Vitamin D-binding protein in cervicovaginal fluid as a non-invasive predictor of maternal and fetal outcome in women with preterm labor

Thesis

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List of Abbreviations

AF : Amniotic fluid

AKI : Acute kidney injury

CKD : Chronic kidney disease

CVF : Cervicovaginal fluid

fFN : Fetal Fibronectin

GalNAc : N-acetylgalactosamine

Gc : Group-specific component

GW : Gestation Weeks

iPTH : Intact parathyroid hormone

MAF : Macrophage-activating factor

pIGFBP-1 : phosphorylated insulin-like growth factor binding protein 1

PPROM : Spontaneous preterm premature rupture of the membranes

RIA : Radioimmunoassay

SPTL : Spontaneous preterm labor and intact membranes

STEMI : ST-Elevation Myocardial Infarction

VDBP : Vitamin D-binding protein

INTRODUCTION

Spontaneous preterm labor and intact membranes (PTL) or spontaneous preterm premature rupture of the membranes (PPROM) accounts for approximately 70 to 80% of all preterm births, and preterm birth, owing to these causes in particular, is strongly associated with significant neonatal morbidity, mortality, and long-term disability **(Goldenberg, et al., 2008)**. Evidence suggests that the impact of preterm birth on adverse neonatal outcomes is directly related to the degree of prematurity and the occurrence of subclinical intra-uterine infection **(Combs, et al., 2014)**. Therefore, the ability to predict the risk of spontaneous preterm delivery (SPTD) and intra-uterine infection more precisely, especially using non-invasive methods, has important clinical implications in terms of the treatment strategy (e.g., administration of medications [i.e., corticosteroid, antibiotics, and magnesium for neuroprotection] and transfer to a tertiary center) and the counseling of patients with PTL or PPROM.

Traditionally, measurement of inflammatory biomarkers in amniotic fluid (AF) sample obtained by amniocentesis has been extensively used for the prediction of intra-amniotic infection and SPTD. However, this measurement is currently limited in clinical practice due to the requirement of invasive AF sampling. In this context, cervicovaginal fluid (CVF), which can be obtained via

noninvasive or minimally invasive methods, is a feasible alternative to the AF, because several studies have demonstrated changes in various inflammatory proteins present in the CVF in association with intra-amniotic infection/inflammation, premature ripening, cervical dilatation, and preterm birth **(Jung et al., 2016)**.

Vitamin D-binding protein (VDBP) is a 58-kDa protein of the albumin superfamily that is mainly synthesized by hepatocytes. The established functions of VDBP include acting as a major carrier protein for vitamin D and its metabolites in serum, sequestering actin, and potentially modulating the inflammatory and immune response, and it is associated with the clinical progression of many diseases **(Gomme et al., 2004)**. In particular, previous studies by **Liong et al. (2015)** and **Hitti et al. (2010)** that used the proteomic and cohort approaches have shown significantly increased expression of CVF VDBP in association with the occurrence of impending PPROM in asymptomatic women and of SPTD and intra-amniotic infection in women presenting with symptoms of PTL. However, these findings have not been confirmed by other studies. Moreover, whether the change in VDBP level in the CVF is associated with intra-amniotic infection and impending SPTD in women with PPROM remains unclear. Hence, the aim of this study was to determine whether the level of VDBP in CVF samples is independently predictive of SPTD within 48 hours in women with PTL.

AIM OF THE STUDY

This study aims to assess accuracy of Vitamin D-binding protein in cervicovaginal fluid in predicting spontaneous preterm delivery.

Hypothesis:

In women with Spontaneous preterm labor and intact membranes, Vitamin D-binding protein level in cervicovaginal fluid may predict spontaneous preterm delivery accurately.

Research Question:

In women with Spontaneous preterm labor and intact membranes, does Vitamin D-binding protein level in cervicovaginal fluid predict spontaneous preterm delivery accurately?

LITERATURE REVIEW

Chapter (1):

Preterm labour is the onset of regular uterine contractions associated with progressive cervical change between viability and 37 completed weeks of gestation. The incidence is between 5% and 10% in most developed nations. In the US, the incidence has increased from 9% to 12% in the past two decades **(Mercer BM, et al., 2006)**.

In 2010, 77% of perinatal deaths were of prematurely born infants **(AQUA, 2010)**. Mortality was especially high (32%) for infants born before GW 28, while late preterm infants, i.e., those born after GW 32, still had 1.3% perinatal mortality (more than ten times that of non-premature infants). In addition to high mortality, very small preterm infants are at high risk for serious long-term complications **(AQUA, 2010)**.

The goal of all attempts to prevent and treat premature labor is to improve newborn infants' chances of surviving with as few complications as possible **(Dudenhausen JW, et al., 2007)**.

Identification of preterm labor

Several biochemical and biophysical markers have been proposed for the identification of patients at risk for spontaneous preterm delivery, in both patients with threatened preterm labor and asymptomatic ones, with the hope that interventions could prevent preterm delivery **(Honest H, et al., 2009)**.

The risk of preterm delivery after one and two previous preterm deliveries has been given as 15% and 41%, respectively **(Mercer BM, et al., 2006)**; however, such figures are difficult to apply to individuals as the risk is dependent on the cause and the gestational age of the previous preterm delivery.

There is now compelling evidence that examination of the cervix with ultrasound is superior to vaginal digital examination **(Gomez R, et al., 2004)** and in patients presenting with preterm labor can assist in determining the risk for preterm delivery before 34 weeks. In general, the shorter the cervix, the higher the risk for preterm delivery and vice versa **(Berghella V, et al., 2008)**. Transvaginal cervical sonography is a good method to assess the risk of preterm delivery in patients presenting with preterm labor, low-risk asymptomatic patients, and patients at high risk for preterm delivery **(Da Fonseca Eb, et al., 2007)**.

Furthermore, in patients with a long cervical length (43.0 cm), the likelihood of preterm delivery is low and, therefore, avoiding aggressive intervention in the setting of premature labor may be justified **(Di Renzo GC, et al., 2006)**. In contrast, patients who have a short cervix would have a higher rate of preterm delivery and may benefit from targeted interventions (i.e. steroid administration and transfer to a centre with a newborn special intensive care unit) **(Di Renzo GC, et al., 2009)**.

A cervical length of 25 mm or less had a sensitivity, specificity, positive predictive value, and negative predictive value of 76%, 68%, 20%, and 96%, respectively, to identify preterm singleton birth at less than 34 weeks of gestation **(Mella MT, et al., 2009)**. It should be also noted that endovaginal sonographic examination of the uterine cervix in women with preterm labor identifies patients at increased risk of intrauterine infections **(Gomez R, et al., 2005)**.

The evidence provided by several studies suggests that the assessment of the risk of preterm delivery in patients with a previous history of preterm birth or mid-trimester pregnancy loss require a longer cervix than those without such a history **(Hayes E, et al., 2008)**.

The assessment of the frequency of uterine contractions has been proposed to identify those at risk for

preterm delivery in both asymptomatic and symptomatic pregnant patients. The rationale for this is that increased frequency of uterine contractions leads to preterm delivery. However, the results of randomized clinical trials have indicated that ambulatory uterine monitoring has not reduced the rate of preterm delivery **(Reichmann JP, et al., 2008)**.

A growing body of evidence indicates that a positive fetal fibronectin (fFN) test in cervical and/or vaginal fluids is associated with preterm delivery both in patients with threatened preterm labor and in symptomatic patients. A negative fFN test identifies patients at very low risk **(Lockwood CJ, et al., 2001)**. A positive fFN test and/or increased cytokine concentrations in cervicovaginal fluid increase the predictive value of cervical ultrasonography to identify patients at risk for preterm delivery **(Ness A, et al., 2009)**.

Actim Partus (phosphorylated insulin-like growth factor binding protein 1 – pIGFBP-1) test can be used for estimating the risk of preterm delivery. The test detects pIGFBP-1 in cervical secretions. Similarly to the fFN test, the Actim Partus test has been shown to efficiently rule out the risk of preterm or imminent delivery. An advantage compared to the fFN test is that the Actim Partus test is not affected by seminal fluid, and can thus also be used on patients with recent intercourse **(Rahkonen L, et al., 2009)**.

However, the test has not been consistently associated to cervical length and scientific evidence is still lacking on its comparison with fFN data.

In a recent systematic review, it has been found that cervicovaginal fFN has limited accuracy in predicting spontaneous preterm birth in both asymptomatic and symptomatic women with multiple pregnancies because the likelihood ratios for positive and negative test results generated only minimal to moderate changes in the pretest probabilities of preterm birth. The test was most accurate in predicting spontaneous preterm birth before 32 weeks' gestation in asymptomatic women with multiple or twin pregnancies, and spontaneous preterm birth within 7 days of testing in women with twin pregnancies and threatened preterm labor **(Conde-Agudelo A, et al., 2010)**.

This meta-analysis suggests that only 1.6% of women with twin pregnancies and threatened preterm labor who test negative for cervicovaginal fFN will deliver in the next week. This finding could be clinically important because these women could be cared for at a primary care center rather than transferred to a tertiary care center.

However, the lack of effectiveness of clinical interventions may be due to: (1) the limitations of the current tests for the diagnosis; (2) inadequate interventions; (3) the