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# The association of chronic endometritis with mid-trimester loss due to cervical incompetence and the outcome of laparoscopic cervical cerclage

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## Abstract

**Purpose** To examine the association of chronic endometritis (CE) with cervical incompetence (CI) in Chinese women with mid-trimester loss, and the impact of the presence of CE on the outcome of laparoscopic cervical cerclage (LCC).

**Methods** This retrospective cohort study included a study group of 293 women with mid-trimester loss due to CI (group I) and a comparison group of 332 women with recurrent first-trimester miscarriage (group II). Immunohistochemical study using CD138 epitope for the diagnosis of CE was completed in all subjects. Pre-conception LCC was undertaken in 247 women in the study group (group I). The study was approved by Institutional Review Board (IRB) (number 2015FXHEC-KY005).

**Results** The prevalence of CE in group I was 42%, significantly ($P < 0.001$) higher than that of 23.5% in group II. Among 247 women in group I, there were no significant difference in mid-trimester loss rate, preterm delivery rate and term delivery rate in women with and without CE (2.2, 12.0, 85.8% vs. 1.8, 10.1, 88.1% respectively) and between women with CE treated and not treated with antibiotics prior to conception (2.3, 9.3, 88.4% vs. 2.0, 14.3, 83.7% respectively).

**Conclusions** Mid-trimester loss due to cervical incompetence is associated with chronic endometritis; However, the presence or not of CE and whether it was treated with antibiotics prior to conception did not appear to significantly influence the obstetric outcomes of women with CI after LCC.

**Keywords** Cervical incompetence · Chronic endometritis · Mid-trimester loss · Pre-conception laparoscopic cervical cerclage

## Introduction

There are several recognized causes of mid-trimester loss, namely uterine malformations, cervical incompetence (CI), infections, fetal and placental anomalies, genetic abnormalities and thrombophilia [1–4]. Environmental co-exposures, such as alcohol consumption, tobacco smoke exposure and socio-economic status are related to recurrent first trimester miscarriage, stillbirth or preterm delivery [5–8] and the risk of miscarriage and preterm delivery may be reduced by modification of these risk factors [7]. Among these underlying conditions, cervical incompetence is an important cause of recurrent spontaneous mid-trimester loss [3, 9]. It typically presents with painless cervical dilation; occasionally it may also present with rupture of membranes or uterine tightening especially if ascending infection has occurred following cervical dilatation. Recurrence mid-trimester loss rates were significantly lower after prophylactic vaginal or abdominal cerclage compared with no cerclage [9].

Chronic Endometritis (CE) is a persistent inflammation characterized by the presence of plasma cell in the endometrial stroma [10]. Recent studies have shown that the immunohistochemical staining for CD138, a cell surface proteoglycan that is expressed on plasma cells, improves the diagnostic accuracy of chronic endometritis [11]. CE is often asymptomatic and has been reported to contribute to recurrent miscarriage and recurrent implantation failure

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[12–14]. However, it is not known if chronic endometritis is also associated with cervical incompetence in women with mid-trimester loss.

In this study, we wish to examine the prevalence of CE among a cohort of women with mid-trimester loss associated with CI, compared to a cohort of women with recurrent first-trimester loss but without a history of mid-trimester loss, and to determine if the outcome of pre-conception laparoscopic cervical cerclage (LCC) is influenced by the presence of CE.

## Methods

### Subjects

This retrospective cohort study was conducted in the Hysteroscopy center, Fu Xing Hospital, Capital Medical University, Beijing, China. A total of 625 Chinese women who had a history of spontaneous mid-trimester loss or recurrent first trimester loss, were referred to the hospital for investigation and management between May 2015 and December 2017. Pregnancy outcomes of women who underwent preconception laparoscopic cervical cerclage were followed up until December 2019. The study was approved by Institutional Review Board (IRB) (number 2015FXHEC-KY005) and written consent was obtained from subjects participating in the study.

Women with spontaneous mid-trimester loss and a clinical diagnosis [15] of cervical incompetence belong to the main study group (group I, $n=293$), which is further divided into two sub-groups: (a) women who presented with a classical history of cervical incompetence characterized by painless cervical dilation (without uterine contractions or pain, or prolonged rupture of membrane) (group Ia, typical group, $n=198$); and (b) women with CI but presented with an atypical history characterized by either irregular uterine tightening or rupture of membranes > 24 h prior to delivery (group Ib, atypical group, $n=95$). Women with recurrent first trimester loss (2 or more clinical miscarriages < 14 week) but without any history of mid-trimester loss constituted the comparison group (group II, $n=332$) for this study.

### Hysteroscopy and endometrial biopsy

During the period of study, women who were referred to our unit because of recurrent first trimester loss or mid-trimester loss underwent routine hysteroscopic assessment and endometrial biopsy to rule out intra-uterine pathology.

Hysteroscopy was performed using a 4.5-mm 30 degree rigid hysteroscope (Olympus, Germany) as an out-patient procedure without the use of any anesthesia. Normal saline solution was used to distend the uterine cavity at 100 mmHg pressure. An endometrial biopsy was routinely obtained after hysteroscopy with the use of a curette.

### CD138 staining for diagnosis of CE

The paraformaldehyde-fixed paraffin-embedded endometrial sections were immune-stained with monoclonal antibody against epitope CD-138 at 1:100 dilution (Biocare Medical, Concord, CA) [10, 16]. The immunoreactive cells were enumerated per 10 high power field (HPF) randomly chosen with non-overlapping stromal areas. The biopsies were graded as positive for chronic endometritis (CE) when there was one or more plasma cell identified per 10 HPF [10, 16]. Regarding observer variability in diagnosis, two competent blinded histopathologists separately reviewed a set of 40 slides, the concordance of result in diagnosis of CE is shown in Table 1 ($K=0.881$, $P<0.001$).

### Antibiotic therapy

Between May 2015 and Nov 2016, CD138 staining was routinely performed along with traditional histological evaluation of endometrial biopsy specimens. During this period, 141 specimens from the study group were examined; subjects whose biopsy specimen showed CE received a course of antibiotics (500 mg levofloxacin (clinafloxacin), once a day and 500 mg metronidazole twice a day) for 2 weeks.

From December 2016 onwards, CD-138 staining ceased to be part of routine histopathological examination and so the diagnosis of CE was no longer available to clinicians. There were 152 specimens in this study in which CD-138 staining was performed retrospectively in archived specimens. In this group of subjects, as the clinicians were not aware of the diagnosis of CE, antibiotic therapy was not administered.

### Laparoscopic cerclage

Among women in group I, 247 subjects underwent preconception laparoscopic cervical cerclage (LCC). The primary indication for LCC was a clinical diagnosis of cervical incompetence resulting in one or more mid-trimester losses; the secondary indications included: (a) failure of a previous vaginal cerclage to achieve a live birth ($n=177$);

**Table 1** Inter-observer variability in the immunohistochemical diagnosis of CE

| First observer | Second observer | | Consistence |
|---|---|---|---|
| | Negative | Positive | |
| Negative | 27 | 2 | $K=0.881$ |
| Positive | 0 | 11 | |

(b) previous cervical trauma or surgery which rendered it difficult to perform transvaginal cerclage ($n=19$); and (c) patient request for pre-conception cerclage ($n=51$).

LCC was performed with the use of simplified laparoscopic cervical cerclage (SLCC) technique as previously described [17]. In brief, the straight needle was inserted into cervical wall 2–3 mm medial to the lateral edge of the cervix at the level of the cervical isthmic junction, without dissecting the bladder off the lower uterine segment and without separating the uterine vessels.

### Follow-up

Clinical and laboratory data was retrieved from hospital record; additionally, telephone contact was made by JL to obtain various reproductive outcome data (211 conceptions confirmed by ultrasound) with a minimum follow-up period of 24 months after the surgery. A flow chart of patient participation and follow-up is shown in Fig. 1.

### Statistical analysis

The various clinical and laboratory data were analyzed with the use of SPSS 21. The difference in demographic characteristics, prevalence of chronic endometritis and delivery and miscarriage rate between groups was analyzed with the use of Pearson Chi-square or Fisher exact tests. Student's $T$ test was used to compare quantitative data between groups. Statistical significance was defined as $P<0.05$. Where appropriate, Bonferroni's correction was applied, in which case the significance level between groups was adjusted to $P<0.0167$.

## Results

### Demographics

The demographics of the three groups of subjects (groups Ia, Ib and II) are summarized in Table 2. There was no difference in age, BMI and previous parity and miscarriage history among the three groups.

### Prevalence of chronic endometritis

The prevalence of CE in group I (123/293, 42.0%) was significantly ($P<0.001$) higher than that of group II (78/332, 23.5%). (OR = 2.36; 95% CI = 1.67–3.32). The difference remained significant after Bonferroni's correction (Fig. 2). Within group I, the prevalence of CE in subgroup Ib (48/95, 50.5%) was significantly ($P=0.040$) higher than that in group Ia (75/198, 37.9). (OR = 1.68; 95% CI = 1.02–2.75). The difference did not reach statistical significance after Bonferroni's correction (Fig. 2).

Within subgroup Ib, the prevalence of CE in subjects who presented with prolonged ruptured membranes (21/39; 53.8%) was not significantly ($P=0.650$) different to that of subjects who presented with tightening (27/56; 48.2%). (OR = 0.798; 95% CI = 0.352–1.810).

### Relationship between CE and number of miscarriages

Within group I, the prevalence of CE in subjects with 1, 2 and ≥ 3 mid-trimester miscarriages were 38/70 (54.3%),

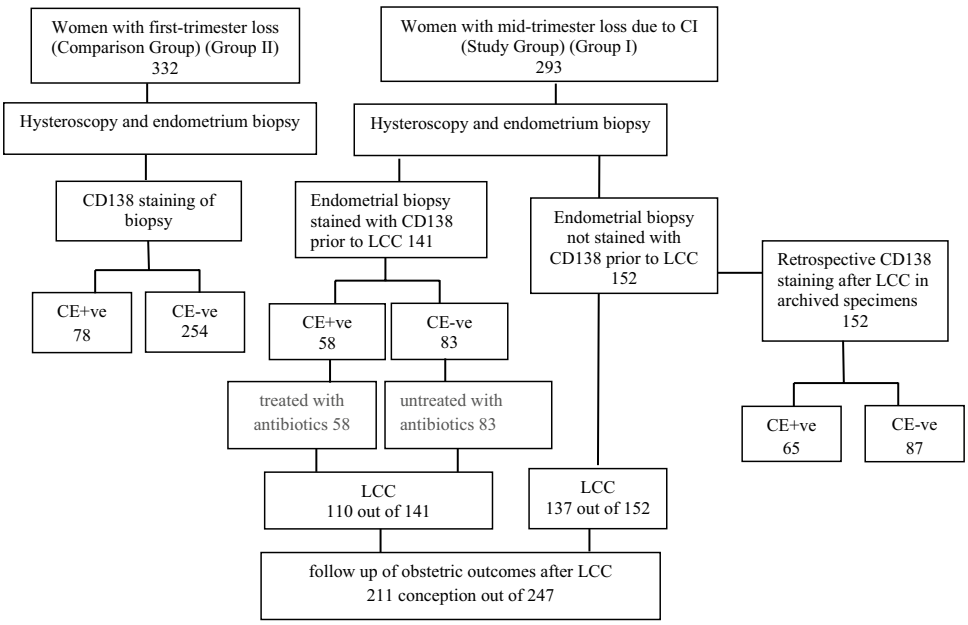


**Fig. 1** Flow chart of the study

**Table 2** Demographic details of subjects included in the study

| | Group Ia $n=198$ | Group Ib $n=95$ | Group II $n=332$ | $P^*$ |
|---|---|---|---|---|
| Maternal age[a], (years) | 32 (21–42) | 31 (25–43) | 30 (23–41) | 0.637 |
| BMI[a], (kg/m$^2$) | 23.1 (19.3–37.8) | 22.6 (18.4–38.5) | 22.2 (18.7–36.2) | 0.453 |
| Parity, *n* | | | | |
| 0 | 178 (89.9%) | 89 (93.7%) | 314 (94.6%) | 0.120 |
| ≥1 | 20 (10.1%) | 6 (6.3%) | 18 (5.4%) | |
| Previous mid-trimester miscarriage, *n* | 2 (1–8) | 2 (1–5) | 0 | 0.550** |
| Previous first trimester miscarriage, *n* | 0 (0–4) | 0 (0–8) | 2 (2–6) | 0.536** |

*$P$ value of the Chi-square test or Fisher's exact test for categorical variables and Student's $T$-test or the Mann–Whitney test for continuous variables

**Comparison between groups Ia and Ib only

[a]Median (range in brackets)

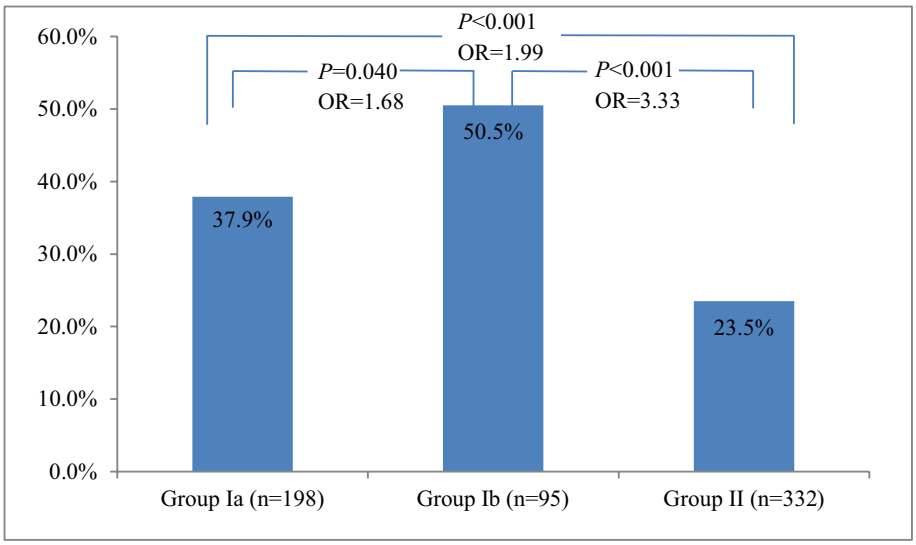


**Fig. 2** A comparison of the prevalence of chronic endometritis in three groups of subjects. Group Ia-women with a classical history of cervical incompetence. Group Ib-women with atypical history of cervical incompetence. Group II-Women with recurrent first trimester loss (the comparison group)

Group Ia-women with a classical history of cervical incompetence
Group Ib-women with atypical history of cervical incompetence
Group II-Women with recurrent first trimester loss (the comparison group)

55/141(39.0%) and 30/82 (36.6%) respectively (3×2 contingency table analysis, $P=0.054$).

Within group II, the prevalence of CE in subjects with 2 first-trimester miscarriages and ≥3 miscarriages were 47/205 (22.9%) and 31/127 (24.4%) respectively (2×2 contingency table analysis, $P=0.757$).

## Factors affecting the prevalence of chronic endometritis in study group

To analyze possible confounding variables, regression analysis was performed using chronic endometritis as dependent variable and age, BMI, parity, number of mid-trimester loss, number of first trimester loss, typical or atypical mid-trimester as independent variables. The prevalence of chronic endometritis was found to be significantly corelated with the type of CI (typical or atypical, $P=0.034$), but not with age, BMI, parity, number of first trimester loss and number of mid-trimester loss.

## Outcomes of subsequent pregnancy after LCC

Among 293 women in Group I, 247 women underwent preconception LCC, of whom 7 women were lost to follow, 29 women had either delayed period or biochemical loss and 211 women had ultrasound evidence of conception. Among the 211 conceptions confirmed by ultrasound, the first trimester miscarriage rate, mid-trimester loss rate, preterm delivery rate and term delivery rate were 2.8, 1.9, 12.3 and 82.9% respectively.

The mid-trimester loss rate, preterm delivery rate and term delivery rate were not significantly different (1) between women with and without CE (2.2, 12.0, 85.8% vs.

1.8, 10.1 and 88.1% respectively), and (2) between women with CE treated and not treated with antibiotics prior to conception (2.3, 9.3, 88.4% vs. 2.0, 14.3 and 83.7% respectively), excluding 4 cases that underwent preterm delivery as a result of other complications (3 cases of pregnancy-induced hypertension syndrome and 1 case of placenta previa).

In addition, there was no difference in first trimester miscarriage rate (2.9% vs. 2.8%), mid-trimester loss rate (0.7% vs. 4.2%), preterm delivery rate (12.2% vs. 12.5%) and term delivery rate (84.2% vs. 80.5%) between groups Ia and Ib.

The relationship between obstetrics outcome (mid-trimester loss or preterm delivery vs. term delivery) and various clinical parameters was analyzed in Table 3. There was no significant difference in any of the parameters between the two groups ($P > 0.05$).

### Adverse events arising from the cerclage

Among the subjects who underwent cerclage, there were 2 cases of intra-operative bleeding of more than 100 ml (0.8%), 1 case of perforation of uterus (0.4%), with no case of bladder or ureteric injury, wound or urinary tract infection, inadvertent placement of suture through the cervical canal, adverse reaction to antibiotic therapy and none required conversion to laparotomy.

## Discussion

This retrospective cohort study aimed to investigate the prevalence of chronic endometritis (CE) among women with cervical incompetence (CI) as a main contributor for mid-trimester loss. We have found that women (group I, 42.0%) with mid-trimester loss associated with cervical incompetence (CI) appeared to have an increased prevalence of CE compared to women (group II, 23.5%) with recurrent early miscarriage but without second trimester loss. Some studies [18, 19] reported that CE was associated with unexplained recurrent first trimester miscarriage, but our study suggests that the association appeared to be even stronger with mid-trimester loss due to CI than recurrent early miscarriage. Monsanto et al. [20] concluded that cervical insufficiency was associated with local inflammation in cervicovaginal fluid.

However, it is uncertain if the association between CE and spontaneous mid-trimester loss due to CI is casual or causal. It is uncertain if pre-existing CE, which is often asymptomatic, may lead to sub-clinical increase in uterine activity in the second trimester which over time causes the cervix to shorten and open up. On the other hand, it is possible that the eventual presentation of CI depends on whether or not there is coexistence of CE. In our study, the prevalence of CE in women presented with an atypical

**Table 3** A comparison of the demographic and clinical details between women who had (1) mid-trimester loss or preterm delivery and (2) term delivery

| | Mid-trimester loss or preterm delivery ($n = 26$) | Term delivery ($n = 175$) | $P$ value |
|---|---|---|---|
| Age*, (year) | 33 (21–43) | 32 (23–42) | 0.524 |
| BMI*, (kg/m$^2$) | 23.4 (18.4–37.8) | 22.7 (18.7–38.5) | 0.438 |
| Parity, $n =$ | | | |
| 0 | 26 | 157 | 0.137 |
| ≥ 1 | 0 | 18 | |
| Previous mid-trimester loss, $n =$ | | | |
| 1 | 5 | 37 | 0.823 |
| ≥ 2 | 21 | 138 | |
| Previous first trimester loss, $n =$ | | | |
| 1 | 23 | 162 | 0.441 |
| ≥ 2 | 3 | 13 | |
| Cervical incompetence type | | | |
| Typical | 16 | 113 | 0.763 |
| Atypical | 10 | 62 | |
| CE type | | | |
| Negative | 13 | 96 | 0.643 |
| Positive | 13 | 79 | |
| Treatment with CE | | | |
| No | 8 | 41 | 0.519 |
| Yes | 5 | 38 | |

*Median (range in brackets); CE, Chronic endometritis

history of CI (50.5%) was significantly higher than that of women presented with a classical history of CI (37.9%). This indicates women with a typical history of CI (painless dilatation of cervix) is less likely to have coexisting CE compared to women with an atypical history.

In women with CI, there may be asymptomatic dilatation of the cervix for some time before the women presented with bulging membranes and expulsion of the fetus (typical cases). During the latent phase of cervical dilatation, however, secondary ascending infection may occur, leading to a variable degree of uterine contraction. In this situation, the presentation may be somewhat atypical, including uterine tightening, backache and rarely strong uterine contractions and ruptured membranes. Following ruptured membranes, the pressure of the fore-water on the cervix is reduced, the degree of cervical dilatation may regress, and cervical dilatation may no longer be as obvious after the membranes have ruptured. The presentation of CI is therefore dependent on the coexistence of any secondary infection. It may also explain why sometimes histopathological examination of the placenta in genuine cases of CI showed evidence of chorion-amnionitis, and why the presence of the latter should not be used as evidence against a diagnosis of CI. It is important to appreciate that the two contributory factors for mid-trimester loss, namely CI and infection, may coexist and together influence the presentation.

In an earlier study, antibiotic therapy in women with chronic endometritis was reported to increase clinical pregnancy rate and live birth rate [12]. In our cohort study, we observed that the term delivery rate of women who did not receive antibiotic therapy for CE (83.7%) was slightly lower but not significantly different to those who did receive antibiotic therapy (88.4%). Nevertheless, the observation should be considered preliminary for a number of reasons, namely, the sample size was not sufficiently powered to address the impact of antibiotic therapy, the retrospective nature of the study makes it more prone to bias and there are confounding variables including the possibility that some subjects may have received prophylactic antibiotic therapy around the time of cerclage or additional courses of antibiotic as guided by the result of high vaginal swab which are more often performed in this group of women.

A limitation of our study was the retrospective nature of the study and the inclusion of various subsets of population; our observation should be used to guide the planning of a prospective study with defined subsets of women with mid-trimester loss to confirm the findings.

The relationship between alteration of cervical microbiome and recurrent miscarriage or preterm labor has recently been examined [21, 22]. In this study, we have examined the relationship between mid-trimester loss and CE based on histological evaluation of the endometrium. However, molecular microbiological study of the genital tract and maternal–fetal interface, a rapidly developing area, may throw further light on the relationship between mid-trimester loss, altered microbiome and specific viral infection such as Covid-19. Our observations lend support to the need to conduct future studies on the relationship between microbiome in endometrial cavity and mid-trimester loss and preterm labor. It remains to be seen if microbiome or its alteration in the endometrial cavity plays an important role in mid-trimester loss and preterm labor.

The current study highlighted that CE should be added to the list of factors including genetic, structural (uterus and cervix), infection and environmental (such as tobacco) which ought to be considered in women at risk of mid-trimester loss or preterm delivery.

## Conclusion

The prevalence of CE in women with mid-trimester loss associated to CI was significantly higher than that of women presented with recurrent first-trimester loss. Women with a typical history of CI (painless dilatation of cervix) is less likely to have coexisting CE compared to women with an atypical history. However, the presence or not of CE and whether it was treated with antibiotics prior to conception did not appear to significantly influence the obstetric outcomes of women with CI after LCC.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00404-021-06029-3.

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**Author contributions** JL Project development, Data collection, Data analyses, Manuscript writing. DS: Project development, Data collection. XF: Data collection, Laboratory supervision. XH: Clinical supervision, manuscript revision. EX: Clinical supervision. TCL: Project development, Data analyses, Manuscript writing.

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## Declarations

**Conflict of interest** The authors declare that they have no conflicts of interest and nothing to disclose.

**Ethics approval** Ethics approval from Fu Xing Hospital, Capital Medical University IRB (Approval Notice Number: 2015FXHEC-KY005) was obtained in April 2015.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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