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History of cervical insufficiency increases the risk of pelvic organ prolapse and stress urinary incontinence in parous women

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ABSTRACT

Objective: A likely contributor to pelvic floor disorders is injury and degradation of connective tissue components such as collagen and elastin, leading to weakening of the pelvic floor. Prior studies have found similar connective tissue component changes in women with cervical insufficiency (CI). However, the connection between pelvic floor disorders and cervical insufficiency has not previously been evaluated. Our objective was to determine whether a history of cervical insufficiency is associated with an increased risk of pelvic organ prolapse and stress urinary incontinence after controlling for confounders.

Study design: The study used de-identified clinical data from a large multi-institution electronic health records HIPAA-compliant data web application, Explorys Inc. (Cleveland, Ohio, USA). Women with a history of at least one prior delivery after at least 20 weeks' gestation between the years 1999 and 2016 were identified. Logistic regression models were used to identify risk factors and adjust for confounders.

Main outcome measures: The primary outcome was subsequent development of either stress incontinence or pelvic organ prolapse.

Results: A total of 1,182,650 women were identified, of whom 30,890 (2.6%) had a history of cervical cerclage or insufficiency. A history of cervical insufficiency was associated with an increased risk of either pelvic organ prolapse or stress urinary incontinence (aOR = 1.93, 95%CI: 1.84–2.02). A history of cervical insufficiency was more strongly associated with an increased risk of pelvic organ prolapse (aOR = 2.06, 95%CI: 1.91–2.21) than with stress urinary incontinence (aOR = 1.91, 95%CI: 1.80–2.02).

Conclusion: A history of cervical insufficiency is associated with an increased risk of development of pelvic organ prolapse and stress urinary incontinence.

1. Introduction

Stress urinary incontinence (SUI) and pelvic organ prolapse (POP) affect millions of women worldwide leading to poor quality of life, increased healthcare costs, and caregiver burden [1–4]. The most common risk factors for stress incontinence and pelvic organ prolapse are increasing parity, operative or spontaneous vaginal delivery, obesity, tobacco use and advancing age [5,6]. Multiple studies have been performed to determine how these risk factors contribute to the pathophysiology of pelvic floor disorders, however, the exact etiology has not yet been elucidated.

A likely contributor to pelvic floor disorders is injury and age related degeneration of connective tissue components such as collagen and elastin. These changes result in weakening of the pelvic floor muscles and endopelvic fascia which leads to clinically evident pelvic organ prolapse and urinary incontinence [7,8]. The importance of connective tissue components in the development of pelvic floor disorders is supported by studies which demonstrating changes in collagen type as well as decreased levels of collagen and elastin in women with pelvic floor disorders compared to controls [9,10]. Additionally, several authors have shown that women with certain connective tissue disorders such as Ehlers-Danlos and Marfan syndrome have higher rates of pelvic floor disorders than controls [11,12].

Cervical insufficiency is defined as painless cervical dilation leading to preterm delivery [13]. This is thought to arise, at least in part, due to degradation of the cervical extracellular matrix leading to loss of

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structural integrity. Previous histologic analysis found similar changes in collagen and elastin in women with a history cervical insufficiency that are found in women with pelvic floor disorders, specifically, decreases in type 1 collagen and elastin have been described in both conditions [14–16]. However, cervical insufficiency has not previously been evaluated as a potential risk factor for subsequent development of pelvic flood disorders. Given similar histologic findings, it is reasonable to believe that women with cervical insufficiency are at increased risk of pelvic floor disorders. The primary objective of this study was to evaluate the impact of cervical insufficiency on the risk of developing pelvic organ prolapse and stress urinary incontinence later in life.

2. Materials and methods

A multi-institution de-identified electronic health record database, IBM®EPM: Explore (IBM Corporation, Somers, NY USA), was utilized to perform a retrospective cross-sectional population study to assess the impact of cervical insufficiency on pelvic floor disorders. EPM: Explore™ is a commercially available analytics platform that collects and standardizes de-identified data from a variety of health information systems including inpatient and ambulatory electronic health records, billing systems, and lab and radiology systems. The de-identified data from participating healthcare organizations are collected into a cloud-based data storage grid, which is updated at least once every 24 h. Each participating healthcare organization has access to a secure, web-based application that allows for exploration and analysis of population-level data. At the time of this study, EPM: Explore™ contained data on over 50 million patients from 26 integrated health systems and 360 hospitals across the US [17]. Detailed information on the EPM: Explore™ platform, data standardization and mapping have been previously published [18].

Between the years 1999–2016 we identified all women over the age of 18 years with a history of undergoing cervical cerclage or cervical insufficiency using search terms containing "cervical cerclage" and "cervical incompetence". Patients with pelvic organ prolapse were identified using terms containing: "enterocele", "rectocele", "cystocele", "uterovaginal prolapse", "vaginal prolapse", "colpopexy", "sacrospinous fixation", "colporrhaphy", and "repair of vagina". Similarly, patients with stress urinary incontinence were identified using terms containing: "stress incontinence", "urinary incontinence/sling operation", "suprapubic sling", "repair of stress incontinence", "bladder neck operation for female stress incontinence", "transobturator tape", "tension free vaginal tape" "urethrocystopexy by levator muscle sling", "fixed suspension procedure of bladder neck", "urethropexy", and "retropubic urethral suspension". The control group included any women over age 18 years with at least one delivery after 20 weeks by any mode resulting in a live born infant.

Only terms which clearly indicated that a birth after 20 weeks occurred were used to identify women with a history of delivery: "vaginal delivery", "vaginal delivery following previous cesarean section", "deliveries by vacuum extractor", "vacuum extractor delivery-delivered", "forceps delivery-delivered", "Deliveries by breech extraction", "classical cesarean section", "multiple delivery, all by cesarean section", "liveborn born in hospital by cesarean section", "extraperitoneal cesarean section", "low cervical cesarean section", "H/O: cesarean section", "Cesarean delivery-delivered", and "Deliveries by cesarean".

Women with a history of congenital connective tissue disorders were identified using the following terms: "Ehlers-Danlos Syndrome", "Hypermobility syndrome", "Marfan's syndrome", "Connective tissue hereditary disorder", and "Inherited disorder of connective tissue". Tobacco users were identified using the terms "smoker", "tobacco dependence syndrome" "tobacco smoking consumption", "tobacco user", cigarette smoker", "moderate cigarette smoker", "heavy cigarette smoker", "heavy smoker (over 20 per day)", "moderate smoker (20 or less per day)".

Because parity is a major risk factor for pelvic floor disorders, including nulliparous women in the control group may result in an overestimation the impact of cerclage or cervical insufficiency has on subsequent development of PFDs simply by virtue of these women having experienced childbirth. In order to avoid this confounder, nulliparous women were excluded. It is also important to note, that all of the women included in this study had a pregnancy related event as their initial visit; cerclage or cervical insufficiency, for the "exposed" group, or for a term delivery, for the "unexposed" group.

The rate of cervical insufficiency was calculated for the entire cohort and for women with and without a history of at least one of the aforementioned pelvic floor disorders. The association between pelvic floor disorders and the following variables were evaluated with univariable logistic regression: cervical insufficiency, BMI $>$ 25 kg/m^{2}at time of initial evaluation, tobacco use, race, history of at least one vaginal delivery, age over 50 years, and a history of congenital connective tissue disease were also assessed. With exception of cervical insufficiency, these variables were selected because they have previously been described as risk factors for pelvic floor disorders [1–4].

The value used for patient age and BMI utilized in this analysis, were the age and BMI at the time a diagnosis or procedure code for PFD or pelvic reconstructive surgery was first entered into the database; and in the case of women without a documented PFD, the last age recorded in the database. The decision to include age over 50 years as a risk factor was based on the fact that women who present with pelvic organ prolapse tend to be older than 50 years and that this age is close to the average age of menopause, a known risk factor for pelvic floor disorders [3–5]. Similarly BMI over 25 kg/m^2 was selected because prior studies have shown that overweight women are at similar risk for developing PFDs as obese women (BMI $>$ 30 kg/m^2).

Because the EPM: Explore™ platform may categorize racial groups with small population sizes into "other" rather than reporting them individually, only women that were identified as either African American or Caucasian were included in the study.

Risk factors that were significant in the univariable analysis ($p < 0.1$) were maintained in the final multivariable regression model. Stepwise backward multivariable logistic regression was used to create the final model. To maintain HIPPA-compliant statistical de-identification, EPM: Explore™ reports population counts rounded to the nearest 10 and does not report sample sizes less than 10 in order to maintain patient confidentiality. In order to determine if such rounding adversely impacted the results, calculations of hat matrix and Pregibon's d-beta were performed to assess for undue influence and leverage respectively. Odds ratios with 95% confidence intervals are presented. The level of statistical significance was set to 0.05. Data analysis was conducted using STATA version 13.1 (College Station, TX).

Studies conducted on the EPM: Explore™ database are considered exempt by our institutional review board. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

3. Results

A total of 1,182,650 women with a history of at least one delivery after 20 weeks gestation were identified. Of these, 30,890 (2.6%) had a history of cervical cerclage or insufficiency; there was a higher rate of cerclage or cervical insufficiency in women with either pelvic organ prolapse or stress urinary incontinence compared to the control group, 5.9% vs 2.5%. In this population of parous women, 1.4% had pelvic organ prolapse and 2.3% had stress urinary incontinence. Women with a history of cervical cerclage or insufficiency had a higher rate of pelvic organ prolapse (2.7% vs 1.4%, $p < 0.001$) and a higher rate of stress urinary incontinence (4.1% vs 2.2%, $p < 0.001$) compared to women without these complications. Women with a history of CI or cerclage also had higher odds of having concomitant POP and SUI (0.9% vs 0.4%, $p < 0.001$).

Women with a history of cerclage were more likely to be younger