is physiologically important and under direct hormonal control (Copp, 1969). There are no marked changes in ultrafiltrable calcium levels in serum during pregnancy (Andersch and Oberst, 1936; Kerr et al., 1962). However, neither the total nor the ultrafiltrable calcium levels provide a reliable index of calcium ion activity in the body (Moore, 1970). The recent introduction of a calcium ion-sensitive electrode has made it possible to measure the free calcium in body fluids in a precise and accurate manner. Since ionic calcium levels during the different stages of pregnancy have not been thoroughly investigated it was decided to examine these with the electrode.

Materials and Methods

One hundred and five women with normal uncomplicated pregnancies attending an antenatal clinic were studied. Most of them were multiparous, and their mean age was 26 years. Seventeen were studied during the first trimester, 55 during the second trimester, and 63 during the third trimester of pregnancy. Sixteen women were followed throughout their second and third trimesters. The women took their normal diets with iron and folic acid supplements during the entire course of pregnancy.

Venous blood was collected without stasis into centrifuge tubes containing 1 ml. of liquid paraffin. After incubation for one hour at 37 °C, the clotted blood was centrifuged and the serum was used for the various chemical determinations. The following chemical estimations were made: total calcium by a photometric method with murexide (Spare, 1964); ionic calcium by a potentiometric method using a calcium flow-through electrode (Model 99-20; Orion Research Inc., Mass., U.S.A.) and an Orion digital volt-meter (Model 801); inorganic
phosphorus by the method of Ammon and Hinsberg (1936); total proteins and albumin by the biuret method (Reinhold, 1953). The globulins were calculated as the difference between the total serum proteins and albumin content. The pH of the serum was measured with a Radiometer pH meter (Model 27) provided with a micro-attachment. All estimations were done at room temperature, 26 °C. ±2 °C. (±SD).

RESULTS

The results are given in Table I. Although it was intended to follow up all the women throughout their entire pregnancies, it was not possible to do so since a number of them defaulted and attendance at the clinic was irregular. However, when the results from women attending the clinic regularly were compared with the results from those whose attendance was irregular, no significant differences were found and it was therefore decided to pool the results.

As can be seen from Table I, the total serum calcium levels showed a slight decrease during the later half of gestation. However, the differences were statistically insignificant and this is in keeping with the observations of others (Nicholas et al., 1934; Watney et al., 1971). When the ionic calcium levels were compared, it was seen that there was a significant decrease in this fraction during the different stages of pregnancy, especially marked between the second and third trimesters. Like total calcium, the inorganic phosphorus levels showed a slight decrease in the later months of pregnancy.

It is generally accepted that hypoproteinaemia develops during pregnancy. In this study the hypoproteinaemia was entirely accounted for by depression of albumin levels throughout gestation, with a maximal decrease from the second to the third trimester. A small elevation of concentration of globulins was found in the early part of pregnancy. These observations agree well with other studies on serum proteins during pregnancy (Mendenhall, 1970; Studd et al., 1970).

The mean pH of the sera during the stages of pregnancy did not differ significantly.

DISCUSSION

The recent introduction of a calcium ion-sensitive electrode has made it possible to measure ionic calcium activity in biological fluids such as serum, plasma, gastric juice, urine, and cerebrospinal fluid. Although no studies have been reported of comparisons of measurements with the electrode with other methods, extensive investigations by Moore (1969) and Sachs et al. (1969) have shown that the electrode responds specifically to calcium ions. Further, by using the electrode ionic calcium values in serum have

<table>
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<th>Calcium, phosphorus and protein concentrations in serum during the different stages of pregnancy (mean±S.E.)</th>
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<td>First trimester</td>
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<tr>
<td>Total calcium</td>
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<td>(mg./100 ml. serum)</td>
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<td>Ionic calcium</td>
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<tr>
<td>Inorganic phosphorus</td>
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<td>(mg./100 ml. serum)</td>
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<td>Total proteins</td>
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<td>Albumin</td>
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<td>Globulins</td>
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Numbers in parenthesis indicate number of women.
been reported in a number of conditions such as cirrhosis of liver and hypercalcaemia of cancer (Moore, 1969), chronic renal failure in patients on haemodialysis (Cameron and Price, 1970), and hyperparathyroidism (Dawkins and Moore, 1970). The electrode has also been used to study the effects of hormones on calcium ion activity in animals (Bernstein et al., 1969; Raman, 1970). It seems that this is a valid method for determining the ionic calcium levels in serum.

In this study it was observed that though the total calcium levels showed only a slight decrease in the later months of pregnancy there was a significant decrease in the ionic calcium levels. According to Kerr et al. (1962) and Hutchin and Kessner (1964) the hypocalcaemia can be explained by concomitant hypoalbuminenaemia. However, this would not explain the lowered ionic calcium levels since this fraction is directly under hormonal control, and changes in serum protein concentration would only affect the amount of protein-bound calcium. Thus, a decrease in serum proteins would result in decreased protein-bound calcium but not a decrease in the ionic calcium levels.

It might be argued that the increased production of certain proteins during pregnancy might be responsible for the decreased ionic calcium levels by increasing the protein-bound calcium. According to Urist et al. (1958) phosphoprotein complexes with increased calcium binding capacities appear in the serum of birds during oestrogen treatment. Studd et al. (1970) have also shown increased levels of $\beta$-lipoproteins in the blood of pregnant women. Although the various calcium fractions in the serum were not determined, ultrafiltration studies by Kerr et al. (1962) have shown that the concentration of protein-bound calcium during pregnancy is in fact slightly decreased. Further, if the increased production of these proteins does affect the calcium-binding properties of maternal serum, they should have similar effects on the fetal serum. However, studies on cord blood in a variety of animals indicate that the total, ultrafiltrable, and ionic calcium levels are all correspondingly greater in the cord than the maternal serum (Bawden et al., 1965; Tan and Raman, 1972). It therefore seems unlikely that increased production of phosphoprotein complexes and $\beta$-lipoproteins are responsible for the lowered ionic calcium levels in maternal serum during pregnancy.

On the other hand, the observed changes could be the result of suppression of the parathyroid glands since ionic calcium levels depend primarily on their activity. However, maternal parathyroid hyperplasia occurs during normal pregnancy (Albright and Reifenstein, 1948) and circulating levels of parathyroid hormone increase with the progress of pregnancy (Cushard et al., 1971). It is nevertheless possible that during pregnancy other factors might antagonize the normal action of parathyroid hormone. In pregnancy there is a greatly increased production of adrenal corticosteroids and of oestrogens, both of which are known to influence calcium metabolism (Nordin, 1966). Adrenal corticosteroids are known to aggravate the hypoparathyroid state as well as antagonize the effects of exogenous parathyroid extract on both calcium and phosphorus metabolism in man (Eliel et al., 1971). Oestrogens also lower the serum calcium and phosphorus levels in man (Nordin, 1966). The antagonistic action by both oestrogens and corticosteroids on the normal action of parathyroid hormone could therefore result in lowering of both total and ionic calcium levels. From a study of the diffusible serum calcium levels in pregnancy, Nicholas et al. (1934) have also suggested that there is disturbance of the parathyroid function during pregnancy. Since it is now possible to measure the parathormone levels in serum, investigation of the activity of the parathyroid glands in pregnancy would probably clarify calcium homeostasis during pregnancy.

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References


