Maternal serum level of ACTH as a predictive marker of preterm labor in patients with threatened preterm labor

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Abstract

Background: The mechanism of preterm labor is still unknown, the hypothalamo-pitutary adrenal axis of the fetus plays an important role in initiation of labor and also premature activation of this axis was reported in cases of preterm delivery. ACTH is the one the hormone of HPA axis so it increases in cases of preterm labor.

Purpose of study: To evaluate the role of maternal plasma ACTH concentration in prediction of preterm delivery in pregnant women presenting with threatened preterm labor.

Subject and Methods: this study was conducted on 262 Egyptian pregnant women aged between 17 and 35 years with singleton pregnancies between 28 and 36 completed weeks of gestation that had been diagnosed with threatened preterm labor.
Patients were subjected to clinical evaluation (history, examination & ultrasound evaluation), serum samples were collected from all women to measure the level of ACTH. Then the women were divided into 2 groups; group of women who delivered preterm and the other of women who delivered at term. The study compared between the 2 groups regarding the level of ACTH.

Results: 61.5% of study population delivered preterm, the median of ACTH level of these women was 23.4 pg/ml compared with 19.3 pg/ml in group of women who delivered at term, this difference in values of hormone between the groups was significant **(p-value < 0.001).**

ROC curve analysis revealed **fair predictive value** of ACTH for prediction of preterm delivery. At the best cut-off value of ACTH in prediction of preterm labor **(>22.6 pg/ml),** the sensitivity was **55.28 %**, the specificity was **86.14%,** positive predictive value was **86.4%** and negative predictive value was **54.7%.**

Conclusion: Maternal plasma ACTH concentration can be used as predictor marker of preterm delivery in pregnant women presenting with threatened preterm labor.

Keywords: Threatened preterm labor - Preterm delivery **(PTD)** - Adrenocorticotropin **(ACTH).**

Contents

List of Abbreviations

ACOG : American College of Obstetricians and Gynecologists
ACTH : Adrenocorticotropin
AFP : α-fetoprotein
ALP : Alkaline phosphatase
Ang II : Angiotensin II
ANOVA : Analysis of variance
ANP : Atrial natriuretic peptide
AUC : The area under the ROC curve
AVP : Arginine vasopressin
B : regression coefficient
BV : Bacterial vaginosis
c AMP : Cyclic adenosine monophosphate
CI : Confidence interval
CLIP : Corticotropin-like intermediate lobe peptide
CNS : Central nervous system
CO : Carbon monoxide
CRF : Corticotropin-releasing factor
CRH : Corticotropin-releasing hormone
CRP : C-reactive protein
CS : Caesarean section
DHEA : Dehydroepiandrosterone
DHEA-S : Dehydroepiandrosterone sulfate
EDTA : Ethylene Diamine Tetra Acetic acid
ELISA : Enzyme linked immunosorbent assay
EMG : Electromyography
FFN : Fetal firbronectin
FTD : Full term delivery
GA : Gestational age
GBS : Group B streptococcus
GHRH : Growth hormone releasing hormone
GHRP-2 : Growth hormone releasing peptide-2
GIT : Gastrointestinal tract
GRO : Growth Regulated Oncogene
HELLP : Hemolysis elevated liver enzyme low platelet count
HPA : Hypothalamus- pituitary–adrenal

HUMA : Home Uterine Activity Monitoring
IAI : Intra-amniotic infection
ICU : Intensive care unit
IGFBP-1 : Insulin-like growth factor binding protein-1
IL : Interleukins
INF-g : interferon-γ
IUGR : Interauterine growth restriction
IVH : Intraventricular hemorrhage
LBW : Low birth-weight
LR : Likelihood ratio
MCP-1 : Monocyte chemotactic protein-1
MMP : Matrix metalloproteinase
NEC : Necrotizing enterocolitis
NO : Nitric oxide
NSAIDs : Nonsteriodal anti-inflamatory drurgs
NVD : Normal vaginal delivery
p CRH : Placental Corticotropin-releasing hormone
p IGFBP : Phosphorylated insulin-like growth factor binding protein
p11β HSD : placental 11β hydroxysteroid dehydrogenase
PAPP : Pregnancy-associated plasma protein
PAS : Periodic acid Schiff stain
PC : Prohormone convertase enzymes
PH : proportional hazards
PHI : Peptide histidine isoleucine
PK-A : Protein kinase A
POMC : Pro-opiomelanocortin
PROM : Preterm Ruptured Membranes
PTB : Preterm birth
PTD : Preterm delivery
PTL : Preterm labor
PV : Paraventricular
RDS : Respiratory distress syndrome
rho : Spearman correlation coefficient
ROC : Receiver operator characteristic
ROM : Rupture of membranes
ROP : Retinopathy of prematurity
s ICAM : Soluble intercellular adhesion molecule

s PTL : Spontanous preterm labor
s VCAM : Soluble vascular cell adhesion molecule
SCN : Supra-chiasmatic nucleus
SD : Standard deviation
SE : Standard error
SEM : Standard error of mean
SGA : Small for gestational age
SLE : Systemic lupus erythromatosis
SLPI : Secretory leukocyte proteinase inhibitor
SOGC : Society of Obstetricians and Gynecologists of Canada
THC : Tetrahydrocannabinol
TLBW : Term low birth-weight
TNF-a : Tumor necrosis factor α
TUV : Transvaginal ultrasound
VIP : Vasoactive intestinal peptide
WHO : World health organization
α MSH : Alpha-melanocyte stimulating hormone
β HCG : Beta-Human chorionic gonadotropin
β LPH : Beta-lipotropin

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Introduction

Preterm birth, defined as birth occurring before 37 gestational weeks ***(Florio et al., 2007).*** Preterm birth is recognized as a worldwide problem responsible for more than 80% of neonatal deaths and more than 50% of long term morbidity in the surviving infants ***(Goldenberg et al., 2008).***

A signal coming from fetal brain promotes a sequence of endocrine events that lead to an effective uterine contractility. At term the first endocrine signal is probably the activation of hypothalamic corticotropin-releasing factor (CRF), which in turn stimulates pituitary adrenocorticotropin (ACTH) and consequently cortisol secretion from fetal adrenal gland (hypothalamus-pitutary-adrenal axis) ***(Reis et al., 1999).***

Near term, placental CRH acts on the fetal pituitary to stimulate the release of ACTH. In turn, fetal ACTH stimulates the secretion of fetal adrenal cortisol sulfate and dehydroepiandrosterone sulfate (DHEA-S), which enter the placental circulation through the umbilical artery and may be converted to cortisol and dehydroepiandrosterone (DHEA) by placental sulfatase. The elevation in dehydroepiandrosterone level could be used for placental estrogen synthesis ***(Sirianni et al., 2005).***

Finally, cortisol stimulates the secretion of placental CRH, thereby completing the positive feedback loop. This progressive stimulation of the placental unit and the hypothalamus- pituitary–adrenal (HPA) axis of both fetus and mother could play an important role in the initiation of parturition ***(Makrigiannakis et al., 2007).*** At term, uterine contractility is proposed to be enhanced by up-regulation of oxytocin receptor expression and communication between oxytocin and CRH receptors ***(Grammatopoulos et al., 2000).***

Preterm labor might be associated with premature activation of placental CRH secretion ***(Challis and Smith, 2001).*** CRH and ACTH maternal serum levels are significantly higher in women who gave preterm birth compared to those giving normal term delivery ***(Makrigiannakis et al., 2007).***

Intrauterine growth retardation is characterized by a reduced maternal uterine blood flow, and consequently, by hypoxemia. The fetus responds to hypoxemia with activation of hypothalamus-pituitary-adrenal activity, as reflected by the increased fetal plasma concentrations of corticotropin-releasing factor, ACTH and cortisol ***(Reis et al., 1999).***

Dexamethasone does not inhibit the effect of corticotropin- releasing factor on placental ACTH so plasma ACTH concentrations are not suppressible by therapeutic dexamethasone administration ***(Makrigiannakis et al., 2007).***

Aim of the Work

To evaluate the role of maternal plasma ACTH concentration in prediction of preterm delivery in pregnant women presenting with threatened preterm labor.

Preterm labor (PTL)

Preterm labor is defined according to world health organization (WHO) as the occurrence of 2 or more uterine contractions within 10 minutes together with cervical effacement and / or dilatation before 37 completed weeks of gestation ***(Wax et al., 2010).***

all infants born weighing < 2,500 g were considered to be premature but now, it was found that not all infants born of low birth-weight (LBW) are in fact born prematurely, the term low birth-weight (TLBW) is often used to include infants born "small for gestational age" (SGA) ***(Charlene, 2011*).**

Goldenberg et al. (2008) subdivided the preterm birth (PTB) according to gestational age**:**

- Extreme prematurity**:** occurs at < 28 weeks (about 5%).
- Severe prematurity**:** occurs at 28-31 weeks (about 15%).
- Moderate prematurity**:** occurs at 32-33 weeks (about 20%).
- Near term**:** occurs at 34-36 weeks (about 60-70%).

Incidence of Preterm Birth

According to Egyptian ministry of health statistics the incidence of prematurity in Egypt reached up to 15.8 % in the year 1985 ***(Kramer et al., 2010).***

The incidence of preterm births have been estimated that approximately 13 million infants are born preterm each year worldwide ***(Goldenberg et al., 2008)***. Preterm

labor preceded approximately 50% of these preterm births ***(ACOG, 2012).***

Etiology and Risk Factors of Preterm Birth

The etiology of preterm birth is still largely unknown. It is likely to be multifactorial, and not all preterm deliveries are the result of the same causes ***(Sayres, 2010).***

1) Maternal characteristics

Race: range of 16-18% for black women compared with 5-9% for white women ***(Simhan and Krohn, 2008).***

Age: The incidence of PTL is higher for women < 20 years and >35 years at first delivery ***(Morgan et al., 2007).***

Body Built: Females with low body weight < 50.8 kg (BMI < 19 kg/m²) are 3 times liable for preterm labor than those weighted > 57.3 kg. Also females shorter than 62" (155 cm) have higher incidence ***(Han et al., 2011).***

2) Socioeconomic and Psychological characteristics

Socioeconomic class and Occupational Factors: The risk of preterm labor was significantly higher in female with low socioeconomic and educational level ***(Díaz-Cueto et al., 2009).*** And women who are performing heavy manual have higher incidence to PTL ***(Mercer et al., 2006).***

Smoking, Alcohol and Cocaine: Tobacco use increases the risk of preterm birth (RR = 1.2 to 1.6). Alcohol abuse has been linked not only to preterm birth but also to high of brain damage in premature infant ***(Sokol et al., 2007).***Cocaine users experience an approximately two folds increased risk of preterm birth compared with that for nonusers ***(Behrman and Butler, 2007).***

Psychological Stress: Mothers experiencing high levels of psychological or social stress are at increased risk of preterm birth (generally >2-folds) ***(Goldenberg et al., 2008).***

Nutrition: Low vitamin C levels are associated with an increased risk of premature rupture of membranes and preterm birth. But an increased level of calcium reduces the risk of preterm birth. Women with low serum concentrations of iron, folic acid, or zinc have more preterm births ***(Goldenberg et al., 2008).*** Intake of larger amounts of the long-chain fatty acids found in certain fish and fish oil might increase the duration of gestation and fetal growth ***(Olsen and Secher, 2002).***

3) Obstetric History

Parity: High incidence of PTL was found between the primigravida ***(Orr et al., 2000).***

Interpregnancy Interval: An interpregnancy interval of less than 6 months confers a greater than two-fold increased risk of preterm birth ***(De Franco et al., 2007).***