AN ANALYSIS OF THE PECULIARITIES AND SIGNIFICANCE OF CHANGES IN THE INTERNAL ENVIRONMENT OF THE ORGANISM DURING PREGNANCY

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The study of environmental factors necessary for the complete formation of the fetus and the newborn organism is of major significance in connection with the problems of antenatal preservation and prophylaxis.

Investigations of the physiological functions of the maternal organism during pregnancy, performed in our laboratory [1, 2, 3] and lasting over many years, have served to establish that the pregnant organism exists in a characteristic state, so-called gestation dominant. The latter determines the endocrine status characteristic for pregnancy, i.e., primarily changes in the gonadotropic functioning of the hypophysis and the functioning of the yellow body. In turn, the endocrinological changes determine, on the one hand, the gravid changes in the uterus, leading to the development and formation of a physiologically complete placenta, and on the other, the specific traits of the metabolism, namely the specific state of the acid-base homeostasis.

It is known that the acid-base equilibrium during pregnancy is significantly altered toward the side of acidosis, especially during various toxicoses of pregnancy [4-6, 10, 16, 22]. However, the question of real changes in the acid-base equilibrium during normal pregnancy has not been resolved until now. The authors of a number of works maintain that normal pregnancy is characterized by a compensatory acidosis [4, 6, 8, 12-14, 16, 17, 22, 23]. These viewpoints have been reflected in obstetrical textbooks and manuals up until the present.

Investigations have appeared in the last 30 years, negating the theory that normal pregnancy carries with it an inherent acidosis, and even asserting the presence of a shift toward the alkaline side [9, 11, 15, 18, 19, 20, 21]. All the literature on this question is based on single observations, which pay absolutely no attention to the state of the newborn as dependent upon the level of the acid-base equilibrium, both during normal pregnancy and during various forms of its pathology.

In this work the goal was to elucidate the state of certain indices of acid-base homeostasis during pregnancy, as related to the question of what is normal in the metabolism during pregnancy, accompanied by complete intrauterine development, and what characterizes pathological pregnancy, terminating with the birth of physiologically immature newborns.

EXPERIMENTAL METHOD

The investigations were performed on non-pregnant and pregnant female rabbits of the chinchilla family. Several of the females were investigated before and after the mating, during the period of the pregnancy, and sometimes, after parturition. The alkaline reserves of the plasma and the urine indices were studied throughout the entire pregnancy, and in several of the rabbits this was done systematically, every nine days. The blood pH was measured 1-3 times (depending on the nature of the experiment) in the second half of the pregnancy, using a positive electrode and the LP-5 potentiometer, on whole blood drawn from the heart under vaseline oil. Determination of the pH was carried out in an apparatus which was carefully prepared prior to the experiment: the compensator for asymmetry of the positive electrode was set according to the buffer solution, the latter being warmed in a water bath to the probable temperature of the blood. The temperature compensator was set to correspond with the temperature of the blood at the

TABLE 1. Characterization of Pregnancy According to Indices of Acid-Base Equilibrium During Normal and Pathological Courses of Pregnancy and Following Experimental Disturbance of Higher Nervous Activity

Physiological condition of the organism	Plasma alkaline reserves (ml) period of pregnancy			pH of whole blood
	first third	second third	third third	
Normal pregnancy. Birth of physiologically mature newborns.	45—51 48±3	47—57 51±3	45—57 49±4	7,41—7,47 7,43±0,02
Pathological course of pregnancy. Birth of physiologically immature newborns or cessation of intrauterine development.	28—43			7,32—7,3
Pregnancy before (numerator) and after experimental neurosis at the beginning of the second half of pregnancy. Birth of physiologically immature newborns or cessation of intrauterine development (denominator).	47—57 24—41			7,41—7,47 7,29—7,39
Non-pregnant females in the diestrus phase.	45—57 49±4			7,32—7,37 7,34±0,02

Note: In the numerator – fluctuation limits, in the denominator – average ± the quadratic error.

moment of the investigation. The blood was studied immediately after being drawn (within 1-2 min). Before and after each measurement of the pH in the pregnant animals, a control pH measurement was performed on the blood of non-pregnant female rabbits; in this case, we tried to obtain a result using the same arrangement of compensators. In this way, we attained the maximum comparative accuracy.

The plasma alkaline reserve was determined by the method of Van Slyke, ammonia by the modified method of Conway (for the photoelectrocalorimeter), urea by the method of Borodin. Titration of the urine was done with 10 normal base and acid. Protein was determined by a qualitative test with nitric acid, ketone bodies by Lange's test with sodium nitroprusside. The urine was collected in a specially constructed metabolism cage, under xylol.

The investigation was carried out on 131 rabbits, of which 91 were pregnant and 40 were non-pregnant (control). In 51 of the rabbits the pregnancy ran a normal course, while in 40 there was some pathology. For the formation of this pathology, we created experimental neurosis in 21 of the pregnant rabbits, a method adopted in our laboratory; in a special chamber, the animal is subjected to the action of a loud noise (automobile siren) and an electrical induction current passed through the floor of the chamber. This form of stimulation can be termed "extreme" (according to I. P. Pavlov) or "stressing" (according to Selye). Stimulation in short intervals was continued for 30 min to 1 h. It was applied twice on various days, more rarely three times or even once. After this, the rabbit was placed in the metabolism cage for collection of the urine, and 2-3 days after the first stimulation we carried out the first blood analysis.

After the births, we investigated a total of 320 newborn rabbits. If the births did not occur at the proper time, the rabbit was sacrificed, autopsied, and the uterus and yellow bodies studied. In the newborns, we investigated the weight, rectal temperature, ECG, cardiac and respiratory rhythms, thermoregulatory reaction to cold stress (chilling at 20° for 20 min). The surviving rabbits were studied periodically for up to 4 months and longer.

EXPERIMENTAL RESULTS

In the normal pregnancy, the pH of the whole blood was characterized by figures of from 7.41 to 7.47, with an

TABLE 2. Indices of Acid-Base Equilibrium and the Outcome of Pregnancy in Rabbits with Experimental Neurosis

Experiment No.	Weight of the rabbits (in grams)	Day of pregnancy on which the stimulation was carried out	Before stimulation		After stimulation				Outcome of the pregnancy
					in the first days		in the subsequent days		
			pH	alkaline reserve (in ml)	pH	alkaline reserve (in ml)	pH	alkaline reserve (in ml)	
20	4,000	16th, 17th, 18th	7.44	51	7.29	24	–	–	Undeveloping pregnancy. Rabbit died on the 24th day of pregnancy. On autopsy – resorption of the fetuses.
56	3,500	16th	7.44	49	7.34	24	–	–	Undeveloping pregnancy. Rabbit died on the 22nd day of pregnancy. On autopsy – resorption of the fetuses.
63	3,500	18th	7.44	56	7.32	29	–	49	Birth at term. Newborns physiologically immature.
65	3,300	18th	7.44	52	7.30	24	–	49	The same.
96	3,100	18th	7.42	50	7.29	25	–	–	Undeveloping pregnancy. Rabbit died on the 25th day of pregnancy. On autopsy – resorption of the fetuses.
100	3,950	20th	7.47	54	7.52	36	7.40	40	Birth at term. Newborns physiologically immature.
103	2,850	15th	7.42	49	7.30	30	7.34	–	Undeveloping pregnancy. Rabbit sacrificed. On autopsy – resorption of fetuses.
115	3,150	18th, 21st	7.43	49	7.37	39	–	–	Birth at term. Newborns physiologically immature.
118	3,500	20th, 21st	7.42	47	7.47	37	7.38	39	The same.
121	3,600	16th, 18th	7.44	52	7.37	39	–	–	The same.
122	3,900	17th, 18th	7.44	49	7.35	36	–	–	The same.
123	3,000	16th, 17th	7.42	47	7.37	35	7.35	22	Premature birth (on the 25th day). Newborns miscarried, physiologically immature.
124	3,200	18th, 23rd	7.41	57	7.50	32	7.30	44	Undeveloping pregnancy. Rabbit sacrificed. On autopsy – resorption of the fetuses.
127	3,600	16th, 18th	7.41	53	7.48	39	7.34	41	Birth at term. Newborns physiologically immature.
129	4,000	16th, 21st	7.44	49	7.48	37	7.31	36	The same.
132	4,200	19th, 20th	7.43	55	7.39	41	–	–	Premature birth (on 28th day). Newborns miscarried, physiologically immature.
134	3,800	15th, 17th	7.45	51	7.32	30	–	–	Undeveloping pregnancy. Rabbit sacrificed. On autopsy – resorption of the fetuses.
137	3,500	17th, 18th	7.44	50	7.37	41	–	–	Premature birth (on 26th day). Newborns miscarried, physiologically immature.
139	3,500	16th, 17th	7.43	51	7.43	51	–	–	Birth at term. Newborns physiologically mature.
140	3,500	17th, 21st	7.43	49	7.49	40	–	–	Rabbit sacrificed on 23rd day of pregnancy. Fetuses corresponded to their calendar age.
141	3,100	16th, 17th, 21st	7.42	50	7.44	35	7.35	45	Undeveloping pregnancy. On autopsy – resorption of the fetuses.

average of 7.43. In the control rabbits in the stage of diestrus, the blood pH was equal to 7.32-7.37, with an average of 7.34. Thus, during pregnancy the pH shifts toward the alkaline side by an average of 0.09. The alkaline reserves of the plasma – 45-57 ml before pregnancy, in the diestrus stage, with an average of 49 ml – were the same as those seen during the normal course of pregnancy (Table 1).

Urinary ammonia during normal pregnancy was somethimes considerably elevated, but in a number of cases it remained unchanged.

Analysis of urinary ammonia and urea in the pregnant rabbits leads to the conclusion that changes in this index are dependent upon changes in the general metabolism, regulated by the nervous system, and do not indicate an acidotic shift during pregnancy, as has been assumed. This question merits special attention.

Pregnancy with an alkaline shift in the metabolism terminates in the birth of physiologically mature newborns. In the pregnant rabbits with experimental neurosis, the blood pH shifted from values of 7.41-7.47 to 7.29-7.39, the plasma alkaline reserves – from 47-56 ml to 24-41 ml (see Tables 1 and 2). In this case, in contrast to the normal pregnant rabbits, we sometimes observed the presence of protein and ketone bodies in the urine.

The data obtained permits concluding that we have created an experimental model which reproduces the series of symptoms observed clinically during toxicoses of pregnancy. I. A. Arshavskii and L. A. Pronin [1, 2, 3, 7] established that during experimental neurosis pregnancy is interrupted, or terminates in the birth of physiologically immature newborns. Our experiments confirm this conclusion. Interruption of pregnancy is accompanied by cessation of intrauterine development. In these cases, autopsy discloses the process of resorption or maceration of the fetuses, and in the ovaries one observes yellow bodies in various stages of involution.

In 6 cases it was possible to demonstrate that initially the pregnant organism may even respond to the neurotic action by an increase in the alkaline shift of the blood pH. Subsequently, the initial alkaline shift is replaced by a change-over to the acidotic condition. In these cases, the alkaline reserve of the plasma, as a rule, was reduced even in the alkaline phase, reflecting the tendency toward a shift in the acidotic direction. According to our observations, the rate of development of the acidotic changes depends on the stability of the original pregnancy state, i.e., the resistance of the gestation dominant. In connection with this, experiment No. 139 is of interest (see Table 2), in which the acidotic changes did not occur despite the usual one-time form of stimulation. In this case, the strongly established pregnancy state eventuated in the birth of physiologically mature newborns.

As in the case of the experimental neuroses, in the females with acidotic indices in their metabolism, not having been exposed to the special "stressing" action, the pH level was shifted toward the acid side (to 7.32-7.39), and the alkaline reserve of the plasma was equal to 28-43 ml. In these cases, we observed interruption of pregnancy and intrauterine death of the fetus, or birth of physiologically immature rabbits.

It should be emphasized that in the pregnant rabbits that underwent the "stressing" stimulation, the birth, as a rule, occurred at full term (if the pregnancy was not interrupted altogether). However, they gave birth to physiologically immature newborns. Only in 3 of the animals with experimental neurosis did we observe premature birth. In this case, the newborns were miscarried, and in their physiological characteristics they did not correspond to their calendar age, i.e., were physiologically immature. In these instances, we also recorded acidotic shifts in the pregnant rabbits.

SUMMARY

Experiments were staged on gravid and nongravid female rabbits (chinchilla breed).

The data obtained showed that normal gravidity is characterized by alkalotic changes in the metabolism, which is a necessary condition for normal fetal development and birth of physiologically mature offspring.

An acidotic shift in metabolism during gravidity is characteristic of pathological processes, resulting in the birth of immature newborns or arrest of fetal development. An acidotic derangement in metabolism during gravidity can be induced by experimental neurosis, i. e., suppression or inhibition of the gestation dominant.

LITERATURE CITED

1. I. A. Arshavskii, Works of the Scientific-Research Institute of Biology [in Russian]. Kharkov, 1956, Vol. 24, p. 161.
2. I. A. Arhsavskii, Works of the Institute of Normal and Pathological Physiology of the Acad. Med. Sci. USSR [in Russian]. M., 1959, Vol. 3, p. 220
3. I. A. Arshavskii, Works of the A. I. Severtsev Institute of Animal Morphology [in Russian]. 1957, No. 22, p. 37.

4. G. A. Baksht, Pregnancy and Metabolism [in Russian], M., 1929.
5. L. S. Galeeva, in the book: Questions in Obstetrics and Pediatrics [in Russian]. Sverdlovsk, 1958, Vol. 2, p. 71.
6. I. T. Mil'chenko and O. S. Monoilova, Acid-Base Equilibrium During Various Physiological and Pathological Conditions of the Female Sex and in Kidney Patients [in Russian]. Kuibyshev, 1956.
7. L. A. Pronin, Works of the Institute of Normal and Pathological Physiology of the Acad. Med. Sci. USSR [in Russian], M., 1959, Vol. 3, p. 187.
8. V. I. Skvortsov, Acidoses and Alkalosis in Medicine [in Russian]. M., 1928.
9. H. Behrend, J. Berberich, and H. Eufinger, Arch. Gynäk., 1931, Bd. 143, S. 537.
10. O. Bokelman and J. Rother, Z. Geburts. Gynäk., 1924, Bd. 87, S. 584.
11. G. K. Doering, H. H. Loeschke, and B. Ochwadt, Citing P. H. Rossier, M. Hotz.
12. S. A. Gammeltoft, Skand. Arch. Physiol., 1913, Bd. 28, S. 325.
13. K. A. Hasselbalch, Biochem Z., 1912, Bd. 46, S. 403.
14. K. A. Hasselbalch and S. A. Gammeltoff, Ibid., 1915, Bd. 68, S. 206.
15. I. Heerhuberg, H. H. Loeschke, and U. Westphal, Pflüg. Arch. ges. Physiol., 1948, Bd. 250, S. 42.
16. M. Labbe and F. Nepvë, Acidosis and Alkalosis [in Russian]. M., 1931.
17. A. Leimdörfer, J. Novak and O. Porges, Z. klin. Med., 1912, Bd. 75, S. 301.
18. M. Nice, J. W. Mull, E. Muntwyler, et al., Am. J. Obstet., 1936, v. 32, p. 375.
19. P. H. Rossier and M. Hotz, Schweiz. med. Wschr., 1953, Bd. 83, S. 897.
20. H. Siedentopf and W. Eissner, Z. Geburtsh. gynäk., 1929, Bd. 96, S. 76.
21. W. Umbricht and H. Mean, Zbl. Gynäk., 1942, Bd. 66, S. 714.
22. Wieser, Cited by G. A. Baksht.
23. L. Zuntz, Arch. Gynäk., 1908, Bd. 78, S. 106; 1912, Bd. 96, S. 188.