THE GENESIS OF PHYSIOLOGICAL IMMATURITY AND ITS RELATIONSHIP TO KETONURIA IN THE MOTHER DURING PREGNANCY

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 50, No. 8, pp. 75-80, August, 1960
Original article submitted July 1, 1959

Numerous investigations [1-6] have shown that the normal intrauterine development of the fetus is controlled by the regulating influence of a gestational dominant, developing at the beginning of pregnancy.

The regulating action of the gestational dominant determines the pituitary's gonadotropic function, specifically for pregnancy, and thereby the hormonal function of the corpus luteum. The latter makes possible the implantation and the formation of a physiologically efficient placenta, ensuring the normal development of the embryo and fetus. I. A. Arshavskii [2, 3, 4, 5] drew attention to the fact that inhibition of the gestational dominant, caused by the formation (at suitable times during pregnancy) of a new dominant, in association with the action of a variety of pathogenic agents, leads to disturbance of the normal formation of the placenta and also to metabolic changes, characterized by a significant shift toward acidosis.

Reports in the literature [8, 10, 12, 16, 20] testify to the fact that the most essential component of the acidotic state of the blood in pregnant females is incompletely oxidized products of the breakdown of lipids, namely, ketone bodies (β-hydroxybutyric and acetoacetic acids, and acetone). A factor of secondary importance is the formation of lactic acid. The problem of the transfer of ketone bodies from the maternal blood to the fetal blood (in abnormal pregnancy) has not yet been solved, on account of the impossibility of estimation of ketone bodies in the fetal blood, whether in man or laboratory animals (owing to the difficulty of obtaining plasma or serum in sufficient quantities, especially in the early stages of pregnancy). For these purposes it was necessary to choose an animal in which the fetus is characterized by the presence of a large enough allantois. Accordingly, the fetus of cattle was selected as test object.

The aim of the present investigation was to study the possibility of the transfer of ketone bodies from the maternal blood to the fetal blood, the development of the placenta and the characteristics of the fetus in relation to the presence or absence of ketonuria in the mother during pregnancy, and the state of physiological maturity of newly born calves in relation to the presence or absence of ketonuria in the mother.

EXPERIMENTAL METHOD

The material to be investigated was collected directly from the Moscow Mikoyan Meat Combine and from the Voskresenskoe and Ramenskoe collective farms in the Moscow region.

At the meat combine, the fetuses, placenta, and corpora lutea were carefully extracted from cows slaughtered at different periods of pregnancy. In each case the urinary bladder was removed from the cow for collection of the urine, and samples of the allantoic and amniotic fluids were collected from the fetuses. All these fluids were subjected to qualitative analysis for ketone bodies by Roser's test [19]. Attention was paid to the rate of development of the reaction – instantaneous, or developing after not more than 3-5 minutes, by which the degree of ketonuria could be judged.

In the collective farms, newly born calves and their placentas were studied. A short time after their delivery from the mother, urine was collected, and during calving the allantoic and amniotic fluids were obtained (also for analysis for ketone bodies).

The investigation of the fetuses and their placentas was carried out in the following order: the fetuses were weighed, and their length from the occiput to the base of the tail, and the length of the tail, were measured. The external morphological condition of the fetuses was assessed from the following signs: ossification of various parts of the skeleton, the presence and distribution of the hair cover, the length of the limbs, opening of the palpebral fissure and the presence of eyelashes and teeth, and descent of the testicles into the scrotum.

The age of the fetus was determined from these findings. For this purpose we used the indices recommended by G. A. Shmidt [14] and A. P. Studentsov [12]. Since the placenta in cattle consists of separate cotyledons (placenta multiplex), all the fetal placentas were counted, weighed, and measured. The placentas were subdivided into three groups in accordance with their size: large, medium, and small. Within the limits of each group, the arithmetic-mean surface area of the individual placenta was calculated, and the total surface area deduced. The total weight of the placentas and the weights of the three groups were determined. The material thus obtained was distributed in accordance with age groups. Within the limits of each age group, we compared the results obtained in the mothers whose urine contained ketone bodies with those in the mothers in whose urine ketone bodies were not detected. Altogether 45 fetuses and 15 calves were investigated.

EXPERIMENTAL RESULTS

Of the 60 pregnant cows investigated, only in 29 was ketonuria not found (normal pregnancy); in the remaining 31 ketonuria was present. When no ketone bodies were found in the mother's urine, they were also absent from the allantoic and amniotic fluids of the fetuses and the newly born calves. The presence of ketone bodies in the mother's urine was accompanied by their appearance in the allantoic fluid, but they were not present in the amniotic fluid. Thus, in the presence of ketonuria in the mother, ketone bodies pass from the maternal blood to the fetal blood, and thence, through the kidneys, into the allantoic fluid.

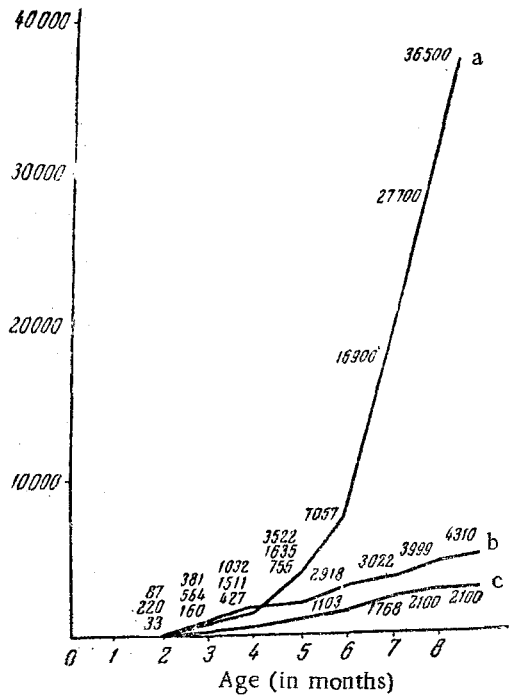

Fig. 1. Changes in the weight of the fetus, and the weight and surface area of the placenta at different periods of normal pregnancy. a) Weight of fetus; b) surface area of placenta; c) weight of placenta.

Let us consider the findings relating to the placentas and the weights of the fetuses obtained from mothers in which ketonuria was not present. In our investigations the earliest age of the fetuses corresponded to two months of intrauterine development (duration of pregnancy in cows is on the average 285 days).

In Fig. 1 are given the results showing the changes in the weight of the fetus (a), the total weight of the placenta (c), and the total surface area of the placenta (b) at different times during pregnancy. Between the end of the second month (87 g) and the end of the pregnancy (36,500 g), the weight of the fetuses increased roughly 420 times. Between the end of the second month of pregnancy (33 g) and the end of pregnancy (2100 g), the weight of the placentas increased only 64 times. The greatest increase in the body weight of the fetus took place during the last months of pregnancy. The greatest increase in the total weight of the placenta occurred during the first months (up to the 4th or 5th) of pregnancy, after which the further growth in the weight of the placenta followed an exponential curve. At the end of the second month of pregnancy, the number of cotyledons was 67; at the end of the third month, 71. Beginning with the fourth month, the number of cotyledons became more or less constant until the end of pregnancy, amounting on the average to 80-90. In isolated cases, over 100 cotyledons were found (as many as 140). The greatest portion of these cases occur in large and medium-sized placentas, and only very few in small placentas.

The same lack of correlation was thus found with respect to the fetuses of cattle, between the increasing dimensions of the total delineated area of the placental surface (which is judged by the weight of the placenta) and the increasing weight of the fetus, as has been established with respect to the fetuses of other mammals by Barcroft [15], Huggett and Hammond [19], and I. A. Arshavskii [1]. The researches of I. A. Arshavskii and his co-workers [6, 7, 11] showed that this lack of correlation during normal pregnancy is compensated by corresponding reactions of the developing fetus, namely, by the adaptive functions of its cardiovascular, respiratory, and musculoskeletal systems. In the cows in whose urine no ketone bodies were found, the corpus luteum of pregnancy acquires its greatest weight at the end of the third month, and in different cows its weight varies between 6.3 and 7.2 g. Starting with the second half of pregnancy a fall in the weight of the corpora lutea takes place, on account of their commencing involution. The subsequent repeated enlargement of the corpus luteum is known to be due to proliferation of connective tissue, supplanting the reducing lutein cells [13, 17].

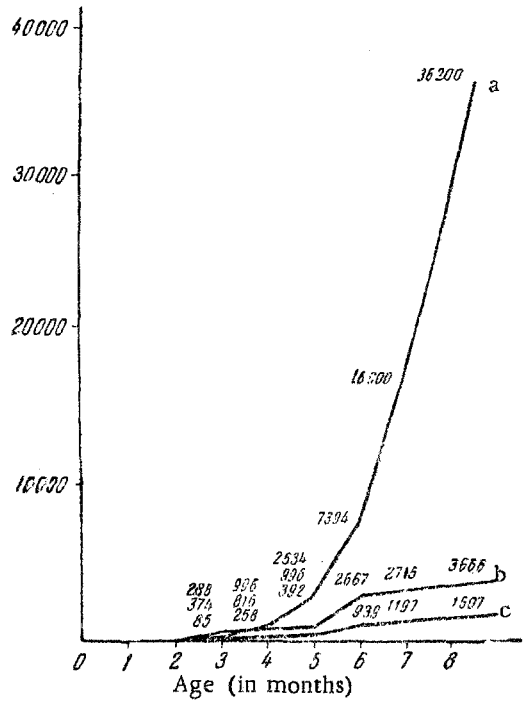

Fig. 2. Changes in the weight of the fetus and in the weight and surface area of the placenta at different times during pregnancy in the presence of ketonuria. a) Weight of fetus; b) surface area of placenta; c) weight of placenta. In these cases no fetuses less than 3 months old, or 7 months old or older, were investigated.

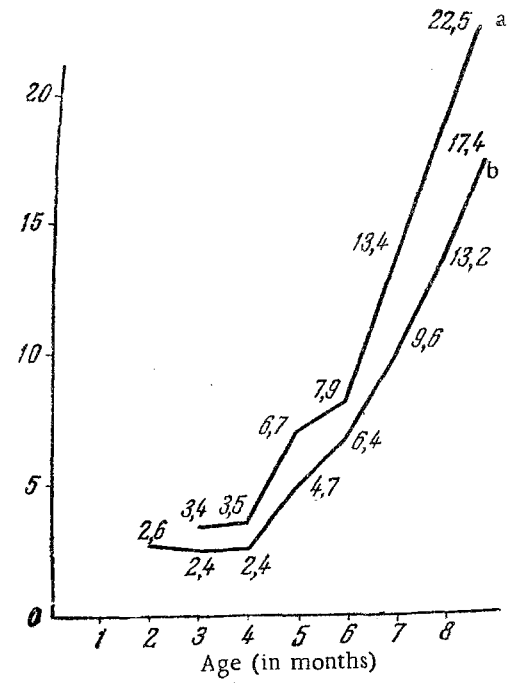

Fig. 3. Relationship between the weight of the fetus and placenta at different times during pregnancy. a) During pregnancy with the presence of ketonuria; b) during normal pregnancy.

The data shown in Fig. 2 show the change in the weight of the fetus (a), the total weight of the placenta (c), and the total surface area of the placenta (b) at different times during pregnancy in cows in whose urine ketone bodies were found. In the first place, attention is drawn to the fact that the weight and surface area of the placenta during all the months of intrauterine development have appreciably smaller values than the placenta in the previous group of cows. At the same time, the weight characteristics of the developing fetus differ only slightly from those of the fetuses of the previous group. Nevertheless, the fetuses in which ketonuria was demonstrated by such signs as the presence and distribution of the hair cover, the time of opening of the palpebral fissure, the time of appearance of the teeth, and the time of descent of the testicles into the scrotum, were characterized by clearly marked signs of physiological immaturity, by comparison with the fetuses of the previous group. When ketonuria was present during the first half of pregnancy, the corpora lutea were appreciably smaller in weight, varying between 4.5 and 5.5 g. Partial involution of the corpora lutea will naturally account for the less perfect placentation in the cows showing ketonuria. The less perfect placentation is shown, not so much by the number of cotyledons formed, as by their size. In cows with ketonuria, a considerable number of the placentas are of the small group, and comparatively few, of the large and medium-sized groups. The small size of the cotyledons corresponds to the small size of the caruncles, i.e., of the maternal part of the placenta.

In Fig. 3. are shown the results characterizing the changing relationship between the weight of the fetus and the weight of the placenta at the various months of intrauterine development in fetuses with the presence (a) and absence (b) of ketonuria. It can be seen that, at all stages of intrauterine development in fetuses with ketonuria, the weight of fetus per unit weight of placenta is far greater. This difference in the relative proportions shows that such fetuses are in much less suitable conditions as regards the supply of oxygen and nutrient substances than fetuses without ketonuria. As investigations carried out in our laboratory show, however, the physiological immaturity of fetuses with a less perfect placentation is created, not so much by their more limited supply of oxygen and nutrient substances, as by changes in their nerve centers due to acid metabolic products passing from the maternal to the fetal blood. It is evident that the ketone bodies play an important part in the induction of these changes in the fetal nerve centers.

We observed one special case in which, in the presence of a high degree of ketonuria and concentration of ketone bodies in the allantoic fluid (instantaneous reaction), the placenta began to undergo complete absorption, and death of the fetus took place at the age of about four months. The corpus luteum in this case was in a stage of almost complete involution.

Newly born calves were investigated during the course of one month (January, 1957). All the cases of ketonuria were observed in one of the collective farms (Ramenskoe) where not only was it possible to take note of this condition, but also, in contrast to the observations at the meat combine, more detailed information was available on the feeding conditions and general care of the animals, and on the physiological state of the newly born calves.

It is clear from the findings described above that newly born animals, developing in the presence of ketonuria in the mother, are smaller in weight and in the surface area of the placenta at each month of intrauterine development than newly born animals with a normal pregnancy. They are smaller in weight on the average by 493 g, and in surface area by 644 cm^2. The weight of the newly born animals is roughly the same in the two groups, and this naturally makes a much worse correlation between the weight of placenta and fetus (see Fig. 3). Newly born animals from mothers with ketonuria are characterized by lower indices of the heart rate, the respiration rate, and the body temperature, and also by a considerably weakened and sluggish sucking reflex.

All these calves developed a toxic dyspepsia within a few days of birth; three of nine calves investigated, from cows with ketonuria, died.

SUMMARY

The aim of this work was to investigate the peculiarities of placentation and characteristics of the fetus in relation to the presence or absence of ketonuria during pregnancy; the possible transfer of the ketone bodies from maternal into the fetal blood and the state of physiological maturity of the newborn with relation to the presence or absence of maternal ketonuria was also studied. The investigation was conducted on cows. The corpus luteum and placenta in cows with absence of ketonuria are characterized by normal development. The fetuses and newborn calves show signs of physiological maturity, i.e., specific features of their physiological functions correspond to their actual calendar age.

The presence of maternal ketonuria is associated with partial involution of the corpus luteum and with signs of imperfect placentation. In this case the ketone bodies pass from the maternal into the fetal blood.

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