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Original Article

Chronic Endometritis in Cases with Cesarean Section Scar Defect

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ABSTRACT

Background: The appearance of unhealed cesarean section scar defect (CSD) has brought extensive attention in the last two decades. This study aimed to assess the relation between chronic endometritis and CSD. **Methods:** This study was performed on a total of sixty women who have a CSD diagnosed either by transvaginal ultrasound (TVUS) or accidentally during hysteroscopy. minute biopsies were taken from the site of the cesarean section (CS) niche and other uterine walls if it was possible. Further, histopathological examination was done, and the diagnosis of chronic endometritis was confirmed when at least one plasma cell was detected in the endometrial biopsy. **Results**: fifteen percent of the patients showed chronic endometritis by histopathology, while (85%) of the patients had normal histopathology. There was a statistically significant difference between histopathological findings and symptoms of CSD among studied patients, as (66.7%) of the patients who had chronic endometritis on histopathology had infertility compared to (23.5%) of patients with normal histopathology. As regards pelvic inflammatory disease, (66.7%) of the patients who had chronic endometritis had Pelvic inflammatory disease (PID) compared to (33.3%) of patients with normal histopathology. **Conclusions**: cesarean section scar defect may be associated with the development of chronic endometritis and may be the cause of CSDs such as infertility and PID
Keywords: Endometritis; Cesarean section scar defect; hysteroscopy.

INTRODUCTION

The prevalence of cesarean sections has been consistently increasing in recent decades. In the United States, the rate escalated from 21.1% to 32.8% between 1990 and 2011. A similar worrisome trend has been observed in Egypt, where there has been a continuous rise in cesarean deliveries. This upward trajectory is associated with the growing utilization of private healthcare facilities for childbirth**. [1].**

Unresolved cesarean section scar defects (CSD) have garnered significant interest in recent decades. The term CSD is utilized to encompass any irregularities marked by a gap in the myometrium, indicating a breach at the location of a previous cesarean section exceeding 2 mm, according to Delphi criteria **[2]** in TVUS examination and/or as a pouch at the anterior uterine wall at the site of the CS incision using hysteroscopy**.** Endometritis is characterized by an infection or inflammation of the endometrium. It is commonly understood that the typical endometrium is free from microorganisms; however, bacteria from the cervix and vagina can migrate upwards, causing inflammation and infection of the endometrium. Additionally, chronic endometritis is often a subtle condition identified during investigations for secondary amenorrhea and infertility **[3].** It has been stated that patients delivered by CS, especially those who had CSD, were associated with endometrial changes especially chronic endometritis when compared to patients delivered vaginally **[4].**

It has been proposed that there is an association between CSD and endometritis, as pathological alterations were observed in the vicinity of the CSD using a paraffin block extracted from a collection of hysterectomy samples. These alterations consisted of an excess of congested endometrium, a moderate to significant presence of lymphocytes infiltrating the area, the presence of free red blood cells in the scar's endometrial stroma, and iatrogenic adenomyosis limited to the scar **[4].**

So, this study aimed to assess the relationship between chronic endometritis and cesarean section scar defect.

METHODS

All the study details were explained to patients then they signed an informed written consent before inclusion in the study. The research was accepted by the Institutional Review Board of the Faculty of Medicine-Zagazig University (ZUIRB: 10656-4-4-2023). The study was done according to the Code of Ethics of the World Medical Association (Declaration Helsinki) for Studies involving humans. This cross-section study was conducted at the endoscopy and infertility unit, obstetrics and gynecology department at Zagazig University Hospitals from April 2023 to January 2024 and performed on a total of ٦٠women who enrolled for operative hysteroscopy and had CSD diagnosed either by TVUS (an indentation more than 2 mm at the site of the CS scar) **[2]** or accidentally discovered during hysteroscopy (a pouch seen at the site of CS scar). patients who received any antibiotics within one month before the procedure, those with uterine cavity abnormalities such as sub mucous fibroid, endometrial polyps, or uterine adhesions, patients with pelvic inflammatory disease (PID), and patients with chronic diseases such as diabetes mellitus or systemic lupus erythematous were excluded from the study.

All women were subjected to the following: History taking, Clinical examination, and preoperative investigations. A transvaginal ultrasound was done a couple of days before the hysteroscopy. Operative hysteroscopy was conducted "during the follicular phase of the menstrual cycle ”under general anesthesia, using saline (NaCl 0.9%) as a distension medium. An experienced endoscopic surgeon performed the hysteroscopic procedures. The panoramic view of the whole cavity was used to explore any cavitary lesion then special attention was given to the site of the CS scar. Further, a 3mm grasper was used to obtain minute biopsies from CSD mainly and from other uterine walls if possible then sent in formaldehyde solution10% for histopathological examination (HPE). These sections were stained with standard histological stains like Hematoxylin and Eosin (H&E) according **to Bancroft et al. [5]** for general histological structure visualization.

The uterine tissue was immersed in 10% normal saline and fixed for 48 hours. The saline solution was made a day in advance to ensure formaldehyde polymers were depolymerized adequately. The samples underwent dehydration using increasing concentrations of alcohol (50%, 70%, 90%, and 95%) for one hour each, followed by two changes of absolute alcohol (100%) for one hour each. Subsequently, they were cleared in xylene for two hours. Subsequently, the samples were embedded in soft paraffin wax at 55 ºC for two hours, followed by hard paraffin at 60ºC for an additional two hours. Sections of 5 mm thickness were then obtained and subjected to xylene clearing for 5 minutes, followed by rehydration in decreasing concentrations of alcohol (100%, 90%, 70%, 50%) for 3 minutes each. The sections were stained with Hematoxylin for 5 minutes and rinsed in running tap water for 3 minutes until a blue color appeared. Subsequently, the sections were stained with Eosin for 10 minutes, rinsed in running tap water for 3 minutes, dehydrated using increasing concentrations of alcohol, cleared in xylene, and finally mounted in Distyrene Plasticizer Xylene (DPX). The diagnosis of chronic endometritis by histopathological examination is confirmed by the presence of at least one plasma cell or more seen by (high power field) through endometrial biopsy **[6]**.

STATISTICAL ANALYSIS

The data obtained was coded, organized, and subjected to statistical analysis using IBM SPSS Statistics software version 22.0 by IBM Corp. in Chicago, USA, 2013, along with Microsoft Office Excel 2007. Descriptive statistics were utilized to present quantitative data, including the range (minimum and maximum values) and mean±SD (standard deviation) for normally distributed quantitative data. For qualitative data, descriptive statistics included counts and percentages. Inferential analyses for quantitative variables involved normality testing using the Shapiro-Wilk test and the independent t-test for comparisons between two independent groups with normally distributed data. In the case of qualitative data, inferential analyses for independent variables were conducted using the Chi-square test to assess differences in proportions and Fisher’s Exact test for variables with small, expected numbers. The significance level was set at a P value < 0.050 to indicate statistical significance; otherwise, the results were considered non-significant.

RESULTS

This is a cross-sectional study including sixty-five patients. Five cases were excluded as their biopsies showed only fibrous tissue in HPE. Fifteen percent of patients showed chronic endometritis (CE) in histopathological examination **Figure (1).** There was no significant difference between histopathological findings and demographic and personal history as shown in **Table (1)**. There was a statistically significant

difference between histopathological findings and the number of cesarean sections, as most of the patients who had normal histopathology (62.7%) had only one cesarean section as shown in **Table (2)**. Moreover, there was a statistically significant difference between histopathological findings and symptoms of CSD, as (66.7%) of the patients who had chronic endometritis **Figure (2)** had infertility in comparison to (23.5%) of patients with normal histopathology **Table (3).** As regards pelvic inflammatory disease, (66.7%) of the patients who had chronic endometritis had PID in comparison to (33.3%) of patients with normal histopathology while there was no significant difference between those with chronic endometritis and those without as regards postmenstrual spotting as presented in **Table (3).**

Table (1): Demographic and personal history among studied patients

Variables *(N. %)*	**All patients (n=60)**
Age *(years)*	
Mean* ± *SD.	**31 ± 6.6**
Range	**(20 – 42)**
Age groups *(N.%)*	
20 – 30 years	**23 (38.3%)**
30 – 40 years	**28 (46.7%)**
>40 years	**9 (15%)**
Post menstrual spotting	**19 (31.7%)**
Infertility	**18 (30%)**
Mild PID	**23 (38.3%)**

Table (2): Comparison of histopathological findings as regard personal history

Variables *(N.%)*	**Absent (n=51)**	**Present (n=9)**	**P value**
Number of cesarian sections			
One	**32 (62.7%)**	**2 (22.2%)**	
Two	**12 (23.5%)**	**3 (33.3%)**	**0.02**
Three	**7 (13.7%)**	**3 (33.3%)**	
Four	**0 (0%)**	**1 (11.1%)**	

Table (3): Comparison of histopathological findings as regard symptoms of cesarian scar niche

Variables *(N.%)*	**Absent (n=51)**	**Present (n=9)**	**P value**
Post menstrual spotting	**16 (31.4%)**	**3 (33.3%)**	**0.91**
Infertility	**12 (23.5%)**	**6 (66.7%)**	**0.01**
PID	**17 (33.3%)**	**6 (66.7%)**	**0.01**

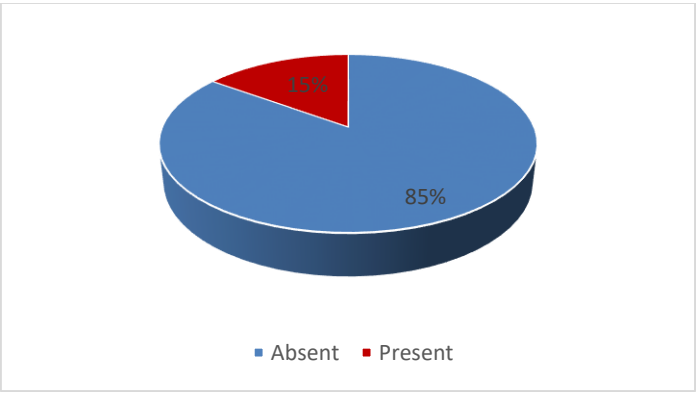

Figure (1): Histopathological findings among studied patients

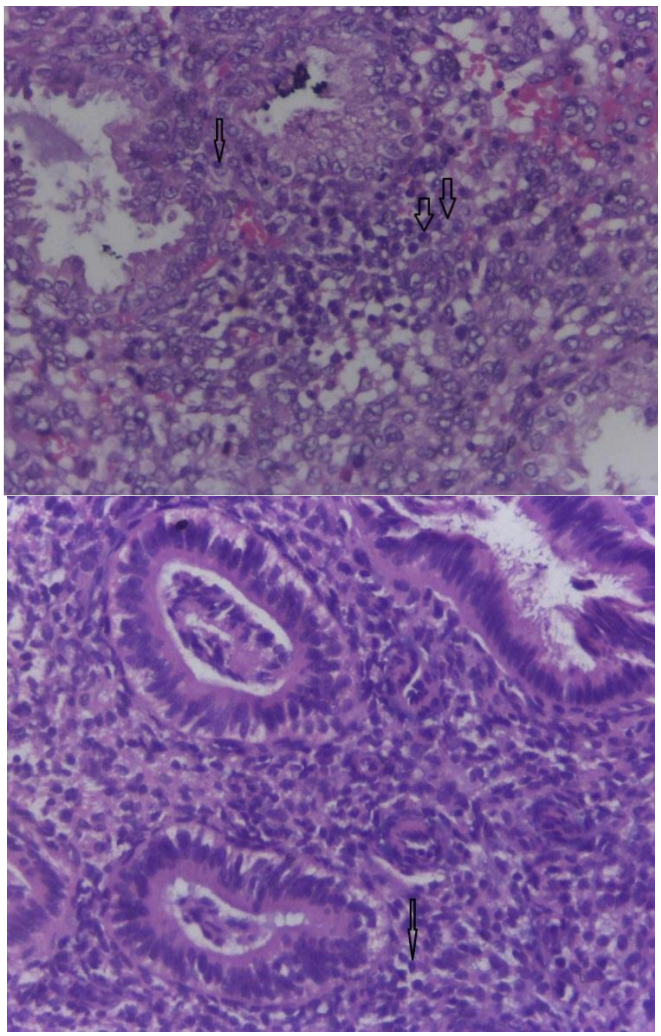

Figure (2): Endometritis: endometrial glands are surrounded by a mixed inflammatory infiltrate mainly formed of lymphocytes, eosinophils and plasma cells (marked by arrows). Hematoxylin and eosin stain magnification: original magnification x 400

DISCUSSION

Over the past ten years, increasing evidence has indicated that chronic endometritis (CE) is linked to infertility. While there is no universal agreement on how to diagnose CE, it is generally understood as a persistent inflammatory state characterized by the presence of plasma cells in the endometrium**.[7].** Since (CE) following cesarean section represents major conflict and is often associated with complications of infertility and menstrual irregularities, evaluating the role of having a cesarean scar defect in a person's susceptibility to (CE) was highlighted as a main point of interest **[8].**

Consequently, this study aimed to assess the relationship between (CE) and CSD. This cross-section study was conducted at Zagazig University Hospital from April 2023 to January 2024

Our data revealed that the mean age of the women was 31 ± 6.6 years, and the Body mass index (BMI) was 25.2 ± 2.3. The most frequent symptom was mild pelvic inflammatory disease found in (38.3%), followed by post-menstrual bleeding in (31.7%) of the patients, while the least frequent symptom was infertility in (30%) of the patients. We also reported that (CE) was confirmed in 15% of patients with CSD.

Regarding CSD symptoms, our study results reported a statistically significant difference between histopathological findings of (CE) and post-CS complications among studied patients, as (66.7%) of the patients with (CE) on histopathology had infertility and mild PID in comparison to 23.5% and 33.33% of patients with normal histopathology, respectively (p value=0.01), while there was no significant difference between the patients with or without (CE) as regards the bleeding p value=0.91).

To the best of our knowledge, there is a paucity of studies in literature correlating between (CE) and CSD, and that represents a strong point of our study.

This aligns with the findings presented in the study by **Xiang et al. [7],** where they carried out a retrospective analysis involving 118 patients with postmenstrual spotting as the primary symptom and 224 asymptomatic patients. The study aimed to investigate the association between cesarean section scar defect (CSD) and chronic endometritis (CE), particularly in cases presenting symptomatic CSD with postmenstrual spotting. The results indicated a higher prevalence of CE in group A (patients with postmenstrual spotting symptom) compared to group B (asymptomatic patients) (P=0.006).

Furthermore, these results align with the findings of Wei et al. [8], who conducted a retrospective study involving 331 patients with cesarean scar defects and 170 controls to investigate the association between CSD and chronic endometritis (CE). Their study revealed that the prevalence of CE in the CSD group was 28.8%. This suggests that the presence of CSD may elevate the likelihood of developing CE ($p = 0.003$). Even after adjusting for potential confounders such as age and BMI, logistic regression analysis indicated that CSD remained an independent risk factor for the prevalence of CE (OR, 1.571; 95% CI, 1.021–2.418; $p = 0.040$).

Consistent with our results, a retrospective study by **Nobuta et al. [9]** examined 201 patients, with 38 in the cesarean scar syndrome (CSS) group and 163 in the non-cesarean scar syndrome (non-CSS) group. Their research aimed to explore the influence of uterine cavity inflammation in women with cesarean scar syndrome on infertility. While there were no significant differences in age among the participants, a notable increase in the number of cesarean sections was observed in the CSS group compared to the non-CSS group ($p< 0.0001$). The prevalence of chronic endometritis (CE) in the CSS and non-CSS groups was 65.8% and 46.0%, respectively, with a significant difference in the occurrence of CE between the two groups ($p = 0.0315$).

The prevalence of CE ranges from 8% to 72% **[10]**. **Wei et al., [8]** reported that 28.8% of patients with CSD were identified with chronic endometritis (CE), indicating a relatively high occurrence. Additionally, the prevalence of CE in the control group was 20.54%. A study by **Nobuta et al.** revealed that 65.8% of patients with CSS were diagnosed with CE, showing a high occurrence. Furthermore, the frequency of CE in the non-CSS group was also notable. It was speculated that this correlation could be attributed to the patient selection criteria, as all women in these studies were experiencing infertility.

Chronic uterine cavity inflammation was detected in patients with cesarean section scar defects through the measurement of proinflammatory cytokines. A prior study indicated a significant increase in TNF-α levels in menstrual fluid from women with chronic endometritis**.[10]**. This finding is consistent with **Nobuta et al., [9]** who stated that the levels of inflammatory cytokines in the group with cesarean section scar defects were notably elevated compared to those in the control group, as determined through the measurement of TNF-α and IL-1β using ELISA.

Higuchi et al., [3] reported the presence of chronic inflammatory markers, such as CD138, in the CSD area. CD138 is the marker of plasma cells and is used for the diagnosis of (CE) **[10].** These findings strongly indicate the existence of chronic inflammation within the CSD region.

In instances of chronic endometritis, there is an elevation of proinflammatory cytokines like interleukin-6, interleukin-1β, and tumor necrosis factor α in menstrual discharge. These proinflammatory cytokines are believed to be contributing factors to infertility. The release of these cytokines could result in the buildup of fluid in the lower part of the uterus, hindering the chances of conception **[3].**

Moreover, we reported a statistically significant difference between histopathological findings and symptoms of CSD, as (66.7%) of the patients who had chronic endometritis had infertility. meanwhile, (66.7%) of the patients who had chronic endometritis had PID.

Consistent with our results, **Hsu et al**. conducted a retrospective analysis involving 363 women experiencing secondary infertility (172 with a prior cesarean section (CS) and 191 without) to explore bacterial presence at cesarean section scar defects in women dealing with secondary infertility. Their study uncovered that CSD was detected in 60.4% of women with a history of CS. A considerable proportion (60%) of women with a prior CS faced secondary infertility, partially attributed to issues stemming from CSD. Among women who had a previous cesarean section, bacterial colonies were detected in 89.6% of those with CSD and 69.8% of those without CSD. Consequently, most women with a history of cesarean section and secondary infertility had bacterial colonies present at the cesarean section scar. Gram-positive cocci, particularly Group B Streptococcus and Enterococcus species, were frequently identified (almost 90%), while Gram-negative rods like E. coli and Pseudomonas species were prevalent among isolates from CSD**. [4].**

According to findings from **Moreno et al., [11]** it was revealed that the endometrial cavity contains non-sterile microorganisms, and the presence of non-Lactobacillus-dominant bacteria in the uterine cavity can impact the outcomes of in vitro fertilization, as well as pregnancy and live birth rates. Additionally, the colonization of bacteria in cesarean section scar defects (CSD) and their potential release of harmful substances could be significant factors influencing the fertility of women with CSD.

Notable pathological alterations, such as deformation and enlargement of the lower uterine segment, congested endometrium, presence of polyps, infiltration of lymphocytes, remnants of suture material, dilation of capillaries, presence of free red blood cells, fragmentation, and deterioration of scarred endometrium, and iatrogenic adenomyosis, could all potentially hinder successful conception by acting as causative factors**. [12].**

Moreover, the occurrence of bacteria in the uterine cavities could account for typical complications following a cesarean section, such as abdominal discomfort, continuous vaginal discharge, and potentially long-term effects like higher risks during subsequent pregnancies**. [4].**

Glukhov and colleagues conducted a study that divided participants into Group A consisting of 26 patients with chronic endometritis (CE) and Group B comprising 24 patients without CE. The study aimed to investigate the influence of CE on the development of Cesarean section scar defect (CSD). Their findings indicated that the symptoms of CSD, such as dysmenorrhea, were present in 19.2% and 20.8% of patients in each group, respectively. Postmenstrual spotting was reported in 57.7% and 33.3% of patients, respectively, with a statistically significant difference ($p = 0.04$). The study also highlighted the impact of undiagnosed and untreated mild forms of postpartum endometritis on the progression to chronic endometritis, observed in 52% of patients, potentially contributing to the development of partial CSD. The notably high occurrence of chronic endometritis (52%) supports its potential involvement in the development of uterine scar weakness following Cesarean section [13].

However, research is still required to determine whether (CE) is the underlying cause or a consequence of (CSD), Numerous studies indicate that using standardized antibiotics can effectively eliminate chronic endometritis (CE) and enhance the reproductive outlook for patients **[8].**

This study's strengths lie in its cross-sectional study design and the absence of any patients lost to follow-up throughout the study duration. The research offers insights into the positive impact of hysteroscopy and endometrial biopsy on infertile women with (CSD).

The history of vaginitis and cervicitis was considered based on the patient's statements which may be unreliable and considered as a study limitation.

CONCLUSIONS

Based on current evidence, CSD may be associated with the development of post-cesarean section chronic endometritis and may result in complications following CSD such as infertility and PID. Consequently, hysteroscopy and endometrial biopsy in infertile women with a CSD as early as possible might be beneficial. This study may highlight a cause of secondary infertility in women with CS niche: embryo implantation failure due to chronic endometritis and chronic inflammation in the pelvis, such as PID.

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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