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CHAPTER 5

Variation in preterm birth rate and the role of short cervical length across two populations; a comparative cohort study

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Manuscript in preparation

ABSTRACT

Objective
To examine variation in preterm birth rates between nulliparous women from two different populations and to investigate the contribution of short cervical length to any observed variation.

Study design
A comparative study between two cohorts of singleton nulliparous women from the Netherlands and Chicago, USA was performed. Women with a non-anomalous singleton pregnancy who underwent routine transvaginal cervical length measurement between 16+0 and 21+6 weeks of gestation with a known pregnancy outcome were selected. Fetuses with congenital anomalies, intra-uterine fetal deaths and deliveries before 24+0 weeks were excluded. Total, spontaneous, and iatrogenic preterm birth rates were calculated for both populations and compared with univariable and multivariable logistic regression.

Results
We included 3,409 women from the Netherlands and 3,334 women from Chicago. The median cervical length was slightly lower in the Netherlands compared to Chicago (42 vs. 44 mm, P<0.0001), but the rate of cervical length of 25mm or less was comparable (0.9 vs. 0.8%, p=0.69 respectively). The total rate of preterm birth prior to 37 weeks was comparable between locations (8.0% in the Netherlands vs. 7.3% in Chicago, p=0.27) but preterm birth prior to 32 weeks was higher in the Netherlands (1.3% vs. 0.54%, p=0.002). Multivariable regression revealed that women from the Netherlands, compared to women from Chicago, are at increased risk for spontaneous PTB between 28-31 weeks and between 24-27 weeks (adjusted odds ratio 3.1, 95% CI 1.2-8.3 and 5.3, 95% CI 1.5-19, respectively).

Conclusion
Despite similar percentages of short cervix, there are marked differences in early preterm birth rates between the Netherlands and Chicago, possibly indicating different phenotypes of preterm birth.

INTRODUCTION

Annually, preterm birth is responsible for the death of 1.1 million neonates worldwide [1]. In addition, it is significantly associated with morbidity: 70% of neonates born before 25 weeks who survive, will have long-term neurologic or developmental disabilities[2]. Infants born late preterm (34-36 weeks) are also at increased risk of cerebral palsy, respiratory problems, developmental delay and long term disabilities [3-5] albeit to a lesser absolute risk. The economic consequences of preterm birth are considerable[6] .

Marked differences between populations in total preterm birth rates have been described [7-9]. Within high income countries, the US is notable for its relatively high preterm birth rate of 12%[10] and for the trend in increasing preterm birth rate over the years[11]. The Netherlands, on the other hand, have a relatively low preterm birth rate of 6% [12] and is considered one of the countries that has had the greatest reduction in preterm birth over the last decade [11].

It has been suggested that preterm birth is not one disease but a syndrome with a variety of mechanisms including intrauterine infection/inflammation, uterine over-distension, and abnormal allogenic recognition[13]. However, the biological mechanism that is responsible for specific instances of preterm birth is not clear in most cases. In addition, it is not clear whether the variation in preterm birth rates can be explained by differential contributions of mechanisms of disease.

A short cervical length in the mid-trimester has been shown to be associated with preterm birth, representing an early initiation of parturitional changes. Accordingly, in some centers, it is measured routinely to identify women at increased risk of spontaneous preterm birth. The incidence of short cervical length is known to differ across countries [14-16] but it is not clear whether these differences directly correlate to rates of spontaneous preterm birth. Our objective was to examine variation in preterm birth rates between nulliparous women from populations in two different high income countries and to investigate the contribution of short cervical length to any observed variation.

MATERIALS AND METHODS

We performed a comparative study between two cohorts of singleton nulliparous women from the Netherlands and Chicago, USA. Women with a non-anomalous singleton pregnancy who underwent routine transvaginal cervical length measurement between 16+0 and 21+6 weeks of gestation with a known pregnancy outcome were selected. Fetuses with congenital anomalies, intra-uterine fetal deaths and deliveries before 24+0 weeks were excluded from the analysis.

Populations

In the Netherlands, women were selected from the nationwide Triple P screening study[17]. Between 2010 and 2011 at the standard fetal anomaly scan, transvaginal sonography was performed to identify women with a short cervical length. Pregnancy outcomes were collected by linkage with the Dutch Perinatal Registry (PRN) using zip code, maternal

date of birth and estimated date of delivery.[18;19]. Details on validation of information in the Perinatal Registry are published elsewhere [18;19]. The Dutch Perinatal Registry gave approval for linkage (approval number 13.07) and all women signed informed consent for measurement of their cervical length and linkage with the Perinatal Registry. The Triple P screening study was approved by the institutional review board of the Academic Medical Center, Amsterdam, The Netherlands (MEC AMC 08/374).

In a tertiary care hospital in Chicago, during the same period as the Triple P study in the Netherlands, transvaginal sonography was a routine part of the second-trimester ultrasonographic examination. The records of all women who received a second-trimester examination between 2010 and 2011 were identified through a query of the electronic records derived from clinical sonography reports, in which all cervical lengths obtained during the study time period were recorded. Eligible women's medical records were abstracted for demographic information and for obstetric outcomes. The Institutional Review Board of Northwestern University approved this study.

Outcome measures

For purpose of the analysis, preterm birth (PTB) was categorized as spontaneous (either preterm labor or preterm premature rupture of membranes) or iatrogenic (either induced labor or caesarean section without labor). In addition, gestational age at birth was categorized as extremely preterm (24+0-27+6 weeks), very preterm (28+0-31+6 weeks), moderately preterm (32+0-33+6 weeks) and late preterm (34+0-36+6 weeks).

Statistical analysis

We compared baseline characteristics between the two geographic populations with student's t-test, Mann-Whitney U Test or chi-square analysis, as appropriate. Total, spontaneous, and iatrogenic PTB rates were calculated for both populations and compared with univariable logistic regression. Multivariable logistic regression was performed to assess whether the geographic location was independently associated with PTB. Risk factors were added to the multivariable model if they were associated with PTB at a $p<0.10$ level in the univariable analysis. Neither database contained information regarding prior spontaneous miscarriages or induced abortions. To ensure that found differences were not due to unknown differences in these characteristics, a post-hoc sensitivity analysis was performed in which only women pregnant for the first time were analyzed.

To compare discriminative ability of cervical length in the prediction of spontaneous PTB between both countries, receiver-operating characteristics (ROC) curves were constructed. Area under the curves (AUC) were compared between the two populations using a method proposed by Hanley *et al*. through the z statistic [20]. All tests were two-tailed and $p<0.05$ was chosen as the threshold for statistical significance. Analyses were performed with IBM SPSS Statistics for Windows, version 20.0 (Armonk, NY: IBM Corp).

RESULTS

In The Netherlands, we identified a total of 3,423 nulliparous women who had a cervical length measurement between January 2010 and December 2011. Women with a delivery before 24+0 weeks gestation (n=5) or with an intra-uterine fetal death (n=9) were excluded leaving 3,409 women for the final analysis. In Chicago, we identified 3,383 nulliparous women who had had a cervical length measurement during the same study period. Women with a fetus with congenital anomalies (n=32), a delivery before 24+0 weeks (n=2) or an intrauterine fetal death (n=15) were excluded leaving 3,334 women for final analysis.

Baseline characteristics of both populations are shown in table 1. Women from Chicago were more often black (11% vs. 3.2%, p<0.0001) and experienced more hypertensive disorders of pregnancy (9.1% vs. 6.1% p<0.0001). In addition, pregnancies in Chicago had more often been conceived through IVF (5.1% vs. 3.0%, p<0.0001).

Table 1 | Baseline characteristics of both nulliparous cohorts

	Netherlands (N=3409)	**Chicago (N=3334)**	***P* value**
Maternal characteristics*			
Maternal age, mean (SD)	30.4 (4.8)	30.6 (5.1)	0.17
Ethnicity N (%): White	2961 (86.9)	1610 (61.3)	<0.0001
Black	109 (3.2)	286 (10.9)	
Other	335 (9.8)	732 (27.9)	
Smoking during pregnancy, N (%)	20 (0.6)	22 (0.7)	0.62
Pre-existing + pregnancy induced hypertension	209 (6.1)	295 (9.1)	<0.0001
Conception through IVF	78 (3.0)	164 (5.1)	<0.0001
Spontaneous births	2520 (73.9)	2365 (70.9)	0.006
Pregnancy characteristics			
Median GA at cervical length measurement (IQR)	19+5 (19+2-20+0)	20+1 (19+6-20+4)	<0.0001
Median cervical length , mm (IQR)	42 (38-48)	44 (39-49)	<0.0001
Cervical length ≤25 mm, N (%)	31 (0.9)	27 (0.8)	0.69

*IVF information available in 5,840 women, race/ethnicity available in 6,033, hypertension available in 6,663, smoking available in 6,628 women.

The total rate of PTB prior to 37 weeks was comparable between locations (8.0% in the Netherlands vs. 7.3% in Chicago, p=0.27) but PTB prior to 32 weeks was higher in the Netherlands than in Chicago (1.3% vs. 0.54%, p=0.002). As illustrated after stratification by type and gestational age of PTB, the higher risk of early preterm birth in women from the Netherlands is primarily related to a higher risk of early spontaneous PTB. This difference becomes even more pronounced after adjustment for other risk factors for preterm birth. Multivariable regression revealed that women from the Netherlands,

compared to women from Chicago, are at increased risk for spontaneous PTB between 28-31 weeks and between 24-27 weeks (adjusted odds ratio (aOR) 3.1, 95% CI 1.2-8.3 and aOR 5.3, 95% CI 1.5-19, respectively, Table 2). Analysis of only women in their first pregnancy did not change these results (aOR 5.7 95% CI 1.6-20 and aOR 8.6 95% CI 1.1-70, for spontaneous PTB between 28-31 and 24-27 weeks respectively).

The shape of the cervical length distributions in the two locations is fairly similar (Figure 1). Although the median cervical length was slightly lower in the Netherlands compared to Chicago (42 vs. 44 mm, P<0.0001), the rate of cervical length of 25mm or less was comparable (0.9 vs. 0.8%, p=0.69). Prediction of spontaneous PTB using only cervical length is poor, with AUCs ranging of 0.63 (95% CI 0.59-0.67) and 0.65 (95% CI 0.54-0.75) for spontaneous PTB less than 37 and 32 weeks in the Netherlands, respectively, and of 0.64 (95% CI 0.59-0.68) and 0.72 (95% CI 0.58-0.86) for spontaneous PTB less than 37 and 32 weeks in Chicago, respectively (Figure 2). There was no difference between the populations in discriminative ability of cervical length for preterm birth (p=0.88 and p=0.41 for comparison of AUCs of spontaneous PTB <37 and <32 weeks respectively).

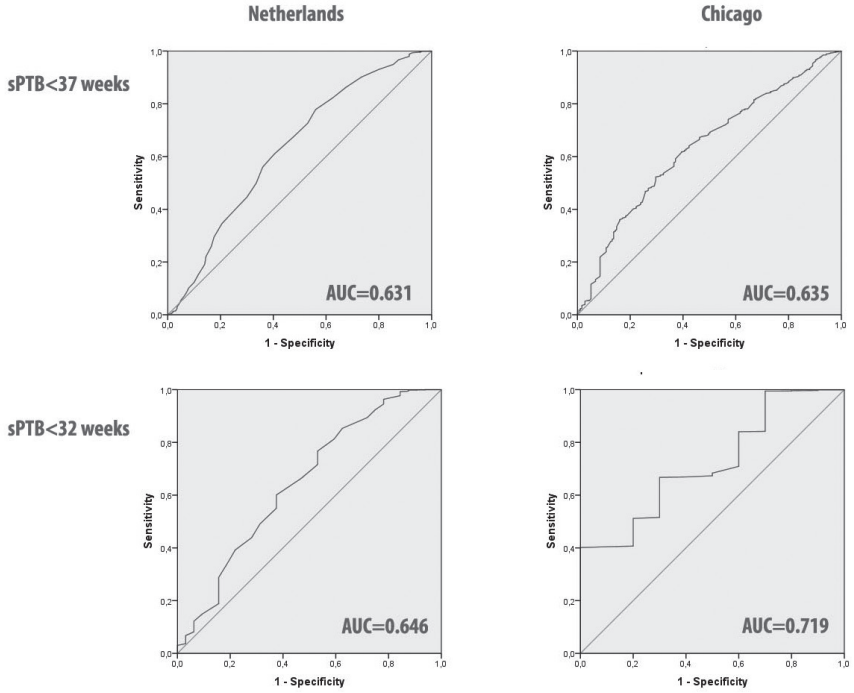

Figure 2 | Receiver operating curves for cervical length in the prediction of spontaneous PTB in both populations.

Table 2 | Rates of preterm birth in women from the Netherlands and Chicago. Risk of living in the Netherlands expressed as Odds Ratios adjusted for other risk factors for PTB.

		Netherlands N	%	Chicago N	%	Unadjusted OR	95%CI	Adjusted OR	95%CI
Total	34+0-36+6*@	191	5.6	192	5.8	0.97	0.79-1.2	1.3	1.0-1.6
	32+0-33+6*$%	38	1.1	32	0.96	1.2	0.73-1.9	1.2	0.69-2.0
	28+0-31+6$%	25	0.73	12	0.36	2.1	1.0-4.1	2.2	1.0-4.7
	24+0-27+6*	18	0.53	6	0.18	2.9	1.2-7.4	3.3	1.3-8.6
Spontaneous PTB	34+0-36+6*@%	138	4.1	142	4.3	0.95	0.75-1.2	1.1	0.87-1.5
	32+0-33+6$%	28	0.82	23	0.69	1.2	0.69-2.1	0.95	0.53-1.7
	28+0-31+6%	17	0.50	7	0.21	2.4	0.99-5.8	3.1	1.2-8.3
	24+0-27+6*	15	0.44	3	0.09	4.9	1.4-17	5.3	1.5-19
Iatrogenic PTB	34+0-36+6@$%	53	1.6	50	1.5	1.0	0.70-1.5	1.0	0.65-1.6
	32+0-33+6@$%	10	0.29	9	0.27	1.1	0.44-2.7	2.4	0.81-7.2
	28+0-31+6@$%	8	0.23	5	0.15	1.6	0.51-4.8	1.9	0.51-7.4
	24+0-27+6@	3	0.09	3	0.09	0.98	0.20-4.9	1.0	0.18-5.9

OR= Odds Ratio

Adjusted for: * IVF, @ hypertension, $ smoking, % race.

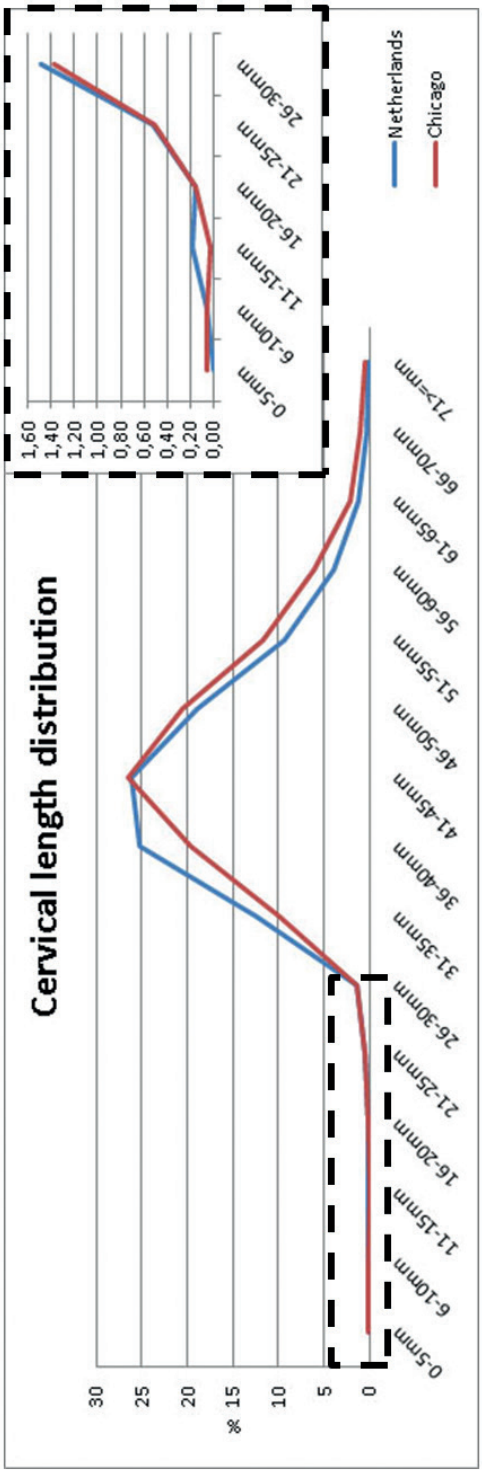

Figure 1 | Cervical length distribution of both cohorts.

DISCUSSION

Main findings

In this study, we have demonstrated that the distribution of cervical length and its predictive value for preterm birth is similar in two geographically distinct populations. Nevertheless, despite these similarities, we found nulliparous women from the Netherlands to have a 3-fold increased risk of spontaneous preterm birth between 28 and 31 weeks and a 5-fold increased risk of spontaneous preterm birth before 28 weeks of gestation. Assuming that cervical shortening is a reflection of one type of pathophysiology leading to spontaneous preterm birth, our data suggest that the increased risk of early preterm birth among women in the Netherlands is indicative of an excess of other pathophysiologic mechanisms.

Strengths and weaknesses

To our knowledge this is the first study that has directly compared differences in preterm birth rates between two geographically distinct populations and correct for differences in known risk factors, including short cervical length. A strength of this study is the relatively large sample of prospectively collected data with cervical lengths measured by certified sonographers in both countries.

A point of discussion is that we compared a population-based cohort (the Netherlands) with a hospital-based cohort (Chicago). Thus, the data in this population cannot be generalized to a general American population. However, this finding supports the notion that within a given country and even between cities, there are marked differences in PTB rates and potentially differences in the balance of mechanisms that account for preterm birth[7].

Secondly, not all known risk factors for preterm birth were available and could be adjusted for in both populations. We were able to correct in our analysis for the most important risk factors such as use of IVF, maternal race, and smoking. Sensitivity analysis in only women with a first pregnancy showed that the differences found in early PTB could not be explained by previous miscarriages and/or abortions. We were unable to correct for differences in BMI or socio-economic status but their total contribution to the risk of preterm birth was found to be fairly low in other studies (BMI=>30 aOR 1.14 95% CI 1.06-1.23 [21], low socioeconomic status aOR 1.10, 95% CI 1.07-1.13[22]) and should not, therefore, account for the differences found in the present study.

Finally, during the study period, a clinical trial was running in both countries comparing the effectiveness of vaginal progesterone [17] or intramuscular 17-OHP [15] to placebo in women with a short cervical length. A subset of women with short cervical length in both populations would therefore have received progesterone/17-OHP or placebo. We expect the influence of treatment for short cervical length on our findings to be minimal since the majority of women with extremely PTB had a normal cervical length measurement and a trial showed no demonstrable reduction in PTB from the use of weekly 17-OHP on women found to have a short cervix [15].

Other studies

Differences in preterm birth rates between populations have been described before. For example, Zeitlin *et al.* found a higher total preterm birth risk in women from the USA compared to women from France which could not be explained by differences in socio-demographic characteristics or higher rates of obstetrical interventions[23]. Also, Morken *et al.* compared PTB rates in singleton nulliparous women from Norway, Denmark and Sweden and demonstrated marked differences in extremely spontaneous PTB rates despite similarities between the three countries in terms of antenatal care, socio-demographic factors and a common Nordic ancestry [24]. This finding, along with our data, indicate that an overall high frequency of preterm birth does not always imply a high frequency of preterm birth at all gestational age subsets.

The rate of short cervical length is low in both the women from Chicago and the women from the Netherlands compared to other studies in nulliparous women (0.9 and 0.8% =<25mm in this study compared to 10.3% <30 mm and 4.9% =<20mm in other studies) [15;25]. It is expected that this frequency is less than reported in other studies, such as by Iams *et al*.[26], given that the gestational age at measurement was earlier. In addition, as has been shown by others[25], populations may differ in the frequency of short cervical lengths depending upon their overall risk status.

Clinical implications and future studies

Our data indicate that there are marked differences in the PTB rate at different gestational age cut-offs in nulliparous women that would not have been identified when comparing total PTB rates. This is important because although the total risk of PTB in the Netherlands is not as high as in other countries, nulliparous women in the Netherlands are at an increased risk of spontaneous extremely PTB, a clinically relevant category considering the associated high rates of mortality and morbidity.

Furthermore, known risk factors could not explain the large differences in the frequency of extremely PTB in two populations with similar cervical length distributions. This indicates that our current understanding of risk factors and etiology for preterm birth is far from complete. Future research should therefore focus on other predictors for extremely PTB in nulliparous women.

In addition, our data underscore that early cervical shortening is a common path for some but not all preterm births. Our data demonstrate that a population with a relatively high frequency of spontaneous early PTB is not accompanied by an increase in the frequency of a short cervix, possibly indicating a different phenotype of preterm birth. Whether these different phenotypes have the same risk of recurrence or even react differently to certain treatments needs to be further evaluated.

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