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Joana Ramalho Carvalho de Aboim Aguiar

Ultrasonographic tools of preterm birth screening

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Doutora Alexandra Matias Pereira Cunha Coelho Macedo

Doutor Rafael José Monteiro da Silva Vieira

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Ultrasonographic tools of preterm birth screening

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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Joana Ramalho Carvalho de Aboim Aguiar, abaixo assinado, nº mecanográfico 201705519, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

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Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

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Joana Aguiar

Ultrasonographic tools of preterm birth screening

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Abstract

Preterm birth, delivery before 37 weeks of gestation, it's a global public health concern, leading to significant mortality and long-term health issues.

Objective: To assess the effectiveness of the uterocervical angle compared to cervical length, measured through transvaginal ultrasonography in the second trimester of pregnancy, for predicting spontaneous preterm birth.

Methods: This observational retrospective cohort study included all women with singleton pregnancies who presented for the second-trimester ultrasound in the Obstetrics and Gynecology Department of Centro Hospitalar Universitário São João, in Portugal, from January 2013 to October 2017. Uterocervical angle and cervical length were measured respecting Fetal Medicine Foundation guidelines.

Results: Among 1,943 women, spontaneous preterm birth prevalence was 5.0%. Uterocervical angle ≥ 105º showed specificity of 87.4%, negative predictive value of 95.7%, sensitivity of 26.5%, and positive predictive value of 10.1%. Cervical length ≤ 25mm demonstrated specificity of 95.5%, negative predictive value of 95.2%, sensitivity of 11.2%, and positive predictive value of 11.8%. Regression models indicated an odds ratio for uterocervical angle of 1.01 (95% CI: 1.00 - 1.02, p = 0.034) and for cervical length of 0.92 (95% CI: 0.88 - 0.97, p < 0.001).

Conclusions: Uterocervical angle performed less effectively than cervical length in predicting spontaneous preterm birth. While both markers had high negative predictive value, indicating a low likelihood of spontaneous preterm birth with a negative screen, sensitivity was low.

Keywords

Uterocervical angle; Cervical length; Spontaneous preterm birth; Preterm birth screening; Transvaginal ultrasound.

Abbreviations

CL, cervical length; PPROM, preterm premature rupture of membranes; PTB, preterm birth; sPTB, spontaneous preterm birth; TVS, transvaginal ultrasonography; UCA, uterocervical angle.

Introduction

PTB, defined as birth before 37 weeks of gestation, is a critical public health concern.[1] In 2020, an estimated 13.4 million PTB occurred on a global scale, with no significant improvement in its rate over the last decade.[2]

Prematurity is the leading cause of neonatal and childhood death below the age of 5 years. Neonates born preterm are at an increased risk of short-term complications attributed to immaturity of multiple organ systems as well as neurodevelopmental disorders, such as cerebral palsy, intellectual disabilities, and vision and hearing impairments. [1, 3, 4] PTB is associated with significant costs to health systems, and families of preterm newborns often experience considerable psychological and financial hardship, and its prevention is one of the United Nations Millennium Development Goals.

PTB can be subdivided according to gestational age: about 5% of PTB occur at less than 28 weeks' (extreme prematurity), about 15% at 28-31 weeks' (severe prematurity), about 20% at 32–33 weeks' (moderate prematurity), and 60–70% at 34–36 weeks' (near term). This classification is crucial as morbidity, mortality and costs inversely correlate with gestational age.[5]

Clinical categorization of PTB includes sPTB (50%), PPROM (25%), and medically indicated (25%).[6] This article specifically addresses sPTB.

sPTB is a complex condition with multifactorial etiologies. A history of previous PTB emerges as the strongest risk factor. Other nonmodifiable factors are cervical insufficiency, multiple gestations, polyhydramnios, and uterine anomalies. Maternal and fetal conditions like infections, hypertensive pregnancy disorders, diabetes

mellitus, and gestational diabetes, as well as lifestyle and environmental factors including smoking, substance abuse, low maternal age, pregnancy weight, or short gaps between pregnancies (< 18 months), contribute to poor pregnancy outcomes, including PTB. [5, 7]

While the mechanisms underlying sPTB remain elusive, various pathways converge on a common trajectory before delivery.[8] The cervix has an important role in pregnancy maintenance, resisting mechanical pressures applied by the growing uterus and the surrounding pelvic organ.[9] As the process of delivery unfolds, the cervix undergoes intensive changes. Consequently, there is a growing emphasis on investigating the role of the cervix in both the etiology and screening of PTB.[10]

The CL is currently the most widely adopted parameter to assess the risk of PTB.[11] The FIGO working group on the best practice in maternal-fetal medicine stated that sonographic measurement of the CL should be performed in all pregnant patients between 19 and 23 weeks of gestation using TVS.[12] A shortened cervix < 25mm has been described as an important indicator of preterm labor.[10] However, the evidence on the use of both this marker and this cut-off in a universal second-trimester screening is inconsistent and it is still not recommended.[13]

More recent studies suggest that the UCA has a higher diagnostic performance and greater potential of being used as screening tool for the prediction of PTB.[14] A wide UCA (greater than 105º), detected in the second-trimester ultrasound, is thought to be associated with a higher risk of PTB.[9, 14] An obtuse UCA is theorized to facilitate the transmission of forces from the expanding uterus and adjacent organs to the cervix, potentially triggering its dilation. Conversely, an acute

UCA is thought to function in the opposite manner, potentially aiding in the maintenance of cervical integrity.[9, 10]

This study was conducted with the aim of evaluating the predictive role of the UCA in sPTB, specifically comparing its efficacy to that of CL in the second trimester ultrasonography.

Methods

This observational, retrospective cohort study was conducted within the Obstetrics and Gynecology Department of Centro Hospitalar Universitário São João (CHUSJ) in Portugal, following approval from the hospital's ethics committee (CES 81-17). The study recruited women attending the outpatient clinic for second-trimester ultrasounds between January 2013 and October 2017. Inclusion criteria were: (1) singleton pregnancy, (2) recruitment between the 18th week and 22nd week + 6 days (determined by the crown-rump length before the 14th week), (3) delivery in the CHUSJ and (4) existence of delivery data. Exclusion criteria were: (1) medically indicated PTB, (2) PPROM, (3) cervical cerclage performed prior to screening, (4) diagnosis of chorioamnionitis and (5) deliveries before the 24th week of gestation.

The ultrasound images were retrieved from the Astraia software (Astraia Software, GmbH, Munich, Germany). All images were reviewed to assess compliance with the Fetal Medicine Foundation guidelines for cervical assessment. The guidelines recommended using a vaginal probe to identify the sagittal view of the cervix, occupying 75% of the image, and locating the internal and external os and the cervical canal. CL measurement involved the space between the internal and external os, considering funneling if present (**Figure 1**). The UCA is the angle between the anterior uterine wall and the endocervical canal (**Figure 2**).

All patients with a short cervix (< 25mm) were recommended either vaginal progesterone or the Arabin (Dr. Arabin GmbH & Co., Witten, Germany) to support pregnancy.

Data were collected from the Obscare Software, then analysed using R (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were

presented as mean ± standard deviation (SD) and analysed by t-test. Categorical variables were presented as frequencies or percentages and analysed by chi-squared test or Fisher's exact test, as adequate. Univariable logistic analyses with clinical and demographic data were performed to determine the variables associated with PTB. Multivariable logistic regression models were created, with PTB as the dependent variable, and using the CL and the UCA as independent variables, first individually and then combined. The main effects of maternal age, previous PTB, cervical insufficiency and conization were also included in the multivariable regression models. A p-value < 0.05 was considered statistically significant. The diagnostic performance of both markers was assessed using receiver operating characteristics (ROC) curve analysis and the trapezoid method was used to calculate the area under the curve (AUC).

Results

A total of 8016 women underwent the second trimester TVS and delivery at CHUSJ. After applying the exclusion criteria, a total of 1943 women were enrolled in our study. The mean age in our cohort was 30.2 ± 5.6 years, 49.0% were primigravidae and 60.1% were nullipara. Only 2.3% had some relevant obstetric history, 1.7% had a previous sPTB and 0.9% had a history of cervical surgery. **(Table 1)**

The prevalence of PTB in our cohort was 5.0% (n = 98), out of which 16.3% (n = 17) occurred before the 34th week of gestation. The mean time of delivery was 39.1 weeks, 66.8% of the women underwent a spontaneous delivery and 79.6% had a vaginal delivery.

The mean UCA was 84.6º and the mean CL was 33.0 mm. The distribution of preterm and term birth rates across different CL and UCA intervals are presented in **table 2**.

The mean UCA was wider in the preterm group compared with the term group (90.4º ± 20.9º vs. 84.3º ± 18.3º, p = 0.006). The percentage of patients who had a UCA of 105º or more was significantly higher in the preterm group (26.5% vs 12.6%, p < 0.001). The mean CL was shorter in those who had PTB (30.9 ± 5.4 mm vs. 33.1 ± 4.6 mm, p < 0.001). The percentage of patients who had CL of 25 mm or less was significantly higher in the preterm group (12.2% vs 4.5%, p < 0.001). In the preterm group the UCA decreases as the gestational age at delivery increases (p < 0.001). Contrary, the CL increases as the gestational age at delivery increases (p < 0.001). **(Table 3 and 4)**

A UCA ≥ 105º showed specificity of 87.4%, negative predictive value (NPV) of 95.7%, sensitivity of 26.5% and positive predictive value (PPV) of 10.1%. A CL ≤ 25mm showed a specificity of 95.5%, NPV of 95.2%, sensitivity of 11.2% and PPV of 11.8% **(table 5)**. Regarding the diagnostic performance of both markers, in the ROC curve analysis, the UCA had an AUC of 0.581 ($p = 0.007$) and the CL had an AUC of 0.606 ($p < 0.001$) **(table 6)**.

In univariable logistic regression analysis, maternal age ≥ 40 years old, history of PTB and cervical insufficiency were the main variables associated with PTB.

In multivariable logistic regression analysis evaluating the impact of the CL (**table 7**) and the UCA (**table 8**) individually and combined (**table 9**) as predictors of PTB, the CL demonstrated an odds ratio (OR) of 0.92 (95% CI: 0.88 - 0.97, $p < 0.001$), which shows a small and statistically significant negative association between the CL and PTB. On the other hand, the estimated OR for the effect of the UCA on PTB was 1.01 (95% CI: 1.00 - 1.02, $p = 0.034$), suggesting no significant association between the UCA and PTB.

Discussion

PTB represents a significant concern in public health as it is the foremost cause of mortality among children below five years of age.[1]

Although the mechanisms underlying sPTB remain elusive, it is well-established that cervical changes are the ultimate outcome in various pathways. Ultrasound evaluation of the cervix has been the most widely accepted tool to predict PTB.[8, 10] Despite that, screening for PTB must start primarily with a thorough medical and obstetric history to identify any risk factors.

A CL < 25mm measured by TVS has been described as a reliable predictor of PTB.[15] This shortening is attributed to proximal cervical effacement, involving the incorporation of muscle fibers from the internal os into the lower uterine segment. However, some studies propose that a shortened cervix might just be a sign that accompanies the true factors that lead to sPTB, rather than being a cause itself.[10]

More recently, the UCA has been identified as a tool to predict PTB. The theory is that a wider angle might alter the mechanical forces exerted on the cervix, increasing the likelihood of premature cervical ripening or weakening, inducing early cervical shortening and dilation, which consequentially leads to PTB.[16]

The estimated PTB prevalence in 2020 was 7.9% in Europe and 9.9% globally.[2] In our cohort, this rate was 5.0%. This difference is due to the exclusion of medically induced PTB and PPROM, which represent groups with 50% of PTB in most series.

In this study, the mean UCA was significantly wider in the preterm group compared with the term group (90.4º ± 20.9º vs. 84.3º ± 18.3º, p = 0.006). Furthermore, the UCA showed a gradual decrease as the gestational age at delivery

increased ($p < 0.001$). Khamees et al. also reported a significant decrease in the UCA as the pregnancy advanced, the mean UCA being 124.3º ± 6.2º in the group that delivered between 30 and 32 weeks, 117.9º ± 5.7º in the group that delivered between 32 and 34 weeks, and 107.6º ± 5.7º in the group that delivered between 34 and 37 weeks ($p < 0.001$).[9] Llobet et al. study also showed that mean UCA in the second trimester was wider in the preterm group (105.16º) compared to the term group (94.53º) ($p = 0.015$).[16] This inversive relation is consistent with the theory aforementioned.[9, 10]

A UCA ≥ 105º showed a specificity of 87.4%, negative predictive value (NPV) of 95.7%, but it was limited by a sensitivity of 26.5% and positive predictive value (PPV) of 10.1%, in this study. Khamees et al. reported lower specificity for UCA ≥ 105º (60.4%) but higher detection rate (86.1%) in the prediction of PTB before 37 weeks' gestation.[9] Singh et al. also reported that a UCA higher than 95º has a sensitivity of 86.7% and specificity of 93.0% in the prediction of PTB.[10] The variations in the results could be attributed to a higher prevalence of PTB in the aforementioned studies.

The mean CL was shorter in the preterm group than in the term group (30.9 ± 5.4 mm vs. 33.1 ± 4.6 mm, $p < 0.001$). The percentage of patients who had CL of 25 mm or less was significantly higher in the preterm group (12.2% vs 4.5%, $p < 0.001$). Additionally, the CL showed a significant increase as the pregnancy advanced. This was also documented in other studies.[11, 17]

A CL ≤ 25mm showed a specificity of 95.5%, NPV of 95.2%, sensitivity of 11.2% and PPV of 11.8%. Almeida et al. showed similar results for the same cut-off, in a cohort with 4.0% prevalence of PTB.[18] Iams et al. reported sensitivity of 37.3% and

specificity of 92.2% for CL ≤ 25mm at 24 weeks gestation in a population with a rate of 4.3% PTB before 35 weeks' gestation.[19]

Comparing these markers, both showed high specificity and negative predictive value, which means that with a negative screen, there is a very low likelihood of developing sPTB. On the other hand, both tests showed low sensitivity, with an AUC of 0.581 for the UCA and 0.606 for the CL, which highlights a poor performance in our population. Dziadosz et al. reported similar results regarding the sensitivity and specificity of the CL and an even lower performance of this marker in the prediction of PTB before 37 weeks, with an AUC of 0.372.[20] A CL ≤ 25 mm showed higher diagnostic performance (AUC = 0.606, $p < 0.001$) when compared to the UCA (AUC = 0.581, $p = 0.007$). These results are not concordant with other studies, that report that the UCA is a better predictor of PTB than the CL.[9-11]

In a multiple regression model, the estimated OR for the effect of the CL on PTB was 0.92 (95% CI: 0.88 - 0.97, $p < 0.001$), which demonstrates only a slight negative association. Nevertheless, in this study, the CL performed better than the UCA, which presented an OR of 1.02 (95% CI: 1.00 - 1.03, $p = 0.007$), which suggests that there is no significant association between the UCA and PTB in our population. Shi et al. presented contradictory results. Their study revealed that higher UCA indicated a higher preterm rate (OR = 7.642, 95% CI: 2.748 – 21.021, $p < 0.05$), as well as shorter CL (OR = 4.154, 95% CI: 1.294 – 17.771, $p < 0.05$).[11]

Several limitations, including the retrospective nature of the study, potential bias, and variations in ultrasound measurements, should be acknowledged. All patients with a short cervix were recommended either vaginal progesterone or the arabin to support pregnancy. However, women with wide UCA did not receive this treatment,

as there is no evidence yet supporting the impact of these measures in patients with high UCA, and this represents another limitation of this study as it can act as a confounding factor.

Further prospective trials are necessary to assess the diagnostic performance of the UCA in comparison with the CL, given the limited existing data on this comparison.

Conclusion

In this cohort, UCA demonstrated lower predictive performance than CL for sPTB. Both markers showed high NPV, emphasizing their utility in ruling out sPTB. However, further prospective trials are recommended to establish comparative diagnostic performance. The TVS, combined with medical and obstetric history, remains essential for identifying at-risk women promptly.

Author contributions

All authors were involved in the design and interpretation of the analyses, contributed to the writing of the manuscript, and read and approved the final manuscript.

Declaration of interest

The authors have no conflicts of interest.

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Tables

Table 1 – Demographic data of the studied population.

Maternal features	
Age (years)	
Mean ± SD	30.2 ± 5.6
Min	47
Max	14
Body Mass Index (Kg/m^2)	
Mean ± SD	24.2 ± 4.7
Years of schooling	
< 4^{th} grade	0.6%
4^{th} to 12^{th} grades	64.3%
> 12^{th} grade	35.1%
Smokers	13.3%
Alcohol/drug users	0.3%
Medical background	
None	87.1%
Uterine malformations	0.3%
Psychiatric disorders	1.2%
Sexually transmitted diseases	1.0%
Cardiac or renal disorders	1.0%
Diabetes	0.3%
Hypertension	1.8%
Hypothyroidism	4.8%
Neoplasia	0.4%
Obstetric intercurrences	
Fetal growth restriction	4,5%
Fetal malformation	0.6%
Urinary infection	3.0%
Other infections	1.2%
Hypertensive syndrome	3.0%
Gestational diabetes	8.8%
Surgery on 1^{st}/2^{nd} trimesters	0.1%
Risk factors for preterm birth	
Spontaneous preterm birth	1.7%
Cervical surgery	0.9%
Short CL (≤ 25 mm) on 2^{nd} trimester US	4.9%
Obstetric background	
None	97.2%
Preeclampsia	0.7%
Fetal death	0.6%
Fetal malformation	0.4%
2^{nd} trimester abortion	0.2%

Actual obstetric data	
Primigravida	49.0%
Nullipara	60.1%
Assisted reproduction	2.8%
Labor induction	26.8%
Vaginal delivery	79.6%
Male newborn	51.1%
Time of delivery	
Mean	39.1 weeks
Minimum	24.2 weeks
Maximum	42.0 weeks
Term delivery (≥ 37 weeks)	95.0%
Preterm delivery (< 37 weeks)	5.0%
Early preterm birth (< 34 weeks)	0.8%
Late preterm (≥ 34 weeks)	4.2%

Abbreviations: CL, cervical length; SD, standard deviation; US, ultrasound.

Table 2 – Distribution of preterm and term births across different cervical length intervals.

	Preterm n = 98 (5.0%)	Term n = 1845 (95.0%)	Total n = 1943
CL			
≤ 15 mm	2 (2.0%)	1 (0.1%)	2 (0.1%)
15.1 to 20 mm	4 (4.1%)	8 (0.4%)	12 (0.7%)
20.1 to 25 mm	6 (6.1%)	74 (4.0%)	80 (4.1%)
25.1 to 30 mm	23 (23.5%)	397 (21.5%)	420 (21.6%)
≥ 30 mm	63 (64.3%)	1365 (74.0%)	1428 (73.5%)
UCA			
≤ 90º	51 (52.1%)	1133 (61.4%)	1184 (60.9%)
90.1º to 95º	7 (7.1%)	195 (10.6%)	202 (10.4%)
95.1º to 100º	7 (7.1%)	171 (9.3%)	178 (9.2%)
100.1º to 105º	10 (10.2%)	130 (7.0%)	140 (7.2%)
> 105º	23 (23.5%)	216 (11.7%)	239 (12.3%)

Abbreviations: CL, cervical length; UCA, uterocervical angle.

Table 3 – Uterocervical angle and cervical length across studied population.

	Preterm n = 98 (5.0%)	Term n = 1845 (95.0%)	*p*-value
UCA			
Mean ± SD	90.4 ± 20.9	84.3 ± 18.3	0.006[a]
Range	40.0 – 134.0	34.0 – 149.0	
No. of cases			
≥ 105º	26 (26.5%)	232 (12.6%)	<0.001[b]
< 105º	72 (73.5%)	1613 (87.4%)	
CL			
Mean ± SD	30.9 ± 5.4	33.1 ± 4.6	<0.001 [a]
Range	13.0 – 44.0	13.0 – 51.0	
No. of cases			
≤ 25 mm	12 (12.2%)	83 (4.5%)	<0.001 [b]
> 25 mm	86 (87.8%)	1762 (95.5%)	

[a]t-test; [b]Chi-squared test

Abbreviations: CL, cervical length; SD, standard deviation; UCA, uterocervical angle.

Table 4 - Uterocervical angle and cervical length across studied population.

	< 28 w n = 5 (0.3%)	28 – 31^{+6} w n = 7 (0.4%)	32 – 36^{+6} w n = 86 (4.4%)	≥ 37 w n = 1845 (95.0%)	*p*-value
UCA					
Mean ± SD	110.9 ± 8.8	89.8 ± 22.0	89.3 ± 20.9	84.3 ± 18,.3	<0.001[a]
Range	103.0 – 120.7	75.0 – 131.0	40.0 – 134.0	34.0 – 149.0	
No. of cases					
≥ 105º	3 (60.0%)	1 (14.3%)	22 (25.6%)	232 (12.6%)	<0.001[b]
< 105º	2 (40.0%)	6 (85.7%)	64 (74.4%)	1613 (87.4%)	
CL					
Mean ± SD	26.2 ± 9.0	30.6 ± 7.9	31.2 ± 4.9	33.1 ± 4.6	<0.001[a]
Range	16.0 – 35.0	14.0 – 38.0	13.0 – 44.0	13.0 – 51.0	
No. of cases					
≤ 25 mm	2 (40%)	1 (14.3%)	9 (10.5%)	83 (4.5%)	<0.001[b]
> 25 mm	3 (60%)	6 (85.7%)	77 (89.5%)	1762 (95.5%)	

[a]One-Way ANOVA; [b]Chi-squared test

Abbreviations: CL, cervical length; SD, standard deviation; UCA, uterocervical angle.

Table 5 – Sensitivity, specificity, NPV and PPV of different cut-offs of UCA and CL measurements.

	S	Sp	PPV	NPV
UCA				
≥ 90º	50.0%	60.1%	6.3%	95.8%
≥ 95º	42.9%	70.3%	7.1%	95.9%
≥ 100º	34.7%	79.6%	8.3%	95.8%
≥ 105º	26.5%	87.4%	10.1%	95.7%
CL				
≤ 15 mm	2.0%	100.0%	2.2%	99.7%
≤ 20 mm	6.1%	99.6%	42.9%	95.2%
≤ 25 mm	11.2%	95.5%	11.8%	95.2%
≤ 30 mm	35.7%	74.0%	37.6%	73.8%

Abbreviations: CL, cervical length; NPV, negative predictive value; PPV, positive predictive value; S, sensitivity; Sp, specificity; UCA, uterocervical angle.

Table 6 – Diagnostic performance of the UCA and CL in the prediction of preterm birth.

	AUC	*p*-value	95% CI
UCA	0,581	0,007	0,518 – 0,643
CL	0,606	<0,001	0,548 – 0,664

Abbreviations; AUC, area under the curve; CI, confidence interval; CL, cervical length; SE, standard error; UCA, uterocervical angle.

Table 7 – Multivariable logistic regression analysis to evaluate the association between CL and PTB.

	Odds ratio	95% CI	*p*-value
Cervical length	0.91	0.88 – 0.96	< 0.001
Maternal age ≥ 40 year	1.98	0.78 – 4.32	0.113
Previous PTB	6.38	2.66 – 14.03	< 0.001
Cervical insufficiency	12.87	0.42 – 384.20	0.099
Conization	1.17	0.23 – 21.41	0.879

Abbreviations: CI, confidence interval; CL, cervical length; PTB, preterm birth.

Table 8 – Multivariable logistic regression analysis to evaluate the association between UCA and PTB.

	Odds ratio	95% CI	*p*-value
Uterocervical angle	1.02	1.00 – 1.03	0.007
Maternal age ≥ 40 year	1.85	0.73 – 4.01	0.149
Previous PTB	6.74	2.85 – 14.67	< 0.001
Cervical insufficiency	15.07	5.84 – 388.62	0.058
Conization	0.92	0.18 – 16.85	0.937

Abbreviations: CI, confidence interval; PTB, preterm birth; UCA, uterocervical angle.

Table 9 – Multivariable logistic regression analysis to evaluate the impact of the CL and the UCA as predictors of PTB.

	Odds ratio	95% CI	*p*-value
Cervical length	0.92	0.88 – 0.97	< 0.001
Uterocervical angle	1.01	1.00 – 1.02	0.034
Maternal age ≥ 40 year	1.89	0.74 – 4.15	0.143
Previous PTB	5.94	2.46 – 13.16	< 0.001
Cervical insufficiency	10.21	0.33 – 313.95	0.140
Conization	1.22	0.24 – 22.41	0.850

Abbreviations: CI, confidence interval; CL, cervical length; PTB, preterm birth; UCA, uterocervical angle.

Figures

Figure 1 – Transvaginal ultrasound measurement of the cervical length.

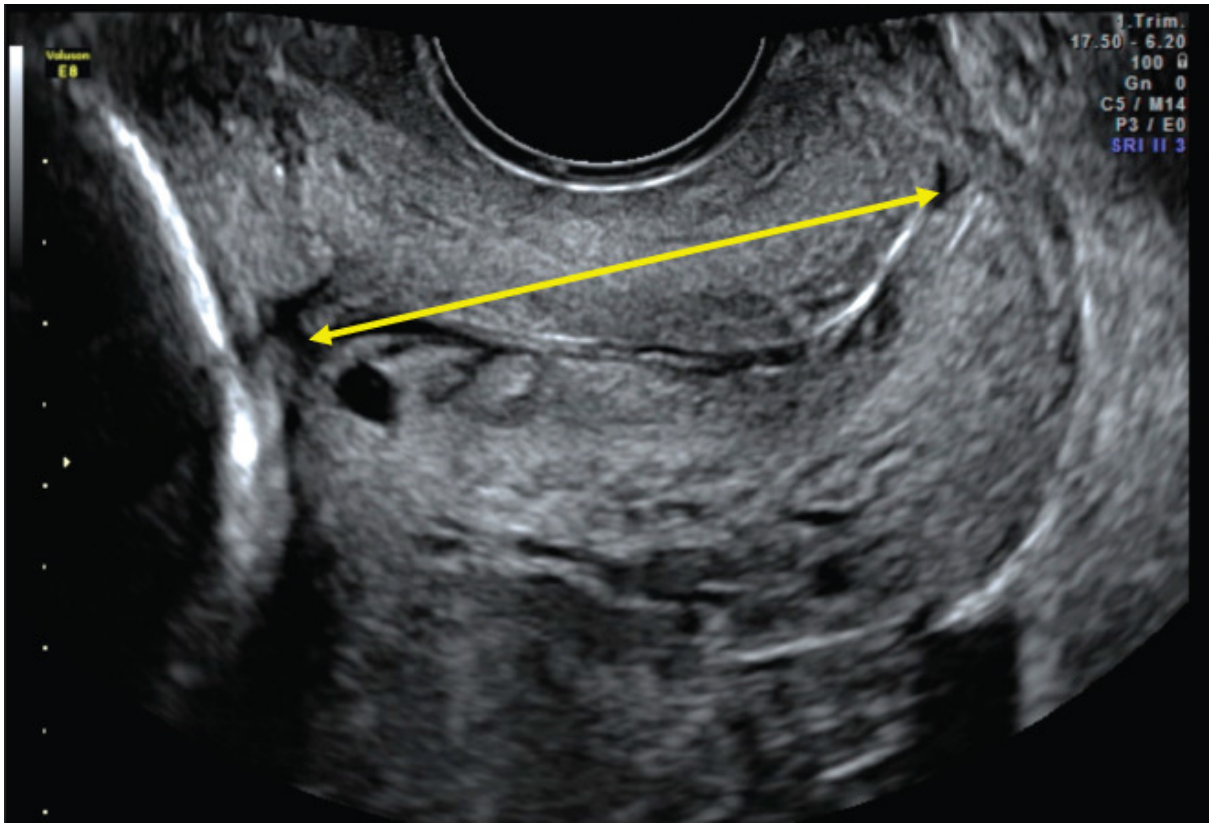
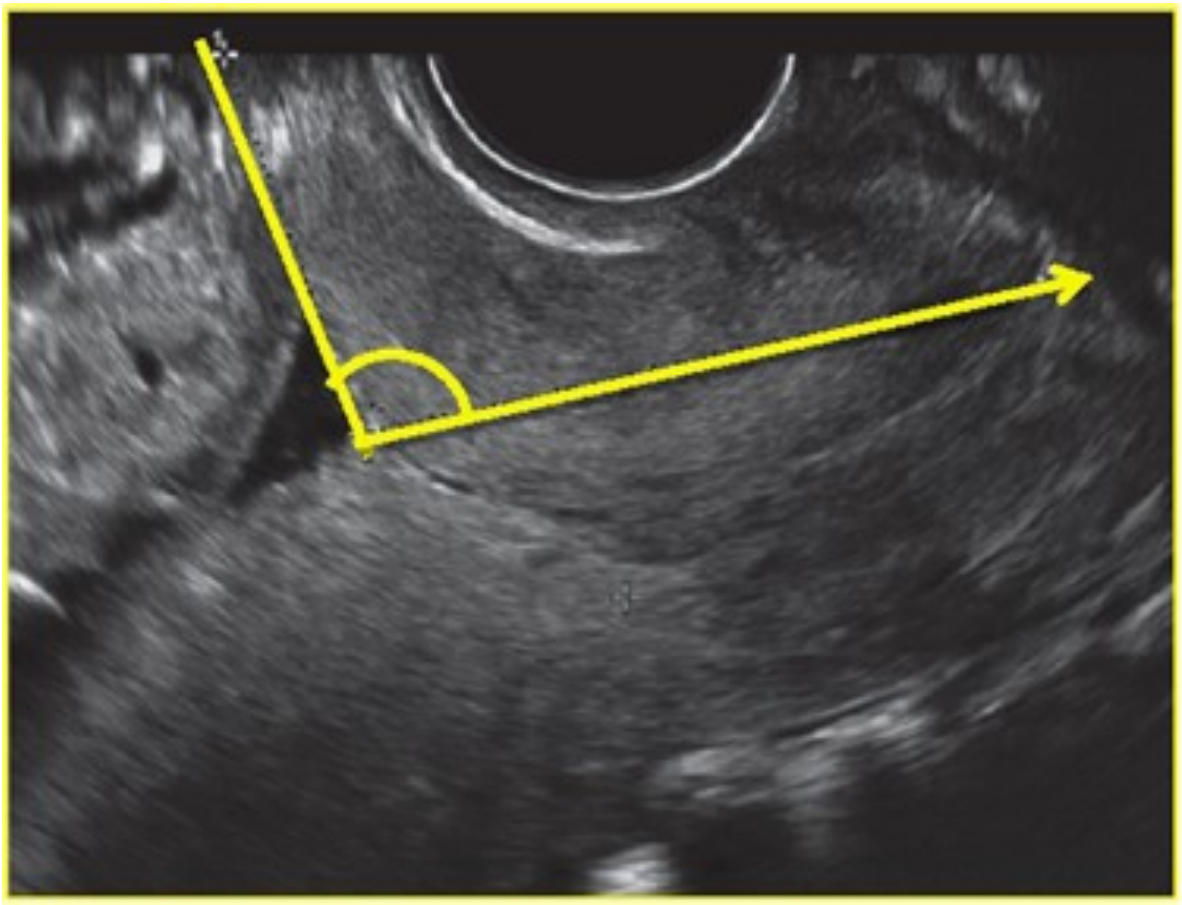


Figure 2 - Transvaginal ultrasound measurement of the uterocervical angle.



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(c) Explain how missing data were addressed	n.a.
		(*d*) If applicable, explain how loss to follow-up was addressed	n.a.
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	n.a.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

1 (a): Página 2 – “This observational retrospective cohort study (…)”.

1 (b): Página 2 – “Methods: This observational retrospective cohort study included all women with singleton pregnancies who presented for the second-trimester ultrasound in the Obstetrics and Gynecology Department of Centro Hospitalar Universitário São João, in Portugal, from January 2013 to October 2017. Uterocervical angle and cervical length were measured respecting Fetal Medicine Foundation guidelines. Results: Among 1,943 women, spontaneous preterm birth prevalence was 5.0%. Uterocervical angle ≥ 105o showed specificity of 87.4%, negative predictive value of 95.7%, sensitivity of 26.5%, and positive predictive value of 10.1%. Cervical length ≤ 25mm demonstrated specificity of 95.5%, negative predictive value of 95.2%, sensitivity of 11.2%, and positive predictive value of 11.8%. Regression models indicated an odds ratio for uterocervical angle of 1.01 (95% CI: 1.00 - 1.02, p = 0.034) and for cervical length of 0.92 (95% CI: 0.88 - 0.97, p < 0.001).”.

2: Página 5/6 – “While the mechanisms underlying sPTB remain elusive, various pathways converge on a common trajectory before delivery. The cervix has an important role in pregnancy maintenance, resisting mechanical pressures applied by the growing uterus and the surrounding pelvic organ. As the process of delivery unfolds, the cervix undergoes intensive changes. Consequently, there is a growing emphasis on investigating the role of the cervix in both the etiology and screening of PTB. The cervical length (CL) is currently the most widely adopted parameter to assess the risk of PTB.

The International Federation of Gynecology and Obstetrics (FIGO) working group on the best practice in maternal-fetal medicine stated that sonographic measurement of the cervical length should be performed in all pregnant patients between 19 and 23 weeks of gestation using transvaginal ultrasound (TVS). A shortened cervix < 25mm has been described as an important indicator of preterm labor. However, the evidence on the use of both this marker and this cut-off in a universal second-trimester screening is inconsistent and it is still not recommended. More recent studies suggest that the uterocervical angle (UCA) has a higher diagnostic performance and greater potential of being used as screening tool for the prediction of PTB. A wide UCA (greater than 105º), detected in the second-trimester ultrasound, is thought to be associated with a higher risk of PTB. An obtuse UCA is theorized to facilitate the transmission of forces from the expanding uterus and adjacent organs to the cervix, potentially triggering its dilation. Conversely, an acute UCA is thought to function in the opposite manner, potentially aiding in the maintenance of cervical integrity.".

3: Página 6 – "This study was conducted with the aim of evaluating the predictive role of the uterocervical angle (UCA) in spontaneous preterm birth (sPTB), specifically comparing its efficacy to that of cervical length (CL) in the second trimester ultrasonography.".

4: Página 7 – "This observational, retrospective cohort study (…)".

5: Página 7 – "(…) was conducted within the Obstetrics and Gynecology Department of Centro Hospitalar Universitário São João (CHUSJ) in Portugal, following approval from the hospital's ethics committee (CES 81-17). The study recruited women attending the outpatient clinic for second-trimester ultrasounds between January 2013 and October 2017.".

6 (a): Página 7 – "Inclusion criteria were: (1) singleton pregnancy, (2) recruitment between the 18th week and 22nd week + 6 days (determined by the crown-rump length before the 14th week), (3) delivery in the CHUSJ and (4) existence of delivery data. Exclusion criteria were: (1) medically indicated PTB, (2) PPROM, (3) cervical cerclage performed prior to screening, (4) diagnosis of chorioamnionitis and (5) deliveries before the 24th week of gestation.".

6 (b): Não aplicável.

7: Página 7 – "The ultrasound images were retrieved from the Astraia software (Astraia Software, GmbH, Munich, Germany). All images were reviewed to assess compliance with the Fetal Medicine Foundation (FMF) guidelines for cervical assessment. The guidelines recommended using a vaginal probe to identify the sagittal view of the cervix, occupying 75% of the image, and locating the internal and external os and the cervical canal. Cervical length (CL) measurement involved the space between the internal and external os, considering funneling if present. The uterocervical angle (UCA) was measured as the angle between the anterior uterine wall and the endocervical canal.".

8: Página 7 – "The ultrasound images were retrieved from the Astraia software (Astraia Software, GmbH, Munich, Germany). All images were reviewed to assess compliance with the Fetal Medicine Foundation (FMF) guidelines for cervical assessment. The guidelines recommended using a vaginal probe to identify the sagittal view of the cervix, occupying 75% of the image, and locating the internal and external os and the cervical canal. Cervical length (CL) measurement involved the space between the internal and external os, considering funneling if present. The uterocervical angle (UCA) was measured as the angle between the anterior uterine wall and the endocervical canal.".

9: Página 7/8 - "Data were collected from the Obscare Software, then analysed using R (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as mean ± standard deviation (SD) and analysed by t-test. Categorical variables were presented as frequencies or percentages and analysed by chi- squared test or Fisher's

exact test, as adequate. Univariable logistic analyses with clinical and demographic data were performed to determine the variables associated with PTB.".

10: Página 7 - "The study recruited women attending the outpatient clinic for second-trimester ultrasounds between January 2013 and October 2017. Inclusion criteria were: (1) singleton pregnancy, (2) recruitment between the 18th week and 22nd week + 6 days (determined by the crown-rump length before the 14th week), (3) delivery in the CHUSJ and (4) existence of delivery data. Exclusion criteria were: (1) medically indicated PTB, (2) PPROM, (3) cervical cerclage performed prior to screening, (4) diagnosis of chorioamnionitis and (5) deliveries before the 24th week of gestation.".

11: Página 7/8 – "Continuous variables were presented as mean ± standard deviation (SD) and analysed by t-test. Categorical variables were presented as frequencies or percentages and analysed by chi- squared test or Fisher's exact test, as adequate.".

12 (a) (b): Página 7/8 – "Data were collected from the Obscare Software, then analysed using R (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as mean ± standard deviation (SD) and analysed by t-test. Categorical variables were presented as frequencies or percentages and analysed by chi- squared test or Fisher's exact test, as adequate. Univariable logistic analyses with clinical and demographic data were performed to determine the variables associated with PTB. Multivariable logistic regression models were created, with PTB as the dependent variable, and using the CL and the UCA as independent variables, first individually and then combined. The main effects of maternal age, previous PTB, cervical insufficiency and conization were also included in the multivariable regression models. A p-value < 0.05 was considered statistically significant. The diagnostic performance of both markers was assessed using receiver operating characteristics (ROC) curve analysis and the trapezoid method was used to calculate the area under the curve (AUC).".

12 (c) (d): Não aplicável.

12 (e): Página 8 - "Univariable logistic analyses with clinical and demographic data were performed to determine the variables associated with PTB. Multivariable logistic regression models were created, with PTB as the dependent variable, and using the CL and the UCA as independent variables, first individually and then combined. The main effects of maternal age, previous PTB, cervical insufficiency and conization were also included in the multivariable regression models.".

13: Página 9 – "A total of 8016 women underwent the second trimester TVS and delivery at CHUSJ. After applying the exclusion criteria, a total of 1943 women were enrolled in our study.".

14: Página 9 – "The maternal and clinical characteristics of the studied population are better described in table 1.".

15: Página 9 – "The prevalence of PTB in our cohort was 5.0% (n = 98), out of which 16.3% (n = 17) occurred before the 34th week of gestation.".

16: Página 9/10 – "The mean UCA was 84.6º and the mean CL was 33.0 mm. The distribution of preterm and term birth rates across different cervical length and uterocervical angle intervals are presented in table 2. The mean UCA was wider in the preterm group compared with the term group (90.4º ± 20.9º vs. 84.3º ± 18.3º, p = 0.006). The percentage of patients who had a UCA of 105º or more was significantly higher in the preterm group (26.5% vs 12.6%, p < 0.001). The mean CL was shorter in those who had PTB (30.9 ± 5.4 mm vs. 33.1 ± 4.6 mm, p < 0.001). The percentage of patients who had CL of 25 mm or less was significantly higher in the preterm group (12.2% vs 4.5%, p < 0.001). In the preterm group the

UCA decreases as the gestational age at delivery increases ($p < 0.001$). Contrary, the CL increases as the gestational age at delivery increases ($p < 0.001$). These results are presented in table 3 and 4. A UCA ≥ 105º showed specificity of 87.4%, negative predictive value (NPV) of 95.7%, sensitivity of 26.5% and positive predictive value (PPV) of 10.1%. A CL ≤ 25mm showed a specificity of 95.5%, NPV of 95.2%, sensitivity of 11.2% and PPV of 11.8% (table 5). Regarding the diagnostic performance of both markers, in the ROC curve analysis, the UCA had an AUC of 0.581 ($p = 0.007$) and the CL had an AUC of 0.606 ($p < 0.001$) (table 6).".

17: Página 10 – "In univariable logistic regression analysis, maternal age ≥ 40 years old, history of PTB and cervical insufficiency were the main variables associated with PTB. In multivariable logistic regression analysis evaluating the impact of the CL (table 7) and the UCA (table 8) individually and combined (table 9) as predictors of PTB, the CL demonstrated an odds ratio (OR) of 0.92 (95% CI: 0.88 - 0.97, $p < 0.001$), which shows a small and statistically significant negative association between the CL and PTB. On the other hand, the estimated OR for the effect of the UCA on PTB was 1.01 (95% CI: 1.00 - 1.02, $p = 0.034$), suggesting no significant association between the UCA and PTB.".

18: Página 11-13 – "In this study, the mean UCA was significantly wider in the preterm group compared with the term group (90.4º ± 20.9º vs. 84.3º ± 18.3º, $p = 0.006$). Furthermore, the UCA showed a gradual decrease as the gestational age at delivery increased ($p < 0.001$). (…) A UCA ≥ 105º showed a specificity of 87.4%, negative predictive value (NPV) of 95.7%, but it was limited by a sensitivity of 26.5% and positive predictive value (PPV) of 10.1%, in this study. (…) The mean CL was shorter in the preterm group than in the term group (30.9 ± 5.4 mm vs. 33.1 ± 4.6 mm, $p < 0.001$). The percentage of patients who had CL of 25 mm or less was significantly higher in the preterm group (12.2% vs 4.5%, $p < 0.001$). Additionally, the CL showed a significant increase as the pregnancy advanced. (…) A CL ≤ 25mm showed a specificity of 95.5%, NPV of 95.2%, sensitivity of 11.2% and PPV of 11.8%. (…) A CL ≤ 25 mm showed higher diagnostic performance (AUC = 0.606, $p < 0.001$) when compared to the UCA (AUC = 0.581, $p = 0.007$). (…) In a multiple regression model, the estimated OR for the effect of the CL on PTB was 0.92 (95% CI: 0.88 - 0.97, $p < 0.001$), (…) the UCA, which presented an OR of 1.02 (95% CI: 1.00 - 1.03, $p = 0.007$)".

19: Página 13/14 – "Several limitations, including the retrospective nature of the study, potential bias, and variations in ultrasound measurements, should be acknowledged. All patients with a short cervix were recommended either vaginal progesterone or the arabin to support pregnancy. However, women with wide UCA did not receive this treatment, as there is no evidence yet supporting the impact of these measures in patients with high UCA, and this represents another limitation of this study as it can act as a confounding factor.".

20: Página 15 – "In this cohort, UCA demonstrated lower predictive performance than CL for sPTB. Both markers showed high NPV, emphasizing their utility in ruling out sPTB.".

21: Página 13/14 – "Several limitations, including the retrospective nature of the study, potential bias, and variations in ultrasound measurements, should be acknowledged.".

22: Não aplicável.

Regras de formatação da revista: *European Journal of Obstetrics & Gynecology and Reproductive Biology*

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81-17

Unidade de Investigação

Face aos esclarecimentos prestados, nada a opor.

28 de Julho de 2017

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

AUTORIZADO

CONSELHO DE ADMINISTRAÇÃO ◉ REUNIÃO DE 10 AGO 2017

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(Dr. António Oliveira e Silva)

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09.03.17 P847

DIRECÇÃO CLÍNICA

Aprovado. Ao CA. 30 / 1 / 2017

(Prof.ª Doutora Ana Azevedo)

Exmo. Senhor

Presidente do Conselho de Administração do

Centro Hospitalar de S. João – EPE

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Joana Patricia Rodrigues Félix Peixoto de Almeida

Título do projecto de investigação: Parto pré-termo: etiologia e rastreio

Pretendendo realizar no(s) Serviço(s) de Ginecologia/ Obstetricia do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 5 / Janeiro / 2017

O INVESTIGADOR/PROMOTOR

Joana Félix

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☑
NÃO APLICÁVEL ☐

8. TERMO DE RESPONSABILIDADE

Eu, Joana Patricia Rodrigues Félix Peixoto de Almeida,
abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 5 / Janeiro / 2017 24/03/17

A Comissão de Ética para a Saúde tendo aprovado o parecer do Relator, aguarda que o Investigador/Promotor esclareça as questões nele enunciadas para que possa emitir parecer definitivo.

Joana Félix
O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de ___/___/___

Centro Hospitalar **São João**

CONSIDERADOS QUE FORAM COMO SATISFATÓRIOS OS ESCLARECIMENTOS PRESTADOS PELO(A) INVESTIGADOR(A), A CES APROVA POR UNANIMIDADE O PARECER DO RELATOR, PELO QUE NADA TEM A OPOR À REALIZAÇÃO DESTE PROJETO DE INVESTIGAÇÃO.

18/04/17

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

Comissão de Ética para a Saúde do C.H.S.João e da FMUP

Parecer

Título do Projecto: Parto pré-termo: etiologia e rastreio

Nome do Investigador Principal: Joana Patrícia Rodrigues Félix Peixoto de Almeida

Promotor do Estudo: NA

Serviço onde decorrerá o Estudo: Serviço de Ginecologia/Obstetrícia do Centro Hospitalar de S. João

Objectivo e Pertinência do Estudo:

Este estudo, visando a elaboração de uma Tese de Doutoramento, tem como escopo:

1. Compreender a fisiopatologia do parto pré-termo (PPT), através da caracterização histológica e imuno-histoquímica do colo uterino
2. Avaliar o papel das alterações placentárias na prematuridade
3. Determinar marcadores ecográficos de risco de PPT

Para o 1º objectivo descrito,

- Serão recrutadas grávidas pré-termo (<37 semanas), cujo parto ocorra neste Centro Hospitalar ou no Hospital Pedro Hispano entre 1 Março 2017 e 31 Dezembro 2018, com critérios de inclusão e de exclusão adequadamente definidos. Tendo em consideração a preocupação expendida pela investigadora aquando da avaliação que faz dos riscos de participação no estudo, foram clarificados os "*critérios de inclusão obrigatórios*"!
- Serão constituídos 2 grupos de controlo: grávidas com idade gestacional (IG) >=39 semanas; outro, constituído por amostras do colo uterino de mulheres não grávidas, seleccionadas aleatoriamente e de forma retrospectiva, da população de biopsias existentes no Serviço de Anatomia Patológica, ambos com adequados critérios de inclusão/exclusão

Para o 2º objectivo descrito, serão avaliadas retrospectivamente as características anatomo-patológicas das placentas de partos prematuros ocorridos entre 2010 e 2015, com recolha de dados dos respectivos Processos Clínicos, seleccionando-se para grupo controlo,

também retrospectivamente, placentas do Serviço de Anatomia Patológica do CHSJ com malformações fetais e as resultantes de cesarianas programadas.

Para o 3º objectivo descrito, será efectuado um estudo retrospectivo com todas as medições de colo uterino nos sectores de ecografia do CHSJ e do HPH de Janeiro 2013 a Dezembro de 2016.

Os objectivos definidos e a metodologia que lhe está dedicada justificam a realização deste projecto de investigação, que poderá trazer novidade científica a esta área de grada relevância assistencial.

A informação dos processos clínicos será acedida pela investigadora e mediada pelo Elo de Ligação do Serviço

Os custos dos estudos das biopsias do colo uterino será suportado pelos investigadores, assim está afirmado pelos mesmos.

Os Senhores Directores de Serviço deram a sua anuência à realização deste projecto de investigação, no que respeita à actividade no Centro Hospitalar de S. João.

Benefício/risco: Não desproporcionados os riscos

Respeito pela liberdade e autonomia do sujeito de ensaio: Será solicitado consentimento informado aos participantes, com a utilização do modelo institucional neste Centro Hospitalar de S. João

Confidencialidade dos dados: Os dados recolhidos serão anonimizados na origem

Elo de ligação (para o Centro Hospitalar de S. João): Profª Doutora Alexandra Matias

Indemnização por danos: NA

Continuação do tratamento: NA

Propriedade dos dados: Os dados serão propriedade do Investigador. Adverte-se porém o investigador de que apenas poderão ser da sua propriedade exclusiva os dados decorrentes da investigação, ou seja, os resultados alcançados, não os dados clínicos dos doentes, em si mesmo. Estes são propriedade inalienável dos doentes, cabendo à

instituição tratá-los de acordo com as suas próprias responsabilidades, sem impedimentos de diferente natureza.

O Centro Hospitalar de S. João e os seus profissionais não ficam impedidos de utilizar dados dos seus doentes, inerentes à actividade assistencial, para qualquer fim, ainda que os mesmos possam ter sido também utilizados no âmbito deste Estudo.

***Curriculum* do investigador**: Adequado ao perfil da investigação

Data previsível da conclusão do estudo: Janeiro de 2019

Conclusão: Considerados os objectivos do estudo e a metodologia que lhe está prevista, e bem assim as alterações efectuadas no sentido do parecer inicial da CES, a CES nada tem a opor à realização deste projecto de investigação na sua actual definição metodológica.

Nota: Releva-se que este parecer abrange a actividade de investigação que se realizará no Centro Hospitalar de S. João. Para a actividade que se desenvolverá no Hospital Pedro Hispano, terá de ser solicitado parecer à respectiva Comissão de Ética institucional.

Porto e C.H.S.João, 2017-04-15

O Presidente da CES

Doutor Filipe Almeida