Research Article

Evaluation of early progesterone use in high risk women to prevent pre-term birth (PTB) predicted with high level of Cervico-Vaginal Fluid (CVF) trappin2/elafin protein

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Abstracts
Introduction: Preterm birth is a global healthcare problem associated with significant neonatal morbidity and mortality and substantial healthcare costs. **Aim of the work:** Evaluate the role of early use of micronised vaginal progesterone at 14 weeks gestation in high risk women for SPTB predicted with high level of trappin2/elaffin protein in Cervico-Vaginal Fluid (CVF). **Patients and Methods:** This is a prospective study included 50 women who are 13 weeks of gestation and had high risk for preterm birth attend to obstetric clinic of Minia university hospital and Abo Korkas hospital during the period from November 2015 to December 2016. The study was approved by the faculty of medicine, Minia university ethical committee. **Results:** A total of 50 women who are 13 weeks of gestation and had high risk for preterm were included in this study. The results were presented as descriptive and analytical statistics and presented in tables. **Conclusion:** *From the obtained results, it could be concluded that:* To the best of our knowledge, very few work was done to study the relation between trappin2/elaffin protein cervical shortening and prediction of spontaneous preterm birth, so very little data is available about this topic.
Keywords: micronised vaginal progesterone, Cervico-Vaginal Fluid,

Introduction
Preterm birth is a global healthcare problem associated with significant neonatal morbidity and mortality and substantial healthcare costs[1]. Spontaneous preterm birth (sPTB) accounts for approximately three quarters of all premature deliveries and the need for early identification of at-risk women is widely recognized, since this would facilitate management and instigation of appropriate interventions[2].

There are several risk factors for preterm labor and premature birth, including ones that researchers have not yet identified, some of these risk factors are "modifiable and other factors cannot be changed[3]. Health care providers consider the following factors to put women at high risk for preterm labor or birth[4]:
1) Women who have delivered preterm before.
2) Multiple gestations or the use of assisted reproductive technology .
3) Women with certain abnormalities of the reproductive organs are at greater risk for preterm labor and birth .

Accumulating evidence suggests that the myometrial activity associated with preterm labor results primarily from a release of the inhibitory effects of pregnancy on the myometrium rather than an active process mediated through the release of uterine stimulants, and progesterone appears to play a central role in this regard. In the first trimester, progesterone produced by the corpus luteum is critical to the maintenance of early pregnancy until the placenta takes over this function at 7 to 9 weeks of gestation, hence its name (progestational steroidal ketone)[5]. Indeed, removal of the source of progesterone (the corpus luteum) or administration of a progesterone receptor antagonist readily induces abortion before 7 weeks (49 days) of gestation[6].

Aim of the Work
Evaluate the role of early use of micronised vaginal progesterone at 14 weeks gestation in high risk women for SPTB predicted with high level of trappin2/elaffin protein in Cervico-Vaginal Fluid (CVF).

Patients and Methods

This is a prospective study included 50 women who are 13 weeks of gestation and had high risk for preterm birth attend to obstetric clinic of Minia university hospital and Abo Korkas hospital during the period from November 2015 to December 2016. The study was approved by the faculty of medicine, Minia university ethical committee. The aim of this study is to evaluate the role of early use of micronised vaginal progesterone at 14 wks gestation in high risk women for Spontaneous preterm birth (SPTB) predicted with high level of trappin2/elaffin protein in Cervico-vaginal fluid (CVF).

Cases were chosen according to the following:
✚ *Inclusion criteria:*
1) Second gravida or more.
2) Previous history of spontaneous preterm birth or late miscarriage.
3) Singleton pregnancy.
4) Gestational age 13 weeks.
✚ *Exclusion criteria:*
1) Primegravida.
2) Previous history of iatrogenic preterm birth.
3) Previous section.
4) Multiple pregnancy.
5) Women with medical disorders.

All cases were subjected to the following:
1. Full history taking including:
1. Personal and demographic data: Name, age and residence.

2. Obstetrical history.
3. History of chronic disease.
2. Examinations:
1. General examination.
2. Gynaecological examination: Including routine ultrasound scanning was done.
3. Ultrasonography examination:
4. Cervico-vaginal fluid (CVF) Sample preparation and AMP analysis.
Dacron swab was obtained from the posterior vaginal fornix in order to obtain a high vaginal sample of CVF at each visit. During speculum examination, the swab was placed in the posterior vaginal fornix for 10 seconds to achieve saturation, then transferred into 750 ml of standard phosphate-buffered saline solution containing protease inhibitors and immediately transported on ice to the laboratory. The swab was removed, placed in a clean tube, vortexed for 10 seconds and centrifuged (2600 g for 10 minutes at 4uC). Resultant fluid was collected and added to the fluid in the original tube. This was mixed and centrifuged for a further 10 minutes to remove cell debris. Cell-free supernatants were divided into aliquots and stored at -80uC until analysis.

Results
A total of 50 women who are 13 weeks of gestation and had high risk for preterm were included in this study. The results were presented as descriptive and analytical statistics and presented in tables.

Cases who developed spontaneous preterm labor of all studied cases.

Parameter		Description (50 cases)
Spontaneous preterm labor	**No**	31 (62.0%)
	Yes	19 (38.0%)

Trappin2/elafin level in cases with and without spontaneous preterm labor

Cases with cervical shortening of all studied cases.

Parameter		Description (50 cases)
Cervical shortening	**No**	18 (36.0%)
	Yes	32 (64.0%)

Trappin2/elafin level in cases with and without cervical shortening .

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Item	Spontaneous preterm labor		P. value (Sig.)
	No (n=31)	Yes (n=19)	
Trappin2/elafin (pg/ml)	68.7 ± 9.5	107.2 ± 15.4	$<0.01**$

Discussion

Preterm birth refers to a delivery that occurs before 37 weeks of gestation., it is a global healthcare problem associated and accounts for more than 85% of all perinatal morbidity and mortality and substantial healthcare costs[5]. The World Health Organization (WHO) estimates that the worldwide incidence of preterm births is 15 million annually; accounting for 11.1% of all births[6]. About 70:80% of preterm births (PTBs) are spontaneous: due to preterm labor (40 to 50%) or preterm pre-mature rupture of membranes (20 to 30%); rarely cervical insufficiency results in spontaneous preterm birth[7].

The underlying physiology and molecular biology of preterm labor is complex and not yet fully understood. The main medications that play an important role in the management of preterm labor are tocolytic therapy, antibiotics and drugs to prevent respiratory distress syndrome of the foetus especially corticosteroids[8].

It has been reported that obesity and advanced maternal age are factors related to a higher risk of preeclampsia, diabetes, chronic hypertension and other pregnancy complications or chronic diseases, and also resultant pi-PTB[9]. The higher the BMI before pregnancy, the higher the pi-PTB risk[10]. In contrast, underweight women before pregnancy and maternal age < 19 were related to a higher sPTB risk for the EMIP population, but not for pi-PTB[11]. Advanced maternal age also increases the need for assisted fertility treatments, elevating the prevalence of multiple pregnancy, an important condition for both pi-PTB and sPTB[12].

In overweight or obese women, the scenario is unfavourable for a healthy pregnancy[13]. Pre-conception care package including nutriational, educational and family planning programs should be considered to prevent this situation[14].

Progesterone is an essential hormone in the endocrinological milieu of women and has many roles at the different stages of human reproduction. Its roles include the proper regulation of menstrual cycle, embryo implanttation and pregnancy maintenance until term[15]. Progesterone supplementation (hydroxyprogesterone caproate) was used during pregnancy to reduce the risk of recurrent preterm birth in women with a history of at least one prior spontaneous preterm delivery[16]. The administration of progesterone was demonstrated to decrease both the number of episodes of uterine contra-ctions and the incidence of preterm birth in women at high risk for preterm delivery [17].

Conclusion

From the obtained results, it could be concluded that:

To the best of our knowledge, very few work was done to study the relation between trappin 2/elaffin protein cervical shortening and prediction of spontaneous preterm birth, so very little data is available about this topic.

Expression of trappin2/elaffin in cervical fluids during pregnancy suggest that they might play essential roles in local tissue homeostasis and immune defense. Also, the elevations in trappin2/elaffin in the women who delivered at preterm might reflect the local response to the pathogen invasion into the cervix preceding preterm labor.

Trappin2/elaffin in Cervicovaginal fluid is a potentially useful tool to screen women for risk

of cervical shortening and SPTB, this is evidenced by the high sensitivity and specificity obtained. So, women with raised CVF Trappin2/elaffin could be stratified to receive more intensive surveillance such as regular cervical length transvaginal ultrasound and test for risk of premature birth.

Early pregnancy recognition of those most likely to develop a short cervix would provide the opportunity for progesterone administration or elective cerclage at an earlier gestation than currently practised.

Use of trappin2/elafin as an earlier test of risk of sPTB could similarly identify women suitable for inclusion in clinical trials assessing prophylactic interventions to prevent prematur labour.

Our study was not without weaknesses, our study was still somewhat small with complete data (ie, biomarker, cervical length, and delivery information). So, future studies are necessary to clarify the functional roles of trappin2/elafin and its role as predictor of cervical shortening and SPTB.

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