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Preterm birth: incidence, risk factors and second trimester cervical length in a single center population. A two-year retrospective study

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Abstract. – **OBJECTIVE:** To report the incidence and the major risk factors (RFs) associated with preterm birth (PTB), combining both maternal RFs and cervical length (CL), and to understand if cervical length measurement is really useful in all the patients.

PATIENTS AND METHODS: The study population consisted of 2048 women admitted to the Department of Obstetrics and Gynecology, University Hospital of Messina, over a 2-year period. Preterm cases represented approximately 8.64% of our total population and, exactly, 65% were late preterm, 32% were preterm and 3% were extremely preterm.

RESULTS: An analysis of PTB sub-categories based on gestational age showed a stronger correlation between gestational age and CL among preterm and extremely preterm, while no correlation was found among late preterm. Between preterm cases and controls, there was a significant difference in pre-pregnancy weight and Body Mass Index (BMI). Moreover, a significant association between PTB and uterine anomalies, poli-oligodramnios and hypertension was found.

CONCLUSIONS: We strongly suggest adding a transvaginal ultrasound CL universal screening to all pregnant women at the time of the second trimester ultrasound. We encourage further studies to identify new RFs of PTB and to define the mechanisms by which risk factors are related to PTB.

Key Words:
Preterm birth, Risk factors of preterm birth, Cervical length, Transvaginal ultrasound.

Introduction

Preterm birth (PTB) is still a serious health and social problem, considered as the first cause of neonatal mortality both in developed and developing countries and characterized by important pathological sequelae[1-4]. Incidence rates are on average higher in low-income countries (11.8%), followed by medium-low income (11.3%) and lowest in countries with high and very high income (9.4% and 9.3%). High rates of incidence of PTB in women in high-income countries are also reported, contributing greatly to neonatal mortality and morbidity. Of the estimated 1.2 million preterm births in high-income countries, more than 0.5 million (42%) were registered in the United States. The high incidence of preterm births in many Western countries could be due to an increase of iatrogenic PTB[5], an improvement of reproductive technology with, consequently, multiple gestations and an increased maternal age[6]. Also, single pregnancies after *in vitro* fertilization are at increased risk of PTB[7]. Some demographic changes (reduced teenage birth rate and fewer multiple births) and/or government policies, which discourage non-medically indicated that births at < 39 weeks' gestation, along with a stricter implementation of smoking bans, have been all added to the decreased rate of PTB in the USA, up to 11.4% in 2013. Research efforts in this field, and therapeutic measures, contributed

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to decreasing this high incidence, demonstrating the importance of identifying populations at higher risk for PLT and, consequently, the need to use multiple types of interventions to prevent it[8,9]. Several risk factors (RFs) have been associated with this pathology, such as maternal demographic characteristics[6], nutritional status, mechanical uterine and cervical factors, maternal comorbidities, infectious etiologies[10-12]. A history of spontaneous PTB is considered by some authors an independent risk factor as it has been shown to increase risk significantly more than others[12-14]. A cervical length (CL) of less than 25 mm is an accurate predictor of increased risk of spontaneous PTB[15-18], in particular when it is combined with a history of spontaneous PTB[19-20]. The primary outcome of this study was to assess the incidence of preterm birth in our Hospital and the major risk factors associated with this condition, combining both maternal RFs and CL, including women with a previous PTB. The secondary outcome was to understand if the CL measurement is really useful in all patients.

Patients and Methods

We performed a single center, observational and retrospective, cohort study. Data were collected in the Department of Obstetrics and Gynecology of the "G. Martino" University Hospital (Messina, Italy) over a 2-year period, from 1 Jan 2013 to 31 Dec 2014. As a standard protocol, each patient, on admission, signed an informed consent allowing data collection for research purposes. The study design was in accordance with the Helsinki Declaration and was approved by the Institutional Review Board of the University Hospital involved. All the design, analysis, interpretation of data, drafting and revisions followed the guidelines for reporting observational studies (STROBE), available through the EQUATOR network. All clinical records of pregnant women who delivered in our Obstetrics and Gynecology Departments during the study period were analyzed. Patient characteristics and probable risk factors for preterm birth collected are reported in Table I. We defined preterm birth all the deliveries before 36 + 6/7 week/day of gestation, according to the World Health Organization (WHO). For this reason, we included only women who delivered before this week, whatever the cause. Multiple pregnancies were excluded. We planned to look at subgroups of PTBs, such as extremely early preterm (i.e. 21 + 5-23 + 6), preterm (i.e. 24-33 + 6) and late preterm (i.e. 34-36 + 6). When medical records were not complete, we tried to contact the women with a phone interview.

Statistical Analysis

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). An exploratory analysis was carried out to determine the distribution of data. Continuous variables are presented as mean ± Standard Deviation (SD) or median and interquartile range (IQR), where appropriate. Distributions of categorical variables are presented as frequencies and percentages. Unpaired Student's *t*-tests were then used to assess differences in demographic and clinical characteristics between control and preterm cases. For cervical length, the only non-normally distributed continuous variable, the Mann-Whitney U test was used. The X^2 or Fisher's exact test was used to compare frequencies. Univariate logistic regression analysis was used to evaluate the prognostic ability of the demographic and clinical variables, individually, to predict the probability of having a preterm birth. Crude odds ratios (OR) with 95% confidence intervals (95% CI) are presented. Variables associated with preterm delivery in the univariate analysis ($p < 0.05$) were included in additional multivariable logistic regression models. We evaluated several models due to collinearity of candidate variables. As additional validation of the model selected, we also used forward stepwise selection with an inclusion criterion *p*-value of 0.10 (the variable was added to the model if the corresponding *p*-value was less than the defined threshold 0.10, otherwise, the variable is not considered sufficiently helpful to enter the model). The overall measure of classification accuracy of the models was assessed using the area under the receiver operating characteristic curve (AUC), also known as c-statistic (C). All hypothesis tests conducted were 2-tailed and a *p*-value < 0.05 was considered significant.

Results

The study population consisted of 2048 women admitted to our Department between 1 Jan 2013-31 Dec 2014. Demographic and clinical characteristics for control and preterm cases are shown in Table I. Preterm cases represent approximately 8.64% (n = 177) of our total population;

Table I. Clinical and demographic characteristics of control and preterm cases.

Characteristics	Controls (n = 1871)	Preterm cases (n = 177)	*p*-value
Maternal age (years), mean (SD)	32.02 (5.68)	32.26 (6.16)	0.6
Race n (%)			
Caucasian	1824 (97.4)	173 (98)	1
Asian	44 (2.4)	4 (2)	
Black or African American	3 (0.2)	–	
P re-pregnancy weight (kg), mean (SD)	63.71 (13.59)	61.39 (11.0)	**0.04***
Maternal BMI, n (%)	25.83 (5.27)	24.73 (4.33)	**0.018***
< 18	31	5	
18-25	742	67	
> 25	783	64	
Marital status, n (%)			
Married	1400 (75)	125 (73)	0.32
Unmarried	461 (25)	49 (27)	
Missing	10	3	
Education			
≤ 12th Grade	1145 (68)	118 (75)	0.1
> 12th Grade	529 (32)	40 (25)	
Missing	197	19	
Parity			
Nulliparous	1064 (57)	103 (58)	0.73
Parous	807 (43)	74 (42)	
Prior history of PTD, Yes, n (%)	52/1819 (2.8)	2/175 (1.1)	0.32
Treatment for cervical dysplasia, Yes n (%)	138 (7)	8 (5)	**0.013***
Cervical length (mm), median (IQR)	37 (33-40)	32 (26-38)	**< 0.0001***
Uterine anomalies, Yes, n (%)	10/1861 (0.5)	4/173 (2.37)	**0.03***
Vaginal infection, Yes, n (%)	52/1819 (3)	2/175 (1)	0.16
Poly/oligoidramnios,			
Yes, n (%)	1780 (95.1)	143 (80.8)	**< 0.0001***
Polyidramnios	49 (2.7)	8 (4.5)	
Oligoidramnios	42 (2.2)	26 (14.7)	
Hypertension, Yes, n (%)	95/1776 (5)	27/150 (15)	< 0.0001*
Thyroid disease, Yes, n (%)	303/1568	27/150 (15.3/84.7)	0.75
Diabetes, Yes, n (%)	225/1646 (12)	24/153 (14)	0.55
Psychological disorders, Yes, n (%)	18/1853 (1)	4/173 (2)	0.12
Smoking, Yes, n (%)	92/1779 (5)	9/168 (5)	0.9

SD: standard deviation; BMI: Body Mass Index; PTD: Preterm Delivery; n: number; IQR: interquartile range.

of these, 81 (45.7%) occurred in 2013 while 96 (54.2%) in 2014. The preterm birth rate was not significantly different between 2013 and 2014. Among PTB, 65% (n = 115) were late preterm, 32% (n = 57) were preterm and 3% (n = 5) were extremely preterm. A significant difference was found in cervical length between preterm cases and controls ($p < 0.0001$) (Table I and Figure 1). Among PTB, gestational age correlated with cervical length ($r = 0.37$, $p < 0.0001$) (Figure 2). But further analysis of preterm birth sub-categories, based on gestational age, showed a stronger correlation between gestational age and cervical length ($r = 0.47$, $p = 0.0007$) among preterm and extremely preterm, while no correlation was found among late preterm ($r = 0.006$, $p = 0.95$).

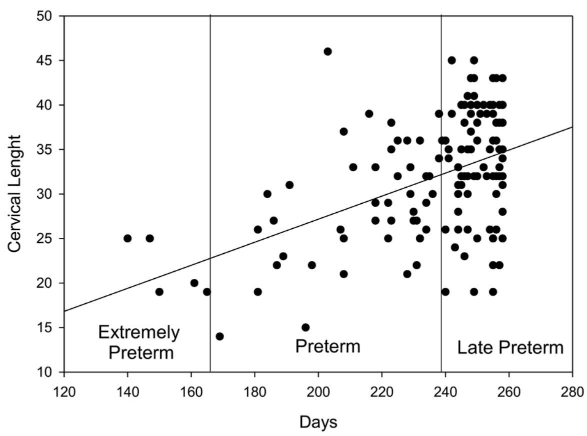

Figure 1. Cervical length in preterm cases and controls.

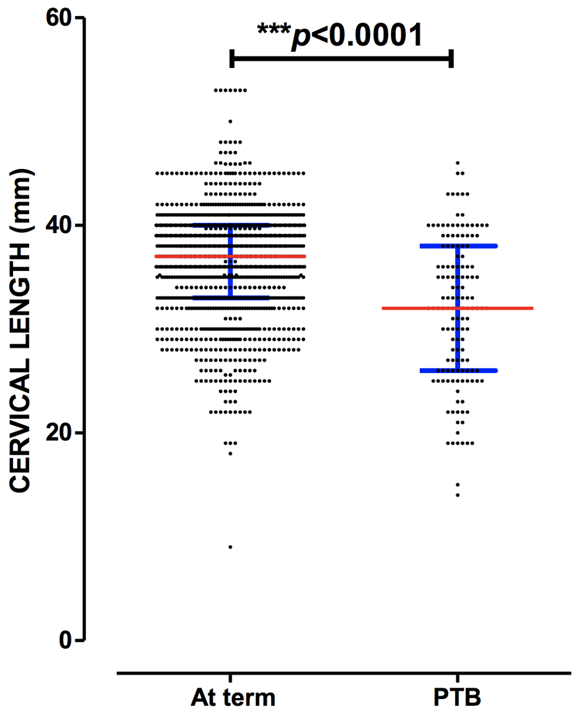

Figure 2. Correlation between gestational age and cervical length.

Among PTB, cervical length was also correlated with Body Mass Index (BMI) (r = 0.22, $p = 0.02$) and age (r = 0.18, $p = 0.03$); no other correlations were found. In addition, between preterm cases and controls, there was a significant difference in pre-pregnancy weight and BMI ($p = 0.04$ and $p = 0.018$, respectively), with control individuals tending to be heavier than preterm cases (Table I). A significant association between PTB and uterine anomalies ($p = 0.03$), poli-oligodramnios ($p < 0.0001$) and hypertension ($p < 0.0001$) was found.

Statistical Analyses

Univariate analysis. Individual logistic regression models examining the association between each demographic and clinical variable and the occurrence of preterm birth were constructed. This analysis revealed that pre-pregnancy weight, maternal BMI, cervical length, oligoidramnios and hypertension, were associated with preterm delivery in our population (Table II). Table II shows crude odds ratios with 95% confidence intervals.

Multiple Logistic Regression Analysis. Forward stepwise logistic regression analysis using an inclusion criterion *p*-value of 0.10 and including all significant variables as covariates, identified several factors to be independently associated with increased odds of preterm delivery. The most prominent independent predictor was cervical length followed by the presence of poly/oligoidramnios, hypertension and maternal BMI (Table III). The area under the curve was 0.74.

Discussion

The incidence of preterm birth in our sample of pregnant women represents 8.64% of total population. This value is high if we consider all the consequences of PTB. It also explains the reasons for many updates on this topic in order to investigate new risk factors or treatment to prevent this pathologic condition. Although we examined many of the variables often correlated with PTB and CL, the list of RFs is quite extensive and we were only able to analyze a few of them. We could not consider important risk factors, such as the urinary infections, which we tried to collect but, since they were inconsistently reported in the medical records, we didn't include in the analysis. Data on alcohol and drug use were also not reported as almost no patient admitted the use or abuse of them, so we could not consider these data reliable. In our analysis, we also included women with a previous PTB (spontaneous or indicated). Our study confirmed some data of the literature on the association between a previous cervical surgery and PTB[1,21,22]. Even if it has been proven that smoking cessation prevents PTB, we did not find any significant statistical association between use of tobacco and risk of preterm delivery. Although a prior PTB is considered the most important RF of PTB[23,24], our data did not reveal any association. Perhaps, these results were influenced by the relatively small sample, which could be a bias of the study. Nulliparous women with a low pre-pregnancy BMI are considered by some authors at increased risk for PTB[25]. Our data reported a lower BMI in PTB then in controls, confirming that a correct nutritional status is necessary to ensure a regular course of pregnancy. Maternal thinness is associated with decreased blood volume and less uterine blood flow; a spontaneous PTB may occur via this mechanism[26]. Some authors have stated that most of the women who deliver preterm have no identifiable RFs[21]. In our sample, almost all the women who had a PTB reported one or more RF

Table II. Unadjusted odds ratios of demographic and clinical characteristics for predicting occurrence of preterm birth, using univariate logistic regression.

Variable	OR (95% CI)	*p*-value	C
Age	1.01 (0.98-1.04)	0.53	0.52
Pre-pregnancy weight	0.99 (0.97-1.00)	**0.045**	0.54
Maternal BMI	0.96 (0.92-0.98)	**0.02**	0.55
Cervical length	0.89 (0.86-0.91)	**< 0.0001**	0.68
Marital status			0.52
Married	1.0	Reference	
Unmarried	1.21 (0.85-1.71)	0.3	
Education			0.53
≤ 12th Grade	1.0	Reference	
> 12th Grade	0.74 (0.51-1.08)	0.17	
Parity			0.51
Parous	1.0	Reference	
Nulliparous	1.07 (0.78-1.5)	0.68	
Prior history of PTD			0.51
No	1.0	Reference	
Yes	0.42 (0.1-1.72)	0.23	
Treatment for cervical dysplasia			0.012
No	1.0	Reference	0.52
Yes	2.37 (1.21-4.62)	**0.012**	
Uterine anomalies			0.51
No	1.0	Reference	
Yes	3.03 (0.84-10.97)	0.09	
Vaginal infection			
No	1.0	Reference	0.52
Yes	0.62 (0.3-1.28)	0.2	
Poly/oligoidramnios			0.58
No	1.0	Reference	
Polyidramnios	2.12 (0.99-4.59)	0.05	
Oligoidramnios	8.07 (4.8-13.56)	**<.0001**	
Hypertension			0.55
No	1.0	Reference	
Yes	3.52 (2.22-5.57)	**<.0001**	
Thyroid disease			0.51
No	1.0	Reference	
Yes	0.88 (0.57-1.37)	0.58	
Diabetes			0.51
No	1.0	Reference	
Yes	1.2 (0.76-1.89)	0.43	
Psychological disorders			0.50
No	1.0	Reference	
Yes	1.75 (0.51-5.96)	0.37	
Smoking			0.50
No	1.0	Reference	
Yes	1.09 (0.54-2.2)	0.81	

BMI: Body Mass Index; PTD: Preterm Delivery; C: C–statistic; OR= odds ratios; ROC curve= receiver operating characteristic curve. C=The area under an ROC curve (also known as c-statistic) provides an overall measure of classification accuracy (representing the overall proportion of individuals correctly classified), with the value of one representing perfect accuracy. * $p < 0.001$, † $p < 0.01$.

for PTB, confirmed data from Berghella's study[27]. Finally, our data confirm that cervical length has a predictive value for subsequent preterm delivery as demonstrated both in C-statistics and within multivariable logistic regression models. In particular, using a stepwise statistical approach we demonstrated that determination of cervical length is a high-ranking predictor of preterm delivery (Table III). Noteworthy, the combination of this factor with other clinical variables led to a significant improvement of c-statistics (0.68 *vs.* 0.74). Specifically, our data report a statistical correlation between gestational age and value of the cervical length in the "extremely

Table III. Adjusted OR of demographic and clinical characteristics for predicting occurrence of preterm birth, using univariate logistic regression, using multivariate logistic regression with forward selection procedures.

Step	Variable	Adj. OR	95% CI	C
1	Cervical length	0.88	0.85-0.91	0.74
2	Poly/oligoidramnios			
	No	1.0	Reference	
	Polyidramnios	3.48	1.41-8.61	
	Oligoidramnios	10.76	5.02-23.05	
3	Hypertension			
	No	1.0	Reference	
	Yes	3.66	1.68-7.99	
4	Maternal BMI	0.91	0.87-0.96	

Adj OR= Adjusted odds ratios; CI: Confidence Interval; C: C-statistic; BMI: Body Mass Index.

preterm" and "preterm" cases. We noted that "late preterm" cases were associated to a wider variation of cervical length. For this reason, we selected only the "late preterm" cases, which were more represented in our sample of women, and we didn't find a positive correlation in this specific sample. So, we confirm that CL measurement helps to identify women at risk for very early PTB[18] and hypothesize that in "late preterm" cases, it could help less as a predicting test. Probably, different risk factors should be also considered in these cases. Maternal disease (i.e.: severe hypertension resistant to medical therapy) or fetal pathological conditions often prompt the gynecologist to induce labor, determining an iatrogenic PTB, more often found in late PTB. Some of the RFs often associated to PTB (i.e.: uterine anomalies, poly/oligohydramnios, hypertension, BMI, treatment for cervical dysplasia), could be easily revealed or detected with an anamnesis or routine exams in pregnancy. On the contrary, if a CL transvaginal screening is not performed, we could not identify, at an early stage, asymptomatic women at risk for spontaneous PTB due to short cervical length, which is about 2-5% of total[28.] In addition, anamnestic risk factors alone are not helpful to predict who would develop a short cervix$_{27}$. An early diagnosis of asymptomatic women at risk of PTB could permit suitable assistance and treatment. For this reason, many authors have supported universal (not based on RFs) screening of pregnant women with CL[29]. It is suggested to perform the exam between 18 and 24 weeks[30], as a measurement of the cervical length at term has moderate value in predicting the onset of spontaneous labor31. Randomized clinical trials reported that vaginal progesterone, at a dose of 200 mg daily, until 36 weeks, in singleton gestations with a short CL (20 mm or less) could reduce neonatal morbidities, decreasing the incidence of spontaneous PTB[19,32,33] by approximately 45%[25,28]. This treatment could be prescribed to all women with a short cervix in order to prevent a PTB, since no adverse effects to the mother or fetus are reported[8,34]. A recent updated meta-analysis35 reported that administration of vaginal progesterone is useful also in asymptomatic women with a twin gestation and a sonographic short cervix in the mid-trimester because reduces the risk of preterm birth occurring at < 30 to < 35 gestational weeks, neonatal mortality and some measures of neonatal morbidity, without any demonstrable deleterious effects on childhood neurodevelopment. As regard singleton gestations with a prior spontaneous PTB, a serial transvaginal ultrasound CL measurement, about every 2 weeks, and weekly if CL is from 25 to 29 mm, between 16 weeks and 23 weeks and 6 days is also suggested. In 40% of these high-risk women, who will develop a short CL of less than 25 mm, cerclage should be offered[28,29,31] as it has been associated with a significant decrease in PTB and perinatal mortality and morbidity36-38. Cerclage seems to be efficacious also in singletons without prior spontaneous PTB with lower CLs, such as < 10 mm, and when tocolytics or antibiotics were used as additional therapy[39].

Conclusions

Despite numerous efforts to prevent preterm birth, the percentage remains high and neonatal complications are still too many. Thus, it is important to continue to study new strategies for screening and implementation of current treatment in this field. Since also a recent meta-analysis reported a significant association between knowledge of cervical length and lower incidence of PTB[40], we strongly suggest adding a transvaginal ultrasound CL universal screening to all pregnant women at the time of the second trimester ultrasound[2,8,33]. Moreover, we encourage further studies to identify new RFs of PTB in otherwise "low-risk" women and to define the mechanisms by which risk factors are related to PTB. In this way it could be possible to apply appropriate risk-specific interventions to reduce the incidence of PTB and related fetal and neonatal morbidity and mortality.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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