Archives of Reproductive Medicine and Sexual Health
ISSN: 2639-1791
Volume 1, Issue 2, 2018, PP: 8-16

Possible Inflammatory Origin of Endometrial Polyps

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Abstract

***Objective:** Endometrial polyps are the most frequent gynaecological pathology. The growth of endometrial polyps (EP) is though to be related to abnormal hormonal signalling; however, endometrial polyps and chronic endometritis (CE) frequently coexist. The aim of this study was to evaluate the expression of VEGF and TGFβ isoforms in the epithelium and stromal cells from endometrial polyps (P) and in the endometrium from the contralateral side of the cavity in women with or without signs of CE.*

***Design:** Case-control study.*

***Setting:** Academic Centre.*

***Patients:** Forty-six women referring for hysteroscopy were divided into 2 groups on the basis of hysteroscopic findings. Group A with endometrial polyps and normal controlateral endometrium, and Group B with polyps and presence of signs of CE.*

***Interventions:** Office hysteroscopy, polypectomy and endometrial biopsies.*

***Main Outcome Measures:** The immuno-histochemical evaluation of VEGF, TGFβ1, TGFβ2 and TGFβ3 expressions.*

***Results:** VGEF, TGFβ1 and TGFβ2 were expressed more in the glandular epithelium than in stromal cells. VGEF and TGFβ1 levels in women with CE were higher compared to women without CE and in polyps compared to the contralateral endometrium. On the contrary, in the stroma the expressions of TGFβ1 and TGFβ2 showed no inter-group differences. However, TGFβ3 was significantly overexpressed in polyps from group B but not from group A and in particular in the stromal cells with "spindle cell" characteristics.*

***Conclusions:** The different expressions of growth factors may imply the existence of two different kinds of endometrial polyps, one hormone dependent and the other of inflammatory nature. The different nature may result in different symptoms, risk of relapse, reproductive and oncologic consequences.*

Keywords: Endometrial polyps, inflammation, chronic endometritis, VEGF, TGFβ.

Introduction

Endometrial polyps are a common endouterine pathology consisting of benign mucosal outgrowths. In the absence of any symptoms, an endometrial polyp may be an unexpected finding on ultrasound or hysteroscopic examination; however they have been associated with reproductive problems and abnormal uterine bleeding (AUB).

Polyps, indeed, may affect the implantation of the embryo not only by causing the deformation of the uterine cavity , but also by impairing the expression of genes and of the paracrine factors involved in the endometrial receptivity process, such as homeobox A-10, -11, interferon-γ (INF-γ), VEGF etc [1,2,3]. Additionally, in women complaining of AUB, polyps are the most common finding on hysteroscopy [4].

Traditionally, the pathogenesis of endometrial polyps is thought to be related to an imbalance in ovarian steroids and to an abnormal estrogenic stimulation [5, 6]. Obesity is an independent risk factor in the development of endometrial polyps which is in syntony with estrogenic hyperstimulation [7]. Furthermore, polyps show an abnormal paracrine expression compared to a normal endometrium. A significant difference in the cycle-dependent inhibin expression has been demonstrated in a normal endometrium and polyps, suggesting that endometrial polyps may be tumours of dysregulation with mainly proliferating characteristics, being unable to synchronise with the normal endometrium [8].

From a clinical point of view, no medical treatment or prevention for endometrial polyps exist. Only, the prophylactic levonorgestrel-releasing intrauterine system has shown to be effective in preventing de novo endometrial polyps in women using tamoxifen [9]. Moreover, polyps frequently recur even after resectoscopic polypectomy or in women with no evident risk factors [10]. This may suggest that the aetiology and the mechanisms underlying endometrial polyp formation are still not completely known.

Interestingly, in recent years growing evidence has been accumulated about the possible inflammatory origin of endometrial polyps. A higher expression of the inflammation mediator INF-γ has been found in the endometrium of women with endometrial polyps [3]. In women diagnosed with chronic endometritis (CE), fluid hysteroscopy has shown endometrial micropolyps which are small outgrowths typically 1-2 mm in length [11]. On histology micropolyps show an inflammatory origin with a leucocyte infiltrate surrounding the vascular axis. Finally, our great experience of more than 25.000 diagnostic hysteroscopies showed that polyps and/or a polypoid endometrium frequently coexist with micropolyps or with other signs of CE such as stromal edema and hyperaemia [12]. In accordance, it has been suggested that the vessel axis of functional polyps may actually originate from the evolution of the vascular changes associated with endometritis placing functional polyps among the spectrum of inflammatory endometrial diseases [13].

The prevalence of CE in the general population is poorly known as this is a subtle pathology often asymptomatic or only accompanied by mild disturbances (pain, bleeding etc.). Notably, CE may hamper endometrial receptivity and may cause infertility. We demonstrated the presence of CE in 57.8% of women with recurrent miscarriages and in 66% of women with repeated implantation failure after IVF [14, 15].

The present study aims to evaluate the hypothesis of an inflammatory etiology for part of endometrial polyps. For this purpose, we compared the endometrial expression of several inflammatory and paracrine growth factors in the stromal cells and glandular epithelium in samples from patients diagnosed at hysteroscopy and histology with endometrial polyps without signs of CE and with both evidence of CE and endometrial polyps.

Materials and Methods

Records and histological samples were evaluated from women who had referred to our department from December 2013 to June 2014 for an out-patient hysteroscopy on suspicion of endometrial polyps. All patients were in reproductive age, in good general health and free from antibiotics or anti-inflammatory drugs for at least 3 months. Women undergoing hormonal therapies were excluded. Submucous myomas, adenomyosis, placental remnant, potential neoplasms were excluded (Table 1).

The study was approved by the local ethical committee of the Department of Obstetrics and Gynecology, University of Bari, Italy and the all women authorized the treatment of their personal data. There were no known conflicts of interest associated with this study and there was no significant financial support for this work that may have influenced its outcome.

Hysteroscopies were performed using a lens-based 2.7 mm OD mini-telescope, 105° angle of visual field equipped with a 4.5 mm OD double-flow operative sheath (Karl Storz, Tuttlingen, Germany). All hysteroscopies were performed in the follicular phase (cycle day 7-12).

A saline solution was employed to distend the uterine cavity at a pressure generated by a simple drip from a bag, suspended 1 m above the patient. A 300 W light source with a xenon bulb and a High Definition digital camera (Karl Storz, Tuttlingen, Germany) were used.

During hysteroscopy both the anterior and posterior uterine walls were thoroughly examined by passing the hysteroscope parallel to the endometrial surface.

This way, any surface irregularity was easily identified.

All hysteroscopies were performed by two of the authors (E.C., M.M.). Polyps were defined as any outgrowth of the endometrial surface. Particular attention was given to subtle lesions, suggesting the presence of CE and namely to micropolyps, hyperhemia and adhesions [12]. The histological diagnosis of CE was carried out based on the criteria described in the publications from our group. More specifically, the diagnosis was made in the presence of a stromal infiltrate dominated by lymphocytes and plasmacells, "spindle cells" change of stromal cells and glandular lysis aspects [16].

In 17 cases endometrial polyps were found without hysteroscopic signs of CE and the contralateral endometrial wall appearing normal (Group A) (Fig. 1a). In 12 cases, endometrial polyps co-existing with hysteroscopic signs of CE were found (Group B) (Fig. 1b) (Table 1).

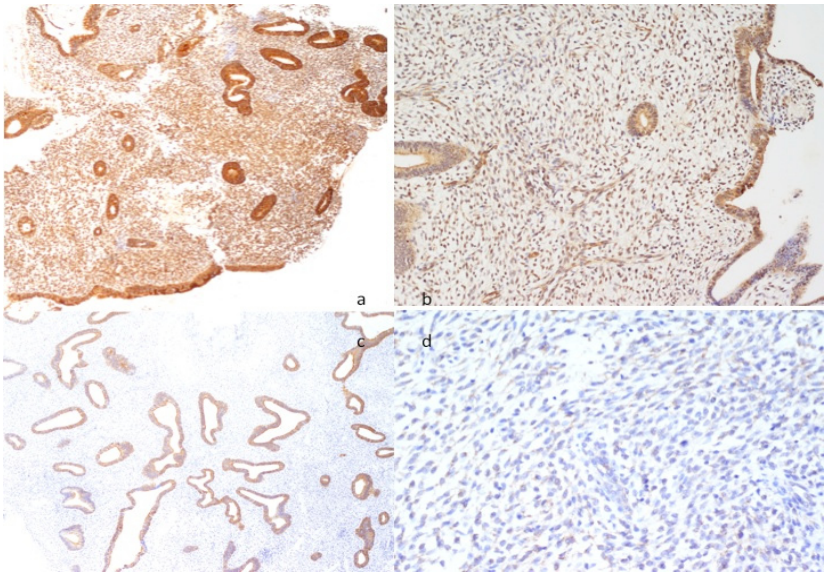

Fig 1. *Immunohistochemistry for VEGF, TGFß1, TGFß2, TGFß3. a) VEGF is immunohistochemically strongly expressed both in epithelium and in stromal cells (x100). b) The expression of TGFß1 is evident in epithelium and in vascular endothelium (x100). c) The TGFß2 is expressed only in the epithelial cells (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
BMI[a]	25.06 ± 2.61	25.08 ± 2.23
Parity (n.)[a]	1.71 ± 0.92	1.50 ± 0.52
Miscarriages	2	5
Intrauterine procedures[b]	3	4

[a]Data are mean ± SD.

[b]With intrauterine procedures, we mean previous D&C, endometrial biopsy, IUD insertion or hysteroscopy

The slides, after being washed in deionized water, were immersed in an antigen retrieval solution (buffered citrate pH 6 for TGFβ 1-3, EDTA pH 8 for VEGF) at 98°C for 15'. After cooling, the slides were incubated with fresh 3% hydrogen peroxide and rinsed in PBS. The incubation with the primary antibody was prolonged overnight at 4°C. After being washed three times in PBS (5' for each rinsing) the slides were submitted to the ENVISION FLEX/HRP automatic revelation system by DAKO. The chromogen used was 3-3i'-Diaminobenzidine and Mayer's hematoxylin was utilized for nuclear counterstaining.

As positive controls were used human placenta sections while as negative controls were used test samples sections not incubated with antibodies.

Sections with the immunohistochemical expression were evaluated by a semi-quantitative scoring method, validated in previous works [17]. The scoring system, applied in two different sequences in the same case (first for the epithelial cells and then for the stromal cells), is a count of positive cells at magnification x 200. Score 0: negative stain; score 1: <1% of positive cells; score 2: 1-10% of positive cells; score 3: 10-33% of positive cells; score 4: 33-66% of positive cells; score 5: >66% of positive cells. In addition, we gave a further score of 0-3 based on the intensity of the stain reaction. Score 0: negative staining; score 1: weakly stained cells; score 2: moderately stained cells; score 3: strongly stained cells. The total score therefore varied from 0 to 8. We evaluated in blinded manner 10 fields for each case, divided by two of the authors (L.R., R.R.), and a mean value ± standard deviation was obtained.

The statistical analysis was performed by an univariate discriminant analysis (Student's t-test) and Chi-square test. A P value < 0.05 was considered the limit of significance for the Chi-square test. The critical value of t for the significance of difference was computed by a Bonferroni's correction from the input value of P<0.05 for 12 comparisons, resulting in P<0.00256. This allowed to reduce the chance of making a type one error in using Student's t-test for multiple comparisons [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, TGFβ1, TGFβ2 and TGFβ3, are displayed in Table 2.

Table 2. The immunohistochemical expression of VEGF and TGF isoforms as assessed with the semi-quantitative scoring method validated in previous works (Xuebing et al 2011).

	VEGF	TGFβ1	TGFβ2	TGFβ3
Group A				
P (glandular epithelium)	7.19 ± 0.65	2.71 ± 0.56	3.12 ± 1.15	3.06 ± 1.12
P (stroma)	5.01 ± 0.99	0.22 ± 0.12	0	0.37 ± 0.50
NP (glandular epithelium)	6.14 ± 0.69	1.43 ± 0.94	2,43 ± 1.51	1.88 ± 1.36
NP (stroma)	3.72 ± 0.95	0.38 ± 0.80	0	0.37 ± 1.06
Group B				
P (glandular epithelium)	7.58 ± 0.51	2.14 ± 0.98	3.08 ± 0.90	2.51 ± 1.18
P (stroma)	6.58 ± 0.67	0.27 ± 0.27	0	2.17 ± 1.27
NP (glandular epithelium)	7.42 ± 0,67	2.73 ± 1.21	2.58 ± 0.90	2.25 ± 1.14
NP (stroma)	6.50 ± 0.67	0.32 ± 0.45	0	2.33 ± 1.30

Data are mean ± 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.

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	TGFβ1	TGFβ2	TGFβ3
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.

1) values of group A: polyps , glandular epithelium
2) values of group A : polyps, stroma
3) values of group A : normal endometrium, glandular epithelium 4) values of group A: normal endometrium, stroma
4) values of group B: endometrial polyps, glandular epithelium
5) values of group B: endometrial polyps, stroma
6) values of group B: endometritis (no polyp area), glandular
7) values of group B: endometritis (no polyp area), stroma

As reported, in all the groups VEGF was expressed more in the glandular epithelium than in the stromal cells. More precisely, VEGF was significantly more expressed in women with CE (Group B) compared to women without CE (Group A) and in polyps compared to the contralateral endometrium, limited to stromal expression.

In accordance with the VEGF expression, also the TGFβ1 and TGFβ2 expressions were higher in the glandular epithelium than in the stroma. The glandular expression of TGFβ1 in all samples from polyps (with and without signs of CE) was comparable and in both cases significantly higher compared to contralateral endometrium in women from Group A.

In the stroma the TGFβ1 expression was weak in two groups. Notably, on immunohistochemistry in the cases with CE (Group B) a weak and diffuse expression of TGFβ1 localized in the endothelium of stromal vessels was observed.

As reported above, the expression of TGFβ2 was observed only in glandular cells but with no differences in the 2 groups.

On the contrary, TGFβ3 showed significant intergroup differences not only in the glandular cells but also in the stroma. More precisely, as observed for TGFβ1, in the glandular cells from polyps, the expression of TGFβ3 was higher than in the contralateral endometrium, without signs of inflammation (Group A). Moreover, in the stromal cells from Group A (cases without signs of CE) the TGFβ3 expression was low on both sites (polyp and contralaterally), while, on the contrary, it was significantly overexpressed in samples from Group B (both from polyp and contralateral areas). Interestingly, in the cases with signs of CE (Group B) TGFβ3 appeared to be over expressed in specific stromal cells with the characteristics of "spindle cells", which were previously found to be correlated to CE [16] (Fig. 1).

Discussion

Endometrial polyps are a very frequent pathology which may cause AUB and reproductive problems. Traditionally, endometrial polyps are considered to be hormone dependent and related to an abnormal estrogenic effect [5]. The results of the present study demonstrate that endometrial polyps does not represent a homogeneous population. In some cases, in fact, they grow in an inflammatory context showing an altered paracrine pattern with overexpression of inflammatory mediators at both both glandular and stromal levels.

In fact, the results of this study demonstrate that in all the polyps of our study stromal VEGF expressions were increased compared to the contralateral endometrium. However, only in the case of polyps grown in an inflammatory context there was a strong stromal activation of TGFβ3 (about 7 times higher than in the polyps without CE).

The higher expression of VEGF in all kinds of polyps with respect to the contralateral areas, is in accordance with the growth factor nature of this molecule. Our data confirm those from Xuebing and colleagues who also found an overexpression of VEGF in polyps compared to the adjacent normal endometrial tissue [17].

Data in literature show that a normal endometrium expresses TGFβ although no conclusive data exist on a cycle dependent production [19, 20]. To date, conflicting data exist on the pathophysiological role of TGFβ1. This is a potent growth inhibitor of epithelial cells, and the identification of inactivating mutations within TGFβ1 signalling pathway in cancers, confirmed that TGFβ1 signalling is a tumour suppressor pathway for early stages of cancer [21]. However, many human carcinomas overexpress TGFβ1 and this has been associated with poor patient prognosis and increased frequency of metastasis. Similar results have been observed in tumour cell lines and experimental animal models. Thus stage specific duality of function is the emerging paradigm for the role of TGFβ1 in cancer [22]. In addition, TGFβ1 is recognized as being involved in angiogenesis and in connective tissue growth [23]. In our study, TGFβ1 was significantly more expressed in the glandular epithelium than in the stroma and in the polyps compared to a normal endometrium suggesting that it may concur to benign endometrial proliferation. Similarly, TGFβ2 was also expressed in the glandular cells but not in the stroma, independently from the inflammatory state. Notably, the TGFβ3 expression was increased in the glandular cells of the polyps from groups A and B compared to the contralateral endometrium from Group A. TGFβ3 is known to be involved in the development of many organs, in cancerogenesis and in the modulation of connective tissue in wound recovery [24]. This finding allows us to speculate on a possible relationship between chronic inflammation and proliferative pathologies. Gold and colleagues found that the glandular epithelium demonstrated a statistically significant stepwise increase in the expression of all three TGF-β isoforms from the normal proliferative endometrium, simple hyperplasia and complex hyperplasia; comparing proliferative endometrium with complex hyperplasia, they found 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 higher expression of VEGF and TGF-β3 in the stroma of samples from Group B as a marker of an inflammatory condition is in agreement with Kazanawa et al. who found an overexpression of VEGF, TGF-β2 and TGF-β3 in inflammatory cells of active inflammatory bowel disease [26].

The inflammatory nature of part of the polyps and the increased expression of growth factors may be related to the possible coexistence of micropolyps, that are small endometrial outgrowths provided with a vascular axis. Micropolyps have been demonstrated to be a reliable marker of CE on both hysteroscopy and histology [11, 12]. Moreover, the strong activation of paracrine factors involved in angiogenesis and epithelial growth, may explain the reported possible relapse of polyps in some patients [27]. In fact, we can speculate that the coexistence of CE may facilitate the regrowth of the polyp, or the growth of a new one.

We have to acknowledge that basing on the data of this study we cannot establish if endometrial polyps may actually have an inflammatory origin as the altered expression of some paracrine factors in Group B may be simply related to the coexisting presence of CE. However, the dual origin of endometrial polyps has been already suggested by Kitaya and coworkers who demonstrated that in infertile women the macropolypoid endometrium and the micropolypoid endometrium show a different proportion of mononuclear cell subsets, suggesting the different nature of the two conditions [28]. More precisely, the authors found that the pan-leukocyte density in the endometrium proliferative phase was significantly lower in endometrial macropolyps than in those with micropolyps or in fertile women. Moreover, they confirmed that the endometrial micropolyps were often concomitant with CE and that in these women the plasmacyte infiltrates were accompanied by an unusual focal B cell invasion. On the contrary, only a few macropolypoid endometrial samples had a plasmacyte infiltration, as macropolyps originate differently from the micropolyps ; endometrial macropolyps should develop under an estrogen-sensitive condition, whereas endometrial micropolyps may grow in an inflammatory microenvironment [28].

We can speculate that endometrial infection with a chronic inflammatory condition may promote and fuel endometrial proliferation playing a role in polyp growth, hyperplasia and possibly in carcinoma pathogenesis. Our data, even if limited to a small number of cases, speak in favour of a link between endometrial inflammation and carcinogenesis as the TGFβ activation has been demonstrated in the case of endometrial hyperplasia and carcinoma [25]; moreover, it is known that an inflammatory status may stimulate aromatase and steroid receptor expression in endometriosis [29].

An interesting new finding of this study, is the stromal expression of TGFβ3 in case of inflammation. In particular, TGFβ3 appears expressed in a particular type of cells with a fusate aspect known as "spindle cells" which we have demonstrated to be helpful in the morphological diagnosis of CE [16]. However, at the moment the nature and functions of such cells are still unknown. The finding that the TGFβ3 expression is particularly evident in spindle cells may suggest the role of these cells in the processes of stimulation and growth of polyps.

As the etiopathogenesis of CE of suspected inflammatory nature is traditionally related to intrauterine manoeuvres. We compared the rate of miscarriage and previous intrauterine procedures (D&C, endometrial biopsy, IUD insertion or hysteroscopy) within the three groups. Interestingly, not only no significant differences were found but only a few patients had previously undergone intrauterine procedures at risk of transporting infectious agents. This finding, even considering the limited number of cases, allows us to speculate that in many cases the origin of endometrial inflammation may be due to spontaneous ascending infections.

In conclusion, the findings of the present study allow us to speculate on the existence of two different kinds of endometrial polyps, one hormone dependent and the other of an inflammatory nature. The different nature may result in different symptoms, risk of relapse, reproductive and oncologic consequences of endometrial polyps.

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Citation: **Resta L, Cicinelli E, Lettini T, et al.** *Possible Inflammatory Origin of Endometrial Polyps. Archives of Reproductive Medicine and Sexual Health. 2018; 1(2): 8-16.*