Maternal Serum Corticotrophin Releasing Hormone Level In Preterm Labour

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ABSTRACT:

BACK GROUND:

Preterm birth still remains a significant management problem and a large number of markers were investigated.

OBJECTIVE:

To assess the increasing of Corticotrophin Releasing Hormone(CRH) level in women diagnosed with preterm labour and are of medical value.

Design: - Case control study .Al-Kadhymia Teaching Hospital.

METHODS:

Plasma samples of 80 women diagnosed with preterm labour were used in this study. Samples were divided into three groups ,according to week of gestation (24^{th}-28^{th}, 29^{th}- 32^{nd}, 33rd-37^{th}). CRH values determined by ELISA . Twenty low risk women of control group were recruited near the end of 2^{nd} trimester, all of them delivered healthy infants at gestational age greater than 37 weeks.

RESULTS:

In a study population of one hundred pregnant women, eighty of them were diagnosed as preterm labour and twenty women as a control group, sixty-four out of eighty high risk women delivered preterm birth while the remaining sixteen of the same group delivered term babies. Our study shows that CRH level is elevated in the women with preterm birth, and ranged between (18.30-95.03)pg/ml., serum values of CRH were significantly lower in women with term birth ,and ranging between (13.5-14.9) pg/ml, , the ($p<0.001$).The sensitivity of CRH was 80% while specificity was 100%

CONCLUSION:

Maternal serum CRH level was elevated in women who gave preterm birth compared with those giving term delivery.

KEYWORD:CRH (corticotrophin relresing hormone), RIA (radio immunioassay)

INTRODUCTION:

Preterm labour is defined as the presence of uterine contractions of sufficient frequency and intensity to cause progressive effacement and dilation of the cervix prior to term gestation between (24- 37) weeks of gestation [(1)].

Peterm labour accounts for over 85% of perinatal morbidity and mortality [(2)];which includes respiratory distress syndrome, intraventricular hemorrhage, sepsis, cerebral palsy. Infection within the uterus has the potential to activate all of biochemical pathology ultimately leading to cervical ripening and uterine contraction[(3)]. 5-10% of patients with preterm labour has infection outside the uterus; most common is urinary tract infection[(4)].

Preterm placental abruption may lead to the onset of preterm labour this is thought to be through the release of thrombin which stimulates myometrial contraction by release protease activated receptors but independently of prostaglandin synthesis[(5)]. Uterine over distension in multiple pregnancies, and polyhydramnios probably lead to preterm labour through premature up regulation of contraction associated protein and factor which mediate cervical ripening, therefore with an earlier rise in placental CRH concentration in the circulation[(6)].

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Corticotrophin-releasing hormone, is a 41 amino acid peptide hormone in the hypothalamus. It acts as the main peptide that controls function of the pituitary-adrenal axis in response to stress[5].

Increase plasma CRH concentration might be associated with the pathogenesis of preterm labour. CRH concentrations seem to be associated with numerous factors, including ethnicity, stress and hormonal placental modifications[7].CRH is expressed in all layers of the fetal membranes and is present in amniotic fluid[8].

There is an important potential interaction between CRH and prostaglandin production in the amniotic compartment. Synthesis of PGE2 and PGF2, potent promoters of cervical maturation and uterine contractility, is induced by CRH in preparations at physiological concentrations [9].

AIM OF STUDY :

To assess the elevation of CRH concentration in serm of pregnant women with diagnosis of preterm birth compared with those of term birth.

PATIENTS AND METHODS:

This is a case control study conducted on one hundred pregnant women attending Al-Kadhymia Teaching hospital over a period of 12 months starting from April 2010 to the end of April 2011. The consent taken from each patient.

From the one hundred pregnant women, eighty patients were admitted to the department of obstetrics and gynecology of the hospital with a diagnosis of threatened preterm labour between (24-36^{+6}) weeks of gestation. Demographic data were obtained for all patients and information regarding birth outcome were recorded in a data base. 64 patients were delivered preterm birth, while 16 patients completed their pregnancy, All cases were followed up recording any complication arising during their current pregnancy. Twenty low risk women were recruited near the end of 2nd trimester of their pregnancy (24-28weeks) in the outpatient clinic.

The control group included healthy women without any medical disease, with singleton viable fetus their serum were used as a control.. All of them delivered healthy infants at a gestational age greater than 37weeks with apgar score more than 7 at one minute. The diagnosis of threatened preterm labor depends on presence of regular uterine contractions and dilatation or effacement of the cervix. Serum samples were collected before any interventions such as tocolysis and or administrations of steroid, pregnant women with preterm premature rupture of membrane. Antepartum hemorrhage, intra uterine growth restriction and fetal death ,cervical dilation more than 4cm were excluded.

Patients included in this study with the range of age from (19-35) years old were divided into three groups according to the gestational age: (24- 28^{th}) weeks, (29-32^{nd}) weeks and (33-36^{+6}) week gestation. Detailed history was taken from each patient, and the gestational age was based on determination of menstrual dates, or first or early 2nd trimester scan. All of them, underwent general &obstetrical examination including both abdominal &pelvic examination and send them for abdominal ultrasound, in addition to the routine investigations. CRH concentrations were measured using a radioimmunoassay (RIA) of DRG Instruments. The assay is based upon the competition of 125I-peptide. Human CRH was used as a reference standard; the cut off for CRH was 10.45pg/ml.

Data were analyzed using Microsoft office excel 2007 and SPSS 16. Data were presented as mean $\pm$SEM. ANOVA test was used to analyze continuous (numeric) data when comparing more than two groups, while student test was used to analyze continuous (numeric) data when comparing two groups. P-value less than 0.05was considered significant. The CRH cut-offs were chosen to provide sensitivity and specificity values. The predictive value of a test is a measure (%) of the times that the value (positive or negative) is the true value, i.e. the percent of all positive tests that are true positives is the Positive Predictive Value.

RESULTS:

This study included one hundred women, eighty patients admitted to the hospital complaining of preterm labour and twenty low risk pregnant women used as a control group.

Table-1 shows the clinical parameters (age, gravidity, parity, gestational age and neonatal birth wt) of the study groups. The mean of gestational ages within the three gestational ages groups (24^{th}-28^{th}, 29^{th}-32^{nd} and 33^{rd}-36^{+6} weeks of gestation) were not different between women who gave preterm birth and those who had a normal delivery at term .There was no significant difference among the groups in the age, gravidity and parity while significant difference was found in the birth weight between term and preterm birth.

Table 1: Demographic maternal variables in the study groups.

Groups	24-28 weeks NO.=20		29-32 weeks NO.=30		33-36^{+6} weeks NO.=30	
Cases	Term 5	Preterm 15	Term 6	Preterm 24	Term 5	Preterm 25
Age	27.25±3.75	27.75±4.08	28.10±4.45	27.93±4.31	27.80±3.75	28.20±4.50
Gravidity	2.75±1.82	2.94±1.95	3.30±2.40	2.94± 1.95	3.30±2.40	2.94±1.95
Parity	1.77±1.65	1.73±1.84	1.77±1.65	2.23±2.30	1.73±1.84	2.23±2.30
Neonatal birth wt.	3450.20±105.6	898.00±89.2	3370.30±115.6	1246.00±105.6	3505.35±85.8	2164.33±89.8

Fig-1- shows that CRH level in maternal plasma which rise significantly near the end of gestation as indicated from the values obtained from the (24-28w),(29-32w) and (33-36^{+6} w) gestational age groups who gave preterm birth (p<0.001).

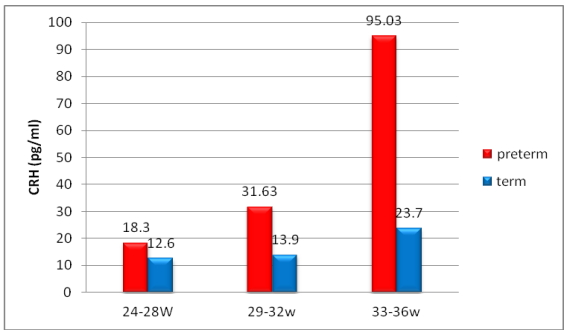

Fig 1: Mean of levels in three gestationl age groups.

Fig-2- shows comparism between CRH levels in patients' diagnosed with threatened preterm labor and the control group in the 24th to the 28th week of gestation. The mean serum CRH concentration is significantly higher in women with preterm birth compared to women with term birth (18.3pg/ml versus 10.1pg/ml respectively). Furthermore CRH values from control women were significantly lower compared to the respective values from the women of the 24-28 week group with preterm birth(p<0.001).

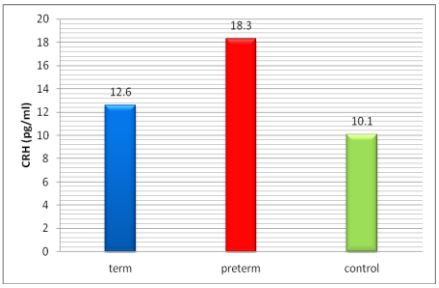

Fig 2:CRH level in(24-28 weeks)patients and control groups.

DISCUSSION:

The finding of this study was demonstrated that CRH concentration in maternal serum was elevated in women with diagnosis of threatened preterm labour .While in women with the same diagnosis but with a term birth serum values of CRH and was significantly lower . Several studies agree with our study like, Markovic D et al(2007). who demonstrated that the placental CRH may enhance fetal cortisol production to provide positive-feedback so that the placenta produces more CRH. Resulting high levels of CRH may modulate myomaterial contractility via interaction with the CRH receptor isoform, this isoform is known to enhance myomaterial contractile response, also cortisol effects on myomaterium indirectly by stimulating the fetal membranes to increase prostaglandin synthesis [(10)].

Kalantaridou SN et al (2010) which focus on the potential roles of CRH on the physiology and path physiology of reproduction and implantation, fetal immune tolerance, parturition and fetal programming of the hypothalamic-pituitary-adrenal axis. It has been suggested that there is a "CRH placental clock" which determines the length of gestation and the timing of parturition and delivery [(11)].

R. Jeanne Ruiz et al (2011). Conducted a study which represents the relationships and predictive abilities of perceived stress, selected clinical risk factors, and corticotrophin-releasing hormone level in maternal plasma were investigated for their association with preterm labour and gestational age at delivery. The measurement of stress combined with the measurement of CRH from maternal plasma may improve the prediction of which pregnant women are at risk for preterm birth [(12)].

Roger Smithet al (2009). Conducted a study of 500 pregnant women who were followed from the time of their first antenatal visit up to birth. Maternal blood samples were tested to measure the ratio of estradiol to estriol, progesterone to estriol, and progesterone to estradiol as well as the association between concentrations of a hormone in the placenta, corticotrophin-releasing hormone (CRH), and estriol during the last month prior to onset of labour. At the 26-week mark, the percentage daily change in levels of CRH was much higher in preterm singletons compared to their term counterparts, and there was a strong positive association between CRH and estriol concentrations in late pregnancy [(13)].

In contrary to our study, Emily.Harville et al (2009). which used indicators of stress and hormones such as cortisol and corticotrophin-releasing hormone have been examined in relation to preterm birth. Although these hormones have been interpreted as biomarkers of stress, it is unclear whether psychosocial measures are empirically associated with biomarkers of stress in pregnant women[(14)].

Also In contrary to our study, Aurelija Klimaviciute et al (2006).conducted as study on 67 women who divided into five groups preterm labour, preterm not in labour ,term not in labour, term labour and non-pregnant. Biopsies were taken from the cervix, while cervical, isthmic and fundal biopsies (from non-pregnant only). Andquantification of mRNA levels and the corresponding proteins were localized by immune histochemical analysis. The levels of CRH-R1 and CRH-R2 mRNA in the pregnant tissues were lower than those in non-pregnant subjects. Therefore no significant differences were observed between preterm and term groups [(15)].

Sibai et al (2005). Analysed a study by which measurement of maternal plasma CRH at 16 to 20 weeks of gestation dose not predict preterm delivery in women at risk for preterm birth [(16)].

Iams JD, et al (2007). Which conducted that the fetus also appear to play a role in parturition. It is hypothesized that the mature fetal hypothalamus secretes more corticotrophin-releasing hormone which in turn stimulates fetal adrenal production of ACTH and cortisol production. Preterm birth results from these pathological changes [(17)].

CONCLUTION:

We Concluded that maternal serum CRH level was significantly higher in symptomatic women with threatened preterm birth who gave preterm labour compared to those giving term delivery. .

So we recommended that maternal serum CRH level can be used in assessment of the relative risk of preterm birth in a woman who has been diagnosed with symptomatic threatened preterm labour.

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