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ORIGINAL ARTICLE

Association of endometrial polyps with STC-1 and STC-2 in infertile patients

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Abstract

Objective: The present study aimed to evaluate the impact of endometrial polyps (EPs) on the endometrium of patients with unexplained infertility using stanniocalcin-1 and -2 proteins (STC), whose effects on endometrial receptivity have been reported recently.

Materials and Methods: A case–control study was performed, consisting of 26 patients who underwent endometrial sampling for diagnosis and/or treatment and diagnosed with EP on biopsy and/or excision material, and 23 patients with normal endometrial findings in the pathology, for a total of 49 patients with unexplained infertility. An immunohistochemistry examination was performed on paraffin-embedded tissue samples from both groups to understand whether there was a relationship between EP and STC. Staining results of the polyp and control groups for STC-1 and STC-2 were compared, and it was investigated whether STCs were predictive for EP.

Results: In the comparison performed between the *H*-score evaluation results of the control and polyp groups after the immunohistochemical staining method, the staining in the polyp group was significantly higher for both STC-1 ($p < 0.001$) and STC-2 ($p < 0.001$). There was more staining with STC-1 than STC-2 in all groups (STC-1: 15.08; STC-2: 8.27; $p < 0.05$). In the logistic regression analysis established with STC-1, STC-2, and age, the predictive effect of STC-1 for EP was statistically significant ($p = 0.040$; odds ratio: 1.66; 95% confidence interval: 1.02–2.68). In EP, according to receiver operating characteristic curve analysis, area under the curve was 0.980 (likelihood ratio: 20.35; $p < 0.05$), and the cut-off value was 18 for STC-1.

Conclusion: In infertile patients, since STC-1, which affects endometrial receptivity, is found to be significantly higher in polyps and has a predictive effect on polyps, in patients with unexplained infertility, routine uterine cavity evaluation and routine excision of polypoid lesions detected during this period may have a positive effect on endometrial receptivity.

KEYWORDS
endometrial polyps, polypectomy, stanniocalcin-1, unexplained infertility

INTRODUCTION

Endometrial polyps (EPs) are localized hyperplastic endometrial growths containing endometrial glands and stroma and are mostly benign. The infrequent occurrence of polyps before menarche and the association between tamoxifen use and EPs suggest that estrogen stimulation of the endometrium plays a vital role in the formation of EP.[1] Estrogen, together with progesterone, provides the secretion of molecules that participate in the formation of the receptive endometrium, in addition to the proliferation and differentiation of endometrial cells, and is necessary for the implantation process.[2]

EPs are detected on hysteroscopy in up to 25% of women with unexplained infertility.[3] Polyps have been hypothesized to affect the endometrial environment by causing abnormal uterine bleeding, mechanical effects on sperm and embryos, or adverse effects at the implantation

site, although their effects on fertility are unclear. Polyps can induce an inflammatory endometrial response, such as an intrauterine device that disrupts the embryo's implantation.[4]

Studies of women with unexplained infertility and polyps have revealed improved spontaneous pregnancy rates after undergoing hysteroscopic polypectomy.[5,6] In contrast, a few studies of women undergoing in vitro fertilization (IVF) did not find a reduction in pregnancy rates in the presence of polyps smaller than 2 cm.[7] Due to these conflicting results, the effects of polyps on infertility need to be further investigated and proven by molecular studies.[8] However, there are very few molecular studies proving the effect of polyps on infertility.

One of the molecules demonstrated to affect the implantation process is stanniocalcin significantly. Stanniocalcin (STC) is a glycoprotein hormone involved in regulating calcium and phosphate, first indicated to be secreted from the Stannius corpuscle in the kidneys of teleost fish.[9] The human homologous STC was first described in 1995, and it consists of STC-1 and STC-2 proteins.[10] The human STC-1 gene is widely expressed in many tissues, but STC-1 is not typically detected in human serum except during pregnancy.[11] This condition suggests that STC-1 acts as a paracrine/autocrine factor rather than an endocrine hormone.[12]

Various studies have reported that STC-1 and STC-2 play a role in calcium regulation, cell proliferation, apoptosis, inflammation, malignancy, oxidative stress, and metabolism.[13–15] Furthermore, because calcium transporter genes are cyclically abundantly expressed in the endometrium and regulated by ovarian steroid hormones, their dysregulation has been suggested to play a critical role in embryo implantation,[16] and the effects of STCs on embryo implantation have also been demonstrated in many studies. Xiao et al., in their study on rats, showed that STC-1, together with STC-2, plays an essential role in implantation and decidualization processes.[17] Also, STC-1 has been suggested as a marker of implantation in pigs.[18] STC-1 is elevated in the mid-secretory phase of the menstrual cycle and is co-expressed with markers of endometrial receptivity in the implantation window.[19] Allegra et al. reported that in women undergoing IVF treatment, STC-1 is one of the genes expressed during the implantation window.[20]

Based on the above findings, it can be argued that the presence of a polyp in the endometrium may alter the endometrial expression of STC-1 and STC-2, and changes in STC-1- and STC-2-mediated endometrial signaling pathways may lead to impaired endometrial receptivity. These findings provide molecular data to support some clinical evidence of improved pregnancy rates after hysteroscopic polypectomy. Therefore, we aimed to investigate the impact of EP formation on STC-1 and STC-2 levels in infertile patients and to provide evidence for its possible effect on endometrial receptivity.

MATERIALS AND METHODS

The presented case–control study was performed in Afyonkarahisar, Turkey, Afyonkarahisar Health Sciences University, Faculty of Medicine, Departments of Obstetrics and Gynecology, Medical Histology, and Pathology. The study was approved by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee Medical Ethics Committee (2021/165). The procedures comply with the terms of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Participants were recruited consecutively between November 2021 and March 2022. Twenty-three patients followed up with the diagnosis of unexplained infertility (with bilateral tubal patency, regular ovulatory cycles, and no male factor infertility) who underwent operative hysteroscopy due to endometrial thickening, polypoid lesion in the endometrial cavity, suspicious uterine intracavitary lesion findings, and pathology evaluation revealed normal endometrial findings and 26 patients with EP were included. Women who smoked and had any infectious-inflammatory-autoimmune and endocrine disease, chronic kidney and/or liver disease, clinical cardiovascular disease, history of malignancy, history of operation, and secondary infertility were excluded. The participants had no confounding medical conditions that affected endometrial receptivity, such as endometriosis, polycystic ovary syndrome, hydrosalpinx, and submucosal fibroids. Enrolled patients had not received any hormonal therapy for at least 3 months before the initiation of the study.

All participants underwent operative hysteroscopy using a 10 mm bipolar resectoscope (Karl Storz, Tuttlingen, Germany) under general anesthesia in the late proliferative phase of the menstrual cycle, just at the end of the menstrual cycle, after the necessary preoperative preparations (anesthesia consultation and routine blood tests) were completed. Hysteroscopy was used for visualization of the uterine cavity in all patients. Macroscopically sized polyps, unipolar, and semi-rigid loop (Bettocchi®) were removed, and immediately afterward, endometrial samples were taken using a 10-mm Karman cannula attached to a plastic syringe. All tissue samples were fixed in 10% formalin for diagnosis and sent to the pathology clinic. Routine hematoxylin–eosin staining was performed in all samples to confirm the diagnosis of the polyp. Immunohistochemistry staining for STC was applied to paraffin blocks whose pathology examination was completed and met the study criteria.

Immunohistochemistry method

After 10% formaldehyde fixation was applied to tissue samples for histopathological examination, paraffin blocking was performed by passing through graded alcohol series and xylene, and 5 μm sections were obtained on polylysine slides. For the antigen retrieval procedure, sections were boiled for 28 min in the microwave with

citrate buffer. After washing, 3% H_2O_2 was applied for 5 min. Sections washed three times for 5 min each with PBS were kept in blocking solution for 1 h for protein blocking. Then, primary antibodies were incubated with anti STC-1 (1/250, FNab08315, Finetest) and anti STC-2 (1/250, FNab08287, Finetest) antibodies overnight at +4°C. Washed sections were incubated with anti-mouse biotin-streptavidin hydrogen peroxidase (Biotinylated Goat Anti-Mouse, LabVision) secondary antibody for 30 min and stained with 3-amino-9-ethyl carbazole (AEC). After staining the nuclei with Mayer's hematoxylin, they were covered with a water-based closure medium, and immunohistochemical evaluations were made under a light microscope.

Histopathological evaluation method

In the immunohistochemical evaluation, a semi-quantitative method was used, and the histological score (*H*-score) was evaluated according to the extent of spread and staining intensities of the stained cells. The mean proportion of cells stained was rated as 0 for <1% of the stained area, 1 for 1%–25%, 2 for 26%–50%, 3 for 51%–75%, and 4 for 75% or more staining. Grading was also performed for staining intensity: 0, negative staining; 1, poor staining; 2, moderate staining; 3, strong staining. The *H*-score was calculated for each sample: *H*-score = degree of stained cell area x mean staining intensity. A total score of 0–12 was given and rated as negative (−, score: 0), poor (+, score: 1–4), moderate (++, score: 5 to 8) or strong (+++, score: 9 to 12).[21]

The primary outcome measure for this study was to determine whether there was a difference in immunohistochemical staining for STC between the polyp and control group. For EP, investigating the predictive effect of STCs was the secondary outcome.

Statistical analysis

After the immunohistochemical staining, the staining intensities were evaluated by calculating the *H*-score, and the distribution of the continuous variables found was expressed as the mean ± standard deviation. Comparison of continuous variables between groups was performed with Student's *t*-test or Mann–Whitney *U* test, depending on the normality of the distribution. After performing logistic regression analysis for STC-1, STC-2, and age, in receiver operating characteristic (ROC) analysis, the area under the curve was calculated to predict polyp probability and evaluate prediction accuracy. Statistical analysis was performed using the Statistical Program for Social Sciences version 20.0 (SPSS, Chicago, IL, USA). The level of significance was $p \leq 0.05$ for all statistical tests.

TABLE 1 Comparison of polyp and control group: STC-1 and STC-2, age.

Parameter[a]	Polyp ($n = 26$)	Control ($n = 23$)	p value
STC-1	21.62 ± 3.25	9.83 ± 4.18	**<0.001**[b]
STC-2	13.19 ± 5.25	4.83 ± 5.02	**<0.001**[b]
Age	32.42 ± 5.21	31.65 ± 5.92	0.653[c]

Note: Bold indicates statistically significant value ($p < 0.05$).
[a]Data are presented as mean ± *SD*, median (interquartile range).
[b]Mann–Whitney *U* test.
[c]Independent samples *t*-test.

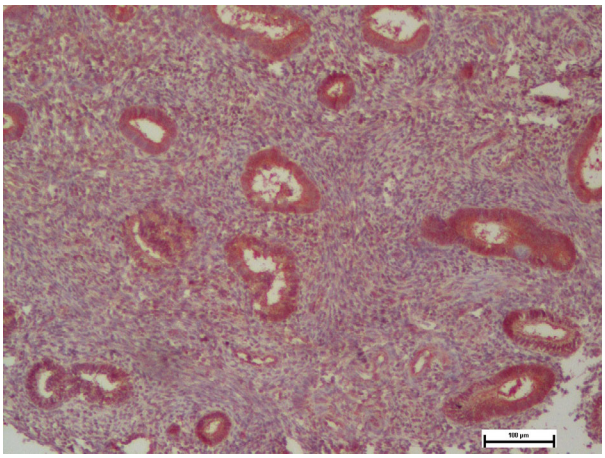

FIGURE 1 Endometrial polyps tissue showing high staining with STC-1 (+3) in the menstrual cycle proliferative phase.

RESULTS

Of the 49 patients with unexplained infertility, 26 constituted the polyp group, and 23 patients with normal endometrial findings formed the control group (late proliferative phase endometrium). There was no difference in mean age between the two groups (mean ± *SD*: polyp: 32.42 ± 5.21; control: 31.65 ± 5.92; $p = 0.653$). For both STC-1 and STC-2, the mean *H*-score in the polyp group was significantly higher than in the control group (for STC-1, polyp: 21.62 ± 3.25; control: 9.83 ± 4.18; $p < 0.001$/for STC-2, polyp: 13.19 ± 5.25; control: 4.83 ± 5.02; $p < 0.001$) (Table 1). In all groups, there was more staining with STC-1 than with STC-2 (STC-1: 15.08; STC-2: 8.27; $p < 0.05$) (Figures 1, 2 and 4). In the logistic regression analysis between polyp and control group, including STC-1, STC-2, and age, it was observed that STC-1 significantly predicted the diagnosis of EP ($p = 0.040$; $B = 0.51$; odds ratio: 1.66; 95% confidence interval: 1.02–2.68) (Tables 2 and 3). The area under the curve (AUC) value of STC-1 was statistically significant in the ROC analysis performed to find the threshold value for the diagnosis of polyp (AUC: 0.980; likelihood ratio [LR]: 20.35), and a threshold value of 18 was determined (Figure 3).

DISCUSSION

In our study, for STC-1 and STC-2, the mean *H*-score in the polyp group was significantly higher than the control group (for STC-1, polyp: 21.62 ± 3.25; control: 9.83 ± 4.18; $p < 0.001$/for STC-2 polyp: 13.19 ± 5.25; control: 4.83 ± 5.02; $p < 0.001$) and in all groups, there was more staining with STC-1 than with STC-2 ($p < 0.05$). In global gene expression profile studies in the human endometrium, increased monitoring of the STC-1 protein in the mid-secretory endometrium is a strong indication of its involvement in the critical implantation process.[22] STC-1 is expressed in rats and pigs before pregnancy in the endometrium and decidua during early pregnancy, and its expression is regulated by estrogen and progesterone. It has been proposed as an implantation marker in swine endometrium.[17,18] STC-1 is also suggested to play a role in implantation in rats and sheep.[23,24] Moreover, the STC receptor (CASR) is induced in the rat uterus during implantation and decidualization.[25] Besides, in another study, transgenic overexpression of human STC-1 in rats resulted in reduced female reproductive capacity.[26] In humans, STC-1 gene expression has been demonstrated in the mid-secretory endometrium in patients conceiving with the aid of assisted reproductive technologies.[20] Again, while STC-1 is upregulated in the mid-secretory phase of the normal menstrual cycle, compared to the early secretory endometrium,[27] microarray analysis of mid-secretory endometrium from women with unexplained infertility found to downregulate STC-1 compared with controls.[28] These findings point to a possible role for STC-1 in human endometrial function and implantation. In our study, endometrial sampling was performed in the late proliferative phase in both groups, and the staining in the polyp group was significantly higher for both STC-1 and STC-2 than in the control group. This result indicates that in the polyp group, the proliferative phase, excessive STC staining and possible impairment in normal endometrial function.

EPs contain estrogen and progesterone receptors, and the receptor concentration is higher in the polyp glandular epithelium and less in polyp stromal cells compared to the normal epithelium.[29] This condition may prevent the stroma of the polyp from undergoing decidual changes and menstrual shedding. Ultimately, this abnormal endometrial architecture may affect the expression and secretion of implantation factors and the molecular mechanisms involved in implantation. However, other unknown factors may cause changes in implantation factor concentrations.[4] One of these factors was STC proteins, which resulted in a high staining rate in polyps in our study.

Buras et al. reported that estradiol increased the expression of STC-2 in breast cancer cells, and the estradiol antibody reversed this effect. The interaction of STC-2 with estrogen and progesterone in breast cancer raises the possibility of possible STC-2 and polyp interaction in EPs where estrogen plays a role in the etiology. Besides, STC-2 has been demonstrated to reduce progesterone biosynthesis through inhibition of 3β-hydroxysteroid dehydrogenase expression.[30] This may be a factor that comes into play in developing polyps. In our study, although less staining was observed in STC-2 compared to STC-1, significantly higher STC-2 staining was observed compared to the control group. Like STC-2, the role of STC-1 in cancer has received much attention. Endometrial cancer is one of them, and STC-1 expression has been reported in endometrial cancer.[31] Malignancy may occur very rarely in EPs, and it has been suggested that malignancy may develop through a mechanism involving aromatase-dependent focal

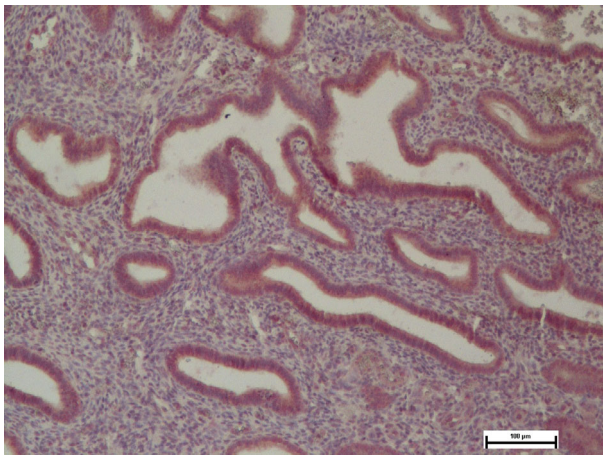

FIGURE 2 Endometrial polyps tissue showing high staining with STC-2 (+3) in the menstrual cycle proliferative phase.

TABLE 2 Predictive effect of STC-1 and 2 on polyps (omnibüs tests of model coefficients: $p \leq 0.0001$).

Independent variable	*p*	OR	95% CI	*B*
STC-2	0.247	1.27	0.85–1.92	0.24
STC-1	**0.040**	1.66	1.02–2.68	0.51
Age	0.679	0.47	0.01–16.79	−0.75

Note: Bold indicates statistically significant value ($p < 0.05$).
Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 3 Logistic regression analysis showing the predictive effect of STC-1 (omnibus tests of model coefficients: $p < 0.001$).

Variable	STC-1 (mean ± *SD*)	*p* value	Nagelkerke R^2	OR (95% CI)
Controls ($n = 23$)	9.83 ± 4.18	**<0.001**	0.905	Reference
Polyps ($n = 26$)	21.62 ± 3.25			1.66 (1.02–2.68)

Abbreviations: CI, confidence interval; OR, odds ratio.

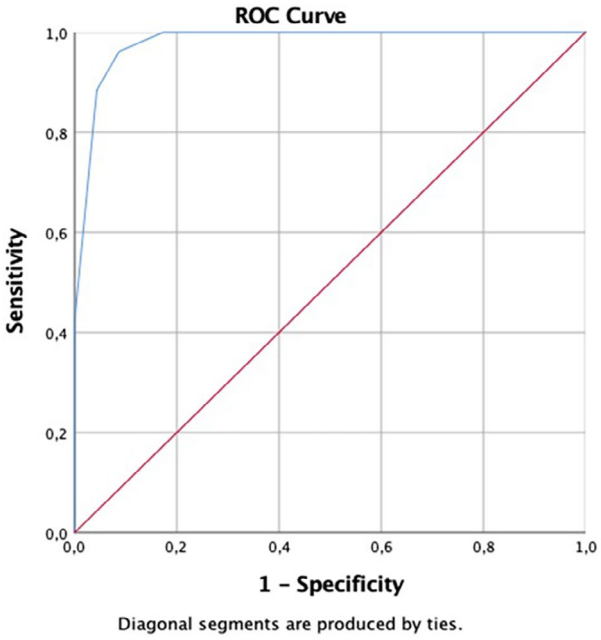

FIGURE 3 Receiver operating characteristic curve for STC-1 for prediction of polyps (AUC: 0.980, LR: 20.35).

hyperestrogenism.[32] Also, similar to its role in endometrial cancer, STC-1 may also play a role in the development of malignant EP.

In a study investigating the role of STC-1 in endometriosis, STC-1 dysregulation suggests that STC-1 is involved in the pathogenesis of decidualization defects. These observations suggested that STC-1 could potentially be a new decidualization marker.[22] Already, decidualization defects have been revealed in polypoid lesions before.

The human endometrium is a dynamic tissue that plays a very important role in implantation, and defects in the implantation window play an important role, especially in unexplained infertile patients. We also included only patients with unexplained infertility in our study. EPs are observed in hysteroscopy in 25% of women with unexplained infertility.[3] Varaste et al.[33] reported the pregnancy rate after endometrial polypectomy as 78.3% in infertile women and 42.1% in those with a normal uterine cavity. In a randomized controlled trial, women who underwent hysteroscopic polypectomy before intrauterine insemination (IUI) significantly improved pregnancy rates compared to women who had polyp biopsy alone

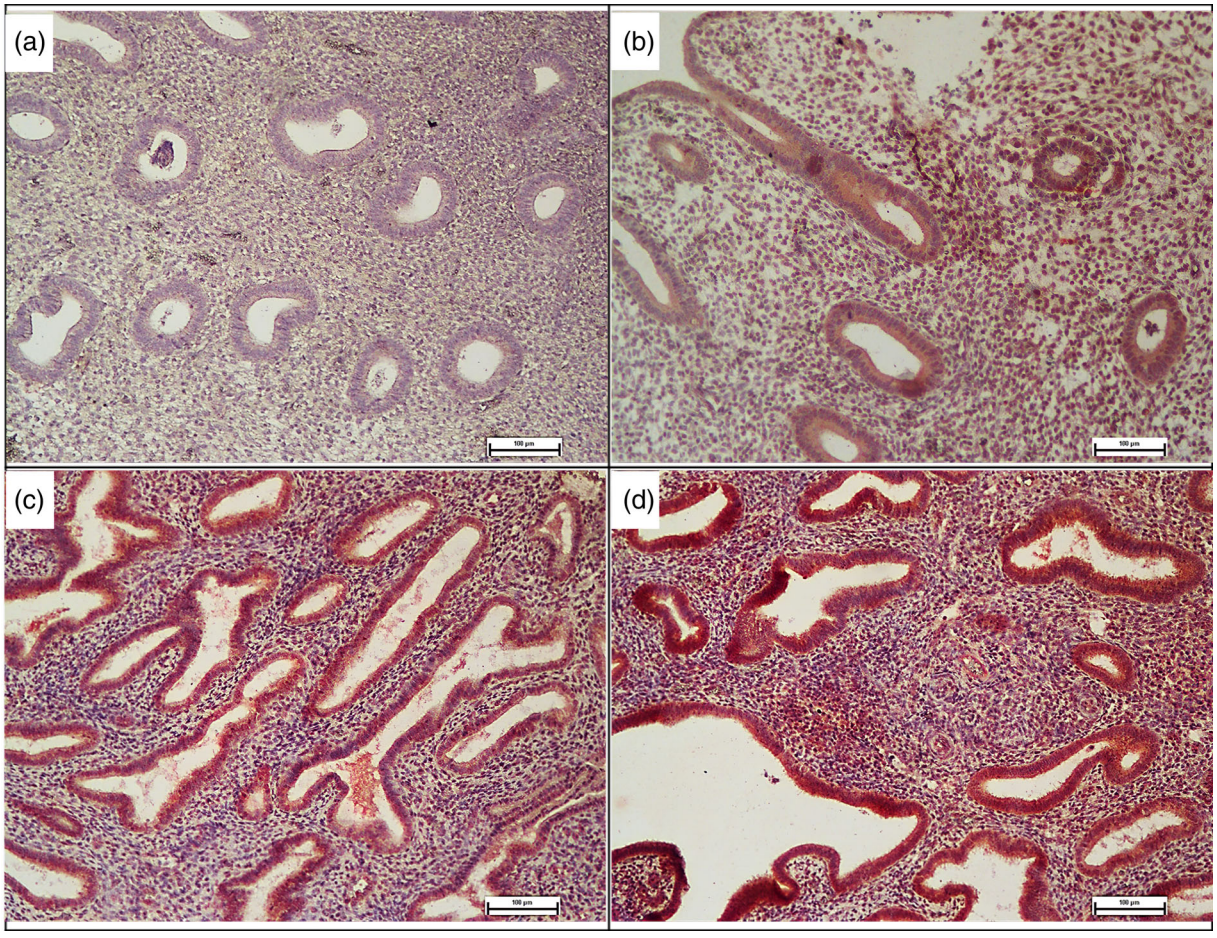

FIGURE 4 Staining intensities used in IHC scoring for STC-1 and -2. (a) Negative staining (control), (b) images indicating + staining, (c) ++ staining, and (d) +++ staining.

(51.4% vs. 25.4%).[5] However, in another study, removing polyps with a maximum diameter of less than 1.5 cm did not improve IVF outcomes, and the authors concluded that EPs do not adversely affect pregnancy and implantation outcomes in IVF cycles.[7] Check et al. also determined a similar clinical pregnancy rate and miscarriage rate among the three groups after IVF cycles, comparing women who had polypectomy, women who had a polyp left, and women who did not have polyps.[34] In the study of Elias et al. in which they retrospectively compared the IVF cycle outcomes of 60 women with EPs and 2933 women without polyps, clinical pregnancy, spontaneous abortion, and live birth rates were similar between the two groups, while the biochemical pregnancy rate was significantly higher in the polyp group than in the nonpolyp group (18.3% vs. 9.6%). The authors concluded that newly diagnosed EPs were associated with an increased biochemical pregnancy rate during controlled ovarian stimulation but ultimately did not adversely affect clinical pregnancy or live birth rates after fresh IVF cycles.[35] The American Association of Gynecological Laparoscopists also states that EPs management can be conservative, especially if they are less than 10 mm in size, with a 25% chance of regression.[36] A systematic review concluded that hysteroscopic polypectomy increased the clinical pregnancy rate in patients undergoing IUI, but no clear benefit was observed for a clinical pregnancy, live birth, miscarriage, and implantation rates in IVF patients.[37] However, as in most IVF centers, clinicians who can easily perform hysteroscopic polypectomy under local anesthesia in the office setting tend to perform the polypectomy routinely. Another IVF study reported an increased abortion rate in the polyp group in the presence of a polyp, and it was recommended to freeze all embryos in the presence of a polyp. However, in this study, the number of participants was insufficient to generalize the results. The authors concluded that EPs smaller than 20 mm did not reduce the pregnancy rate, but there was a trend toward increased pregnancy loss.[38] This study seems to be one of the studies contributing to the trend toward routine polyp removal. Rackow et al. presented evidence that polyps affect endometrial receptivity in their study of HOXA analysis in the uterus with one or more EPs.[8] This result, and the results of our study, supports the results of the randomized trial showing the adverse effect of polyps on fertility.[5]

Despite conflicting results regarding the benefit of polypectomy, the risk of post polypectomy adhesion cannot be completely excluded, even if it is negligible.[39] Also, small EPs are not believed to impact infertility treatments since small polyps often regress spontaneously within 1 year.[40] Considering the recovery time after polypectomy and the surgical cost of the endometrium,[41] the recommendation for routine polypectomy can be discussed. However, one of the critical problems here is that the 1-year observation period is quite long for infertile patients. Therefore, hormonal drug therapy may have a role in polyp management as an alternative to surgery for small polyps.[42] The lack of consensus on the management of EP in infertile patients requires molecular studies to prove a definite adverse effect of EPs on implantation. In studies performed in this direction, there is evidence of increased glycodelin,[43] aromatase,[32] inflammatory markers,[4] and decreased levels of HOXA-10 and 11 mRNA,[8] which are known to have an effective role in endometrial receptivity, in EPs.

In our study, the high staining with STC-1 in EPs suggests that STC-1 activity may affect endometrial receptivity by changing the endometrial environment and that the function and secretion of factors such as homeobox proteins and leukemia inhibitory factors, which are secreted during implantation and have important functions, may also change.[44] STC-1 has also been reported to be a protective factor against oxidative stress and inflammation.[45] As such, it has the potential to affect implantation function. As the studies are conducted, drug treatments for factors such as STC-1 that affect the implantation process may come to the fore in the future. For example, in ovarian cancer, the addition of human recombinant STC-1 promoted cell proliferation and metastasis, while the addition of STC-1 neutralizing antibodies abolished the effects.[46]

To our knowledge, this study is the first to investigate the association of STCs with EP in infertile patients. Although there are limitations for generalization and interpretation of the results due to the relatively small number of patients included in our study and the inability to record EP size, our study provides molecular data supporting clinical findings that pregnancy rates improve after hysteroscopic polypectomy.

This study revealed that in patients with unexplained infertility, STC-1 and STC-2 were significantly higher in polyp tissue than in the control group, and STC-1 predicted polypoid lesions. This result contributes to a possible explanation of the pathophysiological mechanisms that lead to implantation defects and provides new data on STC molecules with many functions described in the literature. Further studies are recommended to reveal whether endometrial receptivity markers return to normal after polyp removal and the precise mechanisms of action of STC-1 in the polyp formation process.

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CONFLICT OF INTEREST STATEMENT

The authors declare that no conflict of interest could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

All data are available in Afyonkarahisar University of Health Sciences IT service. If the data is requested, it can be requested from the Ethics Committee of Afyonkarahisar University of Health Sciences.

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