Review Article

The pathogenesis of endometrial polyps: a systematic semi-quantitative review

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Summary

The pathogenesis and natural history of endometrial polyps are not very clear. The objective of this study was to assess the opinions of international medical literature regarding the factors involved in the pathogenesis of endometrial polyps and to organize the results consistently with what is known about endometrial physiology. *Materials and Methods:* A systematic review was carried out with the following search engines: PubMed, OVID, Scopus, SCIELO, and AJOL. Two hundreds forty-six abstracts were selected from the literature; of these abstracts, 58 factors were extracted and set as causative, non-causative, unclear or protective link with endometrial polyps. This relation is described through a correspondence analysis and tested with a main effect hierarchical log-linear model. *Results:* The log-linear model resulted significant for the correspondence found with the following factors: (i) causative link (ageing, bcl-2 protein, excess weight/obesity, tamoxifen regardless of timing, relationship between estrogen receptors and progestinics, unbalanced estrogen therapy, estrogen-like effect, and unbalance between estrogens and progestinics), (ii) protective link (progestinics, antiestrogenic action), (iii) unclear link (menopause, ki-67 protein, angiogenesis, tamoxifen for a short time, tamoxifen for a long time, hormone replacement therapy (HRT), endometritis/inflammation), and (iv) non-causative link (none of the factors specifically). *Discussion:* Subsequently to a review of the physiology of the endometrium, the onsetting of endometrial polyps was suggested through estrogen-related and non-estrogen related ways; the two ways can overlap. The most implied factors in the development of endometrial polyps are linked with one of these or both ways.

Key words: Endometrial polyps; Pathogenesis; Estrogens; Progesterone; Apoptosis.

Introduction

Endometrial polyps are a very common pathology [1, 2]. They are easily treated through endoscopy [3], they can conceal tumors [4-6], and are often removed.

The endoscopic systematic removal of the polyps has contributed to an increase of publications of clinical studies focusing on risk or protecting factors and on some molecular aspects of pathogenesis. Notwithstanding the timing that polyps need to generate and why, should be taken into account to fully understand the pathogenesis. The time that polyps need to fully develop and their risk factors are unknown. In fact, only deWaay *et al*. [7] analysed the natural development of polyps. This study states that only the small polyps tend to spontaneously recede while the larger ones are more prone to continue growing. This suggests that some factors can play a beginning and promoting role for the polyps' development and these factors act in a synergic or sequential way.

To logically assess and order the vast literature on the endometrial polyps' pathogenesis, the authors undertook a systematic review with a semi-quantitative approach. This should assess the value that has been attributed to epidemiological or molecular risk factors in polyps' development.

Then, according to what is known about the endometrial physiology, the authors examined from a pathogenetic point of view, the most recognised risk factors.

Materials and Methods

On October 11th, 2011 a bibliographic research was carried out with the following search engines: PubMed, SCIELO, OVID, Scopus, and AJOL. The keywords used were the following: "endometrial polyps physiopathology", "endometrial polyps hormone", "endometrial polyps oxidative stress", "endometrial polyps growth factor", "endometrial polyps cytokines", "endometrial polyps inflammation", and "endometrial polyps risk factors".

The research obtained 1,067 references. From this list, duplicates, works of which abstracts were not relative to endometrial polyps, abstracts not directly or indirectly relative to endometrial polyp pathogenesis, and works without an abstract, resulted in a total residue of 246 references. These references are listed in Table 1.

These references' abstracts were read in order to extract any reference to endometrial polyp pathogenesis within the text. Such information is linked to one or more factors implied in endometrial polyp pathogenesis (e.g. tamoxifen use, hormonal unbalance, gene bcl-2 expression, etc.). Fifty-eight factors were identified through the abstracts; these are listed in Figures 1, 2, and 3.

The information can be extracted through logical links within the medical texts sentences [8] and have been used in the medical field to interpret biological processes [9]. Moreover, through this information, the competent readers can assess the relevance of the medical abstracts unbiasedly, similarly to how

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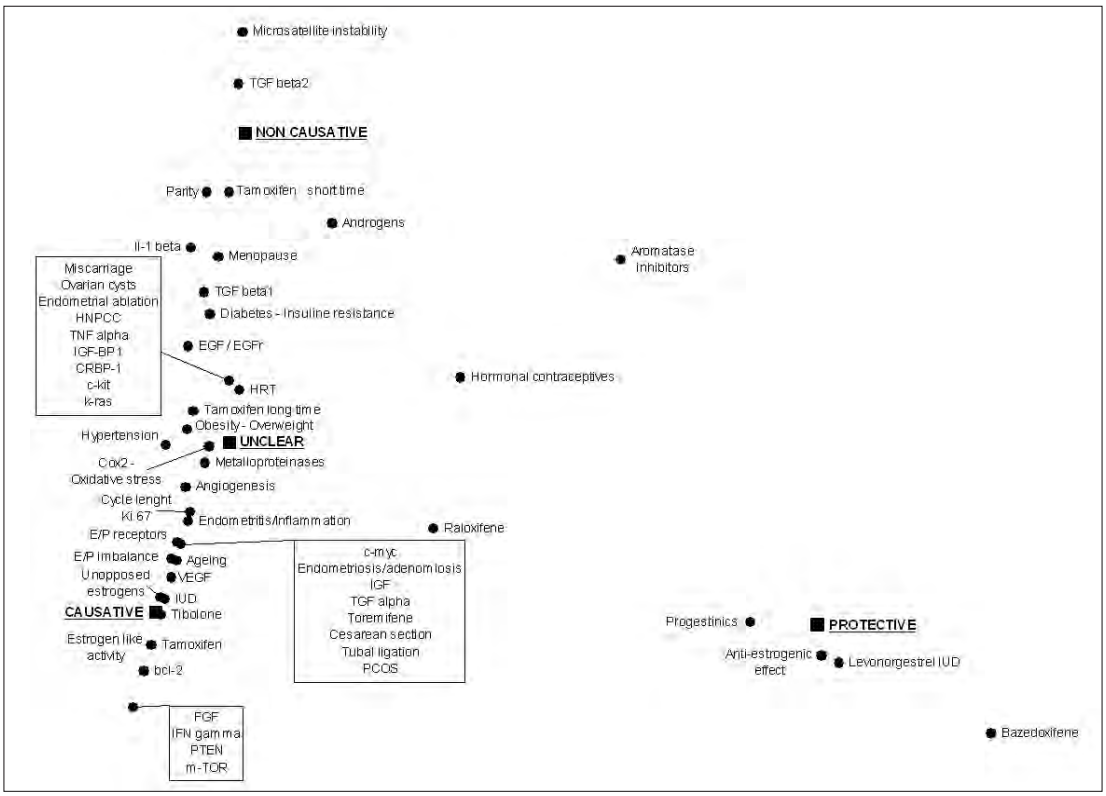

Figure 1. — Perceptual map from correspondence analysis. Causative link, non causative link, unclear link, and protective link are highlighted as the squared points of a bi-dimensional map. Fifty-eight factors are reported as smaller circular points. The closer the factors are to the squared points, the stronger the association is. E: Estrogens. P: Progesterone.
CRBP-1: Cellular Retinol Binding Protein-1. Cox-2: Cyclooxygenase-2. EGF: Epidermal Growth Factor. EGFr: Epidermal Growth Factor Receptor. FGF: Fibroblast Growth Factor. HNPCC: Human Non-Polyposis Colon Cancer. HRT: Hormonal Replacement Therapy. IFN: Interferon. IGF: Insuline Growth Factor. IGF-BP1: Insuline Growth Factor Binding Protein-1. Il-1: Interleuchin-1. IUD: Intra-uterine Device. PCOS: Polycystic Ovary Syndrome. TGF: Transforming Growth Factor. TNF: Tumor Necrosis Factor. VEGF: Vascular Endothelial Growth Factor.

mathematical algorithms would be used [10]. Therefore this information can be used for inference [8].

Based on the logical nexuses present in the sentences of the selected abstracts, every factor was assigned a causative link, a protective link, a non-causative link or an unclear link, with the development of an endometrial polyp.

The frequencies with which every factor was assigned a causative, protective, non-causative or unclear link are described through a two-dimensional correspondence analysis [11]. Such analysis allows to quantify the importance of the association of each factor with each of the four pathogenetic links just mentioned (causative, protective, non causative, and unclear). Such importance is evident in a two-dimensional representation (perceptual map).

The closer the factor is to one of the pathogenetic links and the more distant it is from the others (correspondence), the stronger the importance of the association is. Hence the distances between each factor and the predetermined logical links were calculated. Such distances were represented in a percentage scale, where the closest proximity corresponds to the highest importance according to international literature.

A log-linear model (main effect hierarchical log-linear model) was used to assess whether the correspondence found was significant. The standardized residuals extracted from the model have been graphically represented in order to highlight for which factors the log-linear model is relevant. The higher the standardized residuals are, the more it is agreed upon within the medical literature that the correspondence between that factor and that link is relevant. It is necessary to report the residuals because each factor's frequency relating to each pathogenetic link (causality, protection, indifference, and non-clarity) can bias the importance extracted from the correspondence analysis and represented through the percentage scale. For example, if a factor has been examined in just one study, the possible causative link expressed by the authors of that study in the abstract would result very strong in the correspondence analysis, even if there are no other opinions to support it. SPSS 16.0 was used for statistical analysis, with $p < 0.05$.

Results

In Figure 1 the authors show 58 factors that have been recognised as influencing polyp pathogenesis (perceptual map). After a log-linear analysis, the correspondence shown in Figure 1 appears statistically significant (likelihood ratio 752,154, $p < 0.001$; Pearson Chi-square 849,289, $p < 0.001$).

Figure 2 shows the importance each 58 factors that have been attributed according to the four pathogenetic links (causality, protection, indifference, and non-clarity).

In Figure 3 the highest value of standard residuals shows which factors have a stronger link with endometrial polyps. These factors included the following: ageing, menopause,

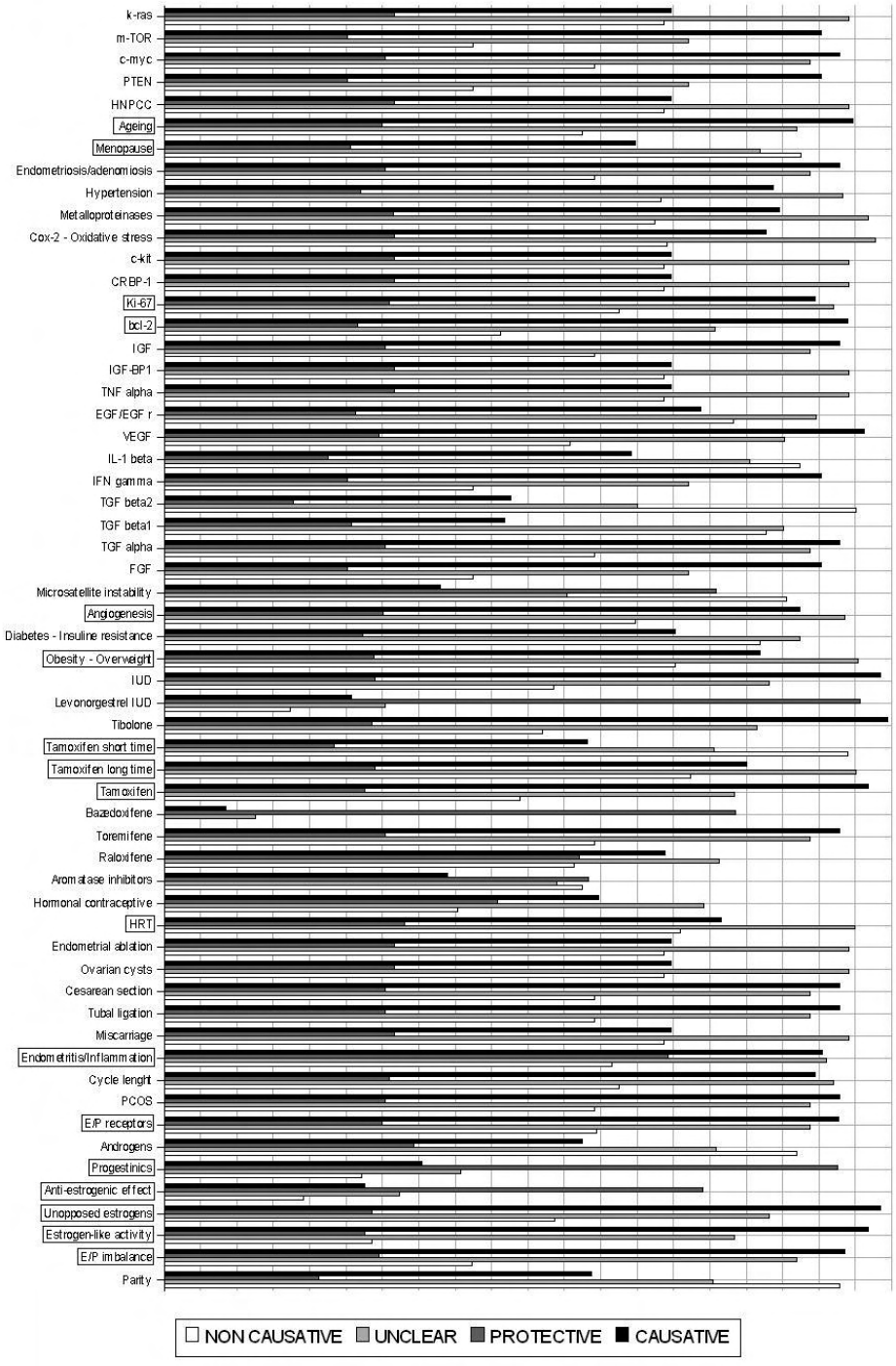

Figure 2. — Graphical representation of the relevance. It was calculated from distances of the perceptual map converted into a percentage scale. Factors more strongly associated with a link are highlighted in boxes.

protein ki-67, protein bcl-2, angiogenesis, obesity/overweight, tamoxifen (for a short time), tamoxifen (for a long time), tamoxifen (regardless of timing), HRT, endometritis/inflammation, relationship between estrogen receptors and progestinics, antiestrogen action, unbalanced estrogen therapy, estrogen-like effect, and unbalance between estrogens and progestinics.

These factors, according to the fixed link, can be ordered as follows: (i) causative link (ageing, bcl-2 protein, excess weight/obesity, tamoxifen regardless of timing, relationship between estrogen receptors and progestinics, unbalanced estrogen therapy, estrogen-like effect, and unbalanced between estrogens and progestinics), (ii) protective link (progestinics, antiestrogenic action),

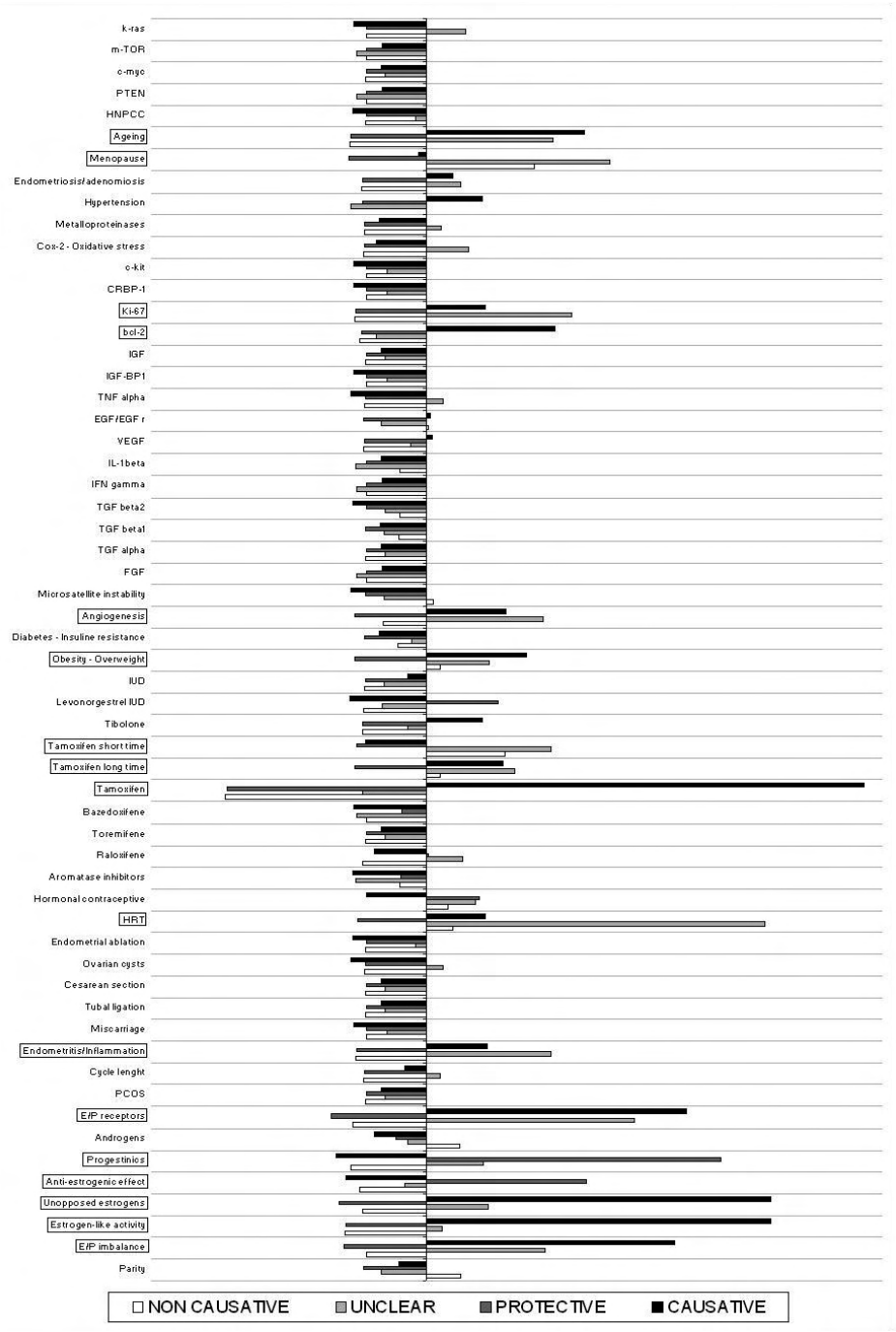

Figure 3. — Graphical representation of standardized residuals for each factors and for each link (causative, non causative, unclear, and protective). Factors with highest standardized residuals (both negative and positive) are considered to be more strongly associated with a link (causative, non causative, unclear, and protective) and are highlighted in boxes. The associative strength of a factor is in relation with the number of abstracts regarding that factor.

(iii) unclear link (menopause, ki-67 protein, angiogenesis, tamoxifen for a short time, tamoxifen for a long time, HRT, endometritis/inflammation), and (iv) non-causative link (none of the factors specifically).

Discussion

The statistical analysis run and the way the authors executed the systematic review (constrained to the availability of the search engines utilised) limit the reliability of the results in relation to the numerous parameters for which there are not many studies. Moreover, by only analysing the abstracts, the authors could not assess the opinions discussed in the full texts. These limitations, however, allow identifying with even more clarity which pathogenetic factors are more relevant as they are acknowledged in several abstracts. Therefore, according

to the results, the authors can conclude that the hormone hypothesis, which states that endometrial polyps develop because of an excess of estrogen activity, in relation to the progestogenic activity on the endometrium, is a widely-accepted hypothesis.

Other studies on the role of additional pathogenetic factors are not entirely conclusive. Some of these could be correlated to hormonal status, for example menopause [12, 13], obesity [14], the expression control of bcl-2 [15], while others cannot have attributed a clear pathogenetic identification (e.g. ageing). Moreover, the literature attributes an unclear link to some factors when their pathogenetic action is not explained even on a presumptive way.

According to what is known on the endometrium physiology, the next section will analyse the pathogenetic action of those factors that are believed to have a nexus with endometrial polyps, with the final aim of summarising in a unique model the endometrial polyps' pathogenesis.

Hormone hypothesis

Menstruation is the clinical expression of the cyclic growth and shedding of the endometrial lining under the control of hormones. Various microarray studies have highlighted how many sets of genes are expressed in the endometrium, during the transition between the advanced proliferative phase and the intermediate secretory phase [16], and how this does not occur in case of endometriosis [17]. The alpha and beta estrogen receptors are expressed in the nucleus of the glandular and stromal cells of the endometrium and tend to decline during the advanced secretory phase within the functional layer of the endometrium [18]. However in the stroma, beta receptor tends to decline less during the secretory phase [19]. For this reason, it is believed that the alpha receptor is the most responsible for the cyclic changes induced by estrogens in endometrium [20]. The expression of progesterone receptors is a consequence of endometrial exposure to estrogens during the first phase of the cycle. The estrogen alpha and progesterone receptors are upregulated during the secretory phase by progesterone [21]. The activation of estrogen beta receptor suppresses the expression of the alpha receptor [22, 23]. It is possible that estrogen alpha receptor may induce the expression of progesterone receptors in the stroma of the endometrium by binding to ovarian estradiol [24]. Finally, within the basal layer, progesterone receptors tend to be consistently expressed during the secretory phase, in the stroma, and close to the vasa [25].

The balance in the expression of estrogen and progesterone receptors at a functional and basal layer in the stroma and in the glandular epithelium regulates endometrial growth and its functions during the menstrual cycle. When an endometrial polyp forms, it is possible that limited areas of the endometrium are estrogen-hypersensitive; this could induce the endometrium to grow also during the second half of the menstrual cycle, thus promoting the growth of a polyp. As the endometrial polyp is formed of a stroma, in which a vascular axis coated in epithelial cells is found [26], the endometrial tissue growth must be specifically related to the endometrial stroma and the vasa, rather than to the epithelial lining. Ludwig *et al*. [27] report that during the proliferative phase, a transitory excess of growth of the endometrial tissue could take place, but the persistence of this during the secretory phase could result in micro polyps. This suggests a low sensitivity to progesterone for some areas of the endometrium. In medical literature, it is generally accepted that a progesterone stimulation of the endometrium or the exposition to substances with an anti-estrogen effect can prevent the onset of endometrial polyps (Figures 2 and 3). On the contrary, there does not seem to be a general consensus regarding the unbalance between estrogen and progesterone receptors as determinant in the development of an endometrial polyp (Figures 2 and 3). Immunohistochemistry studies that searched the link between hormone receptors and polyps in menstruating women have given contrasting results [28-33]. In summary, it seems that polyps in menstruating women are an expression of high levels of estrogen and progesterone receptors in the glandular epithelia, and low progesterone receptors in the stroma, with variable estrogen levels in the stroma.

Some authors [34, 35] have reported the presence of estrogen beta receptors in the nuclei of the vascular endothelial cells of the endometrium, suggesting a direct estrogen-angiogenic role through the beta receptor. As mentioned, the estrogen beta receptor is also the most present in the endothelial stroma during the menstrual cycle. If the estrogen beta receptors' response were to be higher than the alpha receptors, a reduction in the alpha receptor-mediated endometrial response would be expected during the proliferative phase of the menstrual cycle. This implies a reduction in the progesterone receptors' expression and a vascular endothelial and epithelial stroma growth where the estrogen beta receptor is largely expressed. This condition creates the prerequisites for the onset of one or more endometrial polyps. The results of Ye *et al*. [36] support the estrogen receptor imbalance assumption for polyp pathogenesis. These authors have demonstrated that, unlike the estrogen alpha receptor, the estrogen beta receptor is mostly expressed in the endometrial polyps' stroma, compared to a healthy endometrium, and that the extent of such expression is directly related to both serum and local estradiol levels.

Finally, a key point in endometrial polyps' development is the hyperactivation of the estrogen beta receptor, compared to the alpha, during the menstrual cycle's proliferative and secretory phases. This causes a growth of the endometrial stroma, angiogenesis, and progesterone insensitivity.

The role of apoptosis

The endometrial cycle ends with endometrial shedding. The shedding of the endometrial tissue in the basal layer is prevented during the advanced secretory phase by expression of the bcl-2, both on a stromal and on an

epithelial level [37, 38]. The bcl-2 gene expression allows the clonal expansion of the endometrial tissue and the development of a new functional level after endometrial shedding, with the beginning of a new endometrial cycle. Usually, the expression of some proteins of the blc-2 family immortalise the cells, preventing their apoptosis and it is regulated by various cytokines in inflammatory situations [39].

The hypothesis of a deficient apoptosis as a cause determining the onset of endometrial polyps is well-established within medical literature, especially when related to the gene expression for the bcl-2 protein (Figures 2 and 3). Taylor *et al*. [37] state that a pivotal point for the formation of an endometrial polyp is the loss of the regulation of the bcl-2 protein gene expression, concluding that the reason for the polyp's development is not related to an excess of endometrial growth but rather to a loss of physiological mechanisms of apoptosis. Other studies [15, 40-46] have been conducted in relation to the gene expression of bcl-2 when endometrial polyps occur, both in pre-menopause and post-menopause in patients under tamoxifen treatment, HRT, and tibolone therapy. The authors state that there is probably a hormonal implication in the control of the bcl-2 gene expression in endometrial polyps, both in pre- and post- menopause, although a strong quantitative relation between the hormonal receptors and the intensity of the bcl-2 expression has not been found.

The lack of association between hormonal receptors and bcl-2 expression can be explained because immunohistochemical studies provide semi-quantitative evaluations. Moreover, the way the gene expression of bcl-2 at the endometrial level is regulated is in essence not well-understood, although it is intuitive to believe that estrogen and progesterone can indirectly control expression [47]. Maia *et al*. [46] however, state that the bcl-2 gene expression is related to estrogen stimulation during the proliferative phase of the cycle.

It is then necessary to investigate the behaviour of bcl-2 gene when estrogen overstimulation occurs during the first half of the cycle, which continues then in the second half, according to the aforementioned hypothesis of unbalanced estrogen receptors. The patients with endometriosis provide a natural model of over-sensitivity to estrogen of this kind [48, 49]. These patients are over-sensitive to estrogen stimulation via beta receptors [50]. Moreover, the ectopic endometrium is unable to induce apoptosis because the bcl-2 gene is overexpressed. This overexpression is directly related to estrogen receptors [48]. Remarkably, even the eutopic endometrium of patients affected by endometriosis has a less-intense apoptotic capacity compared to the eutopic endometrium of healthy subjects [51]. Bulun [50] has stressed that eutopic endometrium of patients with endometriosis is able to over-express the cyclooxygenase-2 (cox-2), both constituently and via estrogen beta receptor. Cox-2, as known, is an inflammatory marker and induces cellular oxidative stress. Cox-2 expression at the endometrial level increases physiologically when progesterone decreases [52, 53], together with other inflammatory mediators [54-56]. This process has a role in promoting the regeneration of the endometrium after menstrual shedding. It is intuitive and also stated in medical literature [57] that oxidative stress can suppress apoptosis and this can occur also at the endometrial level.

Analysing the endometrium's behaviour in patients with endometriosis, it can be concluded that an inflammatory process is commenced by an excess of estrogen stimulation (via beta receptors) during the entire cycle and this can indirectly lead to inflammation and to the precocious overexpression of bcl-2 gene, via oxidative stress, of which cox-2 is a marker. This generates an exuberant growth of endometrium and angiogenesis and, in absence of apoptosis, endometrial polyps. Some other inflammatory scenarios, independently from hormonal stimulation, can nonetheless generate an endometrial polyp. The literature-established opinion and also deduced in this review support this hypothesis. It is recognised that inflammation can play a role in the generation of endometrial polyps (Figure 2) and there is anecdotal evidence (Figures 1 and 2), that shows a strong causality relation with situations where a stronger inflammation is possible or certain. For example endometrial polyps can be linked to a cesarean section scar [58], with an intrauterine device (IUD) not medicated with levonorgestrel [36, 59], with tubal ligation [60, 61], with endometritis [62], and as already mentioned, with endometriosis [63, 64].

Erdemoglu *et al*. [65], have analysed the cox-2 expression in endometrial polyps in patients during pre- and post-menopause, finding that cox-2 is more expressed in pre-menopause. This tends to be more prominent in epithelium, rather than in the stroma. It also suggests that cox-2 expression in polyps is under hormonal control, and this is indirectly confirmed by Maia *et al*. [66, 67].

The authors can conclude that the presence of an inflammatory state that stops apoptosis in the endometrial functional layer is very likely to be a pivotal point for endometrial polyps' onsetting. The endometrial inflammatory state can be found in various pro-inflammatory conditions (endometriosis/adenomyosis, endometritis, cesarean section scar, tubal ligation, IUD) and when there is an excess of estrogen stimulation. Moreover, given the large incidence of polyps in normal women, the excess of endometrial inflammation is likely to be caused by hormonal dysfunction. This is explainable considering that steroidal hormones normally regulate the mediators' expression of endometrial inflammation [68].

The role of growth factors

Epidermal growth factor/receptor (EGF/EGFr), transforming growth factor alpha (TGFalpha), and platelet-derived growth factor (PDGF) are mitogenic factors for the endometrium's basal layer cells, and are probably controlled by estrogens during the proliferative phase of the menstrual cycle in order to stimulate the endometrium's growth after its shedding [69]. Other cytokines are under progesterone control during the secretory phase, most likely in order to stop expression of metallopro-

teinase – responsible for menstrual shedding [70]. For example, TGFbeta1 suppresses the metalloproteinase at a stromal level [71].

Growth factors could play different roles in endometrial polyps' growth depending on the menstrual cycle's phase and on their localization. There is little evidence throughout international medical literature regarding growth factors' implications in endometrial polyps' growth. Maia *et al*. [72] suggested a role for EGF and for its receptor in both pre-menopausal and post-menopausal endometrial polyp growth, while Gray *et al*. [73, 74] have reported that diethylstilbestrol (DES)-induced TNFalpha's expression can aid in the growth of various types of uterine lesions in rats, including endometrial polyps. However, medical international literature tends to suggest that endometrial angiogenesis does have a role, to some extent, in the growth of endometrial polyps, although it is unclear in what way (Figures 2 and 3).

Physiologically, endometrial vasa growth is mostly controlled by vascular endothelial growth factors (VEGFs). Various isoforms of VEGFs are involved in normal endometrial vasa growth and seem to be constantly produced during the entire cycle [75-77] by the epithelium of the endometrium [78]. It is possible that a source of VEGFs that is important for endometrial vasa growth could be caused by the neutrophils adjacent to the endothelium [79]. Although VEGF's expression is not cyclical, Nayak and Brenner [80] have shown a cyclical growth of the endometrial vasa. This has led to believe that estrogens could induce cyclical expression of VEGF receptors half-way through the proliferative phase [80]. However many other vascular growth factors, including fibroblast growth factor (FGF) and TGFbeta1, control endometrial angiogenesis in a cyclical manner [81], most likely in relation with the hormonal state. It is thus probable that many of these angiogenic growth factors could be under ovarian steroid direct and indirect control, in a not entirely clear way.

Regarding endometrial polyps, Xuebing *et al*. [82] reported that TGFbeta1 is, together with VEGF, involved in their growth, while Hague *et al*. [83] reported that both acid and basic FGF and adrenomedullin are mostly present in the endometria of pre-menopausal women following tamoxifen treatment, suggesting a role for angiogenesis in the pathogenesis of endometrial cancer and endometrial polyps. Cheng *et al*. [84] reported that vasa density and VEGF expression are higher in endometrial polyps compared to healthy endometria, suggesting a physiopathological link between angiogenesis and the growth of endometrial polyps. Maia *et al*. [67] also report a role for VEGF in the development of various uterine pathologies, including endometrial polyps.

Therefore it is believed that a third pivotal reason for which an endometrial polyp develops is the expression of various angiogenic growth factors under hormonal control. The specific role of each of these growth factors in polyps' pathogenesis is yet to be determined, considering the role that the control of cellular apoptosis could play within the growth factors [85].

The role of metabolism and ageing

A specific discussion should be dedicated to the Insulin Growth Factor-I (IGF-I) and to the Insulin Growth Factor Binding Proteins (IGFBPs). Estrogens' control IGF-I during the proliferative phase of the cycle, while during the secretory phase its action is limited by the expression of IGFBP-1 and 3 [86], which sequestrate it and impede its biological action via IGF receptor. Rutanen *et al*. [87, 88] stated that the systemic and endometrial deregulation of IGFs/IGFBPs system can also lead to the onset of malignant and benign endometrial diseases, i.e. endometrial polyps, and the systemic and local deregulation of the IGFs/IGFBPs system can also be determined by metabolic disorders [88, 89]. Ben-Nagi *et al*. [90] have shown a reduction of IGFBP-1 expression in the secretory phase in patients with endometrial polyps. This determines an increase of IGF-I availability for its receptor. IGF-1 regulates apoptosis in various layers controlling the bcl-2 gene expression among others [91]. Keeping in mind that the interruption of apoptosis is considered fundamental in the onset of endometrial polyps, a certain number of polyps can be generated by inhibition of IGF-I mediated apoptosis, explaining why endometrial polyps are related to basal glucose levels [63], diabetes [13], with body mass index (BMI) [92], and arterial hypertension [12, 13, 63]. The regulation of IGFs/IGFBPs could be independent from estrogen activity. Belisario *et al*. [93] stated that polyps' growth is independent from the expression of estrogen receptors in menopausal patients with a high BMI. Therefore, according to the evidence in medical literature, endometrial polyps are, in a percentage of cases, likely to be related to metabolic problems that affect the IGFs/IGFBPs.

Strong evidence in literature is found regarding the link between elderly patients and endometrial polyps (Figures 2 and 3). This relation is independent from menopause, which does not appear as a risk factor in the multivariate analyses [63, 94, 95]. Although in menopause hormonal production is reduced, molecular biological studies have confirmed that even during menopause, endometrial polyps are related to the expression of hormonal receptors [29, 30, 42, 96, 97]. The endometrial polyp's growth in post-menopausal patients is likely to depend on an unbalanced estrogen and progesterone receptor response in some areas of the endometrium. Gul *et al*. [29] have shown that there is a negative correlation between receptors for stromal progesterone and patients' age. Moreover, older studies on animal models and humans [98-101] stated that, when ageing, the diffusion of hormonal receptors for estrogen is more variable within endometrial stroma rather than in the epithelium, and therefore the response to estrogen stimulation is more variable in older animals or humans. Kenemans *et al*. [102] hypothesized that by exposing the endometrium to pulsed estradiol, it is possible to influence the relative abundance of hormonal receptors, with a consequent up-regulation and selective activation of beta receptors. If we embrace this hypothesis, we can expect that during menopause, endometrial polyps can arise from some areas of the endometrium, which are irregularly sensitive to estrogens, with minimal

estrogen hormonal stimulation via beta receptors. Moreover, these polyps in post-menopausal women show deregulation in apoptosis mechanism as they do in pre-menopausal women [15]. Growth factors can also play a role in polyps' development in post-menopause. Loverro *et al*. [103] have shown that TGF beta1 is more expressed in atrophic endometria compared to proliferative and secretory phases.

To conclude, endometrial polyps in post-menopausal patients are likely to develop in a similar way as in pre-menopausal women, taking into account that older patients' sensitivity to estrogen might result in being a lot less predictable compared to pre-menopausal women. The different prognostic relevance of metabolic disorders, suggested by obesity, hypertension, and diabetes, might explain a higher number of polyps in older patients and the oncological implications that polyps have in post-menopausal patients [4, 5, 104].

The role of Selective Estrogen Receptor Modulators (SERMs)

There is large consensus among medical international literature that tamoxifen is determinant in the onset of endometrial polyps (Figures 1, 2, and 3). However, it is still unknown how long it takes for tamoxifen to generate a polyp. In fact, it is still unclear if taking tamoxifen for several months is less dangerous than taking it for years. Few studies have focused on other SERMs with regards to polyps' development. Pinkerton *et al*. [105] have shown that bazedoxifene has a protective effect on the endometrium, as it does not increase the risk of developing polyps when compared to placebo. It has been stated that raloxifene can have a protective effect on the endometrium during menopause [106], while other authors have identified ovarian activation signs in pre-menopausal patients treated with raloxifene, which can lead to the generation of polyps [107]. Finally Zhou *et al*. [108] have shown a similar action spectrum of toremifene to tamoxifen, with the chance of it to lead to endometrial polyps.

Despite the vast literature focusing especially on tamoxifen, it has not been explained in a conclusive way how SERMs can cause the onset of endometrial polyps. Many authors believe that the estrogen effect similar to tamoxifen is responsible for endometrial polyps' development. SERMs' effect on estrogen receptors is variable within different tissues [109, 110]. SERMs' behaviour on the endometrium is presented in the comprehensive review by Cano & Hermenegildo [111]. The biological consequences of stimulation with SERMs on the endometrium will vary depending on the type of SERM, on SERM's metabolism, and on the relative quantity of circulating estrogens and endometrial estrogen receptors. Furthermore, the relative expression of estrogen receptors depends on various factors, such as dysfunctional cycles, hyperestrogenism, previous hormone therapies, inflammatory processes, and ageing. Tamoxifen, and other SERMs likewise, has an influence on the expression of hormonal receptors in a healthy endometrium in post-menopausal women, increasing the quantity of glandular estrogen and stromal progesterone receptors [112, 113]; this effect also occurs in pre-menopausal patients [114]. The estrogen alpha receptor seems to be more expressed than the beta receptor within glandular and stromal epithelia in ovariectomized monkeys treated with tamoxifen in basal and functional layers of the endometria [115]. Tregón *et al*. [116] have shown an immediate increase of ki-67 expression and estrogen receptors after a 21-day tamoxifen treatment, finding simple endometrial hyperplasia through histological examination. Similar results have been revealed by Karack *et al*. [117] for progesterone receptors when treated with tamoxifen. At a later stage, however, the histological effect of endometrial stimulation for patients treated with tamoxifen is variable and seems to be independent from the expression of estrogen receptors [118, 119]. Wang *et al*. [115] hypothesised that during tamoxifen treatment, the activation of the estrogen beta receptor inhibits the expression of the alpha receptor. Therefore the protective effect of tamoxifen on the endometrium could through an estrogen-like activity be more active on the beta receptor when the ERalpha/ERbeta ratio is low. This, as mentioned above, might contribute to the onset of endometrial polyps.

As in a healthy endometrium, also in endometrial polyps of women treated with tamoxifen, there seems to be a variable effect on the expression of estrogen receptors. Dibi *et al*. [120] state that endometrial polyps in women treated with tamoxifen can or cannot express estrogen receptors, and those that do not express these receptors are more frequent when the endometrium is atrophic. Both the estrogen alpha and beta receptors are expressed in endometrial polyps in patients treated with tamoxifen [121]. Schwartz *et al*. [119] also found significant differences in estrogen receptor expression in tamoxifen-related polyps (low stromal levels) compared to non-tamoxifen related polyps (high stromal levels). On the other hand, McGurgan *et al*. [40] have shown that polyps in menopausal women treated with tamoxifen demonstrate a higher amount of progesterone receptors, a higher quantity of bcl-2, and less estrogen receptors, and they have also attributed the most important pathogenetic role for the development of endometrial polyps for patients treated with tamoxifen to apoptosis. As endometrial polyps in patients under tamoxifen treatment do not present high estrogen receptors levels, the assumption of an estrogen-like effect of tamoxifen as a cause of endometrial polyps could not always be valid. Such a possibility is consistent with what has been reported by Cano and Hermenegildo [111] as they highlight how a light tamoxifen stimulation profile on the endometrium could be present regardless of the estrogen-like action. In fact the anti-estrogen effect on the endometrium of tamoxifen increases with time [118, 119], most likely via beta receptors [115]. An unbalanced estrogen-like effect over alpha and beta estrogen receptors is therefore more likely at the beginning of treatment with tamoxifen. As treatment continues, tamoxifen could allow an endometrial polyp to grow by favouring estrogen-independent ways, involving agiogenesis, non estrogen-related apoptosis block, and

cellular proliferation. In fact FGF [83], adrenomedullin [83, 122], and TGFalpha growth factors, TNF-II (113) and EGF receptors, and expression of the ki67 antigene [114, 116], have been higher during tamoxifen treatment. On the contrary, IGFBP-1 is less-expressed during tamoxifen treatment [123].

Concluding, tamoxifen (and most likely other SERMs as well), are able to allow polyps to form probably via two ways: the first is estrogen-related and probably depends very much on the individual endometrial hormonal receptor expression, before and during tamoxifen treatment; the second way is non estrogen-related, that carries angiogenesis, cellular growth, and apoptosis inhibition through unknown mechanisms. This interpretation is justified by the fact that there is no unanimous opinion on how long tamoxifen needs to form endometrial polyps (Figures 2 and 3).

Moreover, the non estrogen-related polyps' oncological meaning during tamoxifen treatment could be different compared to the estrogen-related polyps.

The role of hormone replacement therapy (HRT)

This review's results do not give HRT a clear role in polyps' development. Many studies' abstracts express a pathogenetic role for HRT in endometrial polyps' development. Probably, HRT effect on the endometrium depends on how the hormones are administered [124], on their quantity [125, 126], and on the administration scheme [127]. Moreover, the number of endometrial hormone receptors is variable in post-menopausal women due to the ageing process, so the effect of the same type of HRT should be variable. Hanifi-Moghaddam *et al*. [128] considered the expression of certain sets of genes in endometria in healthy menopausal women under estradiol, tibolone, and estradiol plus medroxyprogesterone acetate treatment over 21 days. Endometrial genes' profile expressed during a balanced hormonal therapy is more similar to the results when no treatment is being administered. On the contrary, gene expression facilitated by tibolone appears to be more similar to that of estradiol, although the expression of some genes is specific only to tibolone. The same authors [129] highlighted how cellular proliferation and stromal and endometrial glandular epithelia apoptosis are at their highest during estradiol treatment, at a medium level during either tibolone or balanced estroprogestinic treatment, and at their lowest when no treatment is being administered. During hormonal treatment, IGFBP-3 is less-expressed, while IGF-I is more expressed. The effect of hormonal treatment on the expression of estrogen receptors (alpha and beta) and for progesterone, seems to be less intense [128]. These data lead to believe that a balanced HRT could be more protective for the endometrium compared to a therapy with just estrogens or tibolone.

Regarding endometrial polyps, McGurgan *et al*. proved that HRT [41] does not influence estrogen and progesterone receptors' expression, and tends to increase bcl-2 levels while inhibiting apoptosis. On the contrary, Maia *et al*. [130] reported that bcl-2 protein and and ki-67 anti-

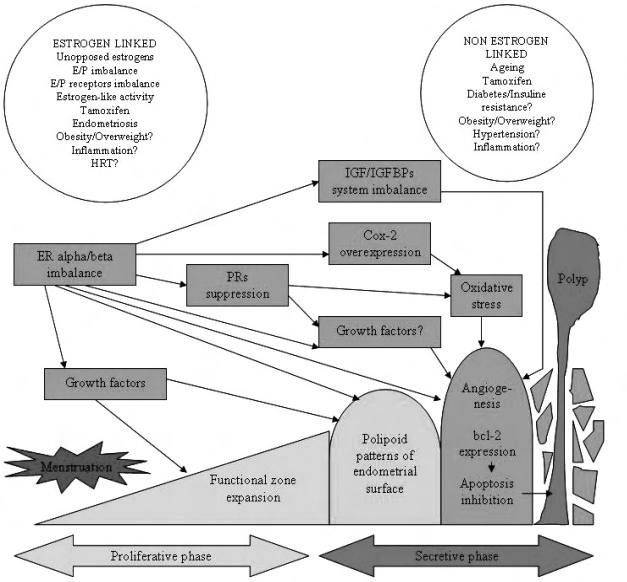

Figure 4. — Proposed model of endometrial polyps pathogenesis. Estrogens may lead to overgrowth of endometrial functional zone via estrogen beta receptor during the proliferative and early secretive phases. This behaviour may trigger oxidative stress via cox-2 and angiogenesis. Angiogenesis is promoted via endothelial estrogen beta receptor and through growth factors in the late secretive phase. When bcl-2 was expressed in the functional zone in the late secretive phase, inhibition of apoptosis saved some islets of endometrium from menstrual breakdown with the onset of polyps. In the succeeding endometrial cycle, polyps may grow in relation to estrogens' sensitivity of both glandular epithelium and stroma and vascular endothelium. Stromal overgrowth could be mainly linked to estrogen beta receptor sensitivity, while glandular epithelium overgrowth could be mainly linked to estrogen alpha receptor sensitivity. Therefore, estrogen-linked endometrial polyps should have a limited growth potential, and their clinical behaviour is set off by hormonal receptors' expression.
Moreover, the IGFs/IGFBPs may have a role in developing endometrial polyps, favouring or causing the onset of polyps independently from hormonal status and hormonal sensitivity. It is unclear if other kinds of growth factors may be able to favour the onset and growth of endometrial polyps independently from hormonal status. The authors suggest to portray this kind of polyp as non estrogen-linked. Some factors may favour polyp onset and growth with both hormonal triggers and non-hormonal triggers. For example, in tamoxifen-linked polyps, the angiogenesis, apoptotis inhibition, and growth of the polyps could be linked both to growth factor/receptor pathways and to estrogen receptor pathway.
Therefore, a double way of endometrial polyps formation is proposed: the most important is the estrogen-related way. Factors mostly involved in this way are listed in the upper-left circle of the Figure. Ageing, metabolic syndrome, and SERMs therapy, may cause endometrial polyp formation through unknown mechanisms. This quote of non-estrogen-linked polyps could have a growth potential and malignant potential differing from the estrogen-linked ones. Factors mostly involved in this way are listed in the upper-right circle of the Figure. Obviously, the estrogen-related and non-estrogen-related ways may overlap.

gene are less-expressed in polyps in women under HRT, concluding that it would allow polyps to grow regardless of bcl-2 and ki-67. Maia *et al*. [131] have also reported that polyps in menopausal patients can express estrogen receptors but are not sensitive to HRT with progestin. These clashing data lead to believe that HRT has a variable effect on the endometrium, sometimes independent of the endometrial hormone sensitivity. In fact if the endometrium was sensitive enough to HRT progesterone, it would be possible to speculate about the balanced HRT as able to prevent the growth of endometrial polyps, in agreement with what international medical literature states regarding progestins (Figures 2 and 3). However, as HRT also has an effect on the IGFs/IGFBPs system [128], it is possible that there is a non-estrogen-related developmental way for endometrial polyps during HRT. In this case as well, endometrial polyps could have a different oncologic potential to those non-estrogen-related.

The role of ki-67

The ki-67 protein is a cellular proliferation indicator [132]. The expression of the ki-67 protein is in an inverse relation with apoptosis in different types of cancer [133, 134]. During the proliferative phase, ki-67 is expressed in the endometrium under the control of estrogen [32], and progestin treatment will reduce its expression [135].

Some studies have considered ki-67 protein's expression in relation to endometrial polyps [15, 37, 40-44, 46, 66, 130, 136]. These studies aimed to assess cellular proliferation through ki-67, in relation to bcl-2 mediated apoptosis in pre-menopausal patients, in post-menopausal patients, during HRT, and during treatment with tibolone or tamoxifen. The results support the assumption of an apoptosis deficit rather than of a direct polyp growth. However an endometrial polyp is not a tumor lesion, that is able to grow independently and freely, in which ki-67 is overexpressed [134]. It is thus explainable how the pathogenic link between ki-67 and polyps, which is probably indirect, remains unclear.

Conclusions

In light of international medical literature's opinion and of the endometrium's physiology, it is concluded that endometrial polyps in most cases arise because of estrogen hypersensitivity in some areas of the endometrium, probably caused by a hyper-activation of the beta estrogen receptor on the alpha receptor during the first phase of the cycle or in post-menopausal women. Furthermore, they do not shed with menstruation because the estrogen-related inflammation could block apoptosis via bcl-2 gene expression (oxidative stress induction, cytokine production). This estrogen-related polyp growth could occur due to angiogenic growth factors' deregulation, produced under hormone control inside the polyp, within a short time, and few cycles. This interpretation explains why small polyps tend to regress, while large ones tend to develop and persist in time [7], and why polyps are clonal lesions [137, 138].

Apoptosis' via bcl-2 control and some endometrial polyps' proliferation, especially if in an elderly patient, during an inflammation or metabolic syndrome, could be independent from estrogens. These endometrial non-estrogen-related polyps could have a different behaviour and neoplastic potential compared to estrogen-related polyps. Moreover, these non-estrogen-related polyps would still be sensitive to hormones whose effect could amplify their growth and neoplastic potential.

This interpretation is summarized in Figure 4 and organizes the vast medical literature regarding endometrial polyps, hoping to guide future studies on their pathogenesis and prognosis in a clinically useful way.

Table 1. — *List of references used for semi-quantitative analysis*

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