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Clinical evidence of positive correlation between intrauterine adhesions and chronic endometritis: a retrospective study

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Abstract. – OBJECTIVE: This study aimed to analyze the potential correlation between chronic endometritis (CE) and intrauterine adhesions (IUA) with its associated risk factors.

PATIENTS AND METHODS: We retrospectively analyzed data from 131 patients who underwent hysteroscopic transcervical resection of adhesions (TCRA) for intrauterine adhesions at our hospital between February 2020 and February 2021. General clinical data were collected and analyzed using univariate, multifactorial, and logistic regression analyses. Patients with mild, moderate, and severe IUA were divided into two groups based on whether they coincided with CE (CE group) or not (NCE group). Logistic regression analysis of the factors associated with IUA was performed and the recurrence rates of IUA after TCRA in the CE and NCE groups were registered.

RESULTS: The risk of severe IUA was higher in patients with a higher number of abortions, higher number of indolent abortions, and CD138 positivity. In addition, the incidence of IUA combined with chronic CE varied when comparing the different IUA stages: 10.70% (3/28) for patients with mild IUA, 25.00% (7/28) for patients with moderate IUA, and 64.30% (18/28) for patients with severe IUA. The recurrence rates of IUA after TCRA in the CE and NCE groups were 69.20% (9/26) and 30.08% (4/67), respectively, in patients with moderate to severe IUA, and the differences were statistically significant (χ^2=12.782, p=0.001).

CONCLUSIONS: A correlation was observed between CE and IUA. Patients presenting both conditions had more severe IUA stage and higher recurrence rates after TCRA.

Key Words:
Intrauterine adhesions, Chronic endometritis, Miscarriage, Retrospective study, Transcervical resection of adhesions.

Introduction

Intrauterine adhesions (IUA), also known as Asherman's syndrome, are defined as a complete or partial damage to the basal layer of the endometrium due to trauma and infection, resulting in fibrous adhesions in the uterine cavity and/or the cervix. IUA can cause clinical symptoms such as decreased menstrual flow, amenorrhea, cyclic lower abdominal pain, recurrent miscarriage, and secondary infertility[1,2]. The pathogenesis of IUA is unclear. However, researchers[3] believe that IUA is related to the damage to the endometrial basal layer and impaired endometrial repair. Chronic endometritis (CE) is a persistent inflammatory disease of the endometrium caused by various pathogens. It can be histologically manifested as endometrial surface edema, high stromal cell density, asynchronous epithelial and mesenchymal maturation, and endometrial interstitial plasma cell infiltration[4]. Studies[5-7] show high incidence of CE in patients with abnormal uterine bleeding[5], endometrial hyperplasia[6], and IUA[7], suggesting its potential role in the development of these diseases. Since CE is caused by inflammatory stimulation of endometrium by various pathogens, it is plausible that this may lead to damage to the basal layer of the endometrium, resulting in the occurrence of IUA. Therefore, a correlation between these conditions is expected. However, there are still few studies on the staging and prognostic association of CE with IUA.

Syndecan-1 (CD138) is a multiligand glycan that is specifically expressed in plasma cells and is used as a marker in diagnostics of CE[8,9].

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The purpose of this study was to investigate the correlation between CE and IUA, using CD138 expression levels in the endometrium of patients with different degrees of cavity adhesions, and to provide new insights into preventing and treating IUA and improving fertility in women of reproductive age.

Patients and Methods

Patient Information and Data Collection

Data were collected from patients with IUA who underwent hysteroscopic transcervical resection of adhesions (TCRA) in our hospital from February 2020 to February 2021. Patients were divided into three groups according to the IUA stage: mild, moderate, and severe uterine adhesions. All participants voluntarily participated in the study and signed a consent form. The study was approved by the Ethics Committee of Fujian Maternity and Child Health Hospital (No. 2020KY142).

The inclusion criteria were as follows: (1) hysteroscopic findings consistent with the diagnostic criteria for IUA; (2) collection of endothelia during the TCRA and related pathological immunohistochemistry were performed; (3) hysteroscopic examination revealing no uterine anomalies such as longitudinal uterus, bicornuate uterus, and saddle-shaped uterus; and (4) no other medical or surgical diseases.

The exclusion criteria were as follows: (1) hysteroscopy results not meeting the diagnostic criteria for IUA; (2) hysteroscopy revealing uterine anomalies such as longitudinal uterus, bicornuate uterus, and saddle-shaped uterus; (3) adverse reactions or complications during the treatment; and (4) incomplete clinical information, affecting the determination of efficacy or safety.

TCRA Procedure and Follow-Up

TCRA procedure was performed in patients with amenorrhea, reduced menstrual flow, or no change in menstrual flow for 3-7 days after the end of the menstruation. The patients were advised to abstain from sexual intercourse from the last menstrual period to the day of surgery to prevent infection.

For the procedure, the patients were routinely disinfected. The procedure was performed with the patient in a bladder lithotomy position and the depth of the uterine cavity was explored. The cervix was dilated to a size of 7-7.5 using a Hagar cervical dilator (Shanghai Medical Equipment (Group) Co., Ltd. Surgical Equipment Factory, Hongkou District, Shanghai, China). A hysteroscope (Carl Storrs Endoscopy GmbH, Berlin, Germany) was placed to observe the whole uterine cavity and to clarify the nature, location, extent, and stage of endometrial adhesions. Micro-scissors were used to cut away the adhesions. Standard saline solution injection (0.9% sodium chloride) (Sinopharm Chemical Reagent Co., Ltd, Shanghai, China) was used as the distention medium, and the dilatation pressure was 20-21 mmHg. A Foley balloon was placed intraoperatively to prevent re-adhesion in cases of moderate and severe adhesions.

Cefmetazole (1.0 g) was administered within 24 h after the surgery to prevent infection. The Foley balloon was removed 1 week after the TCRA. CE was diagnosed by immunohistochemistry as described below, and treated with oral doxycycline (100 mg, twice daily for 14 d). After the surgery, endometrial regeneration was promoted by sequential estrogen and progesterone cycles for 1-3 months, considering the grade and type of adhesions seen intraoperatively and the nature of the scar. Estradiol valerate (2 mg, twice daily) was administered orally from day 2 of the first cycle until the 25th day of menstruation, followed by progesterone capsules (100 mg, twice daily) for the next 10 days. Femoston was administered orally from day 5 of the second and third cycles (two oral estradiol tablets once daily for the first 14 days, and two oral estradiol-digestrol combination tablets once daily for the next 14 days). After a full course of cycled treatment, another hysteroscopy was performed to observe whether the uterine cavity had improved.

The hysteroscopy was repeated within 3-7 days after the menstruation to assess the recovery of the uterine cavity and to determine the efficacy of the treatment. A normal cavity morphology and endometrium without adhesions were categorized as cured. A significantly larger than before uterine cavity with some local adhesions still present was considered an effective treatment. No change in the uterine cavity or further size reduction was categorized as ineffective treatment.

Diagnostic Criteria of IUA and CE

IUAs were graded based on the American Fertility Society Uterine Adhesion Scale (1988)[10]. Cumulative scoring of items was used to define IUA grade: a score of 1-4 was defined as mild

IUA, 5-8 as moderate, and 9-12 as severe. Hysterical adhesions remaining after the post-operative hysteroscopy evaluation were considered a recurrence.

CE was diagnosed using immunohistochemistry. Immunohistochemical staining was performed using a transmembrane acetyl heparan sulfate proteoglycan (CD138) as a specific marker for plasma cells. Pathological specimens were fixed and subsequently paraffin embedded and cut into 4-μm sections (Wuhan Service Biotechnology Co., Ltd, Wuhan, Hubei, China). All chemicals and reagents were purchased from Sinopharm Chemical Reagent Company Limited, Shanghai, China, unless specified otherwise. For immunohistochemical staining, the sections were incubated at 65°C for 45 min in an electric blast box, and permeabilized using xylene I and II for 15 min each, tapered ethanol (anhydrous, 95% and 75%) for 5 min each, and rinsed with water for 3 min. The sections were incubated with ethylene diamine tetra acetic acid (EDTA) antigen retrieval solution (Shanghai Jiehao Biotechnology Company Limited, Shanghai, China) at 95°C for 20 min and cooled at room temperature. Next, sections were washed with phosphate buffered saline (PBS) and incubated at room temperature for another 30 min with 5% sheep serum (Jiehao Biotechnology Co., Ltd, Shanghai, China). Tissues were incubated overnight in the primary CD138 antibody (Fuzhou Maxim Biotechnology Development Co Ltd, Gulou District, Fuzhou, China) diluted in PBS (1:20), at 4°C. The following day, the sections were rewarmed at room temperature for 30 min and incubated with the secondary antibody (Shanghai Jiehao Biotechnology Company Limited, Shanghai, China) at 37°C for 30 min. Section were incubated in the 3,3'-Diaminobenzidine (DAB) chromogen solution and observed under the microscope for 2-3 min until the development of specific staining. The reaction was terminated by washing in PBS. Hematoxylin and eosin staining was performed for 5-15 s, and the sections were rinsed in running water for 15 min. The samples were subsequently dried and sealed. The pathological criteria for a CE diagnosis were defined as >10 CD138. Specific labeled plasma cells per field were visualized at x20 magnification using digital optical microscope (Leica Instruments GmbH, Wetzlar, Germany). Patients with mild, moderate, and severe IUA were divided into two groups based on whether IUA coincided with CE (CE group) or not (NCE group).

Statistical Analysis

Statistical analysis of the data was performed using SPSS (version 26.0, IBM Corp., Armonk, NY, USA). Test for normality of the data was performed. The mean ± standard deviation was used to describe the measures, the Fisher's least significant difference method was used for two-way comparisons, and the Chi-square test was used for rate comparisons. Count data were described as frequencies (percentage, %) and analyzed using Chi-square analysis. $p<0.05$ was considered statistically significant.

Results

A total of 131 patients were included and divided into three groups according to the stage of uterine adhesions: 38 cases were mild, 58 cases were moderate, and 35 cases were severe. There were 28 cases of concurrent CE (CE group) and 103 not presenting CE (NCE group).

We conducted a comparative analysis considering age, weight, body mass index (BMI), number of previous abortions, and number of induced abortions in patients with different stages of IUA. As shown in Table I, age, weight, and BMI values were not significantly associated with IUA ($p>0.05$), while the number of abortions and the number of missed abortions showed significant relationships ($p=0.001$). Immunohistochemical analysis showed that patients with severe IUA showed a higher percentage of CD138 positivity compared to those with mild and moderate IUA ($p=0.001$) (Table I).

A logistic regression analysis of the factors associated with IUA showed a balanced frequency distribution of the IUA stages (Table II). A parallelism test for each of the factors associated with uterine adhesions showed a p-value greater than 0.05, indicating that the factors passed the parallelism test, as shown in Table III. A covariance test was also performed for each of the factors associated with uterine adhesions, with the variance coefficient inflation factor variance inflation factor (VIF) as the statistic, all of which were below 10, indicating no covariance between the factors, as shown in Table IV. The combined analysis showed that the higher number of abortions and the higher number of missed abortions were associated with the higher risk of severe IUA ($p=0.000$). The risk of severe IUA was significantly higher in the CD138-positive population of patients ($p=0.023$) (Table V).

Table I. Single-factor analysis of intrauterine adhesions (IUA).

Index	IUA stage			F/χ^2/H	*p*-value
	Mild (n = 38)	Moderate (n = 58)	Severe (n = 35)		
Age (years)	31.21 ± 4.36	31.26 ± 4.37	31.34 ± 4.51	0.008	0.992
Weight (kg)	57.32 ± 8.05	56.6 ± 10.41	54.38 ± 5.53	1.149	0.320
BMI (kg/m^2)	22.49 ± 3.17	22.16 ± 3.87	22.20 ± 1.85	0.130	0.878
CD138					
(-)	35	51	17	31.049	0.001*
	34.00%	49.50%	16.50%		
(+)	3	7	18	25.909	0.001*
	10.70%	25.00%	64.30%		
Number of abortions	0 (0, 1)	1 (0, 2)	2 (0, 5)	26.851	0.001*
Number of missed abortions	0 (0, 1)	1 (0, 1)	2 (1, 3)	26.851	0.001*

BMI: body mass index; *Significance level was set at $p < 0.05$.

Table II. Frequency distribution of intrauterine adhesions (IUA) stages.

	Categories	Frequency	Percentage (%)
IUA stage	Mild	38	29.0
	Moderate	58	44.3
	Severe	35	26.7

To analyze whether CE affects the severity of uterine adhesions, we compared the incidence of CE (CD138 positivity) in patients with the different IUA grades. Immunohistochemical analysis showed that CE was present in 10.70% (3/28) of patients with mild IUA, 25.00% (7/28) of patients with moderate IUA, and in 64.30% (18/28) of patients with severe IUA (p=0001). Together, these results indicate that the CD138-positivity was associated with more severe IUA (Table VI).

The recurrence rates of IUA after TCRA in the CE and NCE groups in patients with moderate-to-severe IUA were 69.20% (9/26) and 30.08% (4/67), respectively. The differences were statistically significant (χ^2=12.782, p=0.001) (Table VII).

Discussion

In this study, we examined the expression of CD138 in the endometrium of patients with different degrees of cavity adhesions and its association with the recurrence rate of cavity adhesions after surgery. Our study shows that miscarriage and chronic endometriosis (CE) were significantly associated with the formation of intrauterine adhesions (IUA). We found that the severity of IUA correlated with concurrent CE and that IUA recurrence was higher in patients with CE who underwent TCRA. The results of our study may provide new indicators for predicting recurrence of cavity adhesions and new directions for their treatment.

CE is defined as persistent inflammation of the endometrium caused by infection, resulting in its structural and functional disruption. Studies[11-14] show that CE is highly prevalent in infertile women with repeated failure in embryo transfer[10], and its diagnosis and treatment can improve pregnancy and birth rates[12-14]. Intrauterine adhesions are also associated with infertility and recurrent miscarriages. Since both IUA and CE are characterized by the formation of endometrial lesions, there may be a plausible correlation between these conditions.

In this study, we found that the CD138-positive group of patients had more severe uterine adhesions, which is consistent with the higher percentage of CE in patients with uterine adhesions reported in the literature[7]. Severity of the degree of uterine adhesions correlated with the extent

Table III. Multivariants associated with intrauterine adhesions (IUA) tested for parallelism.

Models	-2 log likelihood	Chi-square	Degrees of freedom	*p*-value
Original hypothesis	89.499			
General	84.223	5.277	4	0.26

Table IV. Collinearity tested for the multivariants associated with intrauterine adhesions (IUA).

Variables	Co-linear statistics	
	Tolerances	VIF
Number of abortions	0.897	1.115
Number of missed abortions	0.921	1.085
CD138 (+)	0.405	2.471

VIF: variance inflation factor.

of the surgery-related damage to the uterus and the increased risk of infection. Subsequently, the elevated risk of infection may lead to increased probability of developing CE after the operation, as indicated by their positive CD138 status. CD138 was highly expressed in the endometrium of patients with uterine adhesions and there may be a relationship between the difference in its expression and the recurrence of uterine adhesions. Higher degree of cavity adhesions correlated with the worse recovery of cavity morphology ($p<0.05$), suggesting that CD138 may be used to predict recurrence of cavity adhesions.

Our study demonstrated that the number of abortions and missed abortions increased along with the IUA stage: higher number of abortions and retained abortions correlated with the higher risk of severe IUA. Currently, tissue trauma is recognized as the main cause of IUA. Repeated and multiple surgical operations of the uterus, such as abortion and hysteroscopic operations[15], can cause associated mechanical injury. Most IUA cases occur after pregnancy-related curettage. Excessive curettage tends to cause damage

Table V. Summary of results of multifactor ordered logistic regression analysis of intrauterine adhesions (IUA).

	β	SE	Wald	OR	95% confidence interval of OR		p-value
					Lower limit	Upper limit	
Moderate	-2.201	0.677	10.575		0.029	0.417	0.001*
Severe	1.417	0.636	4.965		1.186	14.339	0.026
Number of abortions	1.181	0.239	24.387	3.258	2.038	5.202	0.000*
Number of missed abortions	1.104	0.260	18.054	3.016	1.813	5.018	0.000*
CD138 (+)	1.325	0.583	5.163	3.762	1.200	11.787	0.023
McFadden R-squared: 0.217							
Cox and Snell R-squared: 0.231							
Negelkerke R-squared: 0.176							

OR: Odds Ratio; *Significance level was set at $p < 0.05$.

Table VI. Comparison of incidence of chronic endometritis (CE) in patients with different intrauterine adhesions (IUA) stages.

	IUA stage			F/χ^2/H	p-value
	Mild	Moderate	Severe		
CD138 (+)	3 (10.70%)	7 (25.00%)	18 (64.30%)	25.909	0.001*
CD138 (-)	35 (34.00%)	51 (49.50%)	17 (16.50%)		

*Significance level was set at $p < 0.05$.

Table VII. Comparison of intrauterine adhesions (IUA) recurrence rate after TCRA between patients with (CE group) or without (NCE group) moderate and severe IUA presenting chronic endometritis.

		NCE Group	CE Group	χ^2	p-value
Recurrence	No. recurrence	63	17	12.782	0.001
		78.80%	21.30%		
	Recurrence	4	9		
		30.80%	69.20%		

to the basal layer of the endometrium, preventing the formation of new blood vessels and resulting in the inability of the endometrium to regenerate and repair, eventually forming adhesions. IUA can be a severe complication of residual products of conception, often occurring in women undergoing postpartum curettage. Missed abortion is a particular type of spontaneous abortion caused by the tight adhesion of the fetal or/and placental tissue to the uterine wall after the spontaneous loss of pregnancy, pregnancy termination or preterm delivery.

We showed that the recurrence rate of re-adhesion after TCRA was 69.2% (9/26) and 30.8% (4/67) in the CE and non-CE groups, respectively, in patients with moderate-to-severe IUA. These results are consistent with those reported by Chen et al[7], suggesting that CE may affect the endometrial repair after the TCRA and increase the recurrence rate of post-TCRA adhesions. CE aggravates the degree of IUA, and consequently increases the recurrence rate after TCRA. Immune response plays an essential role in spontaneous abortion and IUA[16,17]. The endometrium has immunomodulatory activity, providing protection against foreign bacterial invasion, and at the same time, maintaining immune tolerance or protective immunosuppression to allow implantation and embryo development. Immune imbalance leads to activization of immune and mesenchymal cells that subsequently secrete a variety of cytokines, such as interleukin-2, -3, -4, growth factor-α and -β, and interferon-γ. These cytokines participate in the inflammatory response and promote the accumulation of large amounts of extracellular matrix (ECM) in the endometrium, leading to the production of connective tissue and its gradual replacement by endometrial tissue, eventually leading to endometrial fibrosis and the formation of IUA[17].

Our results show the correlation between CE and IUA in terms of promoting fibrous tissue formation and affecting endometrial repair. Recently, a prospective cohort study found that transforming growth factor-β1 (TGF-β1) was significantly higher in patients with CE when compared to those without the condition[18]. TGF-β1 is crucial for ECM deposition and can be related to the development of fibrosis[19]. These results suggested that CE increases the risk of fibrosis in the endometrium *via* TGF-β1-induced increased inflammation. Additionally, CE patients also demonstrated a significant decrease in the expression levels of gelatinase matrix metalloproteinase-9 (MMP-9), an antifibrotic marker that degrades ECM, reduces fibrin deposition, and plays an important role in endometrial repair and reconstruction, including IUA formation[20].

Limitations

Our study has some limitations. Patients with a history of miscarriages, included in our study, may also have a history of abortion or other uterine operations. Hormone cycle therapy after TCRA in our study ranged from 1 to 3 months, introducing variation in the timing of the second postoperative hysteroscopy, which may influence the comparison of IUA recurrence rates. Further experimental studies and randomized controlled trials are needed to verify our findings.

Conclusions

In conclusion, miscarriage and CE are high-risk factors significantly correlated to IUA formation. We found that the degree of IUA tended to be more severe with concurrent CE and that IUA recurrence was higher in patients with CE who underwent TCRA. CE promotes the formation of IUA as well as recurrence. TCRA surgery requires attention to the diagnosis and treatment of CE. Based on the results of our study, we recommend performing endometrial testing of the CD138 expression simultaneously with the surgical treatment of IUA. Additionally, postoperative anti-infection treatment should be actively administered to prevent the recurrence of uterine adhesions.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' Contribution

Conception and design: ZW and XX. Administrative support: XX. Provision of study materials or patients: ZW and MW. Collection and assembly of data: ZW and MW. Data analysis and interpretation: ZW, MW and XX. Manuscript writing: ZW and MW. Final approval of manuscript: All authors.

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Data Availability
Data will be provided upon request to the authors.

Ethics Approval
The study was approved by the Ethics Committee of Fujian Maternity and Child Health Hospital (No. 2020KY142).

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