European Journal of Obstetrics & Gynecology and Reproductive Biology 203 (2016) 245–249

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Cold-knife conisation and large loop excision of transformation zone significantly increase the risk for spontaneous preterm birth: a population-based cohort study

Nina Jančar [a,*], Barbara Mihevc Ponikvar [b], Sonja Tomšič [b]

[a] Department of Human Reproduction, Division of Obstetrics and Gynaecology, University Medical Centre Ljubljana, Slovenia
[b] Health Survey and Health Promotion Department, National Institute of Public Health, Ljubljana, Slovenia

ARTICLE INFO

Article history:
Received 3 March 2016
Received in revised form 2 June 2016
Accepted 11 June 2016

Keywords:
Preterm birth
Cold-knife conisation
Large loop excision of transformation zone
Gestation
Cervical intraepithelial neoplasia

ABSTRACT

Objectives: Our aim was to explore the association between cold-knife conisation and large loop excision of transformation zone (LLETZ) with spontaneous preterm birth in a large 10-year national sample. We wanted to explore further the association of these procedures with preterm birth according to gestation.
Study design: We conducted a population based retrospective cohort study, using data from national Medical Birth Registry. The study population consisted of all women giving birth to singletons in the period 2003–2012 in Slovenia, excluding all induced labors and elective cesarean sections before 37 weeks of gestation (N = 192 730). We compared the prevalence of spontaneous preterm births (before 28 weeks, before 32 weeks, before 34 weeks and before 37 weeks of gestation) in women with cold-knife conisation or LLETZ compared to women without history of conisation, calculating odds ratios (OR), adjusted for potential confounders. Chi-square test was used for descriptive analysis. Logistic regression analyses were performed to estimate crude odds ratio (OR) and adjusted odds ratio (aOR) and their 95% confidence intervals (95% CI) with two-sided probability (p) values.
Results: A total of 8420 (4.4%) women had a preterm birth before 37 weeks of gestation, 2250 (1.2%) before 34 weeks of gestation, 1333 (0.7%) before 32 weeks of gestation and 603 (0.3%) before 28 weeks of gestation. A total of 4580 (2.4%) women had some type of conisation in their medical history: 2083 (1.1%) had cold-knife conisation and 2498 (1.3%) had LLETZ. In women with history of cold-knife conisation, the adjusted OR for preterm birth before 37 weeks of gestation was 3.13 (95% CI; 2.74–3.57) and for preterm birth before 28 weeks of gestation 5.96 (95% CI; 4.3–8.3). In women with history of LLETZ, the adjusted OR was 1.95 (95% CI; 1.68–2.25) and 2.88 (95% CI; 1.87–4.43), respectively.
Conclusions: Women with cervical excision procedure of any kind have significantly increased odds for preterm birth, especially for preterm birth before 28 weeks and before 32 weeks of gestation.

Introduction

Cervical intraepithelial neoplasia (CIN) is caused by persistent Human Papillomavirus infection. CIN is most prevalent in women in their childbearing age and can, in some cases, progress to cervical cancer, if left untreated. Screening programs for cervical cancer are implemented in many countries. As a result, incidence of invasive cervical cancer has fallen substantially in countries with well-organized screening programs [1]. On the other hand, due to growing population of women attending organized screening, more low- and high-grade cervical lesions are detected.

According to national and international guidelines for management of cervical lesions, high-grade lesions, consisting of CIN grade 2 and CIN grade 3, should be treated with excision procedures except in special situations. Large loop excision of transformation zone (LLETZ) and cold-knife conisation are the most frequent procedures used to treat high-grade cervical lesions [2,3]. Several studies and systematic reviews have shown that cervical excision procedures are associated with pregnancy complications such as spontaneous miscarriage, preterm birth and low birthweight [4–6]. Preterm birth is the most important risk factor for neonatal morbidity and mortality. Earlier the preterm birth, greater are possibilities for serious short or long-term complications [7].

* Corresponding author at: Department of Human Reproduction, Division of Obstetrics and Gyanecology, University Medical Centre Ljubljana, Šlajmerjeva 3, SI-1000 Ljubljana, Slovenia. Tel.: +386 1 522 6295; fax: +386 1 439 7590.
E-mail address: nina.jancar@kclj.si (N. Jančar).

http://dx.doi.org/10.1016/j.ejogrb.2016.06.005
0301-2115/

Studies suggest that the risk of preterm birth is associated with more aggressive excision procedures such as cold-knife conisation [4], greater depth of the excised cone [8–13], and the risk of miscarriage is associated with shorter time interval between procedure and pregnancy [13,14]. With the implementation of guidelines for management and treatment of CIN and the use of less invasive excision techniques, pregnancy complications have decreased [3,15]. Studies including women with modern excision techniques, limited to the excision of affected transformation zone and preserving as much healthy cervical tissue as possible, have shown that the risk for pregnancy complications is minimal [5,8,12]. Scientists are investigating a hypothesis whether mere presence of CIN increases the risk of complications in pregnancy [8,16,17].

Slovenia has a national screening program for early detection of precancerous lesions since 2003. There are around 1000 cases of CIN 3 reported every year. Data on CIN 2 lesions is collected by Slovenian Cancer Registry, but not reported in Annual Reports [18].

The aim of our study was to explore the association between surgical procedure for CIN and spontaneous preterm birth in singleton pregnancies in a large 10-year national sample adjusting for some already known important confounders. We wanted to calculate the odds for spontaneous preterm birth in women with a history of cold-knife conisation and women with a history of LLETZ compared to women without any procedure. We wanted to explore further the association of these procedures with preterm birth at different gestation that is before 28 weeks of gestation, before 32 weeks of gestation, and before 34 weeks of gestation.

Materials and methods

We conducted a population-based retrospective cohort study using data from Medical Birth Registry – the National Perinatal Information System of Slovenia (NPIS). NPIS contains data on woman, pregnancy, birth, the postpartum period and the neonate for each mother–infant/infants pair. Data is collected at the time of birth in all 14 maternal hospitals in Slovenia according to standardised methodology and pre-made definitions of variables [19]. Registration is mandatory by law since NPIS also serves as Slovenia's medical birth registry. Data is sent to the Slovenian National Institute of Public Health on a yearly basis, where it goes through statistical quality checks, is edited, and forms the basis for the official perinatal statistics of Slovenia. In the study period 99.9% of women delivered in a hospital.

This study of anonymous entries from administratively collected data was exempt of approval by the ethical committee according to Slovenian law [20].

The study population consisted of women who gave birth to singletons in Slovenia from January 1st 2003 to December 31st 2012. We excluded all induced labors and elective cesarean sections before 37 weeks of gestation, which were carried out due to maternal or fetal illness or condition, such as preeclampsia, maternal chronical illness, intrauterine growth restriction or other critical conditions.

Main exposure variables were cold-knife conisation and LLETZ. Those two variables are recorded in gynecological medical history, which is one of the mandatory groups of variables recorded in NPIS. If one woman had both exposure variables recorded ($n = 56$), we classified it as cold-knife conisation. Women without medical history of cervical excision procedure served as reference group.

Outcome variables were spontaneous preterm birth before 28 weeks, spontaneous preterm birth before 32 weeks, spontaneous preterm birth before 34 weeks and spontaneous preterm birth before 37 weeks of gestation. Gestation was determined by pediatrician assessment of baby after birth, considering also last menstrual period and ultrasound assessment in the first half of the pregnancy.

Four covariates obtained from NPIS were included in the analyses: maternal age, parity, smoking during pregnancy and maternal education. We selected those four covariates, because they have been reported to affect the odds for preterm birth [21]. Maternal age was categorized into seven groups: 19 years or younger, 20–24 years, 25–29 years, 30–34 years, 35–39 years, 40–44 years and 45 years or older. Parity was categorized into three groups: primiparous, women who have given birth for the second time and women who have given birth for the third time or more. Reported smoking during pregnancy was categorized into two groups: no or yes. Maternal education was categorized into five groups: primary or less, vocational, secondary or professional, tertiary and not stated.

Chi-square test was used for descriptive analysis. Logistic regression analyses were performed to estimate crude odds ratio (OR) and adjusted odds ratio (aOR) and their 95% confidence intervals (95% CI) with two-sided probability (p) values. A p value of <0.05 was considered statistically significant. We prepared two models: in the first model, we estimated aOR for spontaneous preterm birth in women with cold-knife conisation and in the second model in women with LLETZ. All other women giving birth to singletons within this period without any cervical excision procedure in their medical history served as a reference group in both models. In both models, we adjusted for maternal age, maternal education, parity and smoking during pregnancy. For statistical calculations, we used IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp.).

Results

In the period 2003–2012 there were 195 471 singleton births in Slovenia. After exclusion of 2738 (1.4%) induced labors and elective cesarean sections before 37 weeks of gestation due to maternal and fetal conditions and three cases with gestation week at the time of birth not recorded, our final sample for the analysis consisted of 192 730 (98.6%) women. Among those 8420 (4.4%) had a preterm birth before 37 weeks of gestation, 2250 (1.2%) before 34 weeks of gestation, 1333 (0.7%) before 32 weeks of gestation and 603 (0.3%) before 28 weeks of gestation. A total of 4580 (2.4%) women with singleton pregnancy had some type of conisation in their medical history: 2083 (1.1%) had cold-knife conisation and 2498 (1.3%) had LLETZ. In the group of women without a history of cervical excision procedure 7949 (4.1%) had a preterm birth before 37 weeks of gestation. In the group of women with a history of cold-knife conisation 267 (12.8%) women had a preterm birth before 37 weeks of gestation, 122 (5.9%) before 34 weeks of gestation, 83 (4.0%) before 32 weeks of gestation and 41 (2.0%) before 28 weeks of gestation. In the group of women with a history of LLETZ 204 (8.2%) women had a preterm birth before 37 weeks of gestation, 76 (3%) before 34 weeks of gestation, 47 (1.9%) before 32 weeks of gestation and 22 (0.9%) before 28 weeks of gestation. Characteristics of women included in our analysis are presented in Table 1.

In the observed period, the percentage of women with singleton births with conisation in their gynecological medical history doubled from 1.5% in 2003 to 3% in 2012. We observed that the type of conisation changed in time. The percentage of cold-knife conisation in the observed period remained rather stable (approximately 1% of all pregnant women), the percentage of women with a history of LLETZ increased from 0.4% in 2003 to 2% in 2012.

The OR and aOR for preterm birth in women with history of cold-knife conisation and LLETZ were significantly higher compared to women without history of cervical excision procedure. We found this to be the case for all types of preterm birth – according to gestational age. OR an aOR were higher for preterm births with lower gestational ages for both types of procedures. OR and aOR were also consistently higher for women with a history of cold-knife conisation procedure when compared to women with a history of