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The association between endometrial polyps, chronic endometritis, and IVF outcomes

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Abstract. – OBJECTIVE: Endometrial polyps (EPs) are one of the most common pathologies detected during the examination of the uterine cavity of infertile women. We aimed to demonstrate the relationship between EPs, chronic endometritis (CE) and in vitro fertilization (IVF) outcomes.

PATIENTS AND METHODS: This retrospective study was performed on 394 hysteroscopically examined infertility cases. We performed polyp resections (PR) and extensive biopsies of the endometrium to demonstrate the association with clinical pregnancy (CP) by IVF. We performed statistical analysis to compare these associations.

RESULTS: The incidence of CE was twice as high in the presence of EPs as in the absence of EPs. The associations between EPs and PR were found to be significant for positive CP outcomes. A significant difference in IVF outcome was found between the group with EPs and the group without EPs. All these associations were statistically significant ($p < 0.05$).

CONCLUSIONS: We found a frequent association between EPs and CE. The pregnancy rate obtained after IVF was negatively affected by the presence of EPs. Treatment of these pathologies improved IVF outcomes.

Key Words:
Endometrial polyps, Chronic endometritis, Hysteroscopy, IVF, Clinical pregnancy.

Introduction

Infertility is a condition of the male or female reproductive system defined by failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse (WHO). It is believed to affect at least 72 million people worldwide[1,2] and practically 8-12% of couples[3].

For couples with infertility problems, the best treatment option is assisted reproductive technology and innovation. These methods include intrauterine insemination, *in vitro* fertilization (IVF), embryo cryopreservation, surgical procedures in men with infertility, oocyte cryopreservation in cancer patients, adoption, and surrogacy. The most commonly used procedure with the best results is IVF. However, the effectiveness of embryo transfer in IVF cycles is only 22.5% for fresh cycles, 31.9% for frozen transfers, and 46.2% for transfers with preimplantation genetic diagnosis[4].

The implantation rate depends not only on the quality of embryos but also on the integrity of the uterine cavity and the receptivity of the endometrium. The most important factor that negatively affects assisted reproduction techniques is the implantation process, even though there are innovations in reproductive immunology, gynecological reproductive surgery, and stimulation protocols[5].

Any pathology of the endometrium, such as a change in hormonal status or inflammation, can alter endometrial receptivity and lead to infertility[6,7]. Endometrial polyps (EPs) are among the most common intracavitary lesions of the uterus[8].

Recent *in vitro* studies suggest that a localized inflammatory process of the endometrium also impairs implantation by negatively affecting decidualization and altering the synthesis of

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proteins responsible for endometrial receptivity[9]. Chronic endometritis (CE) is defined as an infection or persistent inflammation of the endometrium caused by microorganisms in the uterine cavity and diagnosed by the presence of plasma cells in the endometrial stroma. CE is common in patients with unexplained infertility[10].

The current study was necessary because we frequently encountered EPs in the diagnosis and treatment of infertility in our practice. We wanted to find out if they are associated with CE and how common this association is. Finally, we wanted to investigate the impact of this endometrial pathology and treatment on IVF outcomes.

Patients and Methods

We conducted this retrospective study over 3 years (2020-2022). The study overlapped with the COVID-19 pandemic, which negatively impacted fertility and assisted reproductive technology[11]. It included 394 patients with infertility. All patients underwent hysteroscopy by the same gynecologist. We performed the hysteroscopies in cycles during which contraceptives were administered, with decidualization of the endometrium playing a role in obtaining a better view of the endometrium. The hysteroscopies under short-term intravenous anesthesia with propofol (Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany) were performed. A Bettocchi endoscope (Karl Storz SE & Co. KG, Tuttlingen, Germany) with an outer diameter of 5 mm and a channel for biopsy forceps was used, along with a saline solution with a maximum pressure of 100 mmHg to dilate the uterus.

The endocervical canal, uterine cavity, endometrium, and tubal orifices were methodically examined. In all cases, a biopsy of the endometrium and polyp resection (PR) was performed. For PR, we used 5-Fr alligator forceps, 5-Fr scissors, or a bipolar electrode (Karl Storz SE & Co. KG, Tuttlingen, Germany), while for endometrial biopsy, we used a 2-mm endometrial curette from Euro-Med Novak (CooperSurgical Inc., Trumbull, CT, USA).

The resected EPs and the endometrial biopsy were sent to the pathology-anatomy laboratory. There, they were analyzed by the same pathologist specialized in endometrial pathology. The tissue was fixed in a 10% formalin solution for microscopic analysis and processed by the paraffin inclusion method. Blocks were sectioned to a thickness of 3 μm using a Leica 2145 microtome (Leica Microsystems Nussloch GmbH, Nussloch, Germany) equipped with a water-based STS transfer system (Fisher Scientific UK, Loughborough, UK). These were stained with hematoxylin-eosin and examined under a light microscope as described in previous articles[12,13]. We checked for the presence of endometritis lesions according to the Kurman criteria[14]: the presence or absence of inflammatory cells such as neutrophils, lymphocytes, or plasma cells.

In cases diagnosed at CE, both partners were treated simultaneously. A combination of quinolones and nitroimidazole was administered orally twice daily. In all cases studied, IVF treatment was finally performed, and the result could follow. The same gynecological-biological team performed the IVF treatment, and the same protocol was used for stimulation with gonadotropins and inhibition with antagonists.

Embryo transfer was performed with a single blastocyst on day 5 under the conditions of an endometrium prepared with the same therapeutic protocol. We considered positive IVF results according to the definition of clinical pregnancy rate (CP) per aspiration cycle[15].

In addition, the impact of EPs on IVF outcomes and the association between the presence of CE and EPs cases were analyzed.

Statistical Analysis

To determine whether the difference between the results was statistically significant, we used the Chi-square test or Fisher's exact test. $p < 0.05$ was considered statistically significant. We calculated sensitivity, specificity, and positive and negative predictive values for the presence of EPs, CE and IVF results using a 2 × 2 table (Stempel, 1992). StatsDirect 3 software (version 2.8.0, StatsDirect Ltd, Cambridge, UK) was used for significance calculation and data analysis.

Results

Hysteroscopic EPs appear as localized growths of the mucosa protruding from the endometrium and filling small or large spaces in the uterine cavity. They were pedunculated or sessile and had a spherical or cylindrical shape, a smooth surface, and a light brown to yellow color. Many

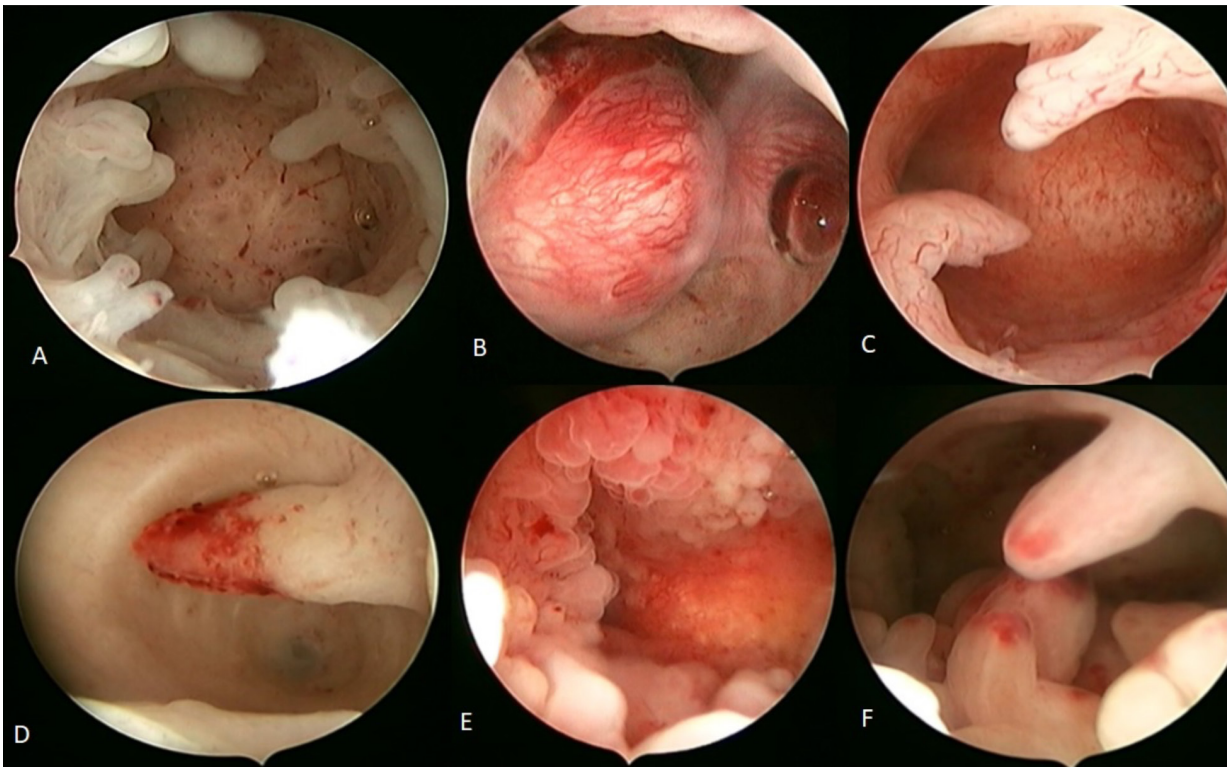

Figure 1. Endometrial polyps – hysteroscopic aspects. **A,** Micro-EPs. **B**, EPs occupying the uterine cavity with marked vascularization. **C**, Pedunculated EPs with CE. **D**, EPs with incipient apical necrosis. **E**, Sessile polyposis with CE. **F**, EPs with apical congestion.

had a purple tip, a sign of apical necrosis due to underlying stromal congestion and poor vascular supply (Figure 1).

Histologically, they consisted of an axis with a stroma of dense fibrous tissue and endometrial glands with a long axis parallel to the epithelial surface and an expanded cystic appearance. In the center, they had a tortuous vascular axis with hyaline, thickened vessel walls, sometimes with fibrinoid degeneration, and the presence of vascular thrombi, suggestive of inflammation-related vasculopathy. On the surface, they were covered by immature endometrial epithelium, a mixture of fragments morphologically distinct from normal cyclic endometrium.

We have frequently encountered nonspecific CE-type lesions that are histologically characterized by the presence of a mixed inflammatory infiltrate composed of lymphocytes, plasma cells, eosinophilic granulocytes, and macrophages. Plasma cells are an important criterion for diagnosis but, in most cases, they constitute only a small portion of the inflammatory infiltrate (Figures 2 and 3).

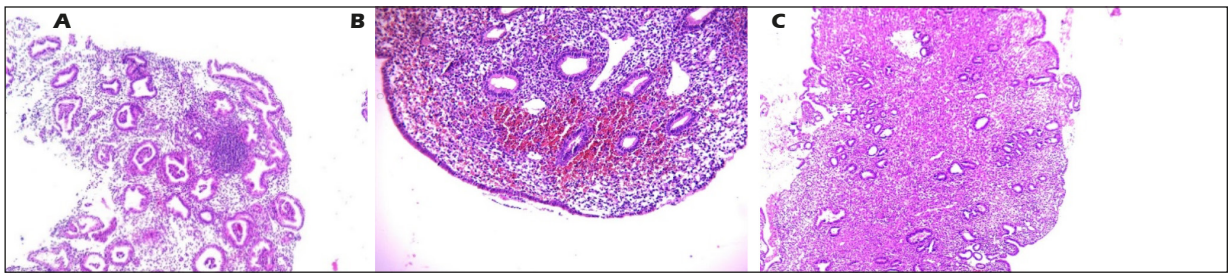

Figure 2. A, EPs with chronic inflammatory lymphoid infiltrate with the formation of lymphoid follicles (×100). **B,** EPs with chronic inflammatory lymphoid infiltrate and areas of stromal hemorrhage (×100). **C,** EPs with cellular stroma and areas of focal glandular hyperplasia (×100).

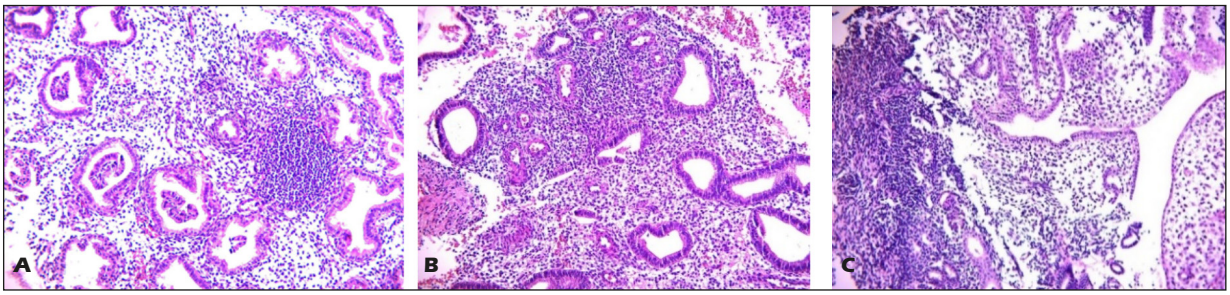

Figure 3. A, EPs with chronic inflammatory lymphoid infiltrate with the formation of lymphoid follicles (×200). **B,** EPs with chronic inflammatory lymphoid infiltrate and vessels with thickened walls (×200). **C,** EPs with abundant chronic inflammatory lymphoid infiltrate and areas with deciduiform transformation (×200).

The inflammatory infiltrates were focal or diffuse (depending on the intensity of the inflammatory process, which could range from discrete to severe). The focal inflammatory infiltrate and plasma cells were more likely to be found under the surface epithelium and around the endocervical glands. In severe endometritis, we noted a mixture of cells, usually consisting of numerous lymphocytes, sometimes with the formation of lymphoid follicles with germinal centers (Figures 2 and 3). Two flow charts of the study are shown in Figure 4 and Figure 5.

In the patients included in the study, we performed 394 hysteroscopies to determine the causes of infertility.

We found EPs in 139 cases (35.28%) of the 394 cases studied. On hysteroscopy, we found a frequent association of EPs with tubal pathology due to a history of pelvic inflammatory disease: 91 cases of 138 cases (65.94%) with EPs were found to have at least unilateral impairment of tubal permeability.

We first investigated the association between two histological findings, EPs and CE. We found CE in 94 of 139 cases cases (67.63%) with EPs, and CE in 118 cases of 255 cases (46.27%) without EPs. We also found that CE was twice as common in cases with EPs as in cases without EPs. The difference was found to be significant ($p < 0.05$) with a p-value = 0.000036 and a Chi-square statistic = 17.095 (Figure 6).

To investigate the impact of EP associated with PR on IVF outcome, the dataset was divided into the group with PR and the group without PR and assessed IVF outcome. In the PR group, pregnancy occurred in 28 cases (39.43%), compared

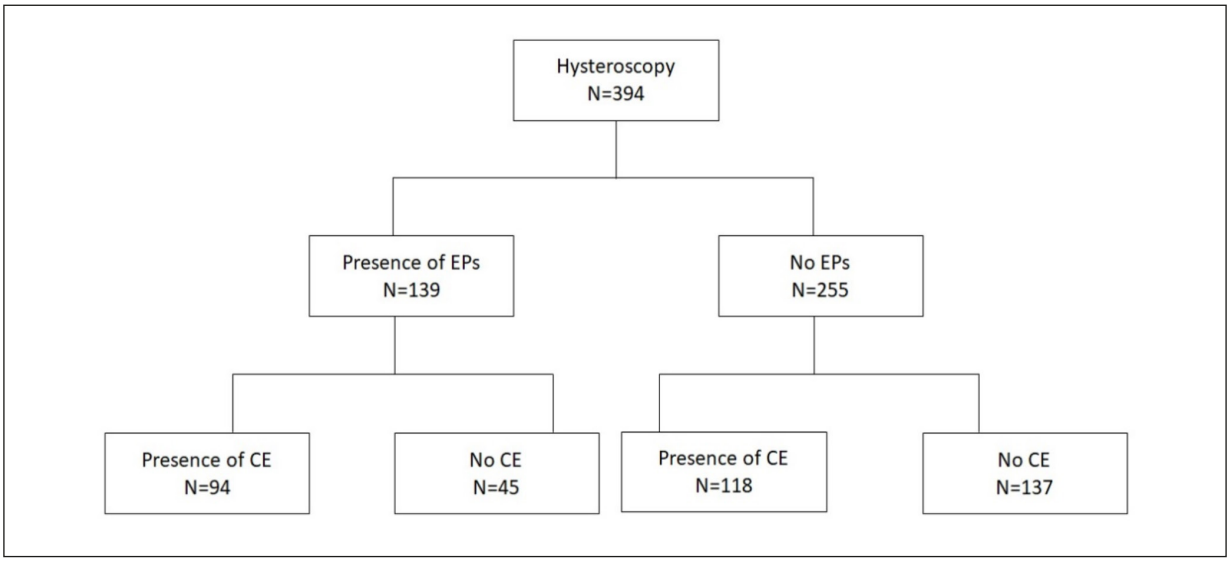

Figure 4. First diagram of study and distribution of cases. EPs, endometrial polyps; CE, chronic endometritis.

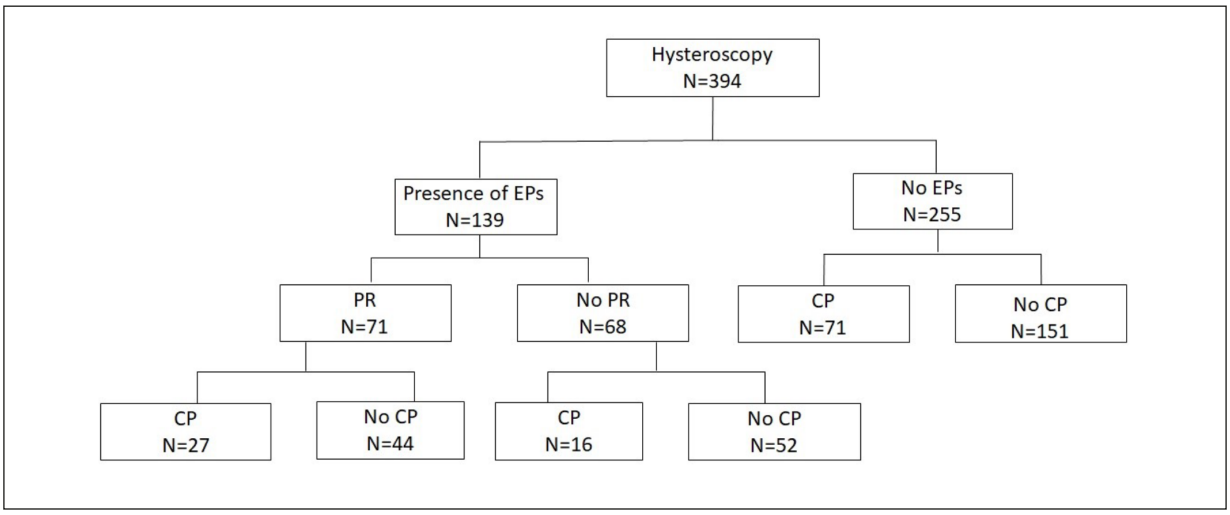

Figure 5. Second diagram of study and distribution of cases. EPs, endometrial polyps; PR, polyp resection; CP, clinical pregnancy.

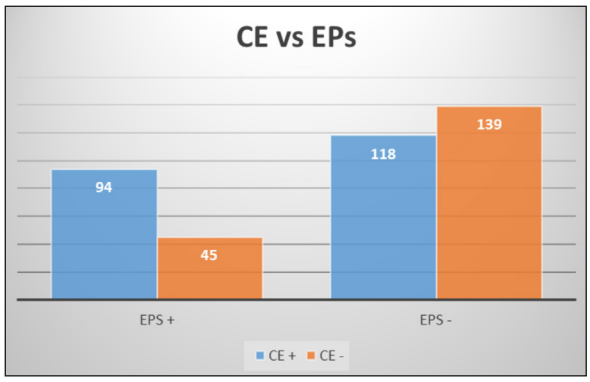

Figure 6. The presence or absence of chronic endometritis (CE+/CE-) in association with the presence or absence of endometrial polyps (EPS+/EPs-).

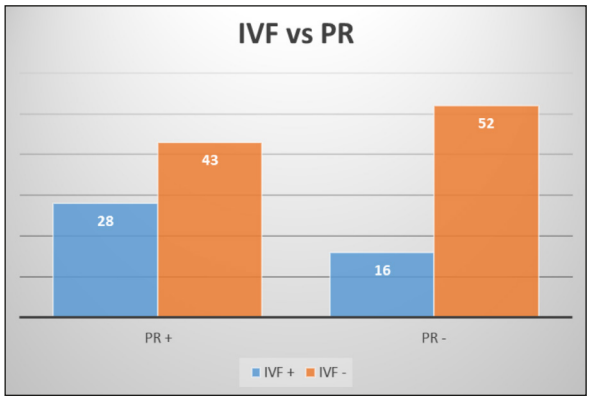

Figure 7. Positive or negative IVF results (IVF+/IVF-) associated with the presence or absence of endometrial polyps (EPs+/EPs-).

to 16 cases (23.53%) in the group without PR. The difference was statistically significant ($p < 0.05$) with a p-value = 0.043845 and a chi-square statistic = 4.0625 (Figure 7).

In a similar approach, we compare IVF outcomes between the presence of EPs without PR and the absence of EPs. In the group with EPs, we obtained a 23.52% CP. In the group without EPs, we obtained 40.78% CP. There was a significant difference ($p < 0.05$), with a p-value = 0.008887 and a chi-square statistic = 6.8454 (Figure 8).

Discussions

Polyps are commonly found on examination of the uterine cavity, but their exact prevalence

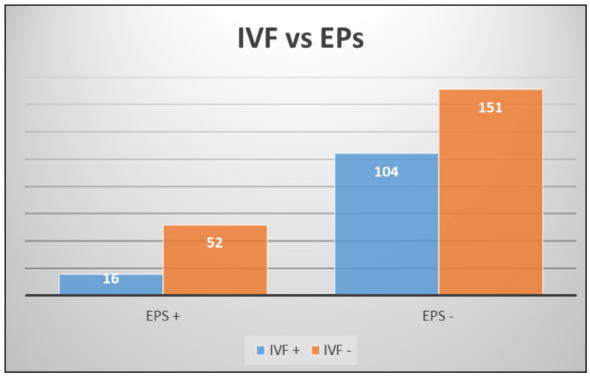

Figure 8. Positive or negative IVF results (IVF+/IVF-) in correlation with the presence or absence of endometrial polyps (EPs+/EPs-).

is not known because polyps may be asymptomatic. However, they have been diagnosed hysteroscopically in 4% of women with unexplained infertility and 14.8% of infertile women with eumenorrhea[16,17].

Originally, it was simplistically assumed that the etiopathogenesis of EP was hormonal: an imbalanced hypoestrogenism that occurs, for example, in polycystic ovaries, premenopausal women, obesity, and gonadotropin therapy for infertility[18,19]. Endometriosis is also associated with the presence of EPs[20].

Less commonly, endometrial polyps consist of a functional endometrium that undergoes cyclic histologic changes. However, many EPs consist of an immature endometrium that is unresponsive to hormonal stimuli. These EPs occur as cystic hyperplasia at all stages of the menstrual cycle and are not shed at the time of menstruation[21,22].

In our study, we frequently encountered histologic aspects of immature epithelium, cystic gland degeneration, and vascular changes specific for an inflammatory response that we associated with concurrent EPs. Other authors have also observed similar vascular tissue changes in EPs and CE.

When studying functional EPs in patients with asymptomatic infertility, Carvalho et al[23] found that all cases with vascular changes had signs of CE.

Recently, there have been more studies[24-26] suggesting an association between EPs and CE. In premenopausal women, EPs and CE correlate with each other and may represent two successive stages of a common pathological process. Immunoreactive CD-138 plasma cells specific for CE have also been detected[27] in the tissues that comprise EPs.

In addition, chronic inflammation is the cause of polyps occurring in other systems of the human body: the digestive tract, the respiratory tract, or the urinary tract[28-30].

In patients with CE, the expression of genes in the endometrium is altered, which are involved in inflammatory, cell proliferation and apoptosis processes, and determine the activation of some cytokines (vascular endothelial growth factors, epidermal growth factors), interleukins, and interferon. All of these substances have proliferative and anti-apoptotic effects, which have already been demonstrated in the pathogenesis of colorectal polyps in inflammatory bowel disease[31,32].

An etiopathogenetic relationship between EPs and CE is also suggested by indirect observations[33]. Thus, a higher frequency of EPs was found in patients with tubal obstruction compared to the control group (42.9% *vs.* 20.1%), $p < 0.000133$[33]. This is also in agreement with our observations regarding tubal permeability damage in EPs: in 91 cases (65.9%), at least unilateral tubal permeability impairment was found. This suggests that EPs are more common in patients with a history of pelvic inflammatory disease. Studies[23,34,35] show that the presence of micro polyps has a 93.7% probability of being associated with the presence of CE and that their presence is a sign of CE. If the presence of micro polyps in the population is about 11.7%, it is 2.1 times higher in infertile patients undergoing hysteroscopy and 3.2 times higher in those who also have an associated uterine malformation.

We found that CE was twice as common in EPs present (67.63%) as in EPs absent (46.27%). EPs were thus positively associated with CE, with a statistical correlation ($p < 0.05$).

EPs are associated[36] with primary infertility in 3.8-38.5% of cases and with secondary infertility in 1.8-17% of cases. In our study, we found EPs in 35.28% of cases evaluated for infertility by hysteroscopy.

Several etiopathogenetic causes of infertility have been described. One is mechanical obstruction with blockage of the fallopian ostium or cervical canal into which sperm can ascend. Another effect would be that of a foreign body or space-occupying lesion[37]. Another way EPs can cause infertility is through biochemical effects. The increased levels of glycodelin, metalloproteinases, and cytokines inhibit embryo implantation[38]. Interferon-gamma has a toxic effect on sperm and embryo development. Glycodelin inhibits sperm-ovum interaction[39]. Placental protein 14, which promotes embryo implantation through its immunosuppressive effects, has lower concentrations in EPs than in normal endometrium[40].

EPs cause an inflammatory response of the endometrium, which negatively affects the endometrial implantation process. In terms of endometrial susceptibility, mRNA expression of *HOXA10* and *HOXA11* is decreased in the endometrium of uterine cavities with polyps compared to normal cavities, and these results were independent of polyp size (8 mm) and polyp number[41]. EPs can also lead to infertility due to repeated implantation failure[42].

Numerous studies[43-46] have shown that hysteroscopic polypectomy has a positive effect on natural pregnancy rates[43]. This would also have

a positive effect on embryo implantation. Endometrial polyps can be a cause of unexplained infertility, as shown in a retrospective study by Stamatellos et al[47], in which the spontaneous pregnancy rate in women with primary and secondary unexplained infertility after hysteroscopic surgery reached 61.4%; interestingly, there was no difference in pregnancy rate depending on the size (1 cm) or the number of polyps present. A retrospective study[48] of polyp location in 230 infertile women found that removal of polyps at the utero-tubal junction provided the greatest chance of pregnancy (57.4%); however, a more recent study[27] of 69 cases found no difference in clinical pregnancy rates after polypectomy.

More than 70% of polyps persist after one year with expectant management, and because time is crucial for infertility patients, most of whom will undergo gonadotropin stimulation, hysteroscopic polypectomy is recommended to restore normal anatomy before fertility treatment[49,50].

The results of intrauterine insemination are 2-4 times better after hysteroscopic polypectomy, and natural pregnancies can even be achieved while waiting for insemination[51,52].

As for the procedure of IVF, there are very few studies in literature dealing with hysteroscopy. Studies[53,54] are comparing the outcome of IVF after polypectomy with the time elapsed until embryo transfer of previously vitrified embryos. Another study[55] concludes that in women randomly diagnosed with endometrial polyps during the IVF cycle, removal of the polyps and subsequent transfer of vitrified and warmed embryos resulted in a comparable outcome to controls without endometrial polyps who received a fresh embryo transfer. Patients diagnosed with polyps during an IVF cycle should be informed of the possible increased risk of miscarriage[56].

In a meta-analysis[57] of five randomized controlled trials, routine hysteroscopy before IVF appears to have modest benefits in terms of clinical pregnancy rates. Another study by Ghaffari et al reached[58] the same conclusion.

Only 2 studies[59,60] recommend prior hysteroscopic polypectomy before IVF. In a 2017 review, Mouhayar et al[61] found in 3 studies that the average pregnancy rate after IVF was 35.6% in the group in which polyps had been removed *vs.* 25.2% in the group in which they had not been removed. However, none of these studies demonstrated statistical significance in favor of the benefit of hysteroscopic polypectomy before IVF.

In our study, we obtained a clinical pregnancy rate of 38.02% in the cases in which the EPs were removed, compared with 23.52% in the cases without the removal of the EPs. In addition, the group without EPs had better clinical pregnancy outcomes after IVF (40.78%) than the group without removal of EPs (23.52%). In both cases, there was a statistically significant difference between the studied groups ($p < 0.05$).

Hysteroscopy itself may also have an additional benefit by facilitating subsequent embryo transfer by widening the cervix or by increasing endometrial receptivity through endometrial injury[62].

Conclusions

The presence of EPs has a negative impact on pregnancy rates after IVF. EPs are usually associated with the process of CE. EPs negatively alter endometrial receptivity, and hysteroscopy with polypectomy improves IVF outcomes.

Further randomized controlled trials with many cases are needed to evaluate the success rate of IVF after polypectomy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

This study was approved by the HitMed Medical Centre Ethics Committee (Decision Number: 08/10, 2022).

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Availability of Data and Materials

The data sets generated and/or analyzed in this study are available on request from the corresponding author.

Authors' Contribution

CCV (conceptualization, methodology, and writing of the original draft); MS, LD, and CC (investigation, data maintenance, formal analysis) MS and MDO (methodology, writing, review and editing); CCV and ACV (monitoring, project management, validation). All authors have read and agreed to the published version of the manuscript.

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