# GLUCOCORTICOID FUNCTION OF THE HUMAN ADRENALS AND ITS PRENATAL AND IMMEDIATE POSTNATAL REGULATION

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The chief glucocorticoid hormone in man is cortisol, which is produced by the fetal adrenal cortex in the prenatal period [9]. During intrauterine development the adrenals undergo morphological and functional changes. Positive correlation is found between the secretory activity of the adrenals and the increase in their weight, especially toward the end of the prenatal period. However, factors affecting the increase in weight and functional activity of the adrenals have received little study. The decrease in weight of the adrenals found in anencephalic fetuses [5] and the reduction of steroid production in the fetal adrenals after injection of exogenous glucocorticoids [6] indicate that the ACTH of the fetal pituitary gland is a possible factor regulating normal growth and development of functional activity of the fetal adrenals.

Most investigations of the secretory activity of the human fetal adrenals have been carried out in experiments in vitro [6, 7] or they have been restricted to periods of neonatal [11, 13, 15] or early postnatal ontogeny [1].

The aim of this investigation was to study the trends of changes in the human fetal blood cortisol level during the prenatal and early postnatal periods, and also to determine blood ACTH concentrations in neonates and during the first week of life.

## EXPERIMENTAL METHOD

Blood from 82 human fetuses at 11-34 weeks of development and of 50 infants from the 1st through the 7th day of life was tested. The fetuses were obtained from obstetric and gynecologic clinics in Moscow after termination of pregnancy or as a result of abortion, from mothers free from endocrine diseases. The fetuses were autopsied not later than 6 h after death. The age of the fetus was determined from its length, the presumed time of ovulation, and the gynecologist's examination. Blood samples were obtained from neonates during birth from clinically healthy mothers and during postnatal examinations. The blood samples collected were centrifuged at 4000 rpm for 25 min, and the resulting serum was treated with 1-2 drops of 4 mM EDTA and kept until required for testing at −15°C. The concentration of cortisol and ACTH was determined by radioimmunoassay using kits from CEA-Sorin (France) in accordance with the instructions. The sensitivity of the method for cortisol assay was 4 ng/ml and for ACTH assay 10 ± 4 pg/ml.

## EXPERIMENTAL RESULTS

The results of cortisol radioimmunoassay in human fetal blood serum are given in Table 1. At the age of 11-13 weeks the cortisol concentration in fetal blood was low (20 ng/ml). With an increase in age it rose sharply, to reach 113.4 ± 29.4 ng/ml by the 19th-20th week, a more than fivefold increase. Later, until the age of 29-31 weeks, the blood cortisol concentration remained virtually unchanged at between 90 and 110 ng/ml. After the 31st week the cortisol level again rose sharply and reached its highest value (174.7 ± 21.8 ng/ml, $p < 0.02$) at birth.

Comparison of the time course of the change in cortisol concentration with the ACTH level in human fetal blood showed a parallel increase in the ACTH and cortisol concentration

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TABLE 1. Serum Cortisol Level (in ng/ml) in Human Fetuses at 11-34 Weeks of Prenatal Development

| Age of fetuses, weeks | Number of observations | Cortisol level |
|---|---|---|
| 11—13 | 2 | 20,0 |
| 14—16 | 5 | 40,0±12,8 |
| 17—18 | 7 | 77,1±21,6 |
| 19—20 | 11 | 113,4±29,4 |
| 21—22 | 14 | 112,3±24,6 |
| 23—24 | 12 | 92,8±16,5 |
| 25—26 | 11 | 95,6±22,3 |
| 27—28 | 10 | 95,4±28,9 |
| 29—31 | 6 | 87,0±14,3 |
| 32—34 | 4 | 152,0±39,3 |

TABLE 2. Serum Cortisol and ACTH Levels (in ng/ml) in Newborn Infants

| Age of infants, days | Cortisol | ACTH |
|---|---|---|
| Neonates | 174,7±21,8 ($n = 7$) | 0,49±0,18 ($n = 7$) |
| 1 | 95,9±10,1 ($n = 11$) | 1,40±0,26 ($n = 5$) |
| 3 | 73,2±16,8 ($n = 12$) | 1,66±0,29 ($n = 11$) |
| 5 | 58,2±8,4 ($n = 12$) | 1,26±0,32 ($n = 10$) |
| 7 | 60,0±4,1 ($n = 4$) | 1,19±0,12 ($n = 4$) |

Legend. n) Number of infants.

in human blood during the first third of the prenatal period [2]. During this period of development the pituitary-adrenal system (PAS) of the fetus is evidently still immature and there is no feedback between pituitary and adrenals.

Some workers consider that the physiological stimulator of the germinative zone of the human adrenal in the first 3rd of the prenatal period is chorionic gonadotrophin (CG) [9, 12]. The human fetal adrenals do in fact begin to function in the first 3 months of pregnancy, when the CG concentration in fetal blood is maximal [3] and the ACTH level is still fairly low [2]. We also know that development of the adrenals in anencephalic fetuses usually takes place normally until the 5th month [5]. After injection of high doses of CG into the amniotic fluid of a human fetus morphological changes were found in the fetal adrenals, evidence of increased secretory activity of the gland [10]. Experiments in vitro also have shown that CG stimulated the formation of dehydroepiandrosterone sulfate in human fetal adrenals [9] and also stimulated the conversion of pregnenolone and cholesterol into dehydroepiandrosterone [12]. All these data confirm that CG may have a regulatory influence on secretory activity of the fetal adrenals in the first 3rd of prenatal ontogeny.

After the 17th-18th week negative correlation was found between the blood ACTH and cortisol levels (Fig. 1). During this period of development the ability of the adrenals to synthesize cortisol in vitro is considerably increased [9], and sensitivity to physiological concentrations of ACTH rises [7]. The present writer also showed previously [4] that cultured cells of the human fetal adenohypophysis in the middle of the prenatal period can react intensively to corticotrophin releasing hormone (CRH), which is present at that time in sufficiently high concentration in the fetal hypothalamus. By the middle of the prenatal period of human development, the feedback mechanism between adrenals and pituitary has evidently matured, and CRH, which may play its own specific role, is secreted from the fetal hypothalamus.

Since cortisol is known to pass through the placenta, some investigators [6] have compared the time course of changes in the cortisol level in maternal and fetal blood throughout pregnancy. They found no positive correlation between the hormone levels in mother and fetus, and they therefore consider that cortisol discovered in the fetal blood is mainly produced by the fetal adrenals. This view is further supported by data showing that the

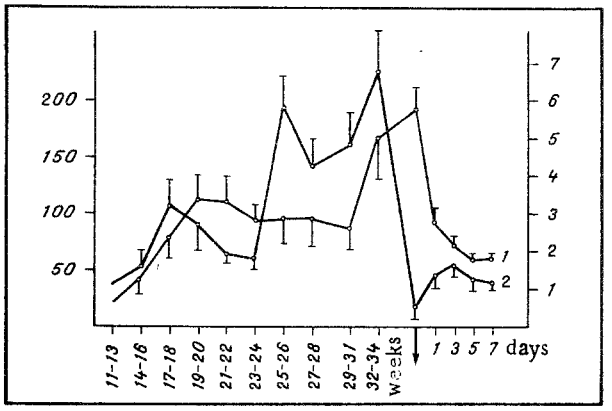


Fig. 1. Serum cortisol and ACTH concentrations (in ng/ml) in human fetuses at 11-34 weeks of development and neonates during the first week of life. Abscissa, age of fetuses (in weeks) and neonates (in days); ordinate: left — cortisol concentration, right — ACTH concentration. Arrow indicates time of birth.

cortisol level in the umbilical artery of the human fetus before birth is higher than in the vein [13] and also by data indicating a significantly higher cortisol concentration in the blood of normal neonates than of anencephalics of the same age, despite its equal concentration in the mothers of anencephalic and normal fetuses [8].

The blood cortisol concentration rises rapidly after the 21st-31st week of development, and in neonates at birth amounts to 174.7 ± 21.8 ng/ml. The ACTH level, on the other hand, fell, so that at birth it was only one-tenth of its concentration at the 32nd-34th week of intrauterine development, whereas in neonates it was 0.49 ± 0.18 ng/ml (Fig. 1). Changes found in the blood cortisol and ACTH levels in the neonate were evidently the result of birth stress. This is supported by data showing that the cortisol concentration in fetal blood and amniotic fluid rises only only during spontaneous birth [11]. A definite relationship also was found between the duration of labor and the cortisol level in the child's blood. Longer labor was accompanied by an increase in the blood cortisol concentration of the newborn infant.

These findings suggest that the PAS has reached a certain level of maturity in man by the time of birth, and that the sensitivity of the adrenals to ACTH is increased.

During the first day of life there was a sharp fall in the cortisol level ($p < 0.02$) and a considerable rise in the ACTH concentration ($p < 0.02$) in the blood (Table 2). The cortisol concentration continued to fall until the 5th day, after which it remained at the same level until the 7th day. The ACTH level, on the other hand, rose a little until the 3rd day of life (1.66 ± 0.29 ng/ml), but by the 7th day it showed a very small decrease (1.19 ± 0.12 ng/ml).

The rapid fall in the blood cortisol concentration of infants in the first days of life is evidently the result, on the one hand, of excretion of cortisol of maternal origin and, on the other hand, of extinction of the reaction to birth stress. It is clear from Fig. 1 that as the blood cortisol concentration falls in infants during the first 3 days of life, the adrenocorticotrophic activity in the blood rises somewhat. This fact is further evidence of the fairly high sensitivity of the feedback mechanism of the PAS in infants in the first days after birth.

Functional interrelations are thus established between the adrenals and pituitary in the middle of human prenatal development, and by the time of birth PAS has reached a certain degree of maturity, as is shown by its marked response to birth stress.

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# EFFECT OF THE MODE OF EXTRAPULMONARY GAS EXCHANGE ON LUNG SURFACTANT FUNCTION AND METABOLISM

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The extensive use of oxygenators of both contact and membrane types for extrapulmonary gas exchange became possible only after a comprehensive study of their action on the body [3, 6, 8]. Until recently, however, little attention had been paid to the study of the relationship between the mode of extrapulmonary gas exchange (the type of oxygenator) and the onset of changes in function and metabolism of the lung surfactant (LS) [1, 6]. However, attention is increasingly being paid at the present time to disturbances in the surfactant system, for it plays an essential role in the development of postoperative pulmonary complications [9, 10].

This paper gives an account of a quantitative and qualitative assessment of changes in LS function and metabolism during the use of a foam-film oxygenator (FFO) and the Sever membrane oxygenator (MO) during venoarterial perfusion.

## EXPERIMENTAL METHOD

Two series of experiments were carried out on 28 mongrel dogs of both sexes weighing 21.4 ± 2.1 kg. Changes in LS under the influence of FFO were studied in series I, changes under the influence of the Sever MO in series II. Under conditions of normothermia, trimeperidine–hexobarbital anesthesia, and artificial ventilation of the lungs (AVL), and after intravenous injection of heparin (8–10 mg/kg for the initial dose, and 0.5 mg/kg every 30 min during the experiment), venoarterial perfusion was carried out with extracorporeal blood oxygenation for 120 min according to the following scheme: right atrium–gas exchanger–left femoral artery. The priming volume of the perfusion system was 500–700 ml (Ringer-Locke, 5% glucose, and rheopolyglucin solutions in equal proportions). Blood was returned to the animals by means of the roller pump unit of the ISL-4 apparatus. The average volume velocity of perfusion in the experiments of series I was 47.8 ± 3.7 ml/min•kg and in series II 46.3 ± 5.8 ml/min•kg. The volume velocity of the gas ($O_2$) flow was 2–6 liters/min. The adequacy of perfusion and oxygenation was monitored by measuring the partial pressure of $O_2$ and the acid-base balance (ABB) of the blood, by the micro-Astrup method (AME-1 analyzer, from Radiometer, Denmark). During the experiments the arterial pressure (BP) was recorded by the

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