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NGUYEN THI HOANG TRANG

RESEARCH ON UTEROCERVICAL ANGLE VALUE AT THE ULTRASOUND AND RESULTS OF UTEROCERVICAL ANGLE ADJUSTMENT IN PREVENTING PRETERM BIRTH IN SINGLETON PREGNANT WOMEN

SPECIALITY: OBSTETRICS AND GYNAECOLOGY
CODE: 9 72 01 05

SUMMARY OF MEDICAL DOCTORAL DISSERTATION

HUE - 2024

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INTRODUCTION

1. Introduction

The World Health Organization defines a preterm birth (PTB) as a live birth that takes place between 20^{+0} and 36^{+6} gestational weeks. An estimated 15 million babies are born prematurely each year worldwide, more than 60% of which occur in Africa and South Asia. According to UNICEF (2014), Vietnam's PTB rate was 9%, placing it 21st globally. Although research efforts on PTB have been ongoing, PTB rates have remained unchanged over the past decade in every region worldwide. Two-thirds of PTBs are due to spontaneous preterm labor, which is still a challenge in obstetric care. This is a significant contributor to neonatal morbidity and death, primarily because of immature respiratory systems, brain bleeding, and infection. These conditions can result in long-term neurological abnormalities such as intellectual disability, cerebral palsy, chronic lung disease, deafness, and blindness. Therefore, PTB preventive measures' effective and safe application is clinically important.

Until now, the cervical length (CL) measurement via transvaginal ultrasound (TVS) in the second trimester has been consistently shown to be a recommended strategy in the prediction of PTB, with the recommendations for the prevention of PTB being the use of micronized progesterone in patients with a short cervix. Currently, cervical length measurement through transvaginal ultrasound in the second trimester is the most common screening strategy. In the case of a positive finding, vaginal progesterone treatment is highly recommended for preventing preterm birth. For singleton pregnancies, a cervical length of 25 mm or less is considered to increase the risk of preterm birth; however, the preterm birth detection rate before 32 weeks of gestation is only approximately 55%, with a false-positive rate of 10%. In recent years, uterocervical angle (UCA) has been proposed as a potential predictor of PTB. The more obtuse the UCA, the more gravity from the uterus, and the fetus acting on the internal os tends to be along the length of the cervical canal, which can lead to a shortened cervix, which is one of the factors causing PTB. Moreover, there is still a lack of in-depth studies evaluating the real distribution of UCA values in pregnant women with term or preterm deliveries, and there is still no consensus on the appropriate gestational age during the second trimester at which to perform UCA measurement to identify women at risk of preterm birth. Another non-invasive method

of preventing PTB is using a cervical pessary, with the hypothesis that it narrows the UCA, which disperses the impact force from the uterus and the fetus down to the cervix. However, the results of these studies are controversial. Due to the discrepancy in the results of the studies above and the hypothesis that a biochemical treatment (progesterone) in combination with a mechanical treatment (cervical pessary) would be additionally effective in reducing the incidence of PTB in the group of women with an obtuse UCA. We conducted this study with two objectives:

1. Investigate the distribution of uterocervical angle values in singleton pregnant women at 16^{+0} - 23^{+6} weeks gestation.

2. Evaluate the results of adjusting the uterocervical angle by using cervical pessary in preventing preterm birth in singleton pregnant women with short cervical length.

2. Scientific significance and contributions of the thesis

This is the first study in Vietnam to establish the uterocervical angle measurements percentile chart in singleton pregnant women at 16^{+0} - 23^{+6} weeks gestation and in specific subgroups of pregnant women (full-term delivery and PTB groups, not at risk and risk of preterm birth groups), thereby providing basic information about normal uterocervical angle values in singleton pregnant women at 16^{+0} - 23^{+6} weeks gestation, and in the above subgroups of pregnant women. The results show that:

- The UCA average value increased statistically significantly with gestational age, an increase of 2.51degrees per week (95% CI: 1.66-2.85).

- The UCA average value of the full-term delivery group increased statistically significantly with gestational age, an increase of 2 degrees per week (95% CI: 1,40-2,61).

- The UCA average value of the preterm birth group increased statistically significantly with gestational age, an increase of 1,91 degrees per week (95% CI: -0,13-3,94).

- The UCA average value of the group not at risk and risk of preterm birth increased statistically significantly with gestational age, an increase of 2,29 degrees (95% CI: 1,67-2,91) and 2,82 degrees per week (95% CI: 0,65-4,99), respectively.

The second objective aimed to evaluate the results of adjusting the UCA by using cervical pessary in preventing preterm birth in singleton pregnant women with short CL, through evaluating the effectiveness of progesterone combined with cervical pessary in pregnant women

with short CL and obtuse UCA and assessing the change in UCA measurements after cervical pessary insertion. The results show that:

- The probability of preterm birth <37 weeks and <34 weeks in the group of pregnant women with a UCA ≥95° treated by progesterone plus cervical pessary decreased in comparison to the progesterone alone group, with an odds ratio (95% CI) of 0.34 (0.15-0.80) and 0,30 (0,09-0,98), respectively.

- In the group of pregnant women with a uterocervical angle ≥105°, the treatment prophylactic by progesterone plus cervical pessary yielded a lower rate of preterm birth <37 weeks and <34 weeks, with an odds ratio (95% CI) of 0.03 (0.01-0.13), and 0.08 (0.02-0.35), respectively.

- In the group of pregnant women treated with progesterone plus cervical pessary, the UCA measurement at time T1 (100.85 ± 16.10 degrees) decreased statistically significantly compared to time T0 (112.35 ± 17.80 degrees). In the group treated with progesterone alone, the UCA measurement at time T1 (101.03 ± 24.37 degrees) increased significantly compared to time T0 (89.92 ± 23.36 degrees).

The study aims to establish the UCA as a physiological constant in singleton pregnant women. Additionally, it shows the significance of the UCA measurement method by using an intervention (cervical pessary combined with progesterone) to change the UCA in pregnant women with a short CL. This research contributes important evidence on the UCA as a potential ultrasound parameter for predicting PTB. This work is meaningful in addressing challenges in prenatal care related to preventing preterm birth.

4. Thesis layout

The thesis is 126 pages including an introduction with 2 study objectives (2 pages), literature review (37 pages), materials and methods (20 pages), results (33 pages), and discussion (30 pages). The conclusion is 2 pages long and includes 4 recommendations.

The thesis contains 39 tables, 45 figures, and 2 diagrams.

The annex has 174 references including 15 Vietnamese documents and 159 English documents, including 52 documents updated in the past 5 years.

Chapter I:
LITERATURE OVERVIEW

1.1. DEFINITION, AND CLASSIFICATION OF PRETERM BIRTH

According to the World Health Organization, preterm birth is defined as a live birth occurring between 20^{+0} and 36^{+6} gestational weeks. In Vietnam, according to the National Guidelines on Reproductive Health Care Services, the gestational age of premature birth ranges between 22 weeks and 36^{+6} weeks gestation.

1.2. MECANISM OF PRETERM BIRTH

1.2.1. Early activation of the hypothalamus-pituitary-adrenal endocrine axis of mother and fetus

1.2.2. Infection or inflammatory reaction

1.2.3. Decidual hemorrhage

1.2.4. Overdistance of uterus

1.3. THE ROLE OF ULTRASOUND IN PREDICTING PREMATURE BIRTH

1.3.1. The role of ultrasound measuring cervical length in predicting preterm birth

1.3.1.1. Outline

1.3.1.2. Measurement of cervical length

1.3.1.3. Optimal gestational age measures cervical length to screen for preterm birth

1.3.1.4. Cut-off to define short cervix

1.3.1.5. Screening for risk of preterm birth by measuring total or selective cervical length

1.3.1.6. Cervical length and fetal Fibronectin measurement in predicting preterm birth

1.3.2. Other ultrasound findings as predictors of spontaneous PTB

1.3.2.1. Cervical internal os shape

1.3.2.2. Amniotic debris

1.3.2.3. Amniotic membrane separation

1.3.2.4. Elastography in predicting preterm birth

1.3.3. Uterocervical angle

1.3.3.1. Outline

The UCA is defined as the angle between the cervical canal and the lower uterine segment. Changes in uterocervical angle related to the placement of a cervical pessary in the prevention of PTB in a singleton pregnancy and twins. The UCA has recently been proposed as a potential ultrasound parameter for predicting PTB.

1.3.3.2. Assessment of the uterocervical angle

The UCA was measured following previously published protocols, according to the method described by Dziadosz et al. [19]. In short, a first line is placed from the internal os to the external os irrespective of whether the cervix is straight or curved. A second line is then drawn to delineate the lower uterine segment. Ideally, the second line reaches 3 cm up the lower uterine segment to establish an adequate measurement. The angle between the two lines is the UCA value. Specifically, in the study, we measured the UCA along with the CL, on the same cross-section image. We first drew the cervical line and measured CL, which was at least 25 mm in our study population. Then, we measured the UCA, of which the second side length was estimated at least 3 cm according to the CL.

Each participant had three images measured to reduce measurement bias, and the most obtuse UCA from the three images was used.

1.3.3.3. Distribution of uterocervical angle measurements

1.3.3.4. Evidence on the role of uterocervical angle in predicting preterm birth

1.4. PREVENTION OF PRETERM BIRTH IN ASYMPTOMATIC SINGLETON PREGNANCY WITH SHORT CERVIX

1.4.1. Conservative measures

1.4.2. Progesterone

1.4.2.1. Knowlege for using progesterone in pregnant women with short cervical length

1.4.2.2. Evidence of the role of progesterone in the prevention of preterm birth in asymptomatic singleton pregnancy with short cervix

1.4.3. Cerclage

1.4.3.1. Mecanism of cervical cerclage

1.4.3.2. Indication

1.4.3.3. Evidence of effectiveness of cervical cerclage in the prevention of preterm birth

1.4.4. Cervical pessary

1.4.4.1. Studies on cervical pessary

1.4.4.4. Evidence of effectiveness of cervical pessary in the prevention of preterm birth

Chapter II:
SUBJECTS AND METHODS

2.1. SUBJECT OF STUDY
2.1.1. Subject of study of Objective 1
All singleton pregnant women between 16^{+0} and 23^{+6} weeks of gestation with viable fetuses were examined and managed at the Haiphong Hospital of Obstetrics and Gynecology.

The exclusion criteria were as follows: (1) Participants with myoma uteri, retroflexed uterus, or uterine malformation, (2) signs of threatened miscarriage or preterm birth, (3) the use of available preterm birth prevention methods (micronized progesterone, cerclage, cervical pessary).

2.1.2. Subject of study of objective 2
All singleton pregnant women with a live fetus at 16^{+0} - 23^{+6} weeks with TVS CL measurements ≤ 25 mm managed at the Haiphong Hospital of Obstetrics and Gynecology, Vietnam were enrolled in the study.

The following were the exclusion criteria: (1) history of PTB or miscarriage in the 2nd trimester; (2) history of cervical intervention, (3) pregnant women with signs of threatened miscarriage, miscarriage, threatened PTB, or PTB; (4) PTB by medical indication; (5) pregnant women with a cervical cerclage; (6) non-adherence to progesterone treatment; (7) congenital malformations; and (8) loss to follow-up.

2.1.3. Location and time of research
The study was conducted at the Hai Phong Hospital of Gynecology and Obstetrics, from November 2019 to November 2023.

2.2. METHOD OF STUDY
2.2.1. Method of study of objective 1
Descriptive study.

2.2.2. Method of study of objective 2
This was an open-label, quasi-experimental study with a nonequivalent group design. All participants received PTB prophylaxis with vaginal progesterone following recommendations. The choice of combination with a cervical pessary depended on the mother's decision after consultation with a senior obstetrician. Mothers who do not want to make their own decisions could completely follow the opinion of the treating doctor, based on the doctor's clinical experience with the mother's written consent.

2.2.3. Steps to conduct the study
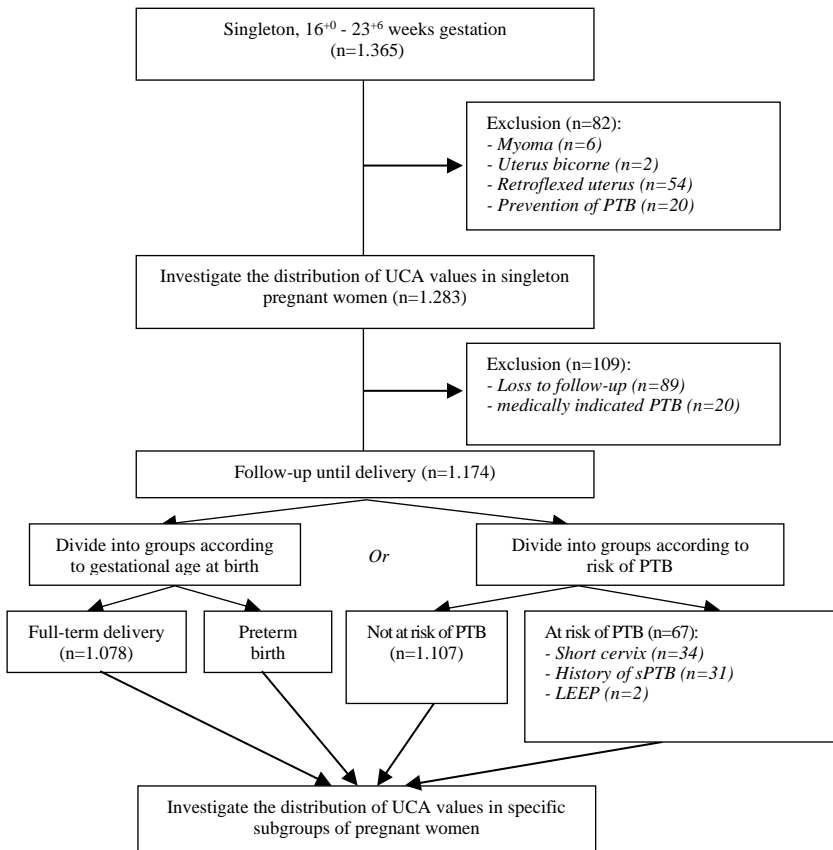### 2.2.3.1. Objective 1
Step 1. Clinical examination, select subjects that meet research criteria.

Step 2. Measurement of CL and UCA via TVS.

Step 3. Investigate the distribution of UCA values in singleton pregnant women at 16^{+0} - 23^{+6} weeks gestation.

Step 4. Follow up until delivery.

Step 5. Investigate the distribution of UCA values in specific subgroups of pregnant women.

Fig.1.1. Study diagram for Objective 1

2.2.3.2. Objective 2

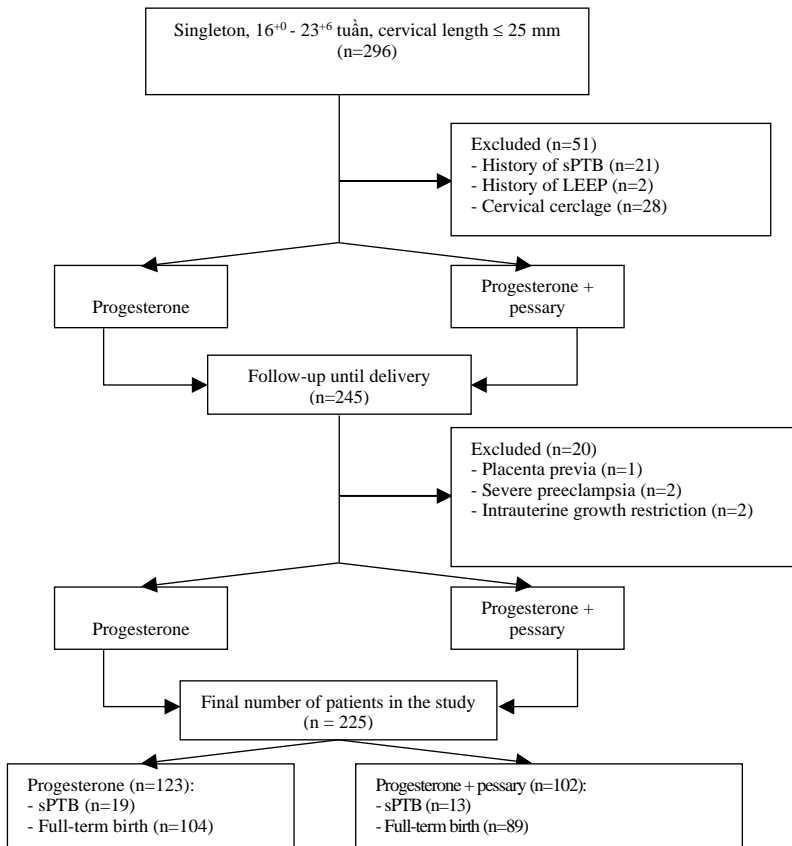 *Step 1. Clinical examination, select subjects that meet research criteria.*
 Step 2. Measurement of cervical length and uterocervical angle via transvaginal ultrasound (The time point of T0).
 Step 3. Explain the objectives, and sign consent to participate in the research.
 Step 4. Distribution of patients into two study groups.
 Step 5. Follow-up until delivery.
Step 6. Follow-up on the results of preterm birth prevention treatment

Singleton, 16^{+0} - 23^{+6} tuần, cervical length ≤ 25 mm
(n=296)

Excluded (n=51)
- History of sPTB (n=21)
- History of LEEP (n=2)
- Cervical cerclage (n=28)

Progesterone

Progesterone + pessary

Follow-up until delivery
(n=245)

Excluded (n=20)
- Placenta previa (n=1)
- Severe preeclampsia (n=2)
- Intrauterine growth restriction (n=2)

Progesterone

Progesterone + pessary

Final number of patients in the study
(n = 225)

Progesterone (n=123):
- sPTB (n=19)
- Full-term birth (n=104)

Progesterone + pessary (n=102):
- sPTB (n=13)
- Full-term birth (n=89)

Fig. 2.2. Study diagram for Objective 2.

2.2.4. Research facilities

2.2.5. Evaluation standards are relevant to the research

2.3. DATA ANALYSIS

2.3.1. Study variables

2.3.2. Data analysis for objective 1

Student's t-test was used to evaluate the difference between the two means, and $p<0.05$ was considered statistically significant. Calculating the correlation between two quantities according to each function $y = f(x)$ (y is anthropometric quantities, x is gestational age), there was a correlation when $r>0.5$. The distribution of UCA values was visualized using a scatter plot against gestational age.

Predicted median and 5th and 95th percentiles of UCA values with 95% confidence intervals according to GA were estimated using quantile regression, which allows the possibility to detect whether the range of UCA values changes with GA, as well as the display of the confidence band around each percentile. Kurtosis and skewness calculations were performed to determine the distribution of cervical angle measurements according to gestational age which is normal when the Kurtosis coefficient $\leq\pm2$ and Skewness coefficient $\leq\pm2$. These distribution characteristics were determined to calculate the values corresponding to the percentile curve. If the distribution was normal, the percentile curve was measured by the following formula: percentile curve= $x \pm k.SD$. The mean values were determined after solving the selective equation (with the highest r), and the values corresponding to the percentiles calculated according to the above formula were the basis for establishing the UCA percentile chart according to gestational age.

2.3.3. Data analysis for objective 1

Categorical variables were denoted by frequencies (n) and percentages (%), while continuous variables were expressed as mean and standard deviation. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of variables. The characteristic differences between the group of patients treated with progesterone alone and the group in combination with a cervical pessary were assessed using the Chi-square test and Fisher's exact test for categorical variables, and T-test and Mann–Whitney U test for continuous variables with normal distribution and non-normal distribution data, respectively. We determined the correlation between

CL, UCA, and gestational age at birth and calculated the OR (95% CI) to determine the association between the output variable and the independent variables. A multivariable binary regression model assessed the association between CL, UCA, and PTB outcomes. Participants were divided into two groups according to UCA values $\geq 95^{o}$ or $\geq 105^{o}$ for analysis. The role of the cervical pessary on the PTB outcome with different UCA measurements was assessed according to the UCA group. The significance level was set to 0.05. The software SPSS version 26.0 (SPSS, Inc., Chicago, IL) was used for all analyses.

2.4. STUDY ETHICS

The research protocol was approved by the Ethics Committee for Biomedical Research of Hue University of Medicine and Pharmacy, Vietnam (IDH 2020/035), and the Scientific Council of Hai Phong Obstetrics and Gynecology Hospital, Vietnam (IEC, 1186/QD-BVPSHP).

Chapter III:
STUDY RESULTS

3.1. INVESTIGATE THE DISTRIBUTION OF UCA VALUES IN SINGLETON PREGNANT WOMEN AT 16^{+0} - 23^{+6} WEEKS GESTATION.

3.1.1. Investigate the distribution of UCA values in singleton pregnant women at 16^{+0} - 23^{+6} weeks gestation.
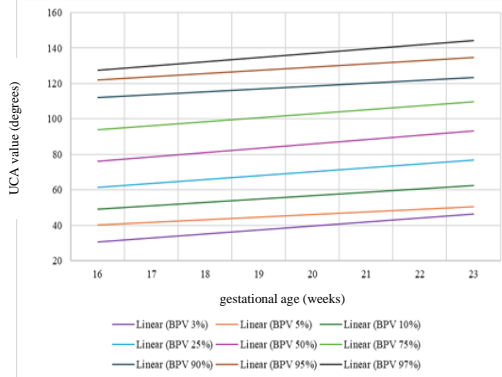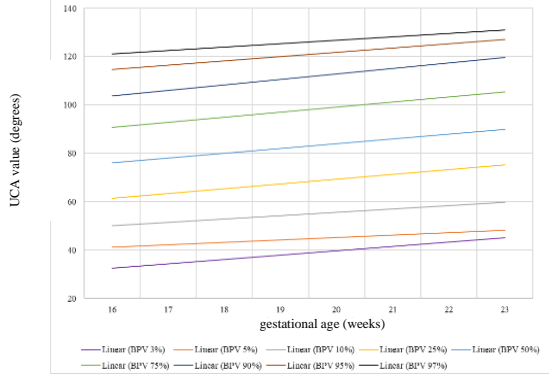

Fig. 3.3. Percentile chart of UCA values in singleton pregnancy women

The UCA average value increased statistically significantly with gestational age from 16^{+0} - 23^{+6} weeks gestation.

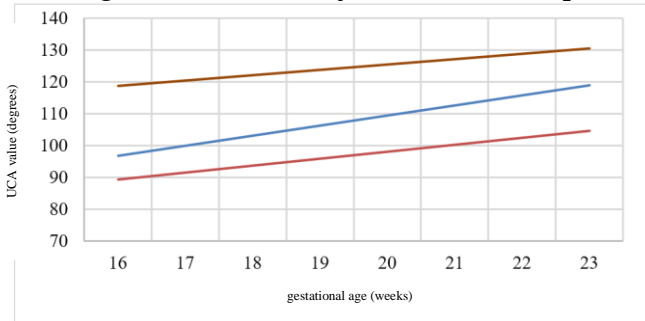*3.1.2. Investigate the distribution of UCA values in specific*

subgroups.
3.1.2.2. Investigate the distribution of UCA values in the full-term group.

Fig. 3.6. Percentile chart of UCA values in full-term group
The UCA average value in the full-term group increased statistically significantly with gestational age from 16^{+0} - 23^{+6} weeks gestation.

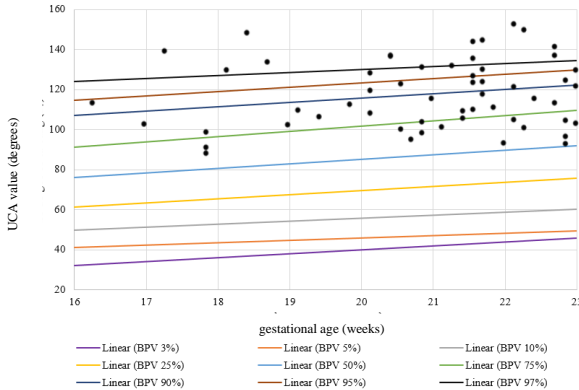*3.1.2.3. Investigate the distribution of UCA values in the preterm group.*

Hình 3.9. Percentile chart of UCA values in the preterm birth group.
The UCA average value in the preterm group increased statistically significantly with gestational age from 16^{+0} - 23^{+6} weeks gestation.

3.1.2.4. Investigate the distribution of UCA values in not at risk of preterm birth group.

Hình 3.12. Percentile chart of UCA values in not at risk of preterm birth group.

100% of women giving PTB before 37 had UCA values above the 50th percentile, and most of them had a UCA value above the 75th percentile (56/67 women, accounting for 83,6%).

Bảng 3.17. Prediction of preterm birth <37 tuần at the UCA's cut-off at 50th và 75th percentile in not at risk of preterm birth group.

Giá trị	50th percentile	75th percentile
RR (95% CI)	-	15,3 (8,1 - 28,7)
p	<0,001	<0,001
Se (95% CI) (%)	100 (93,2 - 100)	83,6 (72,1 - 91,1)
Sp (95% CI) (%)	53,2 (50,0 - 56,2)	78,8 (76,1 - 81,2)
PPV (%)	12,1	20,6
NPV (%)	100	98,7
LR+	2,14	3,9
LR-	0	0,2
ACC (%)	56,0	79,0

At the UCA's cut-off point of the 50th percentile, the sensitivity, and specificity in the prediction of PTB were 100% and 53,2%, respectively, with an accuracy of 56%.

Pregnant women who had UCA measurements above the 75th percentile have a 15,3-fold increased risk of PTB compared to those having UCA measurements under the 75th percentile. The sensitivity,

and specificity in the prediction of PTB were 83,6% and 78,8%, respectively, with an accuracy of 79%.

3.1.2.5. *Investigate the distribution of UCA values in at risk of preterm birth group.*
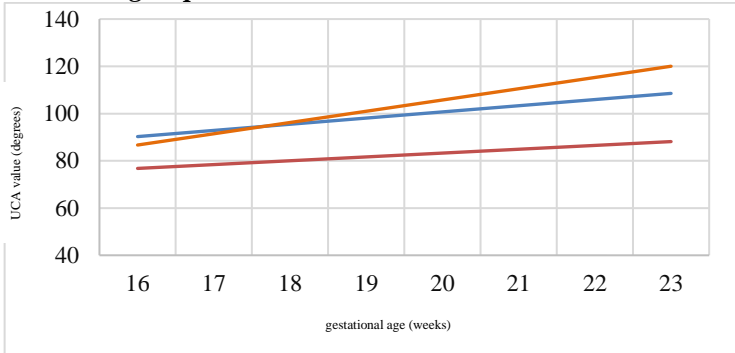
Fig. 3.15. Percentile chart of UCA values in at risk of preterm birth group.

The UCA average value in the at-risk PTB group increased significantly with gestational age from 16^{+0} - 23^{+6} weeks gestation.

3.2. EVALUATE THE RESULTS OF ADJUSTING THE UCA BY USING CERVICAL PESSARY IN PREVENTING PRETERM BIRTH IN SINGLETON PREGNANT WOMEN WITH SHORT CERVICAL LENGTH.

Table 3.24. The UCA change in the two study groups (n = 131).

Intervention time	T0 (degrees)	T1 (degrees)	Difference T1 – T0 (degrees)	p
Progesterone (n = 61)	89,92 ± 23,36	101,03 ± 24,37	+ 11,11	0,001
Progesterone + pessary (n = 70)	112,35 ± 17,80	100,85 ± 16,10	- 11,50	<0,001

In the group of pregnant women treated with progesterone alone, UCA measurements at T1 (101,03 ± 24,37 degrees) increased significantly compared to T0 (89,92 ± 23,36 degrees).

In the group of pregnant women treated with progesterone combined with pessary, UCA measurement at T1 (100,85 ± 16,10 degrees) decreased significantly compared to T0 (112,35 ± 17,80 degrees).

3.2.2. Hiệu quả dự phòng sinh non ở hai nhóm nghiên cứu

Table 3.26. Pregnancy outcomes of study subjects (n = 225).

Outcomes	Preterm birth <37 weeks				Preterm birth <34 weeks			
Prophylactic Treatment	Yes n (%)	No n (%)	OR (95% CI)	p	Yes n (%)	No n (%)	OR (95% CI)	p
Progesterone + pessary	13 (12,7)	89 (87,3)	0,800 (0,374-1,710)	0,563	5 (4,9)	97 (95,1)	0,653 (0,212-2,014)	0,455
Progesterone	19 (15,4)	104 (84,6)			9 (7,3)	114 (92,7)		

There was no statistically significant difference in PTB rates <37 weeks and <34 weeks between the two groups.

Table 3.28. Neonatal characteristics and outcomes of study subjects (n = 225).

Neonatal Characteristics and Outcomes		Progesterone (n = 123)	Progesterone + pessary (n = 102)	p
Gestational age at birth (X ± SD) (weeks)		37,74 ± 2,04	37,86 ± 1,62	0,654
Birthweight (grams)	<1500	2 (1,6%)	2 (2,0%)	0,627
	1500-2499	19 (15,4%)	17 (16,7%)	
	2500 - 3999	100 (81,3%)	83 (81,4%)	
	≥4000	2 (1,6%)	0 (0%)	
	X ± SD	2886,59 ± 523,19	2845,59 ± 504,49	0,553
Apgar scores	≥7	121 (98,4%)	102 (100%)	0,502
	<7	2 (1,6%)	0	
Neonatal Intensive Care Unit admission		6 (4.9%)	5 (4.9%)	1,000

There was no statistically significant difference in neonatal outcomes between the two groups.

3.2.3. The pregnancy outcomes in the UCA ≥≥95º và ≥105º subgroup into two study groups

Table 3.30. The pregnancy outcomes in the UCA ≥95º subgroup (n = 130).

Outcomes Prophylactic treatment	PTB <37 weeks				PTB <34 weeks			
	Yes n (%)	No n (%)	OR (95% CI)	p	Yes n (%)	No n (%)	OR (95% CI)	p
Progesterone	16 (34.8)	30 (65.2)	0.343 (0.15-0.80)	0.011	8 (17.4)	38 (82.6)	0.301 (0.09-0.99)	0.063
Progesterone + pessary	13 (15.5)	71 (84.5)			5 (6.0)	79 (94.0)		

There was a statistically significant relationship between the prophylaxis treatments and PTB <37 weeks in the subgroup of pregnant women with UCA ≥95o. The probability of PTB <37 weeks in the group in combination with a cervical pessary decreased, with an OR (95% CI) of 0.343 (0.147-0.801), in comparison to the progesterone alone group. However, no statistically significant association was found between PTB prophylaxis treatments and outcomes of PTB <34 weeks.

Table 3.31. The pregnancy outcomes in the UCA ≥105° subgroup (n = 81).

Outcomes Prophylactic treatment	PTB <37 weeks				PTB <34 weeks			
	Yes n (%)	No n (%)	OR (95% CI)	p	Yes n (%)	No n (%)	OR (95% CI)	p
Progesterone	14 (87.5)	2 (12.5)	0.026 (0.01-0.13)	<0.001	7 (43.8)	9 (56.2)	0.084 (0.02-0.34)	0.001
Progesterone + cervical pessary	10 (15.4)	55 (84.6)			4 (6.2)	61 (93.8)		

In the subgroup of pregnant women with UCA ≥105°, there was a significant association between the group in combination with a cervical pessary, with a lower rate of PTB <37 weeks with OR (95% CI) of 0.026 (0.01-0.13). Besides that, the patients with combined therapy were associated significantly with a decrease in PTB <34 weeks, with an OR (95% CI) of 0.084 (0.02-0.34).

Bảng 3.32. Multivariable binary regression model to assess the association between cervical length, uterocervical angle, and preterm birth outcomes <37 weeks.

Prophylactic treatment		Beta	OR	95% CI	p
Progesterone (n = 123)	CL	-0.566	0.568	0.318-1.013	0.055
	UCA	0.178	1.195	1.072-1.332	0.001
	Maternal age	0.228	1.256	1.046-1.508	0.015
	Treatment of threatened preterm labor	-2,479	0,084	0,009-0,758	0,027
	Gestational age at ultrasound	-0.267	0.766	0.498-1.177	0.223
	Previous cesarean	-0.597	0.550	0.073-4.160	0.563
	Cervical internal os shape	-0.209	0.811	0.372-1.769	0.599
Progesterone + cervical pessary (n = 102)	CL	-0.190	0.827	0.645-1.060	0.133
	UCA	0.050	1.051	0.999-1.105	0.053
	Maternal age	0.111	1.117	0.960-1.300	0.153
	Treatment of threatened preterm labor	-2.276	1.103	0.021-0.493	0.004
	Gestational age at ultrasound	-0.267	0.766	0.524-1.120	0.169
	Previous cesarean	-0.070	0.933	0,144-6,040	0.942
	Cervical internal os shape	0.372	1.451	0.737-2.857	0.282

[**]*Adjusted with CL, UCA, maternal age, treatment of threatened preterm labor, gestational age at ultrasound, previous cesarean, and cervical internal os shape.*

There was a statistically significant relationship between the UCA at ultrasound and outcomes of PTB <37 weeks in the group treated with progesterone alone, with an OR (95% CI) of 1.195 (1.07-1.33). Meanwhile, in the group in combination with a cervical pessary, no statistically significant relationship was found between CL, UCA, and outcomes of PTB <37 weeks (p>0.05).

Chapter IV:
DISCUSSION

4.1. INVESTIGATE THE DISTRIBUTION OF UCA VALUES IN SINGLETON PREGNANT WOMEN AT 16^{+0} - 23^{+6} WEEKS GESTATION.

4.1.1. Investigate the distribution of UCA values in singleton pregnant women at 16^{+0} - 23^{+6} weeks gestation.

4.1.2. Investigate the distribution of UCA values in specific subgroups.

4.1.2.1. Discuss of study population

4.1.2.2. Investigate the distribution of UCA values in the full-term delivery group

4.1.2.3. Investigate the distribution of UCA values in the preterm birth group

4.1.2.4. Investigate the distribution of UCA values in the not-at-risk preterm birth and clinical application of percentile chart

To demonstrate the clinical applicability of the established UCA percentile chart, we performed the distribution of UCA in the PTB before 37 weeks gestation group on the percentile chart of the singleton pregnant woman at 16^{+0} to 23^{+6} weeks gestation (Fig. 4), and we found that at the UCA's cut-off point of the 50th percentile, the sensitivity, and specificity in the prediction of preterm birth were 100% and 53,2%, respectively, with an accuracy of 56%. Pregnant women who had UCA measurements above the 75th percentile have a 15,3-fold increased risk of preterm birth compared to those having UCA measurements under the 75th percentile. The sensitivity, and specificity in the prediction of preterm birth were 83,6% and 78,8%, respectively, with an accuracy of 79%, most of them had a UCA value above the 75th percentile (57/67 women, accounting for 85.1%). Based on the results of this study, we have the same opinion as some authors that the UCA values in women with PTB are wider than that in women with term delivery. Preterm birth rates are increased in women with obtuse uterocervical angles. Thus, should we consider the 75th percentile on the above UCA percentile chart as a limit to predict PTB before 37 weeks in pregnant women at low risk for preterm delivery? More in-depth studies with a large sample size are necessary to prove the prognostic value of UCA measurements in the prediction

of PTB, especially in combination with a short CL.

In the subgroup of pregnant women not at risk of PTB, women at high risk of PTB were excluded from the size sample, resulting in limited representativeness of the study population. However, this is also an advantage that helps highlight the role of the UCA in predicting PTB, because it eliminates the role and impact of other high-risk factors for PTB that can affect the pregnancy outcomes in this group. In clinical practice, measuring the UCA at the same time as the CL for screening sPTB according to recommendations (at 16-24 weeks gestation) is convenient and may increase the effectiveness of PTB prediction when combining these two parameters.

4.1.2.5. Investigate the distribution of UCA values in the at-risk preterm birth group.

4.2. EVALUATE THE RESULTS OF ADJUSTING THE UCA BY USING CERVICAL PESSARY IN PREVENTING PRETERM BIRTH IN SINGLETON PREGNANT WOMEN WITH SHORT CERVICAL LENGTH.

4.2.1. Discuss of study population

4.2.2. Discuss prophylactic treatment for preterm birth

4.2.3. Discuss the effectiveness of preterm birth prevention in two groups

The combination of progesterone and cervical pessary did not significantly reduce the probability of PTB <37 weeks (OR = 0,80, 95% CI: 0.374-1.710) and <34 weeks (OR = 0.653, 95% CI: 0.212-2.014) compared with progesterone alone. The two groups also had no statistically significant difference in neonatal outcomes.

Micronized progesterone applications have been shown to effectively reduce the risk of PTB and improve neonatal outcomes in singleton pregnancies with short CL measured via TVS in the second trimester. Micronized progesterone is also the best PTB prophylactic intervention in singleton pregnancies with a high risk of PTB. Progesterone is known for its immunomodulatory plus anti-inflammatory effects, inhibiting uterine contractions and prostaglandin production, potent uterotonics, and promoters of cervical ripening. Micronized progesterone administration acts on the immune system by increasing the CD4+ ratio, which determines T-cell regulation.

In some pregnancies, micronized progesterone administration alone has likely been shown to effectively reduce the risk of PTB, so that any

additional benefits of other preventive interventions, such as a pessary, are barely noticeable. Recent studies comparing the use of progesterone alone versus the combination with a cervical pessary in preventing PTB in singleton pregnancies with a short CL showed opposite results. A meta-analysis of five RCTs found that this combination treatment did not reduce the risk of PTB <34 weeks (RR = 0.78, 95% CI: 0.46-1.34), and <37 weeks (RR = 1.09, 95% CI: 0.52-2.27) in comparison with progesterone alone. There was also no difference in neonatal outcomes between the two groups.

In recent years, many studies have evaluated UCA, measured in the second trimester of pregnancy while measuring CL via TVS, as a potential ultrasound parameter predicting PTB. Although there are many complex mechanisms leading to PTB, cervical histological and anatomical variations play a key role in the pathogenesis of preterm birth labor. The pressure from nearby organs and, more importantly, the growing pregnant uterus can impact the cervical internal os and alter cervical function. It seems that an obtuse UCA is associated with a direct force from the pregnant uterus to the cervical internal os, while it is hypothesized that an acute UCA is associated with less direct force action on this os, which plays a supportive role in maintaining integrity as well as preventing the expansion of the internal os.

4.2.4. Discuss the relationship between cervical angle and risk of preterm birth in two study groups

4.2.5. Discuss the value of progesterone combined with preterm birth prevention in cases of obtuse cervical angle

Our results on 225 singleton pregnant women at 16^{+0} - 23^{+6} weeks gestation with a short CL found the added effect of the cervical pessary combined with progesterone in PTB reduction rate was clearly shown in the group of pregnant women with a UCA $\geq105^\circ$.

A possible explanation is that if the UCA is obtuse, the uterus' and the fetus' gravitational pull on the internal os tends to the direction of the cervix, which might shorten it and be one of the causes of PTB. Therefore, a cervical pessary based on this mechanism serves to modify the UCA from obtuse to acute, moving the force of the uterus to the posterior vaginal fornix to prevent shortening the cervix in addition to supporting the cervix and distributing the uterine force uniformly. A study by Cannie et al. revealed that in the high-risk PTB group, the mean UCA value in patients who gave birth after 34 weeks

was significantly lower than it was before the insertion of the Arabin pessary (132º vs. 146º, p = 0.01), but it did not change in patients who gave birth <34 weeks (143° vs. 152°, p>0.05).

The multivariable binary regression model assessing the association between CL, UCA at ultrasound, and outcomes of PTB <37 weeks illustrated that there was a statistically significant relationship between the UCA at ultrasound and outcomes of PTB <37 weeks in the group treated with progesterone alone, with OR (95% CI) of 1.195 (1.072-1.332). We did not find a statistically significant relationship between CL, UCA, and outcomes of PTB <37 weeks in the group of patients treated with progesterone combined with a cervical pessary. The difference in results between the two groups may be that the cervical pessary has partly played a role in narrowing the UCA, thereby reducing the rate of PTB in this group of patients.

To monitor the change in CL and UCA after preventive intervention (time T1) compared to before intervention (time T0), we used the TVS trans pessary described by Goya et al., and we found that in the group of mothers treated with progesterone alone, the UCA measurement at time T1 (101.03 ± 24.37 degrees) increased statistically significantly compared to time T0 (89.92 ± 23.36 degrees), with p = 0.001. Meanwhile, in the combined group, the UCA measurement at time T1 (100.85 ± 16.10 degrees) decreased statistically significantly compared to time T0 (112.35 ± 17.0 degrees), with p < 0.001 (Table 3.24). In contrast, in the progesterone-alone group, the CL at time T1 (24.32 ± 4.78 mm) increased without statistical significance compared to time T0 (23,50 ± 3.48 mm), with p >0.05. In the combined group, the CL measurement at time T1 (22.90 ± 4.94 mm) increased compared to time T0 (22.78 ± 3.12 mm), however, the difference was not statistically significant, with p > 0.05 (Table 3.25).

4.2.6. Discussion of adverse effects in the two study groups
4.3. STRENGTHS AND LIMITATIONS OF THE STUDY
4.3.1. Strengths and limitations of Objective 1
4.3.2. Strengths and limitations of Objective 1

CONCLUSION

Through studying the value of the UCA on ultrasound and the results of adjusting the UCA in preventing PTB in singleton pregnant women, our study came to some conclusions as follows:

1. Investigate the distribution of UCA values in singleton pregnant women at 16^{+0} - 23^{+6} weeks gestation.

- The UCA average value increased statistically significantly with gestational age, an increase of 2.51degrees per week (95% CI: 1.66-2.85).

- The UCA average value of the full-term delivery group increased statistically significantly with gestational age, an increase of 2 degrees per week (95% CI: 1,40-2,61).

- The UCA average value of the preterm birth group increased statistically significantly with gestational age, an increase of 1,91 degrees per week (95% CI: -0,13-3,94).

- The UCA average value of the group not at risk and risk of preterm birth increased statistically significantly with gestational age, an increase of 2,29 degrees (95% CI: 1,67-2,91) and 2,82 degrees per week (95% CI: 0,65-4,99), respectively.

2. Evaluate the results of adjusting the UCA by using cervical pessary in preventing PTB in singleton pregnant women with short CL

- The probability of PTB <37 weeks and <34 weeks in the group of pregnant women with a UCA $\geq 95°$ treated by progesterone plus cervical pessary decreased in comparison to the progesterone alone group, with an odds ratio (95% CI) of 0.34 (0.15-0.80) and 0,30 (0,09-0,98), respectively.

- In the group of pregnant women with a UCA $\geq 105°$, the treatment prophylactic by progesterone plus cervical pessary yielded a lower rate of PTB <37 weeks and <34 weeks, with an odds ratio (95% CI) of 0.03 (0.01-0.13), and 0.08 (0.02-0.35), respectively.

- In the group of pregnant women treated with progesterone plus cervical pessary, the UCA measurement at time T1 (100.85 ± 16.10 degrees) decreased statistically significantly compared to time T0 (112.35 ± 17.80 degrees). In the group treated with progesterone alone, the UCA measurement at time T1 (101.03 ± 24.37degrees) increased statistically significantly compared to time T0 (89.92 ± 23.36 degrees).

RECOMMENDATIONS

1. Research to describe the distribution of UCA with a wider range of gestational ages, to provide changes in normal UCA values , and to investigate UCA measurement changes according to wider gestational age during pregnancy.

2. Consider choosing a combination treatment of progesterone and cervical pessary to prevent PTB in singleton pregnant women with short CL (≤25 mm) and obtuse UCA (≥95°).

3. Conduct a study with a randomized sampling method on a group of pregnant women with obtuse UCA, to evaluate more specifically the role of PTB prevention of the combined treatment of progesterone and cervical pessary.

4. Research to determine the threshold of UCA to predict PTB, and evaluate the effectiveness of UCA combined with CL in predicting PTB, especially in pregnant women with short CL.

LIST OF SCIENTIFIC STUDIES RELATED TO THIS THESIS

A. SCIENTIFIC ARTICLES

1. Nguyen Thi Hoang Trang, Bui Van Hieu, Doi Tu Mai. "Study on the value of preterm birth prediction of transvaginal ultrasound uterocervical angle during the second trimester of single pregnant women and prior spontaneous preterm birth at Haiphong Obstetrics and Gynecology hospital". *Vietnam Medical Journal 2019*; 483(1): 5-8.

2. Nguyen Thi Hoang Trang, Bui Van Hieu, Bui Tung Lam. "Assessing the results of preventing preterm birth in women with short cervical length in Haiphong Obstetrics and Gynecology". *Vietnam Medical Journal 2021*; 503 (special issue): 312-316.

3. Nguyen Thi Hoang Trang, Nguyen Vu Quoc Huy, Vu Van Tam. "Uterocervical angle for preterm birth prediction in singleton pregnancy at a gestational age of 16 - 24 weeks". *Vietnam Medical Journal 2022*; 515(special issue): 386-397.

4. Bui Van Hieu, Nguyen Thi Hoang Trang, Nguyen Van Quan "Cervical length as a prognostic factor for preterm birth by ultrasound in twin pregnancy at Hai Phong Obstetric and Gynecology Hospital". *Journal of Gynecology and Obstetric 2021; 19(3):19-25. DOI:10.46755/vjog.2021.3.1241.*

5. Nguyen Thi Hoang Trang, Nguyen Vu Quoc Huy, Vu Van Tam (2023). "Distribution of uterocervical angles in singleton pregnancy at gestational age 16 - 24 weeks". *Journal of Medicine and Pharmacy, Hue University of Medicine and Pharmacy, 13(7), p. 108. DOI: 10.34071/jmp.2023.7.14*

6. Nguyen Thi Hoang Trang, Nguyen Vu Quoc Huy, Vu Van Tam. "Distribution of uterocervical angles of pregnant women at 16+0 to 23+6 weeks gestation with low risk for preterm birth: first Vietnamese cohort of women with singleton pregnancies" - *BMC Pregnancy and Childbirth (2023) 23:301. DOI:10.1186/s12884-023-05597-3.*

7. Nguyen Thi Hoang Trang, Vu Van Tam, Nguyen Vu Quoc Huy (2024), Uterocervical angle and cervical length measurements for preterm birth prediction in low-risk singleton pregnant women: A prospective cohort study, *Archives of Gynecology and Obstetrics.* https://doi.org/10.1007/s00404-024-07646-4.

B. CONFERENCE REPORTS

1. Nguyen Thi Hoang Trang, Nguyen Vu Quoc Huy, Vu Van Tam (2021). "Distribution of uterocervical angles in singleton pregnancy at gestational age 16 - 24 weeks". The 9th Open Central Vietnam Scientific Congress of Gynecology and Obstetrics, October.

2. Nguyen Thi Hoang Trang, Nguyen Vu Quoc Huy, Vu Van Tam (2022). "Uterocervical angle for preterm birth prediction in singleton pregnancy at a gestational age of 16 - 24 weeks". International PhD Conference, Hue University of Medicine and Pharmacy, July.

3. Nguyen Thi Hoang Trang, Nguyen Vu Quoc Huy, Vu Van Tam (2023). "Distribution of uterocervical angles in singleton pregnancy at gestational age 16 - 24 weeks". National Ultrasound Conference VSUM, March.

4. Nguyen Thi Hoang Trang, Nguyen Vu Quoc Huy, Vu Van Tam (2023). "The uterocervical angle in the prediction of preterm birth: a review of the literature". The 9th Open Central Vietnam Scientific Congress of Gynecology and Obstetrics, November.

5. Nguyen Thi Hoang Trang, Nguyen Vu Quoc Huy, Vu Van Tam (2023). "Prevention of Preterm Birth among Singleton Pregnant Women with an Obtuse Uterocervical Angle: A Quasi-Experimental Study on the Value of Cervical Pessary Combined with Progesterone". Postgraduate Conference, Hue University of Medicine and Pharmacy, November.

6. Nguyen Thi Hoang Trang, Nguyen Vu Quoc Huy, Vu Van Tam (2024). "Prevention of Preterm Birth among Singleton Pregnant Women with an Obtuse Uterocervical Angle: A Quasi-Experimental Study on the Value of Cervical Pessary Combined with Progesterone". Presentation oral at AOFOG, May.

7. Nguyen Thi Hoang Trang, Nguyen Vu Quoc Huy, Vu Van Tam (2024). "Uterocervical Angle Measurement for Preterm Birth Prediction in Singleton Pregnant Women with Low Risk of Preterm Birth: A Prospective Study". Poster report at AOFOG, May.