

ALTERATIONS IN FETAL RABBIT PROTHROMBIN TIME AT DIFFERENT STAGES OF GESTATION AND DURING ASPHYXIA

A.A. Orekhova

From Biochemical Laboratory (Chief-Doctor Biological Sciences A. D. Braun) and Section for Newborn (Scientific Director-Active Member AMN SSSR Prof. A. F. Tur) Institute of Obstetrics and Gynecology (Director-Corresponding Member AMN SSSR P. A. Beloshapko) AMN SSSR, Leningrad

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It is well known that, in comparison with the adult, the newborn has a marked prolongation of its prothrombin time [1, 2, 3, 8].

In the opinion of many authors this is the result of exogenous and endogenous vitamin K deficiency [4, 5, 6, 8, 10].

However, our preceding observations have demonstrated that the prothrombin time in the newborn begins to diminish beginning with the 3rd to 5th day of life even when these infants receive no vitamin K.

In addition, it has been shown that the liver of infants dying as a result of intracranial hemorrhages had adequate amounts of vitamin K even when the prothrombin time during life had been shown as being prolonged. Evidently, the prolongation of the prothrombin time in the newborn must be associated not only with K hypovitaminosis but also with many other factors.

The present study had as its goal the observation of prothrombin time changes in the period of intrauterine ontogenesis and the alterations which occur when the fetus enters into extrauterine life, i.e., starts the period of pulmonary respiration and, also, how prothrombin time is affected in the fetus by asphyxia.

EXPERIMENTAL METHODS

The experiments were conducted upon intratubal rabbit fetuses. The pregnant rabbit received an injection subcutaneously of a 5% solution of hexanastab, the dose being 4 cc per 1 kg of animal weight. After the rabbit had gone to sleep, it was placed into a bath of physiological saline the thermostatic control being set at a temperature of 37.5-38°, the abdominal cavity was opened, the uterine horns brought out and the fetuses removed in turn. The blood for determining the prothrombin times was taken from the fetal heart. The fetal prothrombin time determinations were made by the Kazantseva modification of the Quick method [2, 3].

EXPERIMENTAL RESULTS

Prothrombin time in the period of intratubal ontogenesis. In 16 fetuses aged 20 to 24 days it was not possible to determine the prothrombin time by the Quick-Kazantseva method as the blood did not coagulate even after two hours.

In fetuses at the stage of 26-28 days of intratubal life (35 experiments) the prothrombin time fluctuated between 70 to 20 seconds, averaging 40.4 ± 0.6 seconds. Shortly before birth, i.e., between 29th and 31st days of intrauterine life (40 experiments), the prothrombin time varied from 35 to 15 seconds averaging 26.4 ± 0.8 seconds. In this last group there was observed a definite difference in fetuses at the 29th day of intratubal life and

fetuses at the 31st day of intratubal life. The 29 day fetuses averaged a prothrombin time of 35 seconds while the 31 days fetuses averaged 18-20 seconds.

TABLE 1
Prothrombin Time in Fetuses Between 26-31 Days of Intratubal Life as They Entered Stage of Pulmonary Respiration

No. of exp.	Fetal age (days)	No. of fetuses	Prothrombin time (in seconds)		
			Preg. rabbit	Fetuses (un-tied umbil. cords)	Fetuses (tied umbil. cords)
1	26	4	13	40 35	35 35
2	27	8	12	45 48 45 46	46 48 40 48
3	27	6	15	55 55 55	60 55 60
4	27	8	15	45 48 45 45	45 43 45 40
5	28	8	16	55 60 60 50	55 57 60 53
6	29	4	13	35 33	30 35
7	29	8	12	35 35 30 35	30 33 35 35
8	30	8	14	25 25 23 24	22 25 25 20
9	31	8	12	18 15 20 18	20 15 18 20
10	31	8	14	20 18 18 20	18 20 18 20
Average . . .				35.4 ± 0.7	34.9 ± 2.3

TABLE 2
Prothrombin Time in Fetuses at 26-28 Day of Intratubal Development During Asphyxia

No. of exp.	Fetal age (days)	No. of fetuses	Prothrombin time (in seconds)		
			in preg. rabbit	in control fetus	in asphyx. fetus
1	26	6	14	25 25 25	20 23 20
2	26	6	18	30 32 30	40 40 40
3	27	8	12	40 38 40 42	45 48 45 45
4	28	6	12	27 25 25	32 33 35
5	28	8	15	25 25 23 23	35 36 40 32
Average				29.4 ± 2.02	35.8 ± 1.1

As the fetus becomes older, along with diminution of the prothrombin time, there is also observed a change in the character of the coagulation reaction; in 24-day fetuses the blood does not clot and after 2-4 hours of standing there appear in it only a few scarcely visible grains of fibrin; in the blood of 26-28 day fetuses there was noted the appearance of fibrin clumps settling on the walls of the tube; in the blood of fetuses

in the last stages of gestation there was observed the development of heavy thickenings and clumps, while just before term (31st day) a definite clot floating freely in the tube was present. In the female pregnant rabbit, as the blood coagulated, a firm clot filling the entire lumen of the tube and tightly adhering to its walls was formed.

Alterations in prothrombin time in fetuses during the period of transition from intratubal to extratubal life. In this experimental series 35 animals were studied. After tying the cord the fetus was immediately removed from the mother and placed on a cotton pillow; within several seconds there would begin respiration and movement. Within 10-20 minutes after respiration had begun, blood was taken from the heart to determine the prothrombin time. As controls, the fetuses in the other horn of the mother (that had not been separated from the placenta) were used. The results obtained are shown in Table 1.

As can be seen from this table, there were no significant prothrombin alterations as the fetuses entered into the phase of pulmonary respiration.

Prothrombin time alterations produced by asphyxia. These studies were conducted on fetuses between 26 to 28 days of gestation (17 fetuses) and 30-31st day (30 fetuses).

Twenty minutes after cord ligation blood was drawn from the fetus immersed in the physiological saline solution and the prothrombin time determined. As a control, the fetus in the other uterine horn which had not had its cord tied was used.

TABLE 3
Prothrombin Time in Fetuses at 29-31 Day of Gestation During Asphyxia

No. of exp.	Fetal age (days)	No. of fetuses	Prothrombin time (in seconds)		
			In preg. rabbit	In control fetus	In asphyx. fetus
1	29	8	17	35	45
				35	45
				35	45
				35	45
2	29	8	15	30	35
				25	28
				25	30
				25	30
3	30	6	10	20	30
				20	30
				20	30
4	30	8	12	20	25
				22	26
				22	29
				22	27
5	30	6	10	23	28
				23	28
				24	28
6	30	8	12	20	25
				20	25
				20	25
				20	25
7	30	8	13	20	28
				23	30
				20	25
				25	28
8	30	8	14	25	30
				28	35
				28	30
				30	35
Average				24.6±0.9	30.9±1.1

Tables 2 and 3 demonstrate that prothrombin time lengthens in the fetuses as asphyxia develops. Thus the control fetuses in 26-28 days of gestation had an average prothrombin time of 29.4 seconds, while fetuses of same age that were in a state of asphyxia had an average prothrombin time of 35.8 seconds.

Control fetuses in 29-31 day of gestation had a prothrombin time of 24.6 seconds while in fetuses being in an asphyxial state the time averaged 30.9 seconds.

DISCUSSION OF EXPERIMENTS

The above experiments demonstrate that during intratubal ontogenesis variations in prothrombin time occur; as the fetus matures, the prothrombin time diminishes gradually. This permits us to believe that prolongation of prothrombin time which is observed in the newborn is not associated with the transition to pulmonary respiration but is a continuation of changes which had begun during gestation. To understand the mechanism involved, one must take into account the changes undergone by the blood in the period of intratubal development. A primary consideration is the blood content of fibrinogen the amount of which increases as the embryo grows [9].

The low levels of prothrombin and fibrinogen during gestation point to the liver as not having had time to develop its synthetic function. At birth the increase in blood prothrombin and fibrinogen levels is not terminated but continues. Apparently, the comparative (with adult) decrease in prothrombin which is observed in the newborn is a consequence of an inadequately developed prothrombin capacity of the liver, i.e., the prolongation of the prothrombin time seen in the newborn is a reflection of one of the physiological characteristics of the organism at that stage of life.

SUMMARY

Experiments were conducted which demonstrated that prothrombin time diminishes gradually during gestation of the fetuses. The suggestion is made that

this may be associated with the appearance of the prothrombin formation function of the liver. This function is not fully developed at birth but continues maturing. This and not vitamin K deficiency is suggested as the reason

for the comparatively prolonged prothrombin time seen during the first few days of independent life. Prothrombin time is greatly increased by asphyxia.

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