**PROJECT TITLE**

**PI(s)**

**STATISTICIANS**

**March 24, 2022**

**Questions of Interest:**

***Note questions to be answered in research.***

**Data sources (and version history)/Exclusions:**

***Note what are each of the data sources, and dates; who is excluded and why.***

**Methods:**

***Draft text that may be added to a manuscript – may be more detailed here to be clear.***

**Results:**

***Draft text to explain results in plain language.***

**Tables:**

**Figures:**

**Other/Exploratory results:**

**Refs as needed:**

***Previous Versions and Project Notes***

**Date: March 1, 2022**

**Date:**

**….**

**Project:** **Obstetric History and Risk of Short Cervix in Women with a Prior Preterm Birth**

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June 28, 2019

**Questions of interest:**

1. Assess whether obstetric history in women with prior preterm births (number of PTBs and gestational age of earliest PTB) is associated with incidence of short cervical length before 24 weeks gestation.

**Primary predictors:** Number of prior spontaneous preterm births (1 or 2+), and gestational week of their earliest prior preterm birth (16w0d-23w6d, 24w0d-27w6d, 28w0d-33w6d, 34w0d-36w6d).

**Additional covariates:** Race, maternal age, race/ethnicity, insurance status, BMI, prior D&C, history of cervical excision, prior term births, infertility treatment, tobacco use, progesterone type.

**Primary outcome:** Occurrenceof short cervical length (<25 mm) prior to 24 weeks gestation.

**Methods**

***Data source (from manuscript draft):***

Women were included if they had a previous spontaneous PTB between 16w0d and 36w6d gestation, and were currently pregnant with a singleton fetus. Women who received a history-indicated cerclage in the current pregnancy were excluded. Pregnancies complicated by a suspected major fetal malformation were also excluded. All women included in the study received progesterone prophylaxis. If women had more than 1 pregnancy during the study period, each pregnancy could be included as long as other eligibility criteria were met.

Data regarding each cervical length ultrasound performed in the pregnancy were abstracted from the medical record including gestational age at the time of examination and best shortest cervical length. Cervical length measurements were obtained using the standard techniques as described by Iams et al. (Iams 2013). Outcome data were considered missing for women without cervical monitoring before 24 weeks’ gestation or whose last cervical length was at <20 weeks gestation without short cervix by that point. Women with short cervix before 20 weeks were still included.

***Statistical Methods:***

Patient demographics and medical histories were compared between the primary exposure groups (1 or 2+ prior preterm births). Differences between these groups were assessed using Fisher’s exact test for categorical variables (race, BMI, history of cervical excision, infertility treatment, insurance status, prior D & C, prior term birth, progesterone type, and tobacco use). Differences in age were assessed using t-tests assuming equal variances for both groups. Additionally, the incidence of short cervix for women whose earliest preterm birth was in week 34, 35, or 36 was determined specifically for each of those weeks.

Marginal logistic models were used to evaluate associations between various predictors and the outcome, short cervix before 24 weeks gestation. Separate models for number of prior preterm births, prior term birth, and gestational age of earliest preterm birth as the primary predictor were produced, both unadjusted and adjusted for confounders including age, race, BMI, tobacco use, and history of cervical excision. These models also accounted for women who had multiple pregnancies in the data. An additional model was made including an interaction between gestational age of earliest preterm birth and number of prior preterm births, while adjusting for those same confounders and also prior term births. Four patients were excluded from the logistic regression analyses due to missing data for either BMI or progesterone type. P-values are reported for the adjusted odds ratios. A significance level of 0.05 was used throughout.

The subset of women who were excluded if their last cervical length was at <20 weeks gestation without short cervix by that point were described separately. This included descriptive statistics of number of scans done, the gestational age of their earliest preterm birth, the cervical length measurements, and the gestational age of delivery for this pregnancy. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

**Results**

After exclusions were made, 799 pregnancies remained in the dataset (728 women, some with multiple pregnancies over the study period). In regards to the measurements coming from triage scans, there was a total of 4309 scans made throughout the entirety of each pregnancy, of which 311 (7.2%) were done in triage. In the time period we are interested in, only scans done prior to week 24, 132/2623 (5.0%) of scans were done in triage. Cervical lengths from triage scans were included for the analyses.

There were 25 women excluded due to having no scans at 20 weeks gestation or later and did not have short cervix before 20 weeks. This left 774 pregnancies across 710 women that were included for the primary analyses.

Table 1 provides information on patient demographics and relevant medical histories, comparing women with 1 prior preterm birth and those with 2 or more. Race, infertility treatment use, insurance status, prior D & C, and tobacco use were all significantly associated with the number of prior preterm births.

**Table 1. Patient characteristics compared by number of prior preterm births.**

| **Variable** | **Level** | **1 prior PTB (n=497)** | **2+ prior PTB (n=277)** | **P-value** |
| --- | --- | --- | --- | --- |
| Age, years | Mean (SD) | 29.3 (5.7) | 30.0 (5.3) | 0.0815 |
| African American | Yes | 193 (38.8%) | 151 (54.5%) | <.0001 |
|  | No | 304 (61.2%) | 126 (45.5%) |  |
| BMI | Underweight/  Normal weight | 180 (36.4%) | 99 (35.7%) | 0.88 |
|  | Overweight/Obese | 314 (63.6%) | 178 (64.3%) |  |
| Cervical excision | Yes | 53 (10.7%) | 32 (11.6%) | 0.72 |
|  | No | 444 (89.3%) | 245 (88.4%) |  |
| Infertility treatment | Yes | 14 (2.8%) | 1 (0.4%) | 0.0148 |
|  | No | 483 (97.2%) | 276 (99.6%) |  |
| Insurance | Public | 261 (52.5%) | 220 (79.4%) | <.0001 |
|  | Private | 186 (37.4%) | 42 (15.2%) |  |
|  | None | 50 (10.1%) | 15 (5.4%) |  |
| Prior D & C | Yes | 106 (21.3%) | 88 (31.8%) | 0.0018 |
|  | No | 391 (78.7%) | 189 (68.2%) |  |
| Progesterone type | Vaginal only | 187 (37.7%) | 112 (40.4%) | 0.49 |
|  | 17p | 309 (62.3%) | 165 (59.6%) |  |
| Tobacco use | Yes | 150 (30.2%) | 122 (44.0%) | 0.0002 |
|  | No | 347 (69.8%) | 155 (56.0%) |  |
| Prior term birth | Yes | 232 (46.7%) | 143 (51.6%) | 0.20 |
|  | No | 265 (53.3%) | 134 (48.4%) |  |
| Earliest gestational age at delivery | 16w0d-23w0d | 100 (20.1%) | 101 (36.5%) | <.0001 |
| 24w0d-27w6d | 64 (12.9%) | 41 (14.8%) |  |
| 28w0d-33w6d | 136 (27.4%) | 80 (28.9%) |  |
| 34w0d-36w6d | 197 (39.6%) | 55 (19.9%) |  |

Table 2 provides the incidence of short cervix across the number of prior preterm births, whether they had a prior term birth, and the gestational age of the earliest preterm birth. *These were separate regression models*, one with each exposure-of-interest with and without adjustment for our list of confounders. The number of preterm births was not significantly associated with short cervix (p=0.23). Short cervix occurred in 27% of women with one prior preterm birth, compared to 32% in women with 2 or more prior preterm births. Prior term birth was significantly associated with short cervix (p=0.031), with the relative risk of short cervix being 22% lower in women with a prior term birth. The gestational age at their earliest preterm birth was significantly associated with short cervix (p<.0001). The major difference was between the earliest and latest gestation age brackets; for women whose earliest preterm birth was at 16-23 weeks, the risk of short cervix was 2.05 times that of those whose earliest was between 34-36 weeks. When comparing the 24-27 weeks and 28-33 weeks brackets with the reference of 34-36 weeks, the risks of short cervix were 1.39 and 1.16 times the risks of women whose earliest was at 34-36 weeks, respectively.

**Table 2: Obstetrical history and the relative risk of short cervix**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Cervical length  <25 mm  N=223 | Cervical length ≥25 mm  N=551 | RR  (95% CI) | aRR  (95% CI) | P-value |
| **Number of prior preterm births** | | | | | 0.23 |
| One | 135 (27%) | 362 (73%) | ref | ref |
| Two or more | 88 (32%) | 189 (68%) | 1.20 (0.96-1.51) | 1.15 (0.91-1.45) |
| **Prior term birth** | | | | | 0.031 |
| No | 125 (31%) | 274 (69%) | ref | ref |
| Yes | 98 (26%) | 277 (74%) | 0.79 (0.62-1.00) | 0.78 (0.62-0.98) |
| **Gestational age of earliest spontaneous preterm birth** | | | | | <.0001 |
| 16w0d-23w6d | 89 (44%) | 112 (56%) | 2.28 (1.69-3.08) | 2.05 (1.51-2.79) |
| 24w0d-27w6d | 30 (29%) | 75 (71%) | 1.41 (0.94-2.12) | 1.39 (0.93-2.08) |
| 28w0d-33w6d | 52 (24%) | 164 (76%) | 1.21 (0.85-1.71) | 1.16 (0.83-1.63) |
| 34w0d-36w6d | 52 (21%) | 200 (79%) | ref | ref |

Table 3 provides the odds ratios for the models that included an interaction term between number of prior preterm births and the gestational age of their earliest preterm birth. After adjusting for confounders, the interaction term was not significantly associated with incidence of short cervix (p=0.65). In this model, the individual effects for number of prior preterm births (p=0.57) and gestational age of their earliest preterm birth (p=0.0002) gave similar significance results to those of the separate models for those two variables in Table 2. Again, the relative risks were the highest when comparing women with a very early prior preterm birth to those with only a prior late preterm birth. The relative risks decreased as the gestational age brackets moved closer to the gestational ages of late preterm births.

**Table 3: Additive risk of short cervix based on obstetrical history**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Cervical length  <25 mm  N=223 | Cervical length ≥25 mm  N=551 | RR  (95% CI) | aRR  (95% CI) | P-value |
| **1 Prior PTB** | | | | |  |
| 16w0d-23w6d | 47 (47%) | 53 (53%) | 2.61 (1.82-3.74) | 2.29 (1.59-3.32) | <.0001 |
| 24w0d-27w6d | 18 (28%) | 46 (72%) | 1.48 (0.86-2.53) | 1.45 (0.86-2.44) | 0.16 |
| 28w0d-33w6d | 31 (23%) | 105 (77%) | 1.18 (0.76-1.84) | 1.18 (0.77-1.81) | 0.46 |
| 34w0d-36w6d | 39 (20%) | 158 (80%) | ref | ref |  |
| **2+ Prior PTB** | | | | |  |
| 16w0d-23w6d | 42 (42%) | 59 (58%) | 1.65 (1.00-2.72) | 1.54 (0.93-2.53) | 0.093 |
| 24w0d-27w6d | 12 (29%) | 29 (71%) | 1.07 (0.52-2.19) | 1.08 (0.56-2.09) | 0.81 |
| 28w0d-33w6d | 21 (26%) | 59 (74%) | 1.04 (0.61-1.79) | 0.97 (0.57-1.67) | 0.92 |
| 34w0d-36w6d | 13 (24%) | 42 (76%) | ref | ref |  |

In Table 4, the incidence of short cervix was compared among the 3 weeks that encompass late preterm births, including weeks 32 and 33 as an added reference. Overall, short cervix occurred similarly across the individual weeks of their earliest preterm birth. There was a noticeable difference between weeks 35 and 36, with short cervix occurring in 12% and 31% of women, respectively. However, when all late preterm gestational ages are combined, short cervix occurred similarly to what was seen for those with an earliest delivery at 32 or 33 weeks. The overall incidence of short cervix, regardless of week of earliest prior preterm birth was 29%.

**Table 4. Incidence of short cervix for women whose earliest prior preterm birth was between 32 and 36 weeks gestation.**

|  |  |  |
| --- | --- | --- |
| **Gestational age** | **CL <25 mm** | **CL ≥25 mm** |
| 32 weeks | 16 (26%) | 52 (76%) |
| 33 weeks | 10 (22%) | 36 (78%) |
| 34 weeks | 20 (21%) | 77 (79%) |
| 35 weeks | 10 (12%) | 74 (88%) |
| 36 weeks | 22 (31%) | 49 (69%) |
| 34-36 weeks | 52 (21%) | 200 (79%) |
| 32-36 weeks | 78 (21%) | 288 (79%) |
| 16-36 weeks | 223 (29%) | 551 (71%) |

A subset of 25 pregnancies were excluded due to having their last scan before 20 weeks gestation and did not have short cervix at any of those scans. Of these, 14 pregnancies had only 1 cervical length scan before 20 weeks gestation, 5 pregnancies had exactly 2 scans, and 3 pregnancies had 3 scans. The average gestational age at delivery for this group was 36.4 weeks, ranging from 21.6 weeks to 40.6 weeks. The two earliest deliveries were at gestational ages 21w4d and 22w1d. The next earliest delivery was at gestational age 33w2d. The average cervical length measurement was 35.6 mm, ranging from 25 mm to 50 mm. For the two pregnancies with the earliest deliveries, both had at least 2 measures, with the latest cervical length within about 3 weeks of their delivery.

**Updates June 12, 2019**

**Primary exposures in excluded women**

In the group of 25 women whose last cervical length screening was at <20 weeks gestation without having short cervix, 18 (72%) had 1 prior preterm birth and 7 (28%) had 2 or more prior preterm births. The highest number of prior preterm deliveries among these women was five. There were 2 (8%) women whose earliest prior preterm birth was at 16-23 weeks gestation, none at 24-27 weeks gestation, 9 (36%) at 28-33 weeks gestation, and 14 (56%) at 34-36 weeks gestation. There were 12 (48%) women with no prior term births, 8 (32%) with one prior term births, and 5 (20%) with two or more term births. The highest number of prior term deliveries among these women was seven.

**Sensitivity analysis**

**Table 5: Obstetrical history and risk of short cervix including women without screening at 20 weeks gestation and later.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Cervical length  <25 mm  N=223 | Cervical length ≥25 mm  N=576 | RR  (95% CI) | aRR  (95% CI) | P-value |
| **Number of prior preterm births** | | | | | 0.20 |
| One | 135 (26%) | 380 (74%) | ref | ref |
| Two or more | 88 (31%) | 196 (69%) | 1.22 (0.97-1.53) | 1.16 (0.92-1.47) |
| **Prior term birth** | | | | | 0.027 |
| No | 125 (30%) | 286 (70%) | ref | ref |
| Yes | 98 (25%) | 290 (75%) | 0.78 (0.62-0.99) | 0.77 (0.61-0.97) |
| **Gestational age of earliest spontaneous preterm birth** | | | | | <.0001 |
| 16w0d-23w6d | 89 (44%) | 114 (56%) | 2.36 (1.75-3.18) | 2.11 (1.56-2.87) |
| 24w0d-27w6d | 30 (29%) | 75 (71%) | 1.48 (0.98-2.22) | 1.45 (0.97-2.16) |
| 28w0d-33w6d | 52 (23%) | 173 (77%) | 1.20 (0.85-1.71) | 1.15 (0.82-1.63) |
| 34w0d-36w6d | 52 (20%) | 214 (80%) | ref | ref |

**Table 6: Additive risk of short cervix based on obstetrical history including women without screening at 20 weeks gestation and later.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Cervical length  <25 mm  N=223 | Cervical length ≥25 mm  N=576 | RR  (95% CI) | aRR  (95% CI) | P-value |
| **1 Prior PTB** | | | | |  |
| 16w0d-23w6d | 47 (47%) | 53 (53%) | 2.75 (1.92-3.94) | 2.40 (1.66-3.47) | <.0001 |
| 24w0d-27w6d | 18 (28%) | 46 (72%) | 1.54 (0.90-2.63) | 1.52 (0.91-2.56) | 0.11 |
| 28w0d-33w6d | 31 (22%) | 110 (78%) | 1.20 (0.77-1.87) | 1.19 (0.77-1.82) | 0.44 |
| 34w0d-36w6d | 39 (19%) | 171 (81%) | ref | ref |  |
| **2+ Prior PTB** | | | | |  |
| 16w0d-23w6d | 42 (41%) | 61 (59%) | 1.64 (1.00-2.71) | 1.52 (0.92-2.52) | 0.099 |
| 24w0d-27w6d | 12 (29%) | 29 (71%) | 1.11 (0.55-2.23) | 1.10 (0.57-2.11) | 0.78 |
| 28w0d-33w6d | 21 (25%) | 63 (75%) | 1.02 (0.59-1.76) | 0.94 (0.55-1.63) | 0.84 |
| 34w0d-36w6d | 13 (23%) | 43 (77%) | ref | ref |  |

Overall, the relative risk estimates changed little when including women who did not have cervical length screening at 20 weeks gestation or later and treating them as not having short cervix. These initially excluded women generally fell in the lower risk groups. For example, 18/25 had only 1 prior PTB, 13/25 had a prior term birth, and 14/25 had their earliest prior PTB at 34-36 weeks gestation with 9/25 having it at 28-33 weeks. For the most part, any changes in the odds ratios were slight increases when including this subset of women. Regardless, the same major trend is seen in both methods, with risk of short cervix increasing with earlier prior PTBs.

**Exploratory results of women whose earliest PTB was at 34-36 weeks and had short cervix**

There were 52 women whose earliest prior PTB was between 34-36 weeks and had a short cervical length. Of these women, 11 (21%) received a cerclage while 41 (79%) did not receive a cerclage. In the women with cerclages, their median gestational age at delivery was 36w2d, ranging from 26w3d to 39w1d. For the women without cerclages (2 were excluded due to unknown GA at delivery), the median GA at delivery was 37w4d, ranging from 33w0d to 40w4d. These differences were statistically significant (p=0.034, Wilcoxon rank-sum test).

**Table 7. Comparison of gestational age at short cervix across the primary exposure groups.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | N | Median gestational age at short cervix (range) | P-value |
| **Overall** | 223 | 20 weeks (13-23) | n/a |
| **Number of prior preterm births** | | | |
| One | 135 | 20 weeks (13-23) | 0.31 |
| Two or more | 88 | 19.5 weeks (14-23) |
| **Prior term birth** | | | |
| No | 125 | 20 weeks (14-23) | 0.51 |
| Yes | 98 | 20 weeks (13-23) |
| **Gestational age of earliest spontaneous preterm birth** | | | |
| 16w0d-23w6d | 89 | 18 weeks (13-23) | 0.0003 |
| 24w0d-27w6d | 30 | 19 weeks (15-23) |
| 28w0d-33w6d | 52 | 21 weeks (16-23) |
| 34w0d-36w6d | 52 | 20 weeks (15-23) |

Overall, the week that short cervix occurred in these women was similar when comparing between the number of prior preterm births and whether or not they had a prior term birth. There were significant differences based upon the gestational age of their earliest preterm birth, driven mostly by short cervix occurring earlier in women with earlier prior preterm births. Using a Bonferroni correction to adjust p-values for pairwise comparisons, differences were significant between the 16w0d-23w6d group and the 28w0d-33w6d group (adjusted p<0.0001) and between the 16w0d-23w6d group and the 34w0d-36w6d group (adjusted p=0.048).