CORD BLOOD CORTISOL LEVELS AND RESPIRATORY DISTRESS SYNDROME

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ABSTRACT

Cord blood cortisol levels were analyzed in 121 neonates, using a "Coat a Count" RIA kit. Forty two appropriate for gestation age (AGA) preterms <34 weeks who had not received antenatal dexamethasone constitued Group A, 32 AGA preterms <34 weeks gestation who had received dexamethasone antenatally comprised Group B, while Group C consisted of 47 term normal neonates. Cortisol levels were compared in these 3 groups and correlated Jo the development of respiratory distress syndrome (RDS).

It was observed that preterms (Groups A and B) had significantly ($p<0.005$) lower levels (8.45 ± 6.31 µg/dl) compared to term neonates (11.67 ± 4.68 µg/dl). Antenatal dexamethasone therapy did not significantly alter cortisol levels within the group of preterms. There was a significant difference ($p<0.02$) in cortisol levels between those preterms who developed RDS (5.41 ± 4.91 µg/dl) and those who did not (9.58 ± 6.45 µg/dl). Preterms (Grous A and B) who did not develop RDS had cortisol levels comparable to term neonates.

There was a significant reduction in the incidence of RDS ($p<0.05$) in preterms who had received antenatal dexamethasone. Cord blood cortisol levels ≤ 7 µg/dl had a positive predictive accuracy of 36.59% and negative predictive accuracy of 93.75% in predicting onset of RDS.

Key words: *Preterms, Respiratory distress, Cord blood, Cortisol.*

Respiratory distress syndrome (RDS) is a frequent disorder in preterms with a high mortality rate. It is postulated that the lower incidence of RDS seen in preterms whose mothers received antenatal glucocorticoid is due to increased release of surfactant from granules in alveolar Type II cells(l,2). Animal studies have shown that in response to cortisol, fetal lung fibroblast secrete a heat stable polypeptide called "Fibroblast pneumocyte factor (FPF)"(3). The FPF acts on alveolar type II cells to increase the activity of the choline incorporation pathway and produce increasing amounts of surfactant by a process that includes stimulation of choline phosphate cytidyl transferase which is the rate limiting enzyme in the synthesis of phosphatidylcholine(4,5). Hence, cortisol plays a protective role in the prevention of RDS.

It has been observed that preterms have significantly lower levels of cord blood cortisol compared to normal term newborns and those preterms who developed RDS have significantly lower levels of cord blood cortisol level compared to those who do not develop RDS(6).

The present study hence aimed at establishing the norms of cord blood cortisol levels in preterms and term newborns in the Indian population and to evaluate if any correlation exists between cord blood cortisol

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levels and the presence of RDS. The study also evaluated the relation of antepartum dexamethasone therapy on outcome of RDS.

Material and Methods

Cord blood cortisol level was estimated in 121 newboms who were delivered vaginally. The study population sample consisted of cord blood of preterms appropriate for gestational age (AGA), <34 weeks gestation in whom antenatal dexamethasone had not been administered to the mothers (Group A, n = 42), preterms AGA < 34 weeks gestation whose mothers had received a minimum of 2 doses of 12 mg IM dexamethasone at 12 hourly intervals, the second dose being given at least 12 hours prior to delivery of the neonate (Group B, n = 32). Full term normal newborns > 38 weeks of gestation and weighing more than 2500 g constituted Group C (n = 47).

Neonates whose mothers had endocrinal problems, or in whom antenatal prednisolone therapy was given were not included in the study. Preterms with intrauterine fetal distress, neonates with intrauterine growth retardation and perinatal asphyxia were also excluded from the study.

Cord blood was collected and immediately centrifuged at 2,000-3,000 rpm for 30 minutes to separate the sera, which was then stored at -20°C. A radioimmunosassy Kit "Coat-A-Count" (TKCO1) made by Diagnostic Products Corporation was used to assay cortisol level. The kit had a sensitivity of 0.2 µg/dl. The antisera used were highly specific for cortisol with very low cross-reactivity with other naturally occurring steroid compounds. All newborns were followed up till discharge from the hospital for evidence of RDS which was diagnosed on clinical examination and chest radiographs. Cord blood cortisol levels were compared in the three groups and also correlated with the development of RDS. Statistical analysis was done using Students V test.

Results

The mean and range of birth weights of newborns in Groups A, B and C were 1575 g (1100 g to 1900 g), 1523 g (1260 g to 1800 g) and 2726 g (2500 g to 3400 g), respectively. Thirty eight per cent of newborns in Group A developed RDS as compared to 12.5% in Group B. No newborn in Group C developed RDS. Whereas, there was no mortality in Groups B and C, 19% from Group A expired.

The noteworthy observations made in the study were as follows:

1. Preterms (Group A + B) had significantly lower cord blood cortisol levels ($p < 0.005$) compared to (Group C), and dexamethasone treatment did not significantly alter the levels of cord blood cortisol within the group of preterms *(Table I).*

2. Preterms (Group A + Group B) who

TABLE I-*Cord Blood Cortisol Levels* in *Preterms (Group A and Group B) and Group* C.

Groups	Sample (n)	Mean (µg/dl) ±SD	p value
1. Group A	42	8.59 (±5.44)	<0.005
Group C	47	11.67 (±4.68)	
2. Group B	32	8.28 (±7.40)	<0.005
Group C	47	11.67 (±4.68)	
3. Group A and Group B	74	8.45 (±6.31)	<0.005
Group C	47	11.67 (+4.68)	

developed RDS had significantly lower cord blood cortisol levels (p <0.02) compared to those who did not develop RDS *(Table II).*

3. Preterms who did not develop RDS had lower but comparable levels of cord blood cortisol (p value = not significant) to normal term newborns (Group C) *(Table* II).

4. When results of preterms who were not under influence of exogenous steroids (Group A) were compared with Group C *(Table III)* it was observed that:

(a) These preterms had significantly lower levels of cord blood cortisol level (p <0.005) compared to Group C.

(b) Preterms who developed RDS had significantly lower levels of cord blood cortisol (p<0.05) compared to those who did not develop RDS.

(c) Preterms who did not develop RDS had lower but comparable levels of cord blood cortisol level (p value = not significant) compared to Group C.

5. There was a significant reduction in the incidence of RDS (p<0.05) in those

TABLE II-*Cord Blood Cortisol Levels in Preterms (A + B) With and Without RDS and Group* C

	Groups	Sample (n)	Mean (μ/dl) ±SD	p value
1.	Group A & B (RDS)	20	5.41 (±4.91)	<0.001
	Group C	47	11.67 (±4.68)	
2.	Group A & B (no RDS)	54	9.58 (±6.45)	>0.05
	Group C	47	11.67 (±4.68)	
3.	Group A & B (RDS)	20	5.41 (±4.91)	<0.02.
	Group A & B (no RDS)	54	9.58 (±6.45)	

TABLE III-*Cortisol Levels in Groups A and* C

	Groups	Sample (n)	Mean (g/dl) ±SD	p value
1.	Group A	42	8.59 (±5.44)	<0.005
	Group C	47	11.67 (±4.68)	
2.	Group A (RDS)	16	6.19 (±5.15)	<0.05
	Group A (no RDS)	26	10.06 (±5.17)	
3.	Group A (RDS)	16	6.19 (±5.15)	«0.001
	Group C	47	11.67 (±4.68)	
4.	Group A (no RDS)	26	10.06 (±5.12)	Not significant
	Group C	47	11.67 (±4.68)	

preterms who had received antenatal dexamethasone.

6. Cord cortisol level ranged from 0.7 to 17.9 mg/dl (mean 5.41 ± 4.91) in preterms (Groups A + B) who developed RDS and 0.6 to 29.6 µg/dl (mean 9.58 ± 6.45) in preterms (Groups A + B) who did not develop RDS *(Fig. 1*).

In the present study, RDS observed in preterms (Groups A + B) at the cord blood cortisol level of <7 (µg/dl had a sensitivity of 75% and specificity of 74.26%. The positive predictive accuracy was 36.59% and negative predictive accuracy was 93.75%.

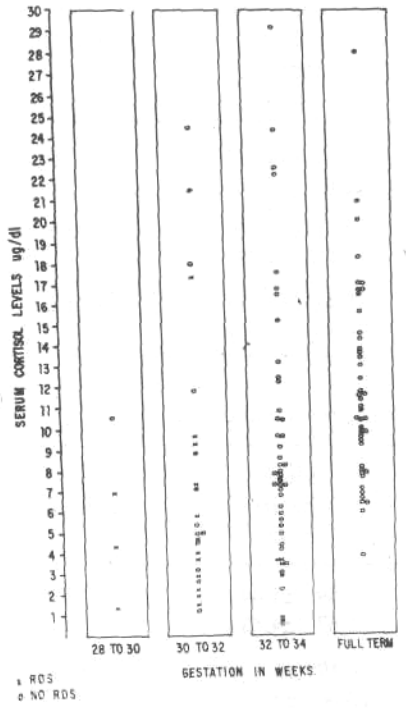

Fig. 1. Lord blood cortisol levels (mg/dl) in relation to gestational age. Levels <7 mg/dl revealed a positive predictive accuracy of 36.59% and a negative predictive accuracy of 93.75% for RDS.

Discussion

Glucocorticoids are produced primarily in the maternal compartment, while the fetoplacental unit complements its production. The majority of the glucocorticoids circulating in the fetal compartment is cortisone while that in the maternal circulation is cortisol(7,8). In the early period of pregnancy, 80-85% of cortisol from the maternal circulation is converted to cortisone in the placenta before entering the fetal circulation(9). In the latter half of pregnancy, there is increased conversion of cortisone to cortisol in the placenta by the 11 B-hydroxyste-roid oxydoreductase enzyme whose activity increase with the increase in gestational age of the fetus, hence preterms may be bom with lower levels of cortisol(7).

Cortisol is responsible for the maturity of fetal lungs(10,ll). The fetal adrenal function and size is inadequate to produce adequate levels of cortisol in preterms who develop RDS as shown by Naeye *et al.* who found that preterms who died of RDS showed smaller adrenal glands than their weight matched controls who did not develop RDS. The difference in adrenal weight was as much as 19%(12). Dickey *et al.* observed that the fetal adrenal function, as reflected by excretion of estriol on day one of life was decreased in preterms who died of RDS(13). In this study, we noted lower but comparable levels of cord blood cortisol level in preterms who did not develop RDS compared to normal term newborns, suggesting that these fetuses although born pre--term had adequate levels of cortisol in the intrauterine life so as to undergo adequate maturation of lung under the influence of cortisol unlike the preterms with RDS who had significantly lower levels of cord blood cortisol.

Murphy's study carried out in the Canadian population noted similar observations as our study, except that the absolute levels of cortisol were lower in the Canadian population. This may have been due to the different methodology (Chromatography-Sephadex LH-20 columns) used by Murphy(14) for estimation of cortisol.

Dexamethasone administration in antenatal period has been shown to be effective in protecting preterms from developing RDS(15-18). Although, the placenta is relatively permeable to all glucocorticoids, the catabolism rate varies for different glucocorticoids and is approximately 67.4% for cortisol, 51.4% for prednisolone, 7.1% for betamethasone and 1.8% for dexamethasone(9). As the catabolism rates for betamethasone and dexamethasone are low and they easily cross the placenta, these drugs can be used to subject the human fetus to high glucocorticoid activity to hasten lung maturity.

From the observations made in the present study, we recommend that all threatened preterm labor should be administered dexamethasone and an attempt be made to prolong pregnancy so as to significantly decrease the incidence of RDS.

We also noted that cortisol levels greater than 7 mg/dl was associated with a very low risk of developing RDS. We suggest that cord blood cortisol levels be estimated in cases where cordocentesis is being done for some other indication to establish cortisol levels at different gestation and perhaps predict the possibility in the neonate for the risk of RDS.

The present study documented cord blood cortisol level in newborns who were delivered vaginally and justifies the use of dexamethasone therapy in the antenatal period for the prevention of RDS. There is need however to document cortisol levels in those delivered by Cesarean section, and compare it with those delivered nonstressed, vaginally, to document the difference if any, in cortisol levels between these two modes of delivery.

We suggest that a larger subset of the Indian newborn population consisting of preterm as well as term SGA and neonates with perinatal asphyxia, meconium aspiration, as well as twins and triplets be studied before a consensus is reached on the exact role of cortisol in protecting the fetus from RDS under different situations.

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