ORIGINAL ARTICLE

DETERMINATION OF RELATIONSHIP BETWEEN PLASMA CORTICOTROPHIN RELEASING HORMONE AND FOETAL DEVELOPMENT DURING NORMAL PREGNANCY

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Background: Corticotrophin releasing hormone (CRH) and subsequent increase in Cortisol during pregnancy may have adverse effects on foetal development. This study is carried out to determine the relation of CRH level on foetal development during normal pregnancy. **Method:** This prospective study was done in the department of physiology and clinical lab of Isra University Hyderabad. 50 cases of normal, singleton uterine pregnancy were selected in their 31–34 weeks of gestation. Blood sample was taken and level of CRH was determined by Elisa method by specific kit. The subjects were followed till delivery. At the time of delivery foetal assessment was done by APGAR score and Ballard maturity chart. **Results:** Mean CRH value in all subjects was 50.03±9.33 ηg/ml. The mean APGAR score in the same subjects was 7.60±0.49. Mean Ballard score in all subjects was 41.70±3.13. Mean Neuromuscular maturity score in the same subjects was 19.51±3.23 and the mean physical maturity score was 22.86±1.56. CRH level revealed a significant negative correlation with mean Ballard score, neuromuscular maturity score and physical maturity score. CRH value did not show any significant correlation with APGAR score. **Conclusion:** It is concluded that high levels of CRH have negative impact on foetal development both physical and neuromuscular.

Keywords: Corticotrophin releasing hormone, APGAR score, Ballard Score

INTRODUCTION

Corticotropin-releasing hormone (CRH) is released from the hypothalamus in response to stress. In primates, it is also produced by placenta. In the second half of pregnancy, there is great increase in maternal CRH blood level. The role of CRH in pregnancy is not clear but it is believed to function in initiation of parturition and regulation of foetal development.[1]

The rising level of placental CRH as gestation advances causes a change in foetal Cortisol concentrations, foetal lung maturation, amniotic fluid proteins, phospholipids, and myometrial receptor expression, which combine, through a set of independent activating pathways, to precipitate labour and delivery.[2]

It is suggested that CRH may influence the development of foetal central nervous system and its organization in the last two trimesters of pregnancy. High levels of CRH lead to an increase in foetal Cortisol level via positive feedback loop. This results in damage to the pyramidal cells of hippocampus and a further increase in CRH level. CRH may then act on parahippocampal and limbic areas and acts as a neurotoxin. Damage to these areas may have adverse effects on the development of the fetus.[3]

Foetal exposure to Glucocorticoids and CRH has both beneficial and detrimental consequences for foetal growth and maturation. Exposure to cortisol in the last trimester is critical for the maturation of foetal systems like cardiovascular, urinary, respiratory and over all foetal growth.[4] Women who use synthetic cortisol during pregnancy are more likely to deliver infants with foetal growth restriction and low birth weight.[5] Similarly, exposure to CRH at 33 weeks gestation has been associated with foetal growth restriction.[6]

APGAR score was developed n 1952, by Dr. Virginia APGAR to evaluate the condition of neonates born at hospitals. This simple system is based on a sum of five numbers obtained 60 seconds after birth. The numbers are determined by objective observations of five signs (heart rate, respiratory effort, reflex irritability, muscle tone, and colour), each of which can be determined easily and without interfering with the care of the neonate.[7]

Ballard newborn maturity rating and classification chart is widely used indicator of post delivery gestational age and has been to assess development. It measures six aspects of neuromuscular maturity (posture, square window of wrist, arm recoil, popliteal angel, scarf sign, and heel to ear) and six aspects of physical maturity (skin lanugo, body hair shed after birth, planter surface of foot, breasts, eye/ear, and genitals.[8]

Present study was conducted to find the relation of CRH level on the overall development of foetus.

MATERIAL AND METHODS

Present study was conducted in the Department of Physiology, Isra University Hyderabad, and its clinical laboratory in collaboration with Liaquat University of Medical and Health Sciences Hospital Hyderabad, and Countess of Dufferin Fund Hospital Hyderabad.

Fifty healthy women with singleton intrauterine pregnancy in 31–34 weeks of gestation were recruited from the antenatal clinics. Mean age of the women was 23.88±4.01 years.

Women with twin or multiple pregnancies, chronic hypertension, chronic heart or renal disease, endocrine disorders, history of foetal congenital or chromosomal anomalies, abnormalities of uterus and cervix were excluded from this study. Smokers and steroid user were also excluded.

Personal information of every individual was recorded on a specifically designed questionnaire after obtaining the informed consent. This was followed by thorough clinical examination.

Gestational age was determined by physical examination, date of last menstrual period and ultrasound data. All subjects were followed until delivery.

Neonatal evaluations were done by APGAR score and Ballard newborn maturity rating score

Plasma CRH level was determined by enzyme immunoassay by commercially available kit EIA-1631 Manufactured by DRG International Inc., USA.

RESULTS

Results are summarised in Table-1–4 and Figure-1–4. 7 subjects were lost to follow-up.

Table-1 shows subject distribution according to CRH level. According to CRH level, subjects were divided into 4 groups. Table-2 shows that mean CRH value in all subjects was 50.03±9.33 ηg/ml. The mean APGAR score in the same subjects was 7.60±0.49. Table-3 shows that mean Ballard score in all subjects was 41.70±3.13. Mean Neuromuscular maturity score in the same subjects was 19.51±3.23 and the mean physical maturity score was 22.86±1.56. Table-4 shows CRH wise distribution of mean Ballard Score. There was a significant difference among the mean Ballard score of each group.

Figure-1 shows correlation between CRH and Ballard score. There is a negative correlation between CRH and Ballard score with *r* value of -0.801 ($p<0.001$). Figure-2 shows correlation between CRH and Physical maturity score. There was a negative correlation between physical maturity and CRH ($r= -0.47$). Figure-3 shows correlation between CRH and neuromuscular maturity score. There was a negative correlation between CRH and neuromuscular maturity with *r* value of -0.56. Figure 4 shows correlation between CRH and APGAR score. There was no significant correlation between these two parameters.

Table-1: Distribution of subjects according to mean CRH value

Group	CRH ηg/ml	n=43
1	Less than 40 ηg/ml	5
2	41–50 ηg/ml	18
3	51–60 ηg/ml	15
4	61–70 ηg/ml	5

Table-2: CRH value and Mean APGAR score in all subjects (n=43)

Variable	n=43
Corticotropin-Releasing Hormone (CRH) ηg/ml	50.03±9.33
APGAR score	7.60±0.49

Table-3: Ballard Score, Mean neuromuscular score, and Mean Physical maturity score of all subjects

Variable	n=43
Mean Ballard Score	41.70±3.13
Neuromuscular maturity Score	19.51±3.23
Physical maturity Score	22.86±1.56

Table-4: CRH wise distribution of Mean Ballard Score

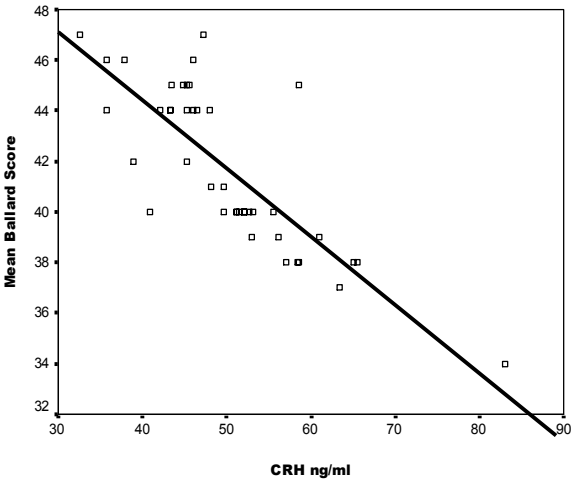
Group	CRH	n	Ballard Score	*p* value
1	<40	5	45.0±2.0	
2	41–50	18	43.6±2.0	0.01*
3	51–60	15	39.8±1.65	<0.001**
4	61–70	5	38.0±0.81	0.05***

Results are expressed as Mean±SD

*p value is statistically significant – between groups 1 and 2

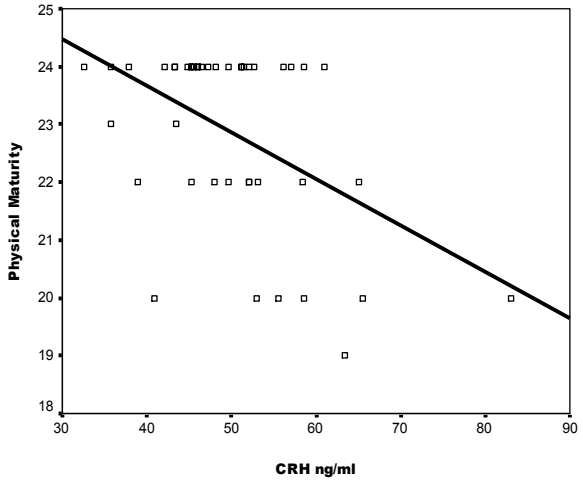
**p value is statistically significant – between group 2 and 3

***p value is statistically significant – between group 3 and 4



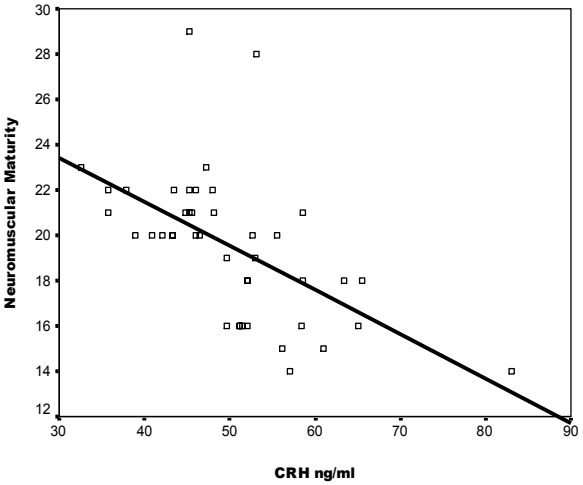
$p<0.001$, $r= -0.801$

Figure-1: Correlation between CRH values and Ballard Score



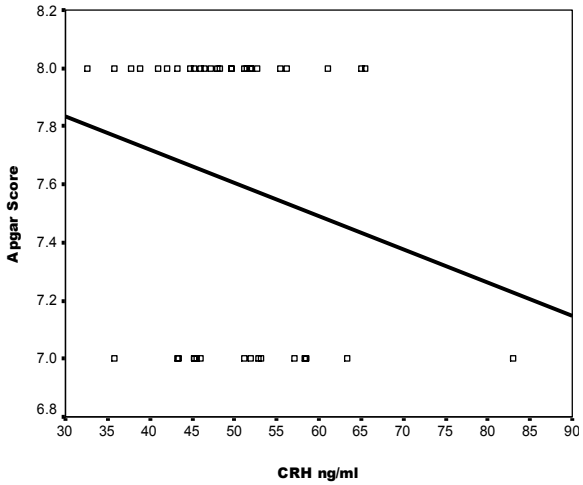
p=0.001, r= -0.47

Figure-2: Correlation between CRH and Physical maturity score



p<0.001, r= -0.56

Figure-3: Correlation between CRH and Neuromuscular Maturity



p=0.16, r= -0.216

Figure-4: Correlation between CRH and APGAR score

DISCUSSION

CRH is a peptide hormone released from hypothalamus during stress. Its levels are undetectable in men and non-pregnant women. It levels increase tremendously during pregnancy, especially in the last trimester. This signifies that it has a definite role in pregnancy/labour.

In the present study we estimated the level of plasma CRH at 31–33 weeks of gestation in normal pregnant women. These women were followed till delivery and at birth assessment of foetal maturation were done by Ballard and APGAR scores.

Of the many functions assigned to CRH during pregnancy one is that it is involved in the development and maturation of the fetus.[1]

CRH stimulates the secretion of glucocorticoids via ACTH. Foetal exposure to glucocorticoids and CRH has both beneficial and detrimental consequences for foetal growth and maturation. Exposure to cortisol in the last trimester is critical for the maturation of foetal systems like cardiovascular, urinary, respiratory and over all foetal growth.[4] Women who use synthetic cortisol during pregnancy are more likely to deliver infants with foetal growth restriction and low birth weight.[5] Similarly, exposure to CRH at 33 weeks gestation has been associated with foetal growth restriction.[6]

In the present study, level of CRH showed a significant inverse or negative correlation with Ballard score, neuromuscular maturity, and physical maturity.

High levels of CRH are associated with low Ballard score. Ellaman *et al*[9] reported that increased CRH at 31 week was significantly associated with decrease in physical and neuromuscular maturation. Each unit increase in maternal CRH (ρg/ml) was associated with a 0.06 decrease (p<0.001) in total Ballard score.

Posen[3] found an inverse correlation between CRH level and neuromuscular maturity but found no correlation of CRH with physical maturity.

CRH may influence the development of foetal central nervous system and its organisation in the last two trimesters of pregnancy. High levels of CRH with associated rise in cortisol result in damage to the hippocampus, parahippocampal and limbic areas.[3,10]

APGAR score was within normal limits and showed no significant correlation with CRH.

It has been observed that there are considerable variations in assigning APGAR score[11], and it has poor interobserver reliability[12].

CONCLUSION

CRH and Glucocorticoids are needed for the development and maturation of foetus at specific windows of intrauterine life. Increased level of both hormones is harmful at times when these are not required in abundance.

REFERENCES

1. Majzoub JA. Corticotrophin-releasing hormone physiology. Euro J Endocrin 2006;155:71–76.
2. Smith R. Parturition. N Engl J Med 2007;356(3):271–83.
3. Posen T, Sandman C. The influence of CRH on neonatal measurement of Neuromuscular and physical maturity. The UCI Undergrad Res J 2001;4:43–8.
4. Murphy VE, Smith R, Giles WB, Clifton VL Endocrine regulation of human foetal growth; the role of mother, placenta, and fetus. Endocrine reviews 2006;27(2):141–69.
5. Bloom SL, Sheffield JS, Mcintire DD, Leveno KJ. Antenatal Dexamethesone and decreased birth weight. Obst Gynaecol 2001;97(4):485–90.
6. Wadhwa PD, Garite TJ, Porto M, Glynn I, Chiczdemet A, Dunkel SC. Placental CRH, spontaneous preterm birth, and foetal growth restriction; a prospective investigation. Am J Obstet Gynecol 2004;191(4):1063–9.
7. Papile LA. The APGAR Score in the 21st Century. N Engl J Med 2001;344:519–20.
8. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers WBL, Lipp R. New Ballard score, expanded to include extremely premature infants. J Pediatr 1991;119;417–23.
9. Ellman LM, Schetter CD, Hobel CJ, Demet AC, Glynn LM, Sandman CA. Timing of foetal exposure to stress hormones: Effects on newborn physical and neuromuscular maturation. Wiley Periodicals, Inc. Dev Psychobiol 2008;50:232–41.
10. Modi N, Lewis H, Naqeeb NA, Obe MA, Dore CJ, Rutherford M. The effects of repeated antenatal Glucocorticoids therapy on developing brain. Pediatr Res 2001;50:581–5.
11. Rüdiger M, Küster H, Herting E, Berger A, Müller C, Urlesberger B, *et al*. Variations of APGAR score of very low birth weight infants in different neonatal intensive care units. Acta Paediatr 2009;98(9):1433–6.
12. O'Donnell CP, Kamlin CO, Davis PG, Carlin JB, Morley CJ. Interobserver variability of the 5-minute APGAR score. J Pediatr 2006;149(4):486–9.

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