Screening for spontaneous preterm birth
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Chapter 8

Is cervical length associated with maternal characteristics?

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Abstract

Objective: Women with a mid-trimester short cervical length (CL) are at increased risk for preterm delivery. Consequently, CL measurement is a potential screening tool to identify women at risk for preterm birth. Our objective was to assess possible associations between CL and maternal characteristics.

Study design: A nationwide screening study was performed in which CL was measured during the standard anomaly scan among low risk women with a singleton pregnancy. Data on maternal height, pre-pregnancy weight, ethnicity, parity and gestational age at the time of the CL measurement were collected from January 2010 to December 2012. Univariable and multivariable linear regression analyses were performed to assess the relationship between CL and maternal characteristics.

Results: We included 5092 women. The mean CL was 44.3 mm. No association was found between CL and maternal height or gestational age of the measurement. Maternal weight was associated with CL ($p = 0.007$, adjusted $R^2 0.03$). Separate analysis for BMI did not change these results. Ethnicity, known in 2702 out of 5092 women, was associated with CL (mean CL in Caucasian women 45.0 mm, Asian 43.9 mm, Mediterranean 43.1 mm, and African 41.8 mm, $p = 0.003$), as well as parity (mean CL multiparous 45.3 mm, nulliparous 43.5 mm, $p < 0.0001$).

Conclusion: Shorter mid-trimester cervical length is associated with higher maternal weight, younger maternal age, nulliparity and non-Caucasian ethnicity, but not with maternal height.
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Introduction

Preterm delivery is a major contributor to perinatal mortality and morbidity\(^1,2\). Accurate identification of women at increased risk for spontaneous preterm birth may allow for timely allocation of preventative therapeutic strategies. Consequently, detection of reliable predictors is of great importance.

A variety of factors have already been assessed to investigate their role as a predictor of preterm birth. Several studies examined the relationship between cervical length and the risk of preterm birth\(^3,4\). Cervical length (CL) measured in the second trimester by transvaginal ultrasound, is inversely related to the risk of preterm birth and is currently one of the most accurate predictors\(^5,6\). Moreover, biochemical tests and biophysical characteristics of the cervix have been explored as well as the impact of infections on the risk of preterm birth\(^7-10\). In addition, several studies assessed maternal demographic, behavioural and anthropometric characteristics as well as maternal nutrition status defined by body mass index (BMI) and its association with preterm birth\(^11-15\). These studies concluded that, although underweight, short statured or younger women were more likely to suffer preterm birth, maternal anthropometric features are poor predictors for the risk of preterm birth. However, evidence concerning the relation between maternal characteristics and CL is limited, and often related to preterm birth and not to CL.

In the course of the Triple P study\(^16\), a prospective cohort study in The Netherlands, in which mid trimester cervical length is measured, we found the prevalence of short CL considerably lower compared to the studies of Heath et al. and Fonseca et al.\(^14,15\). In line with this the mean cervical length was higher\(^17,18\). Dutch women are on average taller than women of non-European origin and the Dutch population is one of the tallest in Europe. We questioned whether there is an association between maternal anthropometry and CL, therefore we decided to analyse CL measurements collected in three centres, while the Triple P study was still ongoing. The aim of this study was to assess the influence of maternal characteristics such as height, weight, age, ethnicity and parity on mid trimester CL, in order to explore if patient specific charts are needed for mid trimester CL to predict preterm birth.
Methods

Design

We performed a prospective cohort study under the acronym Triple P (Progesterone to Prevent Preterm birth). The Triple P study was a nationwide study in which mid trimester cervical length was measured, with subsequent randomization of women with a decreased cervical length.24 The present report was limited to three centres, i.e. two ultrasound centres and one tertiary hospital. At the time of our data collection about 15,000 measurements had been performed between January 2010 and December 2012. These three centres were chosen since they contributed to approximately one third of all CL measurements in the Triple P study. The tertiary hospital was located in Amsterdam South-East, a region which is characterized by the many nationalities of the residents (according to the information of the city council approximately 150). The two ultrasound centres performed the 20 week anomaly scan of all pregnant women in primary care as well as in secondary care in a large region; one was located in a city in the east of the country with a mixed population, and the other in a more rural area with a more conservative population. In this way, these centres can be considered to be a representative sample of the Dutch population. Eligible were women of 18 years or older with singleton pregnancies that underwent a structural sonographic fetal assessment between 18+0 and 22+6 weeks of gestation. Women with a previous spontaneous preterm birth before 34 weeks of gestation, with painful regular uterine contractions or ruptured membranes at the time of screening or with a cervical cerclage were excluded, as were pregnancies in which the fetus had structural anomalies. Prior to the introduction of the study, all participating sonographers were asked to complete an e-learning module, specifically designed to learn the cervical length measurement technique and to enhance the knowledge and skills of the experienced sonographers, thus decreasing the inter- and intra-observer variability. The cervical length was measured in addition to the standard anomaly scan at 18-22 weeks of gestation, which is offered to all pregnant women in the Netherlands. All participants gave informed consent before the measurement. At the end of the standard anomaly scan, women were asked to empty their bladder, to subsequently measure the cervix using a vaginal probe. In order to obtain a sagittal view of the cervix, the probe was placed in the anterior fornix of the vagina, without exerting any pressure, with the echogenic endocervical mucosa along the length of the canal. The calipers were placed at the distance between the triangular area of echo density...
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at the external os and the V-shaped notch at the internal os. This is according to the guidelines of the Dutch society of Obstetrics and Gynaecology (NVOG) as to the methods described by To et al. Each examination was performed during a period of at least three minutes to observe any cervical changes that might arise due to contractions. In such cases, the shortest measurement was recorded. We collected data on height, pre-pregnancy weight, ethnicity, parity and gestational age (GA) at the time of the CL measurement. Height and pre-pregnancy weight were obtained from medical charts. It is common practice in the Netherlands to weight all women at their first visit in pregnancy. The height and weight of our study population were also compared to data in StatLine, the electronic databank of Statistics Netherlands. (Hyperlink: http://statline.cbs.nl/StatWeb/publication/?VW=T&DM=SLNL&PA=81177NED&D1=14-43&D2=a&D3=0&D4=a&HD=121204-1323&HDR=T&STB=G1,G2,G3) of women between 20-40 year, and were consistent. Women without a prior pregnancy progressing after 15 weeks and 6 days were defined as nulliparous. Gestational age was based on ultrasound measurement according to a national protocol. Ethnicity was classified in five categories: European white, African, Asian, Mediterranean and other, following the classification guidelines of the Netherlands Perinatal Registry (PRN). In the PRN database the ethnicity of the women is registered on the basis of race, ethnic and geographical background. White European women are defined as born in the Netherlands or of West European origin. Mediterranean women consist of Turkish and North-African (mainly Moroccan) women. Most of the African-Caribbean women have their origins in the former Dutch colony Surinam, the Dutch Antilles and sub-Saharan Africa (Somalia/Ghana). (Hyperlink: http://www.perinatreg.nl/wat_wordt_geregistreerd?noCache=306;1419264334, code list at generally dataset version 1.3b; B2 Ethnicity) The ethnicity of the women is classified by the care provider during gestation by assigning women to a predefined group.

Statistical analysis

Height and pre-pregnancy weight were used to calculate pre-pregnant body mass index (kg/m²). Maternal height values were plotted against cervical length measurements. The distribution of normality was tested using the Kolmogorov-Smirnov test. We performed univariable linear regression and a subsequent multivariable linear regression analysis to assess the relationship between cervical length and maternal characteristics. Additionally, we dichotomized the database for maternal height, maternal age and BMI and compared CL of the group <P10
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with >P10 and <P90 <P90. Student t-test was used to compare mean cervical length for the different subgroups. Anova test was used to compare mean cervical length across different ethnicities. Since almost 90% of all women in our population were from European origin, ethnicity was dichotomized in the univariable and multivariable regression analysis. All statistical analyses were performed using SPSS version 21.

Results

During the study period CL was measured in the three centres in 5,092 women. Maternal height, weight and BMI were known in 4,454 (87.4%), 4,426 (86.9 %) and 4,415 (86.7%) women, respectively. Parity was known in 4,928 women (96.8%), and 2,880 (56.6%) of these women were nulliparous. Ethnicity was known in 2,702 women, and their majority (2432, 90.0%) was European white, 151 (5.6%) was African, 82 (3.0%) was Asian, 23 (0.9%) was from Mediterranean origin and 14 (0.5%) were classified as other. Maternal age, weight and height were normally distributed; cervical length had some skewness at the lower end of the histogram (figure 1). The median CL was 44.3 mm (table 1) (interquartile range 39 and 49 mm), and the first and fifth percentiles were 26.0 and 32.0 mm, respectively. Only 126 (2.5%) women had a cervical length ≤30mm and 14 (0.27%) had a cervical length ≤15 mm. Women were on average 30 years old and had a BMI of 23.4 (mean maternal height 169.7 cm, mean maternal weight 70.2 kg).

Table 1 Baseline characteristics of the cohort.

<table>
<thead>
<tr>
<th>Maternal characteristics**</th>
<th>Mean* (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.2 (4.9)</td>
</tr>
<tr>
<td>European white, N(%)</td>
<td>2432 (89.6)</td>
</tr>
<tr>
<td>Nulliparous, N(%)</td>
<td>2880 (56.6)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.7 (6.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.3 (13.7)</td>
</tr>
<tr>
<td>BMI (kg/m²), median (range)</td>
<td>23.4 (41.1)</td>
</tr>
<tr>
<td>CL (mm)</td>
<td>44.3 (8.4)</td>
</tr>
<tr>
<td>GA at CL measurement (weeks+days), median</td>
<td>20w+3d</td>
</tr>
</tbody>
</table>

* Unless reported otherwise  
** Age, CL and GA (gestational age) available in 5092 cases, ethnicity in 2702, parity in 4928, maternal height in 4454, weight in 4426 and BMI in 4426 cases.
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Figure 1 Distribution of cervical length (CL in mm)

As a result of our specific interest in the relation between CL and maternal height, we analysed the relation between CL and BMI and the relation between CL and maternal height and weight separately. The results of the univariate and multivariate analysis are shown in table 2.

Table 2 Association between cervical length and maternal characteristics

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>B</th>
<th>95% CI</th>
<th>P-value</th>
<th>R square</th>
<th>Adj R square</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA of CL measurement</td>
<td>-0.17</td>
<td>-0.69 to 0.34</td>
<td>0.51</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Age</td>
<td>0.18</td>
<td>0.13 to 0.22</td>
<td>&lt; 0.0001</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Height</td>
<td>0.03</td>
<td>-0.01 to 0.06</td>
<td>0.114</td>
<td>0.001</td>
<td>0.000</td>
</tr>
<tr>
<td>Weight</td>
<td>0.04</td>
<td>0.03 to 0.06</td>
<td>&lt; 0.0001</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>BMI</td>
<td>0.12</td>
<td>0.07 to 0.17</td>
<td>&lt; 0.0001</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td>European white ethnicity</td>
<td>2.36</td>
<td>1.32 to 3.39</td>
<td>&lt; 0.0001</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>-1.87</td>
<td>-2.33 to -1.41</td>
<td>&lt; 0.0001</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariate analysis</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.11</td>
<td>0.04 to 0.17</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.09</td>
<td>0.02 to 0.17</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European white ethnicity</td>
<td>2.25</td>
<td>1.16 to 3.35</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>-1.77</td>
<td>-2.43 to -1.11</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
We found no association between CL and maternal height (adj $R^2$ 0.00, p-value 0.11). Even after dividing the database in short stature (<P10, <160 cm) versus non-short and tall stature (>P90, >178 cm) versus not tall we found no difference in mean CL and short or tall maternal height: mean CL short stature 43.68 mm versus non-short 44.32 mm $p=0.19$, mean CL tall stature 44.29 versus non-tall 44.25 $p=1.0$. A scatter plot was made to verify and visualize a linear correlation between CL measurements (y-axis, in mm) and maternal height (x-axis, in cm) (Figure 2) the best fit line is almost horizontal and the non-significant Pearson correlation coefficient (adjusted $R^2$ < 0.0001) is included.

Maternal weight was associated with cervical length; CL increases with maternal weight (adj $R^2$ 0.005, p-value <0.001). The same association was present when substituting weight for BMI (adj $R^2$ 0.004, p <0.001). Since BMI is more often used in clinical practice, we used BMI instead of weight in the multivariable regression analysis. After correction, BMI was still associated with cervical length (p-value < 0.0001).

Decreasing maternal age was associated with decreasing CL (adj $R^2$ 0.01, p < 0.0001). Within the period of CL measurement (gestational age $18^{+6}$ – $22^{+6}$ weeks) we found no association between CL and gestational age (adj $R^2$ <0.00, p=0.51).

Nulliparous women were found to have a shorter mean CL than multiparous women (mean CL 43.5 mm versus 45.3mm respectively, (adj $R^2$ 0.012, p-value < 0.0001). European white women had on average a longer mean CL (45.0 mm) than women from other ethnicities, with African women having the shortest cervix (41.9 mm) (table 3, p< 0.0001).
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Table 3 Ethnicity and mean CL

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>N (%)</th>
<th>mean CL (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European white</td>
<td>2432 (89.6)</td>
<td>45.0 (8.0)</td>
</tr>
<tr>
<td>African</td>
<td>151 (5.6)</td>
<td>41.9 (9.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>82 (3.0)</td>
<td>43.9 (8.3)</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>23 (0.9)</td>
<td>43.1 (7.1)</td>
</tr>
</tbody>
</table>

*other N=14

Discussion

The objective of the current study was to investigate if maternal characteristics are responsible for the variance in cervical length. Our results show a relationship between mid-trimester cervical length and BMI, maternal age, maternal ethnicity and parity. However, an association between maternal height and cervical length was not found.

Strengths and weaknesses

The main strength of this study is the large sample size, studying over 5,000 low risk asymptomatic women. It is the first study that explored the influence of maternal anthropometrics on cervical length in such a large cohort.

Not all variables were available for all pregnant women, however data on maternal height, weight and BMI were available for nearly 4,500 women, parity for almost 5,000 women and ethnicity for 2,700 women. Although ethnicity was known in only 53% of the woman in our study population, we have no indication that in our population particularly women of non-European origin specifically were unrecorded. In the population based study in the Netherlands of Schaaf et al.,87% of women were from European white ethnicity compared to 89% in our population. Nevertheless, during the study period, we noticed that women of non-European ethnicity more often refused permission for CL measurement due to the vaginal ultrasound that was needed. Because of the participation of the tertiary centre in Amsterdam, we think the ethnicity of our population was a good representation of the Dutch situation.

According to the inclusion criteria of the Triple P study, parous women with a history of spontaneous preterm birth before 34 weeks of gestation were excluded, thus creating a real low risk study population. However, excluding this group, in
which cervical length could be slightly shorter, has influence on our findings on CL of primiparous women in comparison to CL of multiparous women. Although our conclusion at this paragraph should be interpreted with some reserve, the study of Iams et al.\textsuperscript{17} confirmed a longer CL in multiparous women. A possible limitation of this study is that we did not have data on history of large loop excision of the transformation zone (LLETZ). Although Heath et al.\textsuperscript{21} and Erasmus et al.\textsuperscript{22} reported no difference in CL in patients who previously underwent cervical surgery, Poon et al.\textsuperscript{23} found a shorter mean mid trimester cervical length in women with previous history of LLETZ. Since the total incidence of LETTZ is generally low (<2\%\textsuperscript{21,23}) we do not expect that it may have affected the mean cervical length in our population nor its association with maternal characteristics.

**Relation to other studies**

Our findings of an association between cervical length and BMI, age, ethnicity and nulliparity are supported by some other studies. In comparison to the other studies, our population had a lower BMI, higher height, and on average higher age. Furthermore, the majority of our women were from European origin. Despite these differences, the lack of association between maternal height and CL was supported by two previous studies\textsuperscript{24,25}. In contrast to our findings, Albayrak et al.\textsuperscript{26} showed a trend for increasing second trimester cervical length with increasing maternal height. The correlation was positive but weak (p-value 0.039) in a relative small population (N=114). Our study also confirms the relationship between shorter CL and lower weight and lower BMI\textsuperscript{21,26,27} as well as the increasing risk of short cervix in younger women\textsuperscript{21,27}. The mean CL in our study was shorter in African women (5.6\% of our population) compared to European white (almost 90\%). This was also reported by Heath et al.\textsuperscript{21}. However, Erasmus et al.\textsuperscript{22} concluded that black women did not have shorter CL. An explanation could be that he performed his study in South Africa with 56\% black and only 3.2\% white women.

**Clinical implications**

Despite the significant relationship we found between cervical length and BMI, age, ethnicity and nulliparity, the influence of all these factors on cervical length is marginal. In the multivariate model (predictors: age, BMI, European white and nulliparity) the adjusted $R^2$ was only 0.03, indicating that the combined maternal characteristics explained only 3\% of variation in cervical length between women in our study.
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Conclusion

This study shows that maternal height is not associated with second trimester cervical length. The same applies for gestational age within the period of our cervical length measurement (gestational age 18+0 – 22+6 weeks). Although maternal anthropometric measurements are convenient and easily obtained measures, they are not useful in the risk assessment for preterm birth related to a short cervix. Consequently, when screening for preterm birth by CL measurement, the CL cut-off for increased risk does not need to be adjusted for maternal height.

Statement of contribution

AV, BK wrote the first draft of the paper. BK and CE analyzed the data. AV, BK, EP and BW conceived the study. MO, CG, MH critically revised the manuscript for important intellectual content. All authors approved of the final version of the manuscript to be submitted.
References

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