Plasma Urocortin Level as a Predictor for Pre-term Delivery

Thesis

Submitted for Partial Fulfillment of Master Degree in
Obstetrics and Gynecology

By

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Contents

List of Abbreviations

+LR	*Positive likelihood ratio*
+PV	*Postive Predictive value*
ACTH	*Adrenocorticotrophic Hormone*
ATP	*Adenosine Triphosphate Coenzyme*
AUC	*Area Under the Curve*
cDNA	*Complementary DNA*
cGMP	*Cyclic Guanosine Monophosphate*
CI	*Confidence Interval*
CRF	*Corticotrophin Releasing Factor*
CRH	*Corticotrophin Releasing Hormone*
CRH-R1	*Corticotrophin Releasing Hormone Type 1*
CRH-R2	*Corticotrophin Releasing Hormone Type 2*
CS	*Caesarian Section*
DHEA-S	*Dehydroepiandrosterone – Sulphate*
GIT	*Gastro-Intestinal Tract*
HCG	*Human Chorionic Gonadotropin*
HPA axis	*Hypothalamic – Pituiary – Adrenal axis*
HUAM	*Home Uterine Activity Monitoring*
IL	*Interleukin*
IQR	*Interquartile range*
-LR	*Negative likelihood ratio*
MAPK	*Mitogen-activated Protein Kinase*

Max	*Maximum*
Min	*Minimum*
NICHD	*National Institute of Child Health and Human development*
NO	*Nitric Oxide*
NRDS	*Neonatal Respiratory Distress Syndrome*
PCR	*Polymerase Chain Reaction*
PK	*Protein Kinase*
PPROM	*Preterm Premature Rupture of Membranes*
PROM	*Premature Rupture of Membranes*
PTD	*Preterm Delivery*
PTL	*Preterm Labour*
-PV	*Negative Predictive value*
ROC	*Receiver-operating Characteristic curve*
Rpm	*Revolutions Per Minute*
SD	*Standard Deviation*
TIMP-1	*Metallopeptidase Inhibitor 1*
Ucn	*Urocortin*
Ucn1	*Urocortin 1*
Ucn2	*Urocortin 2*
Ucn3	*Urocortin3*
WHO	*World Health Organization*

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Protocol

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Protocol of Thesis
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Introduction

The world health organization (WHO) recommended that the preterm delivery is defined 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).***

Children who are born prematurely have higher rates of cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses compared with children born at term. The morbidity associated with preterm birth often extends to later life, resulting in enormous physical, psychological and economic costs ***(Petrou et al., 2003).***

The diagnosis of preterm labor has three components ***(Iams, 2003):***

1. The identification of patients at risk of preterm labor.
2. The detection of early warning symptoms of preterm labor.
3. The diagnosis of established preterm labor.

Because the clinical criteria for a diagnosis of preterm labor are inaccurate until labor is well established, over diagnosis is common ***(Iams, 2003).***

Having said that, it must be brought to light that preterm birth is a complex cluster of problems with a set of overlapping factors of influence. Its causes may include individual-level behavioral and psychosocial factors, neighborhood characteristics, environmental exposures, medical conditions, infertility treatments, biological factors, and genetics. Many of these factors occur in combination, particularly in those who are socioeconomically disadvantaged ***(Goldenberg et al., 2008).***

Approximately 45–50% of preterm births are idiopathic, 30% are related to preterm rupture of membranes (PROM) and another 15–20% are attributed to medically indicated or elective preterm deliveries ***(Pennel et al., 2007).***

The pathogenesis of PTD is not yet clear, although PTL might result from an early idiopathic activation of the normal labor process or as a result of various pathological insults ***(Goldenberg et al., 2008)***. In pPROM, focal infection and inflammation play a major role in its pathogenesis ***(Ananth et al., 2005).*** The most severe complication associated with pPROM is the chorioamnionitis, defined as inflammation of the amniochorionic (fetal) membranes of the placenta in response to microbial invasion or due to other pathological process. A strong association exists between infection and earlier PTD ***(Newton, 2005)***: intermembrane cultures in women who delivered at less than 30 weeks are at least two times more likely to be positive than after 30 weeks, with the highest

incidence of subclinical histologic chorioamnionitis in early PTD ***(Andrews et al., 1995)***.

Preterm labour is the single most important complication of pregnancy in the absence of congenital abnormality, as it 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).***

Thus, it is very important to establish a reliable predictor for preterm birth to plan a suitable management strategy. Recent screening strategies for preterm delivery have focused on early identification of patients at risk, enabling earlier intervention for preterm labour. The use of biologic markers to enhance clinical accuracy in predicting preterm birth and to identify those women at risk has been proposed ***(AHRQ, 2000).*** In this context, placenta and fetal membranes are key tissues in the response to infection and in activating the inflammatory pathways leading to PTD through the upregulation of chemokines, cytokines, and corticotropin releasing hormone (CRH), which involves urocortins as well ***(Challis et al., 2009).***

Urocortins (Ucns) are peptides showing sequence homology with CRH; CRH and Ucn are ligands for CRH- type 1 (CRH-R1) and type 2 (CRH-R2) receptors, whereas Ucn2 and Ucn3 specifically bind only CRH-R2 (***Aguilera et al., 2004).*** Ucns are expressed by gestational tissues such as trophoblast and fetal membranes ***(Imperatore et al., 2006)*** and may be

involved in some biological functions during pregnancy ***(Challis et al., 2009)*** as well as modulating immune and placental endocrine function ***(Johnstone et al., 2005).*** A complex cross-talk exists between these placental peptides and the pathways involved in the onset of PTD. Indeed, both CRH and Ucn stimulate ACTH ***(Sirianni et al., 2005)*** prostaglandin ***(Challis et al., 2000)*** and oxytocin ***(Florio et al., 1996)*** release by placental cells in culture, and also exert different effects on myometrial contractility. Moreover, CRH also stimulates uterine contractility when the myometrial intracellular pathways have been already primed by uterotonic agents (oxytocin; prostaglan- dins) ***(Hillhouse & Grammatopoulos, 2002).*** On the contrary Ucn directly ***(Petraglia et al., 1999)*** and indirectly ***(Hillhouse & Grammatopoulos, 2002)*** triggers myometrial contractility.

More specifically, urocortin has a putative role in the modulation of HPA axis and a characteristic interplay with CRF and/or receptors in controlling pregnancy and labor ***(Vaughan et al., 1995).*** Decidua has been shown to be a potential relevant source of urocortin in the events cascade leading to parturition as well as on the competition with CRF on the receptors recruitment and activation in the pregnant myometrium ***(Iavazzo et al., 2009).***

That is why, in this study, we aim to assess the role of measuring urocortin concentrations in maternal plasma of women with threatened preterm labour. The difference in the

urocorin levels between patients who deliver at term and those laboring and delivering preterm will be weighed. We aim to assess whether the measurement of urocortin may be clinically useful as a diagnostic predictor of preterm delivery in women with threatened preterm labour and if there is a cut-off value that can be of clinical use.

Preterm Labour

Preterm birth with its associated morbidity and mortality still represents one of the major unresolved problems in obstetrics and gynecology.

Preterm labor is defined as the presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix prior to term gestation (between 20 and 37 wk) ***(Malgorzata et al., 2013).***

In a systematic review of worldwide research involving all preterm births; 9.6% of all births were preterm, which translates to about 12.9 million births definable as preterm. Approximately 85% of this burden was concentrated in Africa and Asia, where 10.9 million births were preterm. This analysis demonstrates that preterm birth is a significant perinatal health problem across the globe, not only in terms of associated mortality but also with regard to short and long-term morbidity and financial implications for health-care system ***(Stacy et al., 2009).***

Prediction of preterm delivery in women with preterm uterine contractions or signs of preterm labor is critical because if these women are identified they can be referred to appropriate medical centers (***Maryam et al., 2012).***