

Endometrial polyps may have an inflammatory origin.

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Abstract

Goal: The most common gynaecological pathology is endometrial polyps. Although endometrial polyps and chronic endometritis (CE) sometimes coexist, the formation of endometrial polyps (EP) is thought to be associated with aberrant hormonal signalling. The objective of this research was to assess the expression of TGF β and VEGF isoforms in the endometrium from the contralateral side of the cavity and in the epithelium and stromal cells from endometrial polyps (P) in women with or without indications of CE.

Study design: case-control, Academic Center is the setting.

Patients: Based on the results of the hysteroscopy, 46 women who were referred for the procedure were split into two groups. Group B had polyps and symptoms of CE, whereas Group A had endometrial polyps and a normal contralateral endometrium.

Interventions include endometrial biopsies, polypectomy, and office hysteroscopy.

Immunohistochemical analysis of VEGF, TGF β 1, TGF β 2, and TGF β 3 expression is the primary outcome measure.

Findings: Compared to stromal cells, the glandular epithelium produced higher VEGF, TGF β 1, and TGF β 2. Women with CE had greater amounts of VEGF and TGF β 1 than women without CE, and polyps had higher levels than the contralateral endometrium. Conversely, there were no intergroup variations in TGF β 1 and TGF β 2 expression in the stroma. TGF β 3, however, was markedly overexpressed in polyps from group B but not from group A, especially in the stromal cells that exhibited "spindle cell" traits.

Conclusions: The presence of two distinct types of endometrial polyps—one hormone-dependent and the other inflammatory—may be indicated by the various growth factor expressions. diverse symptoms, relapse risk, reproductive, and oncologic implications may arise from the diverse nature.

Keywords: VEGF, TGF β , chronic endometritis, inflammation, and endometrial polyps.

Introduction

Benign mucosal outgrowths make up endometrial polyps, a frequent endouterine disease. Endometrial polyps have been linked to reproductive issues and abnormal uterine bleeding (AUB), but they may also be an unexpected discovery on ultrasound or hysteroscopic evaluation in the absence of symptoms.

In fact, polyps can hinder the implantation of the embryo not only by deforming the uterus but also by affecting the expression of genes and paracrine factors that are involved in the process of endometrial receptivity, such as homeobox A-10, -11, interferon- γ (INF- γ), VEGF, etc. [1,2,3]. Furthermore, polyps are the most frequent finding on hysteroscopy in women who complain of AUB [4].

The pathophysiology of endometrial polyps has historically been linked to inappropriate oestrogenic stimulation and an imbalance in ovarian steroids [5, 6]. In addition to oestrogenic hyperstimulation, obesity is an independent risk factor for the development of endometrial polyps [7]. Additionally, compared to a normal endometrium, polyps have aberrant paracrine expression. Endometrial polyps may be dysregulated tumours with primarily proliferative properties that are unable to synchronise with the normal endometrium, as shown by a considerable difference in cycle-dependent inhibin expression between a normal endometrium and polyps [8].

From a clinical perspective, endometrial polyps cannot be prevented or treated. In women using tamoxifen, only the preventive levonorgestrel-releasing intrauterine device has shown efficacy in avoiding de novo endometrial polyps [9]. Furthermore, polyps often return in women without obvious risk factors or even after resectoscopic polypectomy [10]. This might indicate that there is still much to learn about the aetiology and processes driving endometrial polyp growth.

It's interesting to note that there has been increasing evidence in recent years about the potential inflammatory genesis of endometrial polyps. The endometrium of women with endometrial polyps has been shown to exhibit more of the inflammatory mediator INF- γ [3].

Fluid hysteroscopy has shown endometrial micropolyps, which are tiny growths that are usually 1-2 mm long, in women with chronic endometritis (CE) [11]. Histology reveals that micropolyps have an inflammatory origin, with a leucocyte infiltration around the vascular axis. Lastly, our extensive experience with over 25,000 diagnostic hysteroscopies revealed that polyps and/or a polypoid endometrium often coexist with micropolyps or other symptoms of CE, such as hyperaemia and stromal oedema [12]. Accordingly, it has been proposed that the progression of the vascular alterations linked to endometritis may potentially be the source of the vessel axis of functional polyps, bringing them within the range of inflammatory endometria.

Since CE is a subtle condition that is sometimes asymptomatic or only accompanied by minor abnormalities (pain, bleeding, etc.), nothing is known about its incidence in the general population. Notably, CE may result in infertility and impair endometrial receptivity. We found that 66% of women with repeated implantation failure during IVF and 57.8% of women with recurrent losses had CE [14, 15].

The goal of the current investigation is to assess the theory that certain endometrial polyps have an inflammatory aetiology. In order to do this, we examined the endometrial expression of a number of inflammatory and paracrine growth factors in the stromal cells and glandular epithelium in samples from patients who had both endometrial polyps and signs of CE at hysteroscopy and histology.

Materials and Methods

Women who were sent to our department for an outpatient hysteroscopy on suspicion of endometrial polyps between December 2013 and June 2014 had their records and histological samples examined. Every patient was of reproductive age, in excellent overall health, and had not used any antibiotics or anti-inflammatory medications for at least three months. Women receiving hormonal treatments were not included. Adenomyosis, placental remnants, submucous myomas, and possible neoplasms were not included (Table 1).

The University of Bari, Italy's Department of Obstetrics and Gynecology's local ethics committee accepted the research, and each woman gave permission for their personal information to be handled. This research had no known conflicts of interest, and it received no substantial funding that may have affected the results.

A lens-based 2.7 mm OD mini-telescope with a 105° visual field angle and a 4.5 mm OD double-flow operating sheath (Karl Storz, Tuttlingen, Germany) was used for hysteroscopies. The follicular period (cycle days 7–12) was when all hysteroscopies were carried out.

The uterine cavity was expanded using a saline solution at a pressure created by a straightforward drip from a bag that was hanging one metre above the patient. A High Definition digital camera (Karl Storz, Tuttlingen, Germany) and a 300 W xenon light source were used.

Hysteroscopy included passing the hysteroscope parallel to the endometrial surface in order to completely inspect the anterior and posterior uterine walls.

This way, any surface irregularity was easily identified.

Two of the authors (E.C., M.M.) conducted all hysteroscopies. Any development on the uterine surface was referred to as a polyp. Particular focus was placed on minor lesions, including micropolyps, hyperhemia, and adhesions, which may indicate the existence of CE [12]. The criteria outlined in our group's publications were used to make the histological diagnosis of CE. More precisely, the diagnosis was established in the presence of glandular lysis features, "spindle cells," a shift in stromal cells, and a stromal infiltration dominated by lymphocytes and plasmacells [16].

The contralateral endometrial wall seemed normal in 17 instances (Group A) when endometrial polyps were discovered without hysteroscopic indications of CE (Fig. 1a). Endometrial polyps coexisting with hysteroscopic symptoms of CE were discovered in 12 instances (Group B) (Fig. 1b) (Table 1).

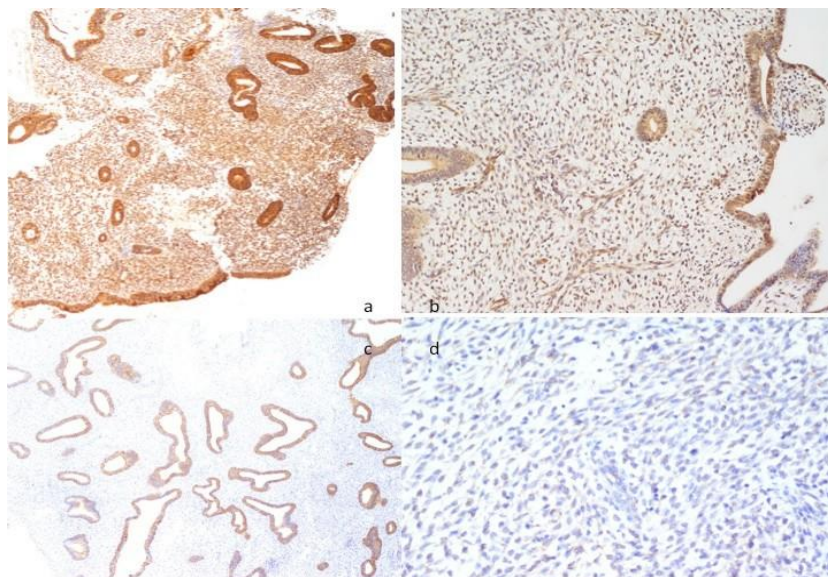


Fig 1. Immunohistochemistry for VEGF, TGFβ1, TGFβ2, TGFβ3. a) VEGF is immunohistochemically strongly expressed both in epithelium and in stromal cells (x100). b) The expression of TGFβ1 is evident in epithelium and in vascular endothelium (x100). c) The TGFβ2 is expressed only in the epithelial cells (x100). d) TGFβ3 appeared to be sporadically expressed in specific stromal cells with the characteristics of “spindle cells”, which had previously been found to be correlated to CE (Resta et al., 2012).

Table 1. Clinical data of women in the 2 groups.

	Group A	Group B
Number	17	12
Age (years)a	35.06 ± 5.87	34.58 ± 6.20
BMIa	25.06 ± 2.61	25.08 ± 2.23
Parity (n.)a	1.71 ± 0.92	1.50 ± 0.52
Miscarriages	2	5
Intrauterine proceduresb	3	4

aData are mean ± SD.

bWith intrauterine procedures, we mean previous D&C, endometrial biopsy, IUD insertion or hysteroscopy

Following a deionised water wash, the slides were submerged in an antigen retrieval solution (buffered citrate pH 6 for TGFβ 1-3, EDTA pH 8 for VEGF) at 98°C for 15 minutes. Following cooling, the slides were washed in PBS and incubated with new 3% hydrogen peroxide. The primary antibody was incubated for an additional nite at 4°C. The slides were sent to DAKO's ENVISION FLEX/HRP automated revelation system after being rinsed three times in PBS for five seconds each. 3-3i' was the chromogen used. For nuclear counterstaining, Mayer's haematoxylin and diaminobenzidine were used. Human placenta sections were employed as positive controls, whereas test sample sections that had not been treated with antibodies were used as negative controls.

A semi-quantitative scoring technique that has been established in other studies was used to assess sections with the immunohistochemistry expression [17]. A count of positive cells at magnification x 200 is the scoring method used in two distinct sequences in the same instance (first for the epithelial cells and subsequently for the stromal cells). Scores are as follows: 0 represents a negative stain; 1 represents less than 1% of positive cells; 2 represents 1–10% of positive cells; 3 represents 10–33% of positive cells; 4 represents 33–66% of positive cells; and 5 represents more than 66% of positive cells. Based on the stain reaction's severity, we also assigned an additional score ranging from 0 to 3. Negative staining is represented by a score of 0, weakly stained cells by a score of 1, moderately stained cells by a score of 2, and highly stained cells by a score of 3. As a result, the overall score ranged from 0 to 8. A mean value ± standard deviation was produced by dividing the ten fields we blindly examined for each example by two authors (L.R. and R.R.).

Table 2. The immunohistochemical expression of VEGF and TGF isoforms as assessed with the semi-

Data are mean $\pm$ SD.

Group A: endometrial polyps and endometrial cavity did not show signs of CE

Group B: cases with signs of CE including micropolyps but with coexistent endometrial polyps.

The Chi-square test and univariate discriminant analysis (Student's t-test) were used for the statistical study. For the Chi-square test, a P value of less than 0.05 was regarded as the limit of significance. Using a Bonferroni's correction, the critical value of t for the significance of difference was calculated from the input value of $P < 0.05$ for 12 comparisons, yielding $P < 0.00256$. This made it possible to use Student's t-test for multiple comparisons with less likelihood of producing a type 1 mistake [18].

Results

Age, BMI, parity, number of miscarriages and previous intrauterine procedures were similar in the 3 groups (Table 1). Histology confirmed in all cases the hysteroscopic diagnosis of CE.

The results of the semiquantitative immunohistochemical evaluation of VEGF, TGF β 1, TGF β 2 and TGF β 3, are displayed in Table 2.

	VEGF	TGF β 1	TGF β 2	TGF β 3
Group A				
P (glandular epithelium)	7.19 $\pm$ 0.65	2.71 $\pm$ 0.56	3.12 $\pm$ 1.15	3.06 $\pm$ 1.12
P (stroma)	5.01 $\pm$ 0.99	0.22 $\pm$ 0.12	0	0.37 $\pm$ 0.50
NP (glandular epithelium)	6.14 $\pm$ 0.69	1.43 $\pm$ 0.94	2.43 $\pm$ 1.51	1.88 $\pm$ 1.36
NP (stroma)	3.72 $\pm$ 0.95	0.38 $\pm$ 0.80	0	0.37 $\pm$ 1.06
Group B				
P (glandular epithelium)	7.58 $\pm$ 0.51	2.14 $\pm$ 0.98	3.08 $\pm$ 0.90	2.51 $\pm$ 1.18
P (stroma)	6.58 $\pm$ 0.67	0.27 $\pm$ 0.27	0	2.17 $\pm$ 1.27
NP (glandular epithelium)	7.42 $\pm$ 0.67	2.73 $\pm$ 1.21	2.58 $\pm$ 0.90	2.25 $\pm$ 1.14
NP (stroma)	6.50 $\pm$ 0.67	0.32 $\pm$ 0.45	0	2.33 $\pm$ 1.30

In Tab. 3 the statistical results of the paired comparisons of the immunohistochemical evaluations in the two groups, are reported. In S1 Table 2 the ratios between the paracrine factor levels in the two groups of patients in correspondence of the polyps (P), the contralateral wall (NP, no polyp) and the levels in the contralateral endometrium in the case of non-inflammatory polyps, are shown (S1 Table 3).

Table 3: The statistical results of paired comparisons of immunohistochemical evaluations in the three groups are reported.

	VEGF	TGF β 1	TGF β 2	TGF β 3
1 vs 3	.001	.001	N.S.	.001
1 vs 4	N.S.	N.S.	N.S.	N.S.
1 vs 6	N.S.	N.S.	N.S.	N.S.
2 vs 4	.001	N.S.		N.S.

2 vs 5	.001	N.S.		.001
2 vs 7	.001	N.S.		.001
3 vs 4	.001	.001	N.S.	N.S.
3 vs 6	.001	.001	N.S.	N.S.
4 vs 5	.001	N.S.		.001
4 vs 7	.001	N.S.		.001
4 vs 6	N.S.	N.S.	N.S.	N.S.
5 vs 7	N.S.	N.S.		N.S.

values of group A: polyps , glandular epithelium

values of group A : polyps, stroma

values of group A : normal endometrium, glandular epithelium 4) values of group A: normal endometrium, stroma

values of group B: endometrial polyps, glandular epithelium

values of group B: endometrial polyps, stroma

values of group B: endometritis (no polyp area), glandular

values of group B: endometritis (no polyp area), stroma

According to reports, the glandular epithelium expressed more VEGF than the stromal cells in all groups. More specifically, only stromal expression of VEGF was seen in polyps compared to the contralateral endometrium and in women with CE (Group B) compared to women without CE (Group A).

TGFβ1 and TGFβ2 expressions were similarly greater in the glandular epithelium than in the stroma, in line with VEGF expression. When compared to the contralateral endometrium in women from Group A, the glandular expression of TGFβ1 in all samples from polyps (with and without evidence of CE) was similar and considerably greater.

Two groups had low levels of TGFβ1 expression in the stroma. Notably, a modest and diffuse expression of TGFβ1 was seen in the endothelium of stromal arteries on immunohistochemistry in the subjects with CE (Group B).

As previously mentioned, TGFβ2 expression was only seen in glandular cells, and there were no changes between the two groups.

Conversely, TGFβ3 revealed significant intergroup variations in both the stroma and glandular cells. More specifically, the expression of TGFβ3 was greater in the glandular cells from polyps than in the contralateral endometrium, without any indications of inflammation, as was shown for TGFβ1 (Group A). Furthermore, TGFβ3 expression was considerably overexpressed in samples from Group B (both from polyp and contralateral regions), but it was low in stromal cells from Group A (patients without symptoms of CE). It's interesting to note that TGFβ3 seems to be overexpressed in some stromal cells with "spindle cell" features in the patients with symptoms of CE (Group B), which were previously linked to CE [16] (Fig. 1).

Discussion

Endometrial polyps are a common condition that may lead to AUB and issues with reproduction. Endometrial polyps have historically been thought to be hormone-dependent and associated with an aberrant oestrogenic impact [5]. The current study's findings show that the population of endometrial polyps is not uniform. In some instances, they really develop in an inflammatory setting with a changed paracrine pattern and overexpression of inflammatory mediators at the stromal and glandular levels.

In fact, the study's findings show that stromal VEGF expressions were higher in all of the polyps than in the contralateral endometrium. However, TGFβ3 was only strongly activated in the stroma of polyps developed in an inflammatory environment (about seven times more than in polyps without CE).

Given that VEGF is a growth agent, its increased expression in all types of polyps relative to the contralateral regions makes sense. Our findings corroborate those of Xuebing and associates, who similarly discovered that polyps had higher levels of VEGF than the surrounding normal endometrial tissue [17].

Although there is no solid evidence regarding a cycle-dependent production, data in the literature indicates that a normal endometrium produces TGFβ [19, 20]. There is currently contradictory information about TGFβ1's pathogenic function. This is a strong growth inhibitor of epithelial cells, and it has been shown that TGFβ1 signalling is a tumour suppressor route for early stages of cancer due to the discovery of inactivating mutations within the TGFβ1 signalling pathway in malignancies [21]. The overexpression of TGFβ1 in many human carcinomas, however, has been linked to a worse prognosis for patients and a higher incidence of metastases. Tumour cell lines and experimental animal models have shown comparable outcomes. Therefore, the new paradigm for TGFβ1's participation in cancer is stage-specific duality of function [22]. Furthermore, TGFβ1 is known to have a role in connective tissue development and angiogenesis [23].

In contrast to a normal endometrium, TGF β 1 was much higher expressed in the glandular epithelium, stroma, and polyps in our investigation, indicating that it may be associated with benign endometrial growth. Similarly, regardless of the inflammatory state, TGF β 2 was likewise expressed in glandular cells but not in the stroma. Interestingly, the glandular cells of the polyps from groups A and B expressed more TGF β 3 than the contralateral endometrium from Group A. Numerous organ development processes, cancer formation, and the regulation of connective tissue during wound healing have all been linked to TGF β 3 [24]. This discovery enables us to hypothesise about a potential connection between proliferative diseases and chronic inflammation. When comparing proliferative endometrium with complex hyperplasia, Gold and colleagues discovered that glandular immunostaining for TGF- β 1, TGF- β 2, and TGF- β 3 was 5.1-, 3.4-, and 2.6-fold higher, respectively [25]. The glandular epithelium showed a statistically significant stepwise increase in the expression of all three TGF- β isoforms from the normal proliferative endometrium, simple hyperplasia, and complex hyperplasia.

Kazanawa et al. discovered an overexpression of VEGF, TGF- β 2, and TGF- β 3 in inflammatory cells of active inflammatory bowel disease [26], which is consistent with the greater expression of VEGF and TGF- β 3 in the stroma of samples from Group B as a hallmark of an inflammatory state.

The presence of micropolyps, which are tiny endometrial outgrowths with a vascular axis, may be connected to the inflammatory character of certain polyps and the elevated expression of growth factors. Micropolyps has been shown to be a trustworthy indicator of CE in both histology and hysteroscopy [11, 12]. Furthermore, the significant activation of paracrine factors involved in angiogenesis and epithelial development may account for certain patients' reported polyp relapses [27]. Indeed, we may hypothesise that the presence of CE might promote the formation of a new polyp or its regeneration.

Since the changed expression of several paracrine markers in Group B may simply be connected to the concurrent existence of CE, we must admit that based on the findings of this investigation, we are unable to determine whether endometrial polyps may genuinely have an inflammatory origin. However, Kitaya and colleagues have already proposed the dual origin of endometrial polyps by showing that the proportion of mononuclear cell subsets in the macropolypoid and micropolypoid endometrium of infertile women differs, indicating that the two conditions are different [28]. More specifically, the scientists discovered that endometrial macropolyps had a much lower pan-leukocyte density in the proliferative phase of the endometrium than either micropolyps or fertile women. Additionally, they verified that in these women, the plasmacyte infiltrates were accompanied by an atypical localised B cell invasion, and that endometrial micropolyps often occurred concurrently with CE. Conversely, only a small number of macropolypoid endometrial samples had plasmacyte infiltration because macropolyps and micropolyps originate differently; endometrial micropolyps may grow in an inflammatory microenvironment, whereas endometrial macropolyps should develop under an estrogen-sensitive condition [28].

We may hypothesise that endometrial infection combined with a long-term inflammatory illness may encourage and feed endometrial proliferation, contributing to polyp formation, hyperplasia, and perhaps the pathophysiology of cancer. Given that TGF β activation has been shown in endometrial hyperplasia and carcinoma [25] and that an inflammatory state may increase aromatase and steroid receptor expression in endometriosis [29], our data, despite being restricted to a small number of cases, support a connection between endometrial inflammation and carcinogenesis.

The stromal expression of TGF β 3 in the event of inflammation is an intriguing new discovery from this investigation. Specifically, TGF β 3 is expressed in "spindle cells," a kind of cells with a fusate feature that we have shown to be useful in the morphological diagnosis of CE [16]. The nature and purposes of these cells are yet unclear, however. The discovery that TGF β 3 expression is more noticeable in spindle cells may indicate that these cells play a function in the stimulation and proliferation of polyps.

Intrauterine movements have historically been linked to the etiopathogenesis of CE of presumed inflammatory character. The three groups' rates of miscarriage and prior intrauterine operations (D&C, endometrial biopsy, IUD implantation, or hysteroscopy) were compared. It's interesting to note that not only were there no discernible changes, but very few individuals had previously had intrauterine operations that may have spread infectious pathogens. This data permits us to hypothesise that spontaneous ascending infections may be the cause of endometrial inflammation in many instances, despite the small number of cases.

In conclusion, the results of this research enable us to hypothesise that there are two distinct types of endometrial polyps—one that is hormone-dependent and the other that is inflammatory. The various types of endometrial polyps may

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lead to varying symptoms, recurrence risk, and oncologic and reproductive effects.

References

Citations

- [1] Bosteels J, Weyers S, Puttemans P, Panayotidis C, Van Herendael B, Gomel V, Mol BW, Mathieu C, and D'Hooghe T. A comprehensive study of hysteroscopy's ability to increase pregnancy rates in infertile women without other gynaecological complaints. *Hum Reprod Update* 2010;16: 1–11. doi: 10.1093/humupd/dmp033. [2] [3] [4] [5] [6] [7] [8] [9] Rackow BW, Jorgensen E, Taylor HS. Endometrial polyps impact uterine receptivity. *Fertil Steril*. 2011 Jun 30; 95(8):2690-2. doi: 10.1016/j.fertnstert.2010.12.034.
- Mollo A, Stile A, Alviggi C, Granata M, De Plaido G, Perrella A, d'Antonio A, Cicinelli Eo elevated levels of interferon-gamma contribute to endometrial polyps in infertile patients? *Fertil Steril*. 96(5):1209-12. doi: 2011 Nov. 10.1016/j.fertnstert.2011.08.001.
- Coutinho Eda S, da Rosa DB, Oliveira MA, Barrozo PR, Lasmar RB, and Dias R. frequency of histologic diagnosis and hysteroscopic findings in individuals with irregular uterine bleeding. *Fertil Steril*. June 2008; 89(6):1803-7.
- Mittal K, Schwartz L, Goswami S, Demopoulos R. Expression of progesterone and oestrogen receptors in endometrial polyps. *Int J Gynecol Pathol* 15(4):345–8, Oct. 1996.
- Zucoloto S, Zambelli Ramalho LN, Candido dos Reis FJ, Sant'Ana de Almeida EC, and Nogueira AA. Immunohistochemical expression of progesterone and oestrogen receptors in postmenopausal women's endometrium and endometrial polyps. maturity. Nov. 15, 2004; 49(3):229-33.
- Serhat E, Cogendez E, Selcuk S, Asoglu MR, Arioglu PF, Eren S. Are endometrial polyps associated with obesity, diabetes mellitus, and hypertension? *Obstet Arch Gynecol*. November 2014; 290(5):937-41. doi: 10.1007/s00404 014-3279-4 Mylonas I, Makovitzky J, Fernow A, Richter DU, Jeschke U, Briesse V, Gerber B, Friese K. Expression of the inhibin/activin subunits alpha (alpha), beta-A (betaA), and beta-B (betaB) in benign human endometrial polyps and tamoxifen-associated polyps. *Arch Gynecol Obstet*. 272(1):59-66, June 2005.
- Yeo W, Yu MY, Tam WH, Wong AW, and Chan SS. Levonorgestrel-releasing intrauterine system prophylactic use in breast cancer patients receiving tamoxifen: a randomised controlled trial. *Archives of Reproductive Medicine and Sexual Health* V1. 12. 2018 14 Possible Inflammatory Origin of Endometrial Polyps [10] [11] [12] [13] [14] [15] [16] [17] *Obstet Paradisi* R, Rossi S, Scifo MC, Dall'O' F, Battaglia C, Venturoli S. Endometrial polyp recurrence. *Gynecol Obstet Invest*. 78(1):26-32. doi: Endometrial micropolyps with fluid hysteroscopy indicate the presence of chronic endometritis (Cicinelli E, Resta L, Nicoletti R, Zappimbulso V, Tartagni M, Saliani N). *Hum Reprod* 2005; 20: 1386–1389.