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ARTICLE

Plasma cortisol and ACTH levels in 416 VLBW preterm infants during the first month of life: distribution in the AGA/SGA population

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Abstract

Objective The aim of this study is to establish the serum level distribution of cortisol and ACTH in VLBW preterm newborns and determine which neonates are ideal candidates for the stimulation test for adrenal insufficiency.

Methods Plasma cortisol and ACTH levels were evaluated in 416 VLBW newborns on days 1, 7, and 30 of life. Gender, gestational age, weight, type of delivery, RDS prophylaxis, and perinatal morbidities were considered as potential variability factors.

Results Cortisol and ACTH levels significantly decreased between 1, 7, and 30 days. Significantly higher cortisol levels were found at lower gestational ages and in infants born by vaginal delivery, whereas lower levels were observed in those born after maternal corticosteroid treatment. The distribution of cortisol and ACTH levels in healthy infants born by cesarian section is presented.

Conclusion Even if high or low levels were not frequently linked to illness, the presented distribution data may indicate that the newborns are ideal candidates for the stimulation test.

Introduction

The fetus can produce cortisol from the 10th week onward of gestation [1]; its investigation, determined by funiculocentesis samples, has revealed stable levels at very early gestational ages (GAs) [2, 3], with an increase starting from week 32 to 37 of gestation [3]. Conversely, ACTH levels in the fetal period display progressive increase from very early GAs until the end of gestation [2].

Cortisol levels in premature newborns, particularly in those born very low birth weight (VLBW), are indeed variables [4–13]. This may be due to several factors, i.e., the different GAs, the type of delivery, the maternal corticosteroid administration for the respiratory distress syndrome (RDS) prophylaxis, the presence of RDS or chorioamnionitis, the need for assisted ventilation, and, not the least, the point in time, in terms of hours or days of life, at which cortisol levels are measured. Thus, many perinatal factors have been considered in the definition of cortisol percentiles for the preterm population [11].

Few data exist so far for basal plasma ACTH levels in VLBW infants during the first month of life; since they do not negatively correlate in preterms infants with 28 weeks median GA, pituitary maturation seems to be more advanced than that of the adrenal glands [12].

Regarding the response of the hypothalamic–pituitary–adrenal (HPA) axis to various pathological conditions, low cortisol levels have been associated to higher incidence of pulmonary bronchodysplasia, mortality, and sepsis [14–16], whereas high levels have been described in ventilated

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versus nonventilated preterm infants [12], even if these data are still debatable.

Preterm infants born small for gestational age (SGA) show lower adrenocortical response to stimulation, which may represent an insufficient response to stress that contributes to higher rates of morbidity and mortality [17]. From a clinical point of view, symptoms of slightly or moderately high cortisol levels could be subtle and the condition of eucortisolism in a distressed VLBW newborn could be difficult to define; on the other hand, it is not easy to identify a cut-off point below which an adrenal insufficiency can be specified.

Thus, we thought it would be useful to establish the serum level distribution in percentage terms that represent a statistical trend of cortisol and ACTH in VLBW preterm newborns not suffering from any diseases worthy of note, to determine in which neonates a stimulation test should be performed and whatcould be the appropriate management in case of neonatal diseases. Cortisol and ACTH plasma levels were evaluated in a large population of VLBW newborns on days 1, 7, and 30 of life, also taking into consideration factors related to GA, weight, gender, type of delivery, RDS prophylaxis with maternal corticosteroid administration, and the presence of RDS or perinatal morbidities.

Methods

Study subjects

Four hundred and sixteen newborns (198 male and 218 female) with BW ≤ 1500 g (in 175 ≤ 1000 g, in 241 > 1000 g, and range 490–1500 g) were enrolled after their admission to four neonatal intensive care units participating at this multicenter study in the period from January 2016 to January 2018. Exclusion criteria were the presence of congenital, chromosomal, metabolic or endocrine disorders, clinical or biochemical signs of infection, and maternal diabetes or corticosteroid therapy during pregnancy. None of the infants was treated with corticosteroids during the first month of life. Antenatal corticosteroids (1–2 cycles of 12 mg of betamethasone given twice in 24 h) administered to the mother in case of preterm membrane rupture or threatened preterm labor was taken into account.

The GA, dated by ultrasonography performed at 17–18 weeks of gestation or by the date of last menstruation and by the New Ballard Score Assessment after birth, varied from 22 to 36 weeks. Adequate for gestational age (AGA) was defined as a birth weight above the 10th and below the 90th percentile and SGA as birth weight below the10th percentile [18].

Infants in wellness (*W*) were considered asthose with O2 requirement ≤ 25% on day 7 of life, and not in wellness (NW) with those in high-frequency ventilation, conventional mechanical ventilation, or requiring continuous positive airway pressure (cPAP) (Table 1).

For the data distribution at day 7 of life, AGA and SGA subjects born by cesarian section (CS), not ventilated for at least 24 h, without hypoglycemia or hyperglycemia, sepsis, symptomatic PDA, and hypotension, who had not received any corticosteroid therapy, and in whom no invasive procedures had been performed at least 12 h before, were considered.

Written consent was obtained from the parents. The study protocol was approved by the ethics committee of each institution or university participating in the study.

Laboratory analysis

One ml of blood in EDTA was taken at 1, 7, and 30 days at 08.00 a.m., at least 1 h after any other stressful events

Table 1 Clinical features of the studied population

	Whole population (n. 416)	BW ≤ 1000 g (n. 175)	BW > 1000 g (n. 241)
Gender (M/F)	198/218	78/97	120/121
Gestational age (weeks)[a]	28.94 ± 3.01	26.57 ± 2.14	30.66 ± 2.30
Birth weight (g)[a]	1095.56 ± 289.65	793.57 ± 136.28	1314.85 ± 129.67
VD/CS	58/358	43/132	15/226
Antenatal corticosteroids (Yes/No)	257/159	102/73	155/86
APGAR score[a]	5.17 ± 2.05	3.85 ± 1.99	5.97 ± 1.62
At 1 min	6.97 ± 1.53	6.06 ± 1.66	7.52 ± 1.14
At 5 min	272/144	107/68	165/76
Well/unwell infants	327/89	133/42	194/47
AGA/SGA	28.94 ± 3.01	26.57 ± 2.14	30.66 ± 2.30

BW birth weight, *VD* vaginal delivery, *CS* cesarian section, *AGA* adequate for gestational age, *SGA* small for gestational age

[a]Reported values represent the mean values ± SDS

(venopuncture or manipulations). The samples were stored at −80 °C and then cortisol and ACTH levels were measured at Siena University to potentiate chemiluminescence (Ortho-Clinical Diagnostics Amersham, UK and Medical Systems, UK, respectively).

Statistical analysis

The comparison of mean values was evaluated by the Student *t*-test, either for independent or for paired data. To obtain the normal distribution, and fundamental postulation of the parametric tests, the logarithmic transformation was performed. In case of inability to obtain the normal distribution, the nonparametric U Mann–Whitney *U* test was used. Pearson coefficient was used to correlate cortisol to ACTH levels. The level of significance was set at $p = 0.05$. All statistical analyses were performed by using the GraphPad release software (GraphPad Software, La Jolla, CA, USA).

Results

Out of 416 newborns included in the study, cortisol levels were examined in 310 newborns at day 1 (C1), in 333 at day 7 (C7), in 237 either at C1 or C7, and in 53 at day 30 (C30) of life. ACTH levels were obtained for 238 subjects at day 1 of life (ACTH1), for 237 at day 7 (ACTH7), for 164 newborns at ACTH1 and ACTH7, and for 43 newborns at day 30 (ACTH30).

Cortisol and ACTH mean levels at day 1, 7, and 30, related to sex, GA, type of delivery, birth weight, illness, and RDS prophylaxis, are represented in Table 2. Pearson correlation coefficients between cortisol and ACTH at day 1 showed strong correlation, being 0.81 in very early preterm (22–27 weeks of GA) and 0.83 in early preterm infants (28–32 weeks of GA) (Fig. 1). Similar data were also observed at day 7 (0.91 and 0.79, respectively). Considering the whole population, no statistical difference was found between C1 and C7 (Table 2); conversely, a significant difference was observed between C1 and C30 ($p = 0.023$) and between C7 and C30 ($p = 0.027$). ACTH levels showed a reduction during the first month of life, reaching a statistical significance when considering ACTH1 versus ACTH7 ($p = 0.006$) and ACTH1 versus ACTH30 ($p = 0.017$).

Significantly higher cortisol levels were found in males compared to females at C7 (8.2 ± 7.46 versus 5.32 ± 5.78; $p = 0.06$), ACTH levels at ACTH7 (28.31 ± 38.88 versus 20.10 ± 14.41; $p = 0.029$) and ACTH30 (24.09 ± 13.89 versus 16.72 ± 7.07; $p = 0.03$) (Table 2).

Cortisol levels were higher at lower GAs, with a negative correlation between days 1, 7, and 30 and GA ($p = 0.009$, $p < 0.001$, and $p = 0.019$, respectively), whereas significantly high correlation with GA was found for ACTH levels either at days 7 and 30 ($p = 0.02$ and $p = 0.001$, respectively).

A negative correlation between cortisol and ACTH levels and BW was only found for C7 ($p = 0.01$ and $p = 0.03$, respectively).

Significantly higher cortisol levels were observed in those born by vaginal delivery (VD) versus those born by CS, at C1 (6.51 ± 16.50 versus 10.52 ± 19.42; $p = 0.006$) and C7 (6.78 ± 12.25 versus 12.19 ± 17.77; $p < 0.005$). A statistically significant difference was recorded for ACTH7 between those born by VD versus CS ($p = 0.03$).

Infants born after maternal corticosteroid administration for RDS prophylaxis present lower cortisol and ACTH levels, even if significant lower levels were present only at day 1 ($p = 0.06$ and $p = 0.03$, respectively).

Significantly higher C1 and C7 were observed in NW versus *W* subjects (8.82 ± 19.89 versus 5.90 ± 15.29; $p = 0.017$ and 7.49 ± 15.05 versus 5.10 ± 12.97; $p = 0.007$, respectively). This difference was not found for ACTH levels.

To minimize the interferences due to the mode of delivery and the SGA condition, data distributions for cortisol and ACTH were obtained by considering separately the *W* infants born by CS, if AGA or SGA; the selected population was then divided into two groups, according to the GA (Table 3). Preterm AGA infants born at 24–27 weeks of GA showed higher C1 and C7 at the 50th percentile than the ones born at 28–32 weeks of GA. For both the considered groups, similar values were recorded for ACTH1 and ACTH7.

Preterm SGA infants born at 24–27 weeks of GA showed lower C1 but higher C7 at the 50th percentile than SGA infants born at 28–32 weeks of GA. ACTH showed a similar trend, being lower at ACTH1 and higher at ACTH7.

Among the *W* AGA infants delivered by CS at 24–27 weeks, 10/38 infants died; they all had cortisol levels at C1 and ACTH1 between the 10th and 90th percentile, but one had C1 levels below the 10th percentile and ACTH1 above the 90th percentile. Among the *W* AGA infants born at 24–27 weeks by VD, 8/21 infants died; they all displayed cortisol and ACTH levels at day 1 between the 10th and 90th percentile, but one had C1 values above the 90th percentile and ACTH in the 25–50th percentile.

Among the *W* AGA infants delivered by CS at 28–32 weeks, 2/159 died displaying cortisol level at C1 and ACTH1 between the 10th and 50th percentile. No AGA infants born with VD within that GA died. Among the NW AGA born at 24–27 weeks by CS, 7/44 died showing C1 and ACTH1 levels between the 10th and 90th percentile, but one had C1 and ACTH1 below the 10th percentile. All the 4/18 NW AGA infants born by VD at 24–27 weeks with a fatal event displayed C1 and ACTH1 levels between the

Table 2 Mean levels of cortisol and ACTH at day 1, 7, and 30 in relation to sex, gestational age, delivery, birth weight, illness, and RDS prophylaxis

	C1	*p*-value	C7	*p*-value	C30	*p*-value	ACTH1	*p*-value	ACTH 7	*p*-value	ACTH 30	*p*-value
Population as a whole	6.27 ± 5.57 ($n = 310$)		7.83 ± 5.56 ($n = 333$)		7.26 ± 5.28 ($n = 53$)		39.46 ± 49.43 ($n = 238$)		23.98 ± 28.93 ($n = 237$)		20.15 ± 11.26 ($n = 43$)	
M	6.53 ± 5.57 ($n = 139$)		8.2 ± 7.46 ($n = 167$)		7.59 ± 5.54 ($n = 25$)		40.1 ± 52.7 ($n = 108$)		28.31 ± 38.88 ($n = 112$)		24.09 ± 13.89 ($n = 20$)	
F	6.07 ± 5.58 ($n = 171$)	0.31	5.32 ± 5.78 ($n = 166$)	0.06	6.97 ± 5.13 ($n = 28$)	0.89	38.85 ± 46.57 ($n = 130$)	0.73	20.10 ± 14.41 ($n = 125$)	0.029	16.72 ± 7.07 ($n = 23$)	0.03
Very early preterm 24–27 weeks	8.9 ± 19.17 ($n = 107$)		11.39 ± 17.81 ($n = 108$)		9.73 ± 14.35 ($n = 38$)		43.91 ± 51.43 ($n = 82$)		25.48 ± 21.66 ($n = 79$)		20.12 ± 12.1 ($n = 33$)	
Early preterm 28–32 weeks	6.3 ± 16.73 ($n = 161$)		4.95 ± 8.28 ($n = 179$)		3.43 ± 2.29 ($n = 15$)		36.82 ± 50.75 ($n = 120$)		22.64 ± 34.13 ($n = 124$)		10.5 ± 12.06 ($n = 10$)	
Preterm 33–37 weeks	5.58 ± 12.23 ($n = 42$)	0.009	4.19 ± 11.81 ($n = 46$)	< 0.001	($n = 0$)	0.019	38.13 ± 39.92 ($n = 36$)	0.16	25.38 ± 22.85 ($n = 34$)	0.02	($n = 0$)	0.001
Cesarian delivery	6.51 ± 16.50 ($n = 271$)		6.78 ± 12.25 ($n = 285$)		7.44 ± 12.51 ($n = 44$)		38.20 ± 47.32 ($n = 206$)		24.67 ± 30.91 ($n = 201$)		19.69 ± 11.16 ($n = 34$)	
Vaginal delivery	10.52 ± 19.42 ($n = 39$)	0.006	12.19 ± 17.77 ($n = 48$)	< 0.005	10.44 ± 12.7 ($n = 9$)	0.13	47.57 ± 61.60 ($n = 32$)	0.23	20.11 ± 12.96 ($n = 36$)	0.15	21.87 ± 12.16 ($n = 9$)	0.5
VLBW	6.20 ± 5.37 ($n = 188$)		7.19 ± 5.16 ($n = 206$)		4.41 ± 2.11 ($n = 3$)		36.36 ± 44.86 ($n = 145$)		23.99 ± 34.32 ($n = 147$)		19.9 ($n = 1$)	
ELBW	6.18 ± 5.58 ($n = 122$)	0.79	8.88 ± 6.03 ($n = 127$)	0.01	5.18 ± 4.12 ($n = 50$)	0.98	44.29 ± 55.72 ($n = 93$)	0.12	24.07 ± 17.31 ($n = 89$)	0.03	20.15 ± 11.4 ($n = 42$)	–
AGA	6.61 ± 17.53 ($n = 244$)		7.06 ± 13.7 ($n = 259$)		8.8 ± 13.5 ($n = 44$)		37.45 ± 46.43 ($n = 180$)		22.53 ± 28.58 ($n = 184$)		20.1 ± 11.4 ($n = 36$)	
SGA	6.18 ± 15.37 ($n = 66$)	0.24	6.2 ± 13.8 ($n = 74$)	< 0.001	3.48 ± 1.14 ($n = 9$)	0.27	45.71 ± 57.77 ($n = 58$)	0.07	29.02 ± 29.87 ($n = 53$)	0.06	20.4 ± 11.22 ($n = 7$)	0.9
W babies	5.90 ± 15.29 ($n = 208$)		5.10 ± 12.97 ($n = 233$)		7.10 ± 17.91 ($n = 33$)		37.82 ± 50.78 ($n = 163$)		23.80 ± 31.98 ($n = 171$)		18.80 ± 24.95 ($n = 28$)	
NW babies	8.82 ± 19.89 ($n = 102$)	0.017	7.49 ± 15.05 ($n = 100$)	0.007	7.89 ± 16.05 ($n = 20$)	0.38	43.03 ± 46.48 ($n = 75$)	0.45	24.44 ± 19.08 ($n = 66$)	0.88	21.74 ± 34.06 ($n = 15$)	0.85
RDS	5.85 ± 5.39 ($n = 180$)		7.97 ± 5.23 ($n = 178$)		5.19 ± 3.97 ($n = 29$)		33.82 ± 41.51 ($n = 129$)		21.64 ± 20.03 ($n = 125$)		20.2 ± 11.92 ($n = 23$)	
NO RDS	6.52 ± 5.30 ($n = 130$)	0.05	7.84 ± 6.07 ($n = 118$)	0.31	5.62 ± 4.65 ($n = 18$)	0.72	43.98 ± 50.68 ($n = 78$)	0.03	26.63 ± 40.52 ($n = 84$)	0.22	19.78 ± 9.83 ($n = 16$)	0.98

C cortisol, *VLBW* very low birth weight, *ELBW* extremely low birth weight, *AGA* adequate for gestational age, *SGA* small for gestational age, *W* in wellness, *NW* not in wellness, *RDS* respiratory distress syndrome

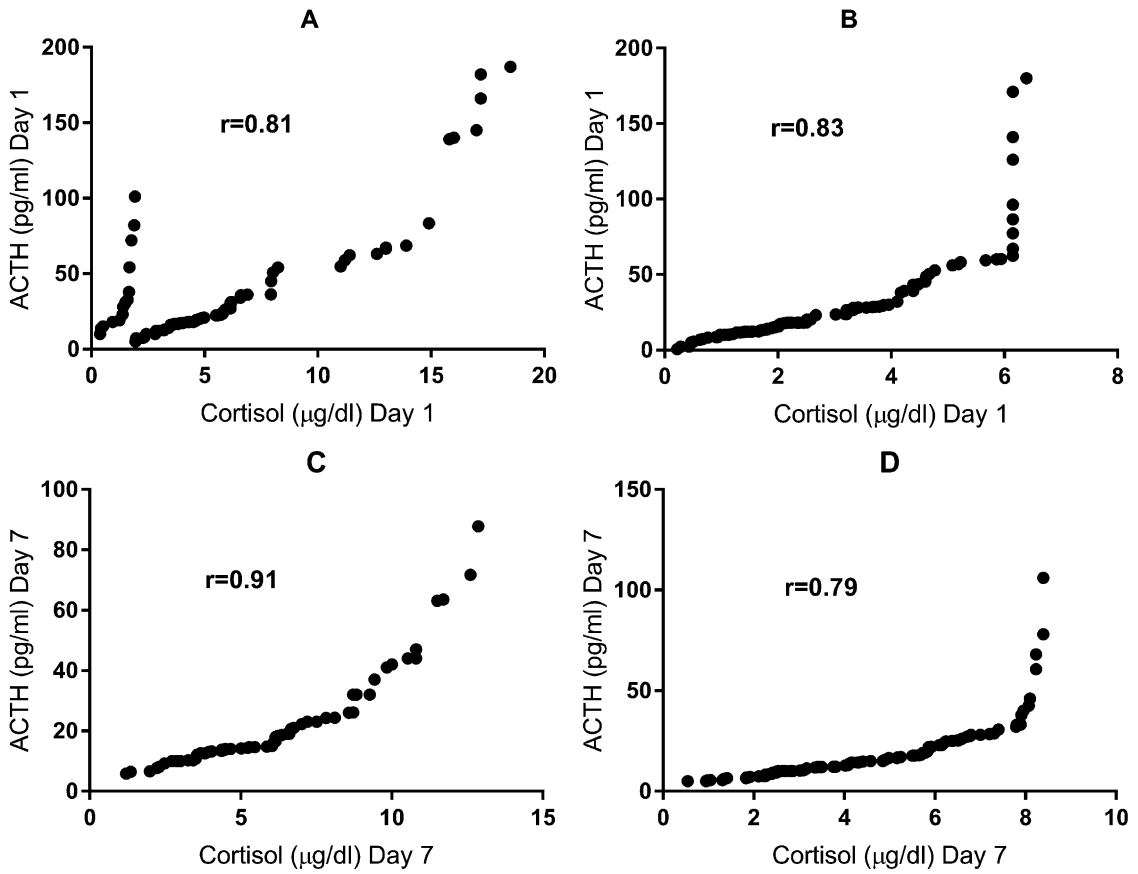

Fig. 1 Correlation between Cortisol and ACTH in day 1 and 7

Table 3 Percentile distribution in healthyAGA/SGA infants born by cesarian section in relation to gestational age

	Cortisol (μg/dl)				ACTH (pg/ml)			
	24–27 weeks		28–32 weeks		24–27 weeks		28–32 weeks	
Percentile	C1 ($n = 33$)	C7 ($n = 28$)	C1 ($n = 124$)	C7 ($n = 126$)	ACTH1 ($n = 26$)	ACTH7 ($n = 21$)	ACTH1 ($n = 90$)	ACTH7 ($n = 92$)
AGA								
10th	1.07	2.85	1.13	2.32	7.47	6.5	8.28	6.89
25th	1.96	6.11	1.94	3.38	12.37	9.61	12.26	10.0
50th	4.5	9.43	3.97	6.08	21.2	15	18.05	14.3
75th	7.45	16.4	7.40	8.76	40.5	37	29.08	27.5
90th	13.5	19.78	11.85	13.26	72.9	59.6	56.6	35.92
Percentile	C1 ($n = 16$)	C7 ($n = 17$)	C1 ($n = 45$)	C7 ($n = 50$)	ACTH1 ($n = 15$)	ACTH7 ($n = 12$)	ACTH1 ($n = 35$)	ACTH 7 ($n = 38$)
SGA								
10th	1.61	1.81	1.03	1.45	12.96	10.0	12	10.0
25th	2.92	2.93	2.98	2.15	18.0	14.5	14.5	11.15
50th	4.62	7.81	5.13	4.57	28.0	24.2	29.22	16.1
75th	9.08	13.95	12.6	8.87	46.05	39.8	52.30	24.22
90th	17.84	16.86	15.66	14.44	85.8	81.7	69.0	55.33

AGA adequate for gestational age, *SGA* small for gestational age

10th and 90th percentile, but one had C1 < 10th and ACTH > 90th percentile. None of the NW AGA infants born at 28–32 weeks of GA had fatal events.

Among the NW SGA delivered by CS at 24–27 weeks of GA, 5/13 died showing C1 and ACTH1 level between the 10th and 75th percentile. Similar data were displayed by the 2/11 infants born at 28–32 weeks of GA. None of the NW SGA born by VD infants had fatal events. No significant differences were observed on cortisol or ACTH levels between the survived and died infants.

Discussion

To date no accepted normal ranges exist for cortisol levels in AGA or SGA preterm newborns; in particular, no reference values have been established for cortisol in well preterm newborns, delivered exclusively by CS at GA < 28 weeks or BW < 1000 g. Neither has any study compared cortisol and ACTH levels on days 1 and 7 of life in newborns with GA < 28 W with those of GA between 28 and 32 weeks. Watterberg et al. have evaluated a similar cohort, even though in their paper AGA and SGA subjects were not distinguished and delivery type was not considered [19].

Compared to the previously reported data [20], the present series showed significantly higher cortisol levels at day 7 in males compared to females and ACTH levels significantly higher at both day 7 and 30, even though these data should have to be strengthened by further studies on a larger population.

The negative correlation between GA, and likewise, between BW and cortisol levels in our series is in agreement with other studies [12, 21]. The discrepancy with the fetal values reported at corresponding GAs [3] may be due to the stress of childbirth, adaptation, extra-uterine life, and to various invasive maneuvers to which an overall ELBW preterm newborn is subjected in the early hours of life. Thus, the high cortisol and ACTH levels at the end of the first week of life in the ELBW infants, even lasting for the whole first month in the very early preterm, might not indicate the basal secretion but a prompt and prolonged HPA response to various stressful events.

Regarding the mode of birth, it is well known that the full-term infant responds to the stress of labor and delivery with hypersecretion of cortisol and ACTH, as is shown by the lower levels found in the cord blood of infants delivered at full term by CS, without labor [22–25]. However, previous reports on cortisol levels after VD or CS in preterm have produced conflicting results [26, 27]; none of these studies has taken into consideration the ELBW newborns either for cortisol or for ACTH [28]. Within our population, markedly higher cortisol levels have been detected in those born by VD, whereas higher but not statistically significant difference was found for ACTH levels. Our data demonstrate that the ELBW preterm newborn also responds to the stress of labor and delivery, similarly to the full-term infant, with hypersecretion of cortisol.

Since their wide utilization in preterm neonates for the prevention of RDS, many studies have investigated the benefits of antenatal maternal corticosteroid treatment and their potential side effects, but only few studies have examined the extent to which this treatment might interfere with the HPA axis function. No uniform results have been provided, even extending the investigation of antenatal corticosteroids effects to 4–6 weeks of life [12, 13]. In our population, the corticosteroid treatment seems to mildly interfere with the cortisol and ACTH levels only at day 1. We can thus hypothesize that in the first day of life the inhibition of the prenatal steroid treatment may persist not only on the adrenal gland but also on the whole HPA axis function.

Undoubtedly, the greatest controversy in the literature concerns the definition of a cortisol level which indicates an adequate response to stress, and below which adrenal insufficiency ought to be considered. In view of the great variability of cortisol levels in the early hours, days, and month of life in the preterm infant [19, 20], we believe that a cut-off point valid for all subjects cannot be determined. Our laboratory data indicate that in the *W* newborns delivered by CS at GA < 28 weeks the 50th percentile at day 7 is equal to 9.43 mcg/dl for AGA infants and 7.81 mcg/dl for SGA infants, whereas in the newborn of GA > 28 weeks it is 6.08 mcg/dl for AGA infants and 4.57 mcg/dl for SGA infants; thus the cut-off point for adrenal insufficiency suspicion should be evaluated differently depending on the GA.

In the studied cohort, an HPA derangement has not been frequently associated to the worst outcome, either in the 24–27 weeks or in the 28–32 weeks of GA population. However, we think that the finding of cortisol levels < 10th percentile, overall if associated to ACTH levels > 90th percentile, and cortisol levels > 90th percentile might indicate the need for further HPA investigation through CRH or ACTH stimulation test. Either low orhigh basal cortisol levels could be the possible indicators of absolute or relative adrenal insufficiency. An absolute adrenal insufficiency is classically characterized by low cortisol levels and a lack of response to dynamic stimulation tests, whereas relative adrenal insufficiency is typically indicated by an adrenal response that is inadequate for the extent of the stress; in this condition, the basal cortisol levels are generally high, but there is a suboptimal response to the dynamic stimulation tests, due to insufficient reserves [28, 29]. Extremely high levels may thus suggest that the adrenal gland is working within its limits and is not capable of further increasing cortisol production, depicting a state of relative insufficiency.

Conclusion

In conclusion, this work reports neonatal cortisol and ACTH evaluation of a large series of AGA and SGA preterm infants, leading to values distribution for those born between 24 and 27 weeks and between 28 and 32 weeks of GA. Even though low or high cortisol levels have not been frequently linked to clinical alterations in the studied population, cortisol and ACTH values might be investigated in VLBW infants, overall during acute or chronic illness, to produce more evidence of their HPA axis status in the different clinical conditions; a dynamic stimulation test should be considered in case of values below the 10th or

above the 90th percentile associated with adrenal insufficiency symptoms, to decide whether and when to administer a replacement therapy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics The study protocol was approved by the Ethics Committee of each Institution or University participating in the study.

Informed consent Written consent was obtained from the parents. The study protocol was approved by the Ethics Committee of each Institution or University participating in the study.

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