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Analysis of risk factors for cervical insufficiency: a retrospective controlled study

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Abstract

Objective:To study the risk factors of cervical insufficiency (CI). Design:Retrospective controlled study. Setting:First Hospital of Shanxi Medical University. Population:209 CI patients with a singleton pregnancy (CI group) and 348 patients randomly selected (control group). Methods and main outcome measures:All patients were required to have records of the whole pregnancy. The general conditions and pregnancy complications of the two groups were collected. A model of logistic regression and ROC curves were used. Results:Patients with a history of multiple pregnancies had a 17.51 times higher risk of CI than negative patients(OR=17.51, 95%CI: 2.16-141.85, P=0.007); patients who were pregnant by IVF-ET/ovulation induction had a 3.26 times higher risk of CI than negative patients(OR=3.26, 95%CI: 1.69-6.30, P<0.001); patients with gestational diabetes (GDM) or pregnancy with diabetes (PGDM) had a 2.88 times higher risk of CI than negative patients(OR=2.88, 95%CI:1.87-4.44, P<0.001); patients with PCOS had an 8.72 times higher risk of CI than negative patients (OR=8.72, 95%CI: 2.33-32.64, P=0.001); and patients with uterine malformations had a 4.00 times higher risk of CI than negative patients(OR=4.00, 95%CI:1.07-14.97, P=0.040) . The ROC curve showed the combination of multiple indicators have a certain predictive ability for CI (AUC=0.728). Conclusions:Previous multiple pregnancy, IVF-ET/ovulation induction conception, diabetes mellitus (GDM or PGDM), uterine malformations, and PCOS are risk factors for the incidence of CI, and the combination of multiple indicators has some predictive ability for CI. Funding:None

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Methods and main outcome measures: All patients were required to have records of the whole pregnancy. The general conditions and pregnancy complications of the two groups were collected. A model of logistic regression and ROC curves were used.

Results: Patients with a history of multiple pregnancies had a 17.51 times higher risk of CI than negative patients(OR=17.51, 95%CI: 2.16-141.85, P=0.007); patients who were pregnant by IVF-ET/ovulation induction had a 3.26 times higher risk of CI than negative patients(OR=3.26, 95%CI: 1.69-6.30, P<0.001); patients with gestational diabetes (GDM) or pregnancy with diabetes (PGDM) had a 2.88 times higher risk of CI than negative patients(OR=2.88, 95%CI:1.87-4.44, P<0.001); patients with PCOS had an 8.72 times higher risk of CI than negative patients (OR=8.72, 95%CI: 2.33- 32.64, P=0.001); and patients with uterine malformations had a 4.00 times higher risk of CI than negative patients(OR=4.00, 95%CI:1.07-14.97, P=0.040) . The ROC curve showed the combination of multiple indicators have a certain predictive ability for CI (AUC=0.728).

Conclusions: Previous multiple pregnancy, IVF-ET/ovulation induction conception, diabetes mellitus (GDM or PGDM), uterine malformations, and PCOS are risk factors for the incidence of CI, and the combination of multiple indicators has some predictive ability for CI.

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Tweetable abstract:

Previous multiple pregnancy, IVF-ET/ovulation induction, GDM or PGDM, uterine malformations, and PCOS are risk factors for CI.

Authors' Contribution:

Yu Han:Statistical analysis and manuscript writing

Wang Na:Data collection

Wang Chao:Data Collection

Hailan Yang:Project development and final manuscript editing

Analysis of risk factors for cervical insufficiency: a retrospective controlled study

Introduction

Cervical insufficiency (CI) is one of the main obstetrical diseases leading to preterm birth, which also afflicts 4% of patients with recurrent miscarriage.[1]CI refers to the abnormal remodeling, premature softening and shortening of the cervix, which is one of the major obstetric disorders leading to preterm birth and recurrent miscarriage in the second trimester, with an incidence of 1%-2% that is increasing.[2] There are known risk factors for CI, such as acquired factors including dilatation and evacuation, dilatation and curettage, induced abortion, previous cervical laceration, LEEP surgery, cold-knife cone biopsy, or other cervical surgeries. Congenital factors include utero diethylstilbestrol exposure, collagen vascular disease, or Müllerian abnormalities.[3]

The Canadian Society of Obstetrics and Gynecology (SOGC) clinical guidelines state that polycystic ovary syndrome (PCOS) is an independent risk factor for CI.[4] In addition, it has been shown that higher BMI is an independent risk factor for CI;[5]however, it has also been shown that obese patients have a lower risk of CI and premature delivery.[6] Therefore, whether BMI is significantly different between CI patients and non-CI patients requires further elucidation. The Royal College of Obstetricians and Gynecologists (RCOG) clinical

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guidelines also consider multiple pregnancies a risk factor for CI.[7] However, whether a previous history of multiple pregnancies is associated with the development of CI has not been shown. Additionally, previous studies have proposed that assisted reproductive technology (ART) is associated with the occurrence of CI.[8] In recent years, though studies have gradually found that the incidence of CI in the ART population is high,[9] whether ART serves as a risk factor for CI has not been clarified. Studies have shown that PCOS, impaired glucose tolerance and type II diabetes, and elevated BMI together constitute 70% of patients with recurrent miscarriage.[1] At the same time, in our previous study, it was found that more than 40% of CI patients had gestational diabetes mellitus (GDM) and pregnancy with diabetes mellitus (PGDM).[10] However, no relevant studies on whether the incidence of GDM and PGDM is different in CI patients versus non-CI patients, as well as whether diabetes can be used as a risk factor to predict the incidence of CI, currently exist.

In this paper, a single-center retrospective cohort study is conducted pertaining to the unspecified risk factors of CI by performing comparisons between the CI population and non-CI population, which may offer significant insight into the comprehensive management of CI patients during pregnancy and may clarify further research directions.

Methods

A total of 209 patients with a singleton pregnancy complicated by CI (CI group) hospitalized in the First Hospital of Shanxi Medical University from July 2013 to June 2020 were enrolled in this study. The control group (non-CI group) was randomly selected at a ratio of 1:2 and the inclusion criteria were: singleton pregnancy and non-cervical insufficiency. All patients were required to have records of the whole pregnancy. A total of 348 patients in the control group who met the criteria were collected. The general conditions, pregnancy complications (subclinical hypothyroidism, GDM and PGDM, PCOS, uterine malformation, uterine fibroids/adenomyoma, hypertensive disorders in pregnancy, anemia, vaginitis, and hyperlipidemia) of the two groups were then collected. A model of logistic regression was used to calculate the prediction probability, produce a combination of multiple indicators of new variables, draw ROC curves, and assess the predictive ability of risk factors for CI.

Statistical tools, such as Excel and SPSS 20, were used for data entry and analysis, while the quantitative data were analyzed by the t-test or analysis of variance and rank sum test. Qualitative data were analyzed using the chi-square test to explore the relationship between the variables, while logistic regression and ROC curves were used for multivariate analysis. $\alpha=0.05$ was set as the test level.

Results

Comparison in the general conditions between women with CI and those without CI

As shown in **Table 1** , there was no statistical difference in age (30.66 ± 3.66 VS 30.28 ± 4.56, P=0.284) and height (1.61 ± 0.05 VS 1.62 ± 0.06, P=0.058) between CI group and non-CI group. Compared with the non-CI group, patients in the CI group had a greater mean body weight (62.49±9.90 VS 58.83±9.17kg, P<0.001), a greater mean BMI (24.20±3.57 VS 22.63±3.63 kg/m^2, P<0.001), and a greater proportion had a BMI of 24 kg/m^2 or higher (50.25%,102/203 VS 29.85%,103/345, P<0.001). Compared with the non-CI group, the CI group had less mean weight gain during pregnancy (10.66±6.11 VS 13.36±5.35kg, P<0.001), and there was no significant difference in the mean BMI at delivery (27.96±3.76 VS 27.77±4.34kg/m^2, P=0.602) and in the proportion of patients with BMI greater than 24 kg/m^2 at delivery between the two groups (88.41%,183/207 VS 84.30%,290/344, P=0.051).

There was no significant difference in the gravidity(2.92±1.20 VS 2.14±1.18, P=1.903), uterine cavity procedures(0.45±0.87 VS 0.50±0.84, P=0.556), or medical abortions (0.09±0.36 VS 0.05±0.26, P=0.154)between patients in the CI and non-CI groups. Patients in the CI group had significantly fewer deliveries(0.26±0.54 VS 0.48±0.59, P<0.001)and more premature deliveries(0.16±0.40 VS 0.01±0.12, P<0.001)and spontaneous abortions (1.19±0.93 VS 0.10±0.39, P<0.001)than those in the non-CI group. The proportion of patients in the CI group who had a history of previous multiple pregnancies was significantly more than that in the non-CI group (7.66%,16/209 VS 0.29%,1/348, P<0.001), while the proportion of patients who concei-

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ved by ovulation induction/IVF-ET was also significantly higher in the CI group than in the non-CI group (23.44%,49/209 VS 4.89%,17/348, P<0.001).

2. Comparison in the comorbidities between women with CI and those without CI

As seen in **Table 2** , in the CI group, the incidence of GDM/PGDM was found to be significantly higher than that in non-CI group (41.21%,82/199 VS 18.39%,64/348, P<0.001), while patients with PCOS accounted for a higher proportion in the CI group (10.55%,21/199 VS 0.86%,3/348, P<0.001). There were no significant differences in the incidence of subclinical hypothyroidism, uterine malformations, uterine fibroids/adenomyomas, hypertensive disorders in pregnancy, anemia, vaginitis, and hyperlipidemia between the CI group and non-CI group. According to **Figure 1** , the distribution of various complications in the two groups of patients can be more clearly understood (the results marked with are statistically significant).

3. Multivariate analysis of influencing factors of cervical insufficiency

Presence or absence of CI (yes = 1, no = 2) was used as the dependent variable, while significant and other relevant variables in univariate analysis (age, gestation, parity, BMI, hypothyroidism, uterine fibroids, pregnancy-induced hypertension, anemia, vaginitis, and hyperlipidemia) were included in the logistic regression model, where α in = 0.05 and α out = 0.1. After conducting a multivariate adjustment for significant factors and possible confounders on univariate analysis, the results demonstrated that patients with a history of multiple pregnancies had a 17.51 times higher risk of CI than negative patients(OR=17.51, 95%CI: 2.16-141.85, P=0.007); patients who were pregnant by IVF-ET/ovulation induction were found to have a 3.26 times higher risk of CI than negative patients(OR=3.26, 95%CI: 1.69-6.30, P<0.001); patients with gestational diabetes/pregnancy with diabetes were noted to have a 2.88 times higher risk of CI than negative patients(OR=2.88, 95%CI:1.87-4.44, P<0.001); patients with PCOS had an 8.72 times higher risk of CI than negative patients(OR=8.72, 95%CI: 2.33- 32.64,P=0.001); and patients with uterine malformations had a 4.00 times higher risk of CI than negative patients(OR=4.00, 95%CI:1.07-14.97, P=0.040), as shown in **Table 3** . Notably, after adjusting for significant factors and possible confounders in the univariate analysis, the multivariate analysis showed that BMI was not associated with the development of CI.

The prediction probability was calculated using the model of logistic regression, in which a new variable and multi-index combination was generated. The ROC curve was then plotted (Figure 2). The larger the area under the ROC curve (AUC), the stronger the prediction ability of the index. The results showed that the area under the ROC curve: multi-index combination (0.728) > GDM or PGDM (0.614) > IVF-ET/ovulation induction (0.586) > PCOS (0.539) > previous multiple pregnancy (0.548) > uterine malformation (0.510). Evidently, the area under the curve following the combination of multiple indicators was 0.728, which was greater than 0.7, and was also significantly greater than the area under the curve of a single indicator, indicating that the model is fair. Accordingly, this once again suggests that previous multiple pregnancy, IVF-ET/ovulation induction conception, diabetes, uterine malformation, and PCOS are related to the occurrence of CI, and the combination of multiple indicators have a certain predictive ability for CI.

Discussion

1. Main findings

The present study demonstrated that previous multiple pregnancy, IVF-ET/ovulation induction conception, diabetes mellitus (GDM and PGDM), uterine malformation and PCOS all served as risk factors for CI. In this study, the multivariate analysis did not find that BMI was associated with the development of CI.

2. Interpretation

(1) History of multiple pregnancy and assisted reproductive technology

This study found that 7.66% of CI patients had a previous history of multiple pregnancies. The RCOG clinical guidelines consider multiple pregnancies as a risk factor for CI; therefore, whether women with previous multiple pregnancies increased the risk of CI in a singleton pregnancy was considered. Eventually, the results showed that a previous history of multiple pregnancies increased the risk of CI by 17.51-fold. Recent

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studies haven't mentioned the effect of previous multiple pregnancies in the occurrence of CI. These points should be further explored and confirmed in subsequent studies, which may also guide our future research to a certain extent. This study also demonstrated a 3.26-fold increased risk of CI via IVF-ET/ovulation induction pregnancy. A population-based study in 2007 showed that ART increased the risk of CI by 6-fold;[8] two retrospective cohort studies in 2010 and 2012 showed that the risk of CI was higher in women treated with ART than in women with spontaneous pregnancy.[11, 12] Meanwhile, a study of 4710 women who became pregnant after IVF/ICSI treatment in 2021 found that a high proportion of patients (2.31%) were diagnosed with CI.[9] In anovulation-related infertility patients, the formation of CI has been shown to be related to ovarian stimulation with gonadotropin and clomiphene citrate, and the use of other reproductive technologies.[13] Hence, attention should be given to the management of pregnancy and timely ultrasound monitoring during continuous pregnancy in patients undergoing assisted reproductive conception. Furthermore, focus should be given to the relationship between CI and infertility in clinical and scientific research.

(2)GDM/PGDM and PCOS

This study showed that diabetes (most patients are GDM) incidence was 41.21% among CI patients and approximately 18.39% among non-CI population. However, literature showed that the total incidence of GDM in mainland China was 14.8%,[14] indicating that the incidence of diabetes in the CI population of this study was significantly increased, while the incidence in the non-CI population was similar to the total incidence in mainland China. A history of diabetes mellitus was identified to be a predictor of CI in 2010,[15] and few studies have been published since then. The present multivariate analysis showed that GDM/PGDM increased the risk of CI by 2.88-fold. Pregnant women with diabetes are known to have a higher risk of adverse pregnancy outcomes, however, no systematic study exists pertaining to the relationship between diabetes and CI, while the association between the two may be explored by searching for a common pathogenesis. Insulin resistance and chronic subclinical inflammatory processes are considered to be the main factors leading to the development of GDM, which may be related to the development of CI.[16-18] The association and mechanism between the two should be further explored via basic experiments. This study also showed that about 10.55% of CI patients had PCOS, which increased the risk of CI by 8.72 times. This was consistent with SOGC clinical guidelines attributing PCOS to risk factors for CI. PCOS is a disease characterized by abnormal menstruation, hirsutism and acne, affecting about 6% -10% of women of childbearing age. PCOS patients have an increased risk of infertility, endometrial hyperplasia, and abnormal glucose metabolism.[19] According to literature, CI patients with PCOS have worse pregnancy outcomes than those without PCOS.[20, 21] Therefore, more attention should be given to the clinical management of such patients as well as the possible intercorrelation between PCOS and CI. Furthermore, supervision of pregnancy and the management of patients should be carried out adequately.

(3)Müllerian anomalies and uterine malformations

Müllerian anomaly is a known risk factor for congenital CI. Abnormalities that occur during development can range from uterine and vaginal agenesis to congenital uterine malformations.[22, 23] In 2011, the prevalence of congenital uterine malformations was reported to be about 5.5% in the general population, 8.0% in the infertile population, and 13.3% in the recurrent miscarriage population.[24] Meanwhile, in 2013, the prevalence of congenital uterine malformations was reported to be about 1.8–37.6% in the recurrent miscarriage population, which largely depended on the choice of methods and diagnostic criteria.[25] According to this study, uterine malformations accounted for about 1.44% in the non-CI population and 4% in CI patients. The incidence of uterine malformations was found to be slightly different from that reported in literature, which may be related to diagnostic methods, racial differences and chronological differences. According to literature, the incidence of CI is about 3.6% -30% in patients with uterine malformation.[26-28] The present study showed that patients with uterine malformations had a 4.00-fold increased risk of CI, which is in line with studies reporting that Mullerian abnormalities may increase the risk of CI by 6.19-fold.[28] Therefore, when encountering cases with congenital uterine malformations, CI may also be associated; hence, the cervical status of these patients must be assessed by serial ultrasonography in the second trimester.

(4)BMI

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Regarding the effect of BMI on CI, a study conducted by German scholars in 2011 showed that gestational obesity accounted for 7.9% of primiparous women, which reduced the risk of CI and preterm delivery. Although this study had a large sample size, it was conducted 10 years ago;[6] In 2015, Chinese scholars pointed out that for each unit increase in BMI, the risk of CI increased by 1.296 times; however, due to its small sample size, its conclusions still need to be verified by studies with a large sample size.[5] A retrospective study with a large sample size done by Yang et al in 2020 showed that BMI[?]25 kg/m^2 increased the risk of CI 3.87 times.[21] Meanwhile, 2 of the three studies in 2017 and 2020 had moderate sample sizes, while one had a large sample size, all suggesting that higher BMI may be related to longer cervical length.[29-31] In this study, although patients in the CI group had a larger mean pre-pregnancy BMI in the univariate analysis, and those with BMI of 24 kg/m^2 and above accounted for more, the multivariate analysis did not find that high BMI was associated with the occurrence of CI. In recent years, few studies have been conducted on the association between BMI and CI with no consistent conclusions. This study's conclusions also require a larger sample size to be further verified.

3. Limitations and advantages

The limitations of the present study are that the findings are not fully generalizable to the Chinese population as it is a single-center study with a moderate sample size. However, a major strength of this study is the direct clinical information gathered from our diverse and contemporary population that reflects current obstetric practice, as well as the large amount of data from 209 women with cervical insufficiency.

Conclusions

Previous multiple pregnancy, IVF-ET/ovulation induction conception, diabetes mellitus (GDM and PGDM), uterine malformations, and PCOS are risk factors for the incidence of CI, and the combination of multiple indicators has some predictive ability for cervical insufficiency.

Declarations:

Funding (information that explains whether and by whom the research was supported): None

Conflicts of interest/Competing interests: None

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