ORIGINAL ARTICLE

CERVICITIS AS A CAUSE OF PRETERM BIRTH IN WOMEN

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ABSTRACT

The aim: To evaluate the prevalence of preterm birth and to determine the role of cervicitis as a cause of preterm birth in women in Ukraine.

Materials and methods: We conducted a retrospective multicentre cohort study from January 1st, 2019 to December 31st, 2021. This study included pregnant women aged 17-50 years admitted to the labor ward at the 13 hospitals from 10 regions of Ukraine.

Results: Of the 8151 participants, the prevalence of preterm birth was 2226 (27.3%, [95% CI 26.8 – 27.8]) whereas 5925 (72.7% [95% CI 72.2-73.2]) delivered at term. Preterm birth associated with cervicitis was 76.3% (4,388/2666). History of cervicitis, maternal age, previous preterm labor or premature birth, and pregnancy with twins, triplets or other multiples were identified as independent risk factors of preterm birth.

Conclusions: Preterm birth in Ukraine is widespread, the number of which tends to increase. Infection and inflammation of the cervix seem to play a significant role for preterm birth. Early detection and treatment of cervicitis can reduce the risk of preterm birth. Women who have a history of poor pregnancy outcomes are at greater risk of poor outcomes in following pregnancies. Health providers should be aware of this risk when treating patients with a history of poor pregnancy outcomes.

KEY WORDS: Pregnancy; Cervix; Cervicitis, Cervical remodeling; Cervical ripening; Spontaneous preterm birth; Ukraine

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INTRODUCTION

Pregnancy loss and preterm birth (also known as premature) in women is an important public health care concern in worldwide Its negative consequences are manifested in many ways in our society, including the monetary costs of its investigation, diagnosis, and treatment as well as the psychosocial stresses it imposes on women.

Each year, around 2.6 million babies are stillborn, 15 million are born preterm (<37 weeks of gestation), and 32 million are born small for gestational age (less than tenth percentile for weight, smaller than usually expected for the relevant pregnancy stage). Being born preterm or small for gestational age can increase the chance of long-term health problems [1]. Preterm labor leading to preterm delivery (<37 weeks' gestation) affects approximately 5-7% of live births in developed countries, but significantly higher in developing countries [2]. More than 60% of preterm births occur in Africa and South Asia. In the lower-income countries, on average, 12% of babies are born too early compared with 9% in higher-income countries. [3].

The term reproductive loss is often associated with miscarriage, which manifests itself as spontaneous abortion during the first trimester of pregnancy before 12 weeks (early miscarriage) or 12 to 24 weeks of gestation (late miscarriage) in women [4]. Miscarriage can be also classified as embryonic loss (or early miscarriage) when it occurs before 10 gestational weeks and fetal loss (or fetal miscarriage) when it occurs after 10 gestational weeks [5]. According to literature, research suggests that between 10% and 20% of women with a medically confirmed pregnancy will end in miscarriage [6]. Early pregnancy loss in women is a relatively common event, occurring in 15%–25% of pregnancies, and increasing in prevalence with maternal age [7, 8]. In an Australian prospective cohort women the rate of miscarriage varied from 11.3 to 86.5 per 100 live births; overall, miscarriage occurred in 25% of the women in the study [9]. According to the American College of Obstetricians and Gynecologists, risk of miscarriage in women aged 45 years but increases to 80% [10].

Pregnancy loss and preterm birth in women is one of the most common yet under-studied adverse pregnancy outcomes [7]. Preterm birth is now recognized as a syndrome associated with multiple pathologic mechanisms, including infection, vascular disorders, uterine overdistension, breakdown in maternal-fetal tolerance, and cervical disease [11, 12]. Preterm birth is also associated with socioeconomic, lifestyle, and environmental factors [13, 14]. Previous studies have shown the association of

advanced maternal age [7, 8], smoking, drinking alcohol, illegal drug use, domestic violence, physical abuse, and exposure to environmental pollutants [13-15].

THE AIM

The aim of this study was to evaluate the prevalence of preterm birth and to determine the role of cervicitis as a cause of preterm birth in women in Ukraine.

MATERIALS AND METHODS

STUDY DESIGN, SETTINGS AND PARTICIPANTS

We conducted a retrospective multicentre cohort study from January 1st, 2019 to December 31st, 2021. This study included pregnant women aged 17-50 years admitted to the labor ward at the 13 hospitals from 10 regions of Ukraine. We compiled list of the 17 women hospitals. Of these, only 13 hospitals from 10 regions (Lviv, Vinnytsia, Zhytomyr, Kyiv, Sumy, Kherson, Dnipro, Kharkiv, Zaporizhzhia, and Odesa) of Ukraine agreed to take part in our study. The inclusion criteria in this study for participants were as follows: 17–49 years old; married or cohabitational; local residents. Te exclusion criteria: not a local resident of the selected regions; cancer; positive serological test for syphilis or other sexually transmitted infections.

DEFINITION

Preterm birth occurs when a baby is born before the 37th completed week of gestation. Pregnant mothers who delivered between 28 and 36 completed weeks of gestation were classified as preterm birth and whereas pregnant mothers who delivered at 37–42 completed weeks were classified as term birth. The gestational age (GA) in the present study was defined in weeks as the duration of pregnancy before birth based on menstrual history (date of the first day of the last menstruation), clinical examination, and ultrasonography (measuring the crown-rump length of the fetus during a first-trimester). Although preterm birth has an unknown cause, its etiologic phenotypes are broadly categorized into spontaneous preterm birth (natural onset of labor or preterm premature rupture of membranes) and provider-initiated preterm birth (induction of labor or pre-labor elective cesarean for maternal or fetal indications). Intrauterine growth restriction (IUGR) was defined as the estimated fetal weight less than the 5th centile along with abnormal Doppler velocimetry values (above 95th centile). IUGR was further examined determined by the measurement of the mother's belly from the top of the pubic bone to the top of the uterus (fundal height).

DATA COLLECTION

Using a simple randomized sampling technique, a total of 8,151 pregnant women who are between 17 and 50 years and had reported for delivery at the labor ward from 2019 to 2021 were selected for this study. This study includes interviews, questionnaires, and examinations medical records. Full text medical records were reviewed for the all women's. A standard data collection form was created to extract demographic and clinical data, and outcome information from routine patient records. Supervision and quality control were conducted throughout the entire study. In this study adopted double entry mode of paper questionnaire data and were analyzed anonymously. Pregnant women who delivered between 28 and 36 completed weeks of gestation were classified as preterm delivery whereas those who delivered after 37–42 completed weeks were described as term. Patients' folders and the hospitals' database were used to obtain all the other information

Table I. Trends of preterm birth among 8,151 pregnant women in Ukraine (2019-2021)

Region of Ukraine (n, medical facilities)	Trend of preterm birth						Total (2019-2021) n (%)	95% CI[a]	Trend (2019-2021)[b]
	2019 (n=696)		2020 (n=756)		2021 (n=774)				
	n	%	n	%	n	%			
Northern region (n=2)	130	18.7	144	19.0	148	19.1	422 (19.0)	18.2 – 19.8	↑
South Region (n=3)	146	21.0	157	20.8	149	19.3	452 (20.3)	19.5 – 21.2	↓
Western region (n=2)	131	18.8	146	19.3	142	18.3	419 (18.8)	18.0 – 19.6	↓
Eastern region (n=2)	131	18.8	147	19.4	146	18.9	424 (19.0)	18.2 – 19.8	↑
Central region (n=4)	158	22.7	162	21.4	189	24.4	509 (22.9)	22.0 – 23.8	↑
Total (n=13)	696	25.3	756	27.3	774	29.4	2,226 (27.3)	26.8 – 27.8	↑

[a] CI, Confidence interval

[b] ↑ and ↓ indicate statistically significant increasing and decreasing trends, respectively;

Table II. Characteristics of women with preterm birth in Ukraine (2019-2021)

Variable	All pregnant women (n=8151)		Term birth (n=5925)		Preterm birth (n=2226		P-value
	n	%	n	%	n	%	
Maternal age (years) category							
17-19	1,041	12.8	933	89.6	108	10,4	<0.001
20-22	1,557	19.1	1,308	84.0	249	16,0	
23-25	1,944	23.8	1,593	81.9	351	18.1	
26-28	1,248	15.3	951	76.2	297	23.8	
29-31	681	8.4	405	59.5	276	40.5	
32-34	549	6.7	261	47.5	288	52.5	
35-37	441	5.4	201	45.6	240	54.4	
38-41	261	3.2	117	44.8	144	55.2	
42-44	189	2.3	75	39.7	114	60.3	
45-47	129	1.6	45	34.9	84	65.1	
48-50	111	1.4	36	32.4	75	67.6	
Place of residence							
Urban	4,984	61.1	3,130	52.8	1,139	51.2	0.523
Rural	3,167	38.9	2,795	47.2	1,087	48.8	
Level of education							
Primary	2,439	29.9	784	13.2	378	17.0	0.374
High school	2,241	27.5	941	15.9	287	12.9	
Junior college degree	1,937	23.8	1,327	22.4	460	20.7	
Bachelor's degree and above	1,534	18.8	2,873	48.5	1,101	49.5	
Marital status							
Married	6,978	85.6	5,028	84.9	1,950	87.6	0.347
Unmarried	1,173	14.4	897	15.1	276	12.4	
Occupation status							
Unemployed	1,118	13.7	773	13.0	345	15.5	0.517
Head of enterprises	1,152	14.1	821	13.9	331	14.9	
Professional worker	2,985	36.6	2,229	37.6	756	34.0	
Clerk	303	3.,7	245	4.1	58	2.6	
Service worker	1,114	13.7	815	13.8	299	13.4	
Agricultural and related worker	217	2.7	148	2.5	69	3.1	
Operator	107	1.3	85	1.4	22	1.0	
Other	1,155	14.2	809	13.7	346	15.5	
Smoking							
Yes	6,141	75.3	4,455	75.2	1,686	75.7	0.564
No, secondhand smoke	1,877	23.0	1,360	23.0	517	23.2	
No	133	1.6	110	1.9	23	1.0	
Drinking							
Yes	7,206	88.4	5,152	87.0	2,054	92.3	0.0582
No	945	11.6	773	13.0	172	7.7	
BMI (kg/m^2)							
Thin	591	7.3	408	6.9	183	8.2	0.311

Normal	5,141	63.1	3,809	64.3	1,332	59.8	
Overweight	1,845	22.6	1,295	21.9	550	24.7	
Obese	574	70.0	413	7.,0	161	7.2	
Previous preterm labor or premature birth	1,728	100.0	474	27.4	1,254	72.6	0.001
Pregnancy with twins, triplets or other multiples	945	100.0	322	34.1	623	65.9	0.009
History of Cervicitis	5,748	100.0	1,360	23.7	4,388	76.3	<0.001
Chronic conditions							
high blood pressure	641	7.9	488	8.2	153	6.9	0.537
diabetes	4,975	61.0	3,544	59.8	1,431	64.3	
autoimmune disease	1,952	23.9	1,465	24.7	487	21.9	
depression	583	7.2	428	7.2	155	7.0	
Stressful life events	711	100.0	343	48.2	368	51.8	0.311

BMI, Body Mass Index

Table III. Logistic multivariate regression analyses of risk factors for preterm birth among pregnant women in Ukraine (2019-2021)

Characteristics	p-value	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)
Age (years)				
	< 0.001		< 0.001	
17–21		Ref		Ref
22-26	0.003	9.379 (2.165–40.619)	0.011	6.862 (1.557–30.247)
27–31	0.012	6.618(1.549–28.274)	0.031	5.036 (1.163–21.83)
32–36	0.025	5.577 (1.244–25.011)	0.109	3.49 (0.758–16.071)
37–41	0.035	5.50 (1.131–26.752)	0.174	3.096 (0.607–15.797)
42–50	0.269	2.297(0.515–10.249)	0.587	1.523 (0.335–6.943)
History of Cervicitis				
No		Ref		Ref
Yes	< 0.001	3.611 (2.234–5.831)	< 0.001	3.063 (1.819–5.158)
Previous preterm labor or premature birth				
No		Ref		Ref
Yes	< 0.001	5.131 (2.662–9.878)	< 0.001	3.835 (1.908–7.712)
Pregnancy with twins, triplets or other multiples				
No		Ref		Ref
Yes	< 0.009	3.623 (2.231–5.841)	0.001	3.081 (1.816–5.157)
Constant			0.003	0.109

OR, Odd Ratio

needed concerning the study participants clinical and obstetric history. Pregnant women who did not give informed consent, those who were medically unstable and those with the twin pregnancies were excluded.

ETHICS

Ethics approval was given by the Committee on Human Research, Publications, and Ethics at the Shupyk National Healthcare University of Ukraine. Written permissions were sought from the management of hospitals in which data and information were collected. This study was performed in line with the principles of the Declaration of Helsinki.

STATISTICAL ANALYSIS

The analysis of statistical data was performed using Excel (Microsoft Corp., Redmond, WA, USA). Results are expressed as median (range), mean standard deviation for

continuous variables, and number and corresponding percentage for qualitative variables. Categorical variables were analyzed and expressed as frequencies and proportions. Chi-square test/Fischer's Exact test and the binary logistic regression analysis were employed to test for associations and the strength thereof between the dependent variable (preterm birth) and independent variables. Significance level of the strength of association was determined at p-value < 0.05.

RESULTS

PREVALENCE OF PRETERM BIRTH

In during study period (2019-2021) we sampled 8,151 pregnant women who were 17–50 years old in 13 hospitals of 10 regions in Ukraine. Of the 8,151 participants, the prevalence of preterm birth was 2,226 (27.3%, [95% CI 26.8 – 27.8]) whereas 5,925 (72.7% [95% CI 72.2-73.2]) delivered at term. This study showed that the situation with preterm birth among pregnant women in Ukraine varies greatly by region (Table I). In general, lower preterm birth percentages were reported by Ukrainian regions in the west while higher percentages were reported in the central region, north, south and east of Ukraine.

Time trend analysis of preterm birth proportions by Ukraine was performed. The results are summarized in the Table I. Considering all hospitals that submitted data both in 2019 and 2021, the overall number of preterm birth reported was lower in 2019 than in 2021. These overall tendencies were not always observed at national level, however all but one hospital (Kyiv city, central region) reported higher numbers of preterm birth among pregnant women in 2021 than in 2019. Looking at preterm birth among pregnant women results in 2021, preterm birth was generally lowest in western part (Lviv city) of Ukraine and highest in eastern part (Kharkiv city).

PATIENT CHARACTERISTICS AND RISK FACTORS

Table II shows association of preterm birth with sociodemographic and obstetric factors. History of Cervicitis ($p<0.001$), Maternal age ($p<0.001$), Previous preterm labor or premature birth ($p<0.001$), and Pregnancy with twins, triplets or other multiples ($p<0.05$) was significantly associated with preterm birth. However, this study did not find any significant association between pregnant women's place of residence ($p=0.523$), marital status ($p=0.347$), occupational status ($p=0.517$), smoking ($p=0.564$), Body Mass Index ($p=0.311$) and preterm birth. Univariate logistic regression indicated that participants who had drinking were at increased risk of preterm birth. However, these factors were not independent risk factors after adjusting for possible confounders on multivariate logistic regression analysis ($p > 0.05$).

In Table III showed the odds ratio (OR) and 95% confidence interval (CI) for the risk factors associated with preterm birth in logistic multivariate regression analyses. After adjusting for possible confounders in the multivariate logistic regression analysis, maternal age, history of cervicitis, previous preterm labor or premature birth, and pregnancy with twins, triplets or other multiples were identified as independent risk factors of preterm birth.

DISCUSSION

This study presents the first estimates data on prevalence of preterm birth in pregnant women and risk factors in Ukraine. Of the 8151 participants, the prevalence of preterm birth was 27.3%, whereas 72.7% delivered at term. In the USA, the preterm delivery rate is 12–13%; in Europe and other developed countries, reported rates are generally 5–9% [16]. However, the rate of preterm birth has increased in many locations, predominantly because of increasing indicated preterm births and preterm delivery of artificially conceived multiple pregnancies. History of cervicitis, maternal age, previous preterm labor or premature birth, and pregnancy with twins, triplets or other multiples were identified as independent risk factors of preterm birth. Preterm birth associated with cervicitis was 76.3%.

Infants are born preterm at less than 37 weeks' gestational age after: (1) spontaneous labour with intact membranes, (2) preterm premature rupture of the membranes (PPROM), and (3) labour induction or caesarean delivery for maternal or fetal indications. Births that follow spontaneous preterm labour and PPROM—together called spontaneous preterm births—are regarded as a syndrome resulting from multiple causes, including infection or inflammation, vascular disease, and uterine overdistension. Risk factors for spontaneous preterm births include a previous preterm birth. A short cervical length and a raised cervical-vaginal fetal fibronectin concentration are the strongest predictors of spontaneous preterm birth [17].

Preterm deliveries are those that occur at less than 37 weeks' gestational age; however, the low-gestational age cutoff, or that used to distinguish preterm birth from spontaneous abortion, varies by location. [17]. It is estimated that 25–40% of PTBs are caused by intrauterine infections [17, 18]. Most intrauterine infections during pregnancy are caused by bacteria ascending from the vagina and the cervix [19]. How the cervix is compromised to cause the ascent of an infectious agent is still not fully understood. Infections during pregnancy may affect a developing fetus. If left untreated, these infections can lead to the death of the mother, fetus, or neonate and other adverse sequelae [19].

Infection and inflammation in the cervix appear to play a role in pregnancy and parturition. Preterm labor occurs when regular contractions result in the opening of your cervix after week 20 and before week 37 of pregnancy. Preterm labor can result in premature birth. According to literature, approximately 40% of cases of spontaneous preterm birth (sPTB) are associated with ascending intrauterine infections [12]. The cervix serves as a physical and immunological gatekeeper, preventing the ascent of microorganisms from the vagina to the amniotic cavity. The cervix undergoes remodeling during pregnancy. It remains

firm and closed from the start until the late third trimester of pregnancy and then dilates and effaces to accommodate the passage of the fetus during delivery. Remodeling proceeds appropriately and timely to maintain the pregnancy until term delivery. However, risk factors, such as acute and chronic infection and local inflammation in the cervix, may compromise cervical integrity and result in premature remodeling, predisposing to sPTB. Previous studies have established bacterial (i.e., chlamydia, gonorrhea, mycoplasma, etc.) and viral infections (i.e., herpesviruses and human papillomaviruses) as risk factors of PTB. However, the exact mechanism leading to PTB is still unknown [12].

Preterm labor can affect any pregnancy. Many factors have been associated with an increased risk of preterm labor. A viable preterm birth is defined as any delivery of a pregnancy at less than 37 completed weeks (< 259 days) and more than 23 completed weeks of gestation. It is a heterogeneous condition where 30–40% of all cases of preterm births are the result of elective delivery for a maternal or a fetal complication. The remaining 60–70% of preterm births occur spontaneously. Preterm birth complicates about 3% of pregnancies before 34 weeks' gestation and between 7 and 12% before 37 weeks' gestation [20].

If women can be identified to be at high risk in early pregnancy, they can be targeted for more intensive antenatal surveillance and prophylactic interventions. When women present with symptoms of threatened preterm labour, if the likelihood of having a spontaneous preterm birth can be determined, interventions can be deployed to prevent or delay birth and to improve subsequent neonatal mortality/morbidity. Several markers have been proposed for the identification of patients at risk for spontaneous preterm delivery, in both patients with threatened preterm labor and asymptomatic ones, with the hope that interventions could prevent preterm delivery. There is now compelling evidence that examination of the cervix with ultrasound is superior to vaginal digital examination [21] and in patients presenting with preterm labor can assist in determining the risk for preterm delivery before 34 weeks. In general, the shorter the cervix, the higher the risk for preterm delivery and vice versa [20, 22]. Transvaginal cervical sonography is a good method to assess the risk of preterm delivery in patients presenting with preterm labor, low-risk asymptomatic patients, and patients at high risk for preterm delivery. It should be also noted that endovaginal sonographic examination of the uterine cervix in women with preterm labor identifies patients at increased risk of intrauterine infections [23].

To protect the health of pregnant women and their offspring, additional research is needed to understand how these intrauterine infections adversely affect pregnancies and/or neonates in order to develop prevention strategies and treatments.

CONCLUSIONS

Preterm birth in Ukraine is widespread, the number of which tends to increase. Infection and inflammation of the cervix seem to play a significant role for preterm birth. Early detection and treatment of cervicitis can reduce the risk of preterm birth. Women who have a history of poor pregnancy outcomes are at greater risk of poor outcomes in following pregnancies. Health providers should be aware of this risk when treating patients with a history of poor pregnancy outcomes.

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