ORIGINAL ARTICLE

ROLE OF CORTICOTROPHIN RELEASING HORMONE IN DETERMINING THE LENGTH OF GESTATION: PLACENTAL CLOCK

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Background: CRH is a hormone of stress and its secretion is greatly increased during pregnancy especially in the last trimester. During pregnancy it is also secreted by the placenta and plays role in determining the length of gestation and initiation of parturition. **Methods:** This prospective study was carried out in the Department of Physiology, and clinical laboratory of Isra University Hyderabad. Fifty 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. The subjects were followed till delivery and length of gestation noted. **Results:** Mean length of gestation in all subjects was 41.85±1.80 weeks. Mean plasma CRH in all subjects was 50.02±9.33 ηg/ml. When length of gestation was measured according to CRH values by dividing the subjects in four groups, it was found that length of gestation decreased significantly as CRH increased. Length of gestation revealed a negative correlation with CRH values with an r value of -0.901. **Conclusion:** CRH level in normal pregnancy has negative correlation with length of gestation.

Keywords: CRH, Gestation, Elisa, placenta, parturition

INTRODUCTION

Corticotropin-releasing hormone (CRH) is a 41-amino acid peptide derived from a 191-amino acid preprohormone. CRH is secreted by the paraventricular nucleus (PVN) of the hypothalamus in response to stress. In primates, it is also released from placenta. The role of placental CRH is not clear, but it may function in initiation of parturition and regulation of foetal development.[1]

In human placenta, CRH seem to modulate vasodilatation, prostaglandin synthesis, and ACTH secretion. It has also been suggested that CRH might act as a placental clock, determining the length of gestation.[2] There are two types of CRH receptors CRH-1 and CRH-2 and both are expressed in human pregnant myometrial tissue.[3]

Through different signalling pathways, CRH-R1 maintains myometrial quiescence whereas CRH-R2 promotes smooth muscle contractility.[4]

Increased maternal ACTH levels promote the production of Cortisol and dehydroepiandrosterone (DHEAS) by maternal adrenal glands. Maternal Cortisol stimulates further placental release of CRH, and DHEAS provides substrate for placental oestrogen synthesis.[3] Oestrogen is essential for production of placental oxytocin and prostaglandins which are major effectors of uterine contraction during labour and delivery.[1]

There is an association between maternal placental CRH level and time of birth. Maternal plasma CRH level increases greatly as pregnancy advances, peaking at the time of delivery. In women, who deliver pre term, the exponential increase is rapid, whereas in women who deliver after the estimated date of delivery, the rise is slower. These findings suggest that a placental clock determines the timing of delivery.[3]

Since no such study has been reported from our country, we designed this study for the women of our region.

MATERIAL AND METHODS

This study was conducted in the Department of Physiology, Isra University Hyderabad, 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 normal singleton intrauterine pregnancy, having no pre-existing medical disease or antenatal complications were included in this study. These were recruited from the antenatal clinics of Isra University Hospital, and Countess of Dufferin Fund Hospital Hyderabad. Women with twin or multiple pregnancies, or having chronic hypertension, chronic heart disease, renal disease, endocrine disorders, etc. were excluded from the study. Women having severe mental problems, history of foetal abnormalities, or abnormalities of uterus and cervix, and smokers and steroid user were also excluded.

Personal information of every individual was recorded on a specifically designed questionnaire after obtaining the informed consent. Gestational age was determined by Physical examination, date of last menstrual period and ultrasound data. All subjects were followed until delivery and length of gestation was noted.

Subjects were divided into 4 groups (group1–4) on the basis of CRH level. Group 1 consisted of subjects with CRH value less than 40 ηg/ml; Group 2 with CRH value between 41–50 ηg/ml; Group 3 with CRH value

between 51–60 ηg/ml and Group 4 consisted of subjects with CRH value between 61–70 ηg/ml.

Five ml of blood was withdrawn from the antecubital vein under aseptic condition. Plasma was obtained by centrifugation at 3,000 rpm, and frozen at -20 ºC. Level of plasma CRH was estimated by enzyme immunoassay by commercially available kit EIA-1631. It was performed on Diamet Elizer Plate Reader machine.

RESULTS

Seven subjects were lost to follow up. Group 1 had 5 subjects, Group 2 had 18 subjects, Group 3 consisted of 15 subjects, and Group 4 had 5 subjects.

Table-1 shows mean length of gestation and mean plasma CRH in all subjects. The mean length of gestation was 41.85±1.80. Mean plasma CRH value was 50.02±9.33. Table-2 shows distribution of length of gestation according to CRH level categories. As the CRH level increased from group 1 to group 4, mean length of gestation decreased and this difference was significant among all groups.

Figure-1 shows correlation between CRH values and length of gestation. Length of gestation revealed a negative correlation with CRH values with an *r*-value of -0.901.

Table-1: Mean length of gestation and mean plasma CRH in all subjects (n=43)

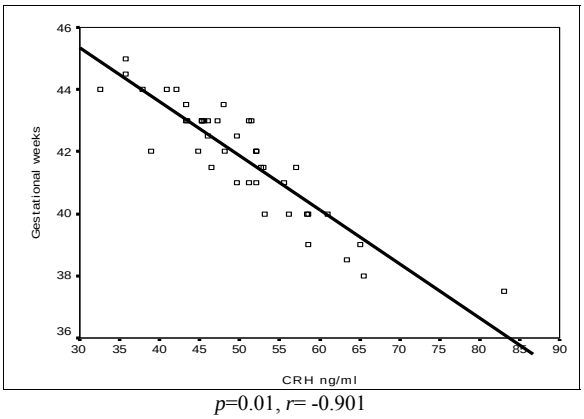
Variable	n=43
Mean Gestational age (week)	41.85±1.80
Mean CRH (ηg/ml)	50.03±9.33

Results are presented as Mean ± Standard Deviation

Table-2 Distribution of length of gestation according to CRH level categories

Group	CRH	n	gestation (weeks)	*p*
1	<40	5	43.9±1.140	-
2	41–50	18	42.8±0.78	0.02†
3	51–60	15	41.1±1.15	<0.001††
4	61–70	5	38.8±0.85	<0.002†††

†*p*-value is statistically significant between group 1 and 2, ††*p*-value is statistically significant between group 2 and 3, †††*p*-value is statistically significant between group 3 and 4



p=0.01, *r*= -0.901

Figure-1: Correlation between plasma CRH and length of gestation

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 measured the level of plasma CRH at 31–33 weeks of gestation in normal pregnant women. These women were followed till delivery and duration of gestation was noted.

Of the many functions assigned to CRH during pregnancy one is that it controls the duration of gestation and initiates and promotes labour. An association has been observed between maternal placental CRH level and time of birth. CRH level increases with advancing pregnancy being maximum at the time of delivery. This rise in plasma CRH is more and rapid in those who deliver preterm as compared to those who deliver at term. This lead to the concept of a placental clock.[3]

In the present study, the duration of gestation was found to be significantly less as the CRH level raises. When plotted, duration of gestation was found to be inversely correlated with CRH level. These results are in agreement with various previous studies.[5–15]

Linton EA *et al*[6] proposed that CRH is a marker of a placental clock controlling the length of gestation. Rising maternal plasma CRH, first detected at mid-gestation, is buffered partially by the presence of an excess of CRH-binding protein (CRHBP) in the circulation. Near the end of normal pregnancy when CRH levels are greatly increased levels of CRHBP fall gradually and more free CRH is available that may stimulate early parturition.

Sandman *et al*[13] in their study on 230 women found that CRH levels increased faster and were higher in women who delivered preterm as compared to those who delivered at term. CRH levels at 31 week of gestation predicted preterm birth. Levels of cortisol were higher at early weeks of gestation in women who delivered preterm and it was suggested that influence of cortisol on birth was mediated by its influence on placental CRH at 31 weeks.

Markovic *et al*[9] found that onset of labour is associated with increased transcription of myometrial CRH-R1 gene and IL-1 appears to be the signal involved in this pathway.

Leung *et al*[15] found a significant negative correlation between gestation at the time of delivery and mid-trimester CRH level among pre-eclampsia subjects.

Sandman *et al*[14] demonstrated that elevation of placental CRH is associated with decreased gestational length and this relationship was independent of foetal gender, parity and medical risk.

Florio *et al*[10] observed that there was a better correlation between maternal CRH and the risk of preterm birth in the 3rd trimester. A single CRH measurement at 33 weeks in asymptomatic women detected a threefold increased risk of preterm birth among those with 'high' CRH levels. Therefore CRH is useful to predict impending birth among women presenting with preterm labour in the third trimester.

Inder *et al*[7] observed that a single measurement of plasma CRH, toward the end of the second trimester, may identify a group at risk for preterm delivery, but over 50% of such deliveries will be unpredicted.

High levels of CRH promote labour by several mechanisms; it stimulates PG synthesis, Increase the release of Oxytocin, and causes vasodilatation in foeto-placental circulation.[2] CRH also potentiates the action of various uterotonins like oxytocin and PG.[3] Increased CRH causes increased secretion of ACTH and DHEA. DHEA is a substrate for oestrogen that in turn is needed for the production of placental oxytocin and PG. This may affects the timing of parturition.[1] A significant inverse correlation was found between mid trimester CRH level and gestation at delivery.[15]

CONCLUSION

It is concluded that CRH level is inversely correlated with length of gestation.

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