PhD Thesis/*tesis doctoral*

Oncological significance of endometrial polyps; *Significado oncológico de los pólipos endometriales*

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Hacemos constar

Que **Don Pietro Gambadauro** ha desarrollado bajo nuestra dirección el trabajo titulado "ONCOLOGICAL SIGNIFICANCE OF ENDOMETRIAL POLYPS; SIGNIFICADO ONCOLÓGICO DE LOS PÓLIPOS ENDOMETRIALES", que reúne las características de originalidad y calidad científica como para ser presentado para optar al grado de DOCTOR.

Para que conste y surta los efectos oportunos, firmamos y certificamos en Santander, Marzo del 2013.

FDO. Dr. Jose Schneider Fontan   FDO.: Dr. Rafael Torrejón Cardoso

"So if you got a trumpet, get on your feet, brother, and blow it"

— Nick Cave

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Abbreviations

AUB	abnormal uterine bleeding
BMI	body mass index
CI	confidence interval
COH	controlled ovarian hyperstimulation
EP	endometrial polyp
ER	estrogen receptors
FIGO	International Federation of Gynecology and Obstetrics
HOXA	homeobox A
HRT	Hormone replacement therapy
IGFBP-1	insulin-like growth factor binding protein 1
IQR	interquartile range
IUI	intrauterine insemination
IVF	in-vitro fertilization
NPV	negative predictive value
OR	odds ratio
PPV	positive predictive value
PR	progesterone receptors
RR	relative risk
SD	standard deviation
SERM	selective estrogen receptors modulator
SIR	standardized incidence ratios
US	ultrasound
VAS	visual analog scale

Abstract

Background: The risk of endometrial hyperplasia and cancer in women with endometrial polyps is low, but still represents a controversial issue. The main objectives of this research were to calculate the frequency of malignant and premalignant endometrial changes, and to identify possible factors associated with malignancy in women diagnosed with endometrial polyp by means of ultrasound.

Materials and methods: Our study population consisted of 1390 consecutive patients referred for hysteroscopy following ultrasonographic diagnosis of endometrial polyps. We have identified all cases of atypical hyperplasia and endometrial cancer, and we have used descriptive statistics to analyze clinical data and stage of disease. Moreover, we have compared lower and higher risk neoplasia, in order to study possible associations. The second part of our research consisted of a case-control study, where the cases of endometrial neoplasia previously identified were compared to controls with benign endometrial polyps. The controls were selected randomly, from the same initial population, and in a ratio of 4:1 (controls:cases). Bivariate statistical analysis and a logistic regression model were used to assess the association between various variables and endometrial neoplasia.

Results: Sixteen cases of endometrial neoplasia were found out of the 1390 patients (1.15%). The frequencies of atypia and cancer in our population were 0.14% and 1.01% respectively. All patients except one were post-menopausal (93.8%). All of them were symptomatic and 93.8% of them had reported bleeding as main symptom. Nine cases had a lower risk disease (56.25%), while 7 had a higher risk cancer (43.75%; ≥stage IA G3). Patients with a higher risk disease were found to be significantly younger, and their polyps were smaller, albeit non-significantly. In our case-control study, 64 controls with confirmed benign endometrial polyps were compared to the 16 cases of endometrial neoplasia. The cases were significantly older (mean age 64.19±9.382 vs 52.03±9.846; $p<0.001$) and had a greater BMI (median 27.66 vs 24.59; $p<0.001$). Other factors significantly associated with endometrial neoplasia were postmenopausal status and bleeding as a main symptom. At multivariate analysis with logistic regression, the only factors that showed a statistically significant association with endometrial neoplasia were older age (OR 1.102; 95% CI 1.015-1.198) and bleeding (OR 13.7; 95% CI 1.486-126.278).

Conclusions: In spite of the common practice to refer all women with an ultrasound diagnosis of polyp for hysteroscopy, the prevalence of endometrial neoplasia in these patients is low (1.15%). Moreover, the malignancy is not confined to a polyp in most of the cases. Among women with an ultrasonographic suspicion of endometrial polyp, bleeding and an older age are independently associated with endometrial neoplasia. In conclusion, our data support the idea that the hypothesized association between polyps and endometrial cancer depends on a detection bias.

Introduction

Endometrial polyps

Pathology

Endometrial polyps are localized, sessile or pedunculated, overgrowths of the endometrial layer, consisting of glands, stroma and blood vessels covered by epithelium and protruding into the uterine cavity (Peterson and Novak, 1956).

The dimension of an endometrial polyp can range from millimeters to several centimeters, and rarely they can protrude from the cervix, and become visible at a speculum examination of the vagina and portio.

While the pathologic diagnosis is relatively clear in case of an intact surgical specimen, such as in case of hysterectomy, endometrial biopsies, obtained by suction or curettage, might be difficult to evaluate, for endometrial polyps. This problem is also common with new, minimally invasive methods for polyp removal, using micro-instruments, some of them electrosurgical. In all those cases, the specimens obtained are often scanty and in fragments, and therefore an endometrial polyp might not be

easily identified. This makes the pathologic assessment difficult, potentially leading to missed or wrong diagnosis. For instance, endometrial polyps might be over-diagnosed as endometrial hyperplasia (Winkler at al., 1984). In view of the possible difficulties of a histological diagnosis, clinical data should always be provided to the pathologist (McCluggage WG, 2006).

An indirect sign of endometrial polyp on bioptic material might be represented by the coexistence of normal and synchronous mucosa with areas of endometrium with a different morphology (Kim et al., 2004).

Often, a fibrous stroma that is also thicker than the normal endometrium is found (McCluggage WG, 2006). Within the endometrial stroma, thick walled blood vessels are commonly seen. The glands are usually irregularly distributed and dilated, and often show signs of proliferative activity (McCluggage WG, 2006). Epithelial metaplasias might be present (McCluggage WG, 2006).

A distinctive microscopic feature of endometrial polyps was described by Kim et al. (2004) consisting in the parallel arrangement of the endometrial glands' long axis to the surface epithelium, a diagnostic feature which was present in 80% of premenopausal women's polyps, while it was not

identified in normal endometrium biopsies used as controls (Kim et al., 2004).

A recent study has addressed the issue of the differential diagnosis of endometrial polyp versus endometrial hyperplasia in difficult cases, such as those where scanty tissue is available (Moritani et al., 2012). By using immunohistochemistry, the authors studied the expression of *p16*, a useful marker in gynecological pathology, on specimens of endometrial polyps and hyperplasia. A significantly higher expression of *p16* was found in the stroma of endometrial polyps (seen in 31 out of 35 cases; 89%), compared to endometrial hyperplasia (1 out of 33 cases; 3%). They concluded that "stromal p16 expression might be a peculiar characteristic of endometrial polyp and constitute a useful marker for the diagnosis, especially in fragmented specimens from biopsy or curettage" (Moritani et al., 2012).

Etiology

The etiology of endometrial polyps is still unknown, although their development and growth seems to be depending on the stimulating potential of estrogens on the endometrium (Lee et al., 2010). This is supported by epidemiological data, such as the rarity of polyp diagnosis in premenarchal women, or the strong association with tamoxifen, a selective estrogen receptor modulator (SERM) (Lee et al., 2010).

Interestingly, the concentrations of estrogen and progesterone receptors (ER and PR) in the glandular epithelium are significantly higher in endometrial polyps than in normal endometrium (Lopes et al., 2007).

On the contrary, the ER and PR concentrations in the stroma are similar in the polyp and endometrium (Lopes et al., 2007).

These findings corroborate the hypothesis of hormonal dependance of endometrial polyps, and also justify the endometrium-like cyclic changes seen in polyps' surface (Maia et al., 2004).

Epidemiology

Medical literature is not univocal on the prevalence of endometrial polyps. This might depend either on the patient groups under study, on the definition of polyp, or on the accuracy of methods used for diagnosis (Salim et al., 2011).

A recent study by Dreisler et al. (2009) found a prevalence of 7.8% of endometrial polyps in a randomly selected population of 619 Danish women, aged 20-74 years old. In this study, the participants were systematically submitted to transvaginal ultrasound and saline contrast hysterosonography. According to the same study, the prevalence of endometrial polyps is positively correlated with age, and is higher in postmenopausal women (11.8 % versus 5.8 % in premenopusal women, p <.01). Interestingly, women younger than 30 years old showed a low prevalence of 0.9% (Dreisler et al., 2009).

Endometrial polyps seem to be more common among infertile women. Hysteroscopy identifies polyps in 16 – 26% of women with unexplained infertility, and in 46% of infertile women with endometriosis (Kim et al. 2003; de Sa Rosa e de Silva et al., 2005).

As mentioned before, the use of tamoxifen is a known, important risk factor for endometrial polyps. Up to 30-50% of women using tamoxifen for breast cancer have been found to have endometrial polyps at hysteroscopy (Dibi et al., 2009; Exacoustos et al., 1995).

Other risk factors for the development of endometrial polyps have been seen in obesity and hypertension (Reslova et al., 1999).

Women using hormonal replacement therapy (HRT) are also considered at higher risk, while the previous use of oral contraceptives seems to represent a protective factor (Dreisler et al., 2009).

An increased risk of endometrial polyps has been reported among patients with cervical polyps (OR 4.83; 95% CI 2.43-9.52; adjusted OR after multivariate analysis 5.42; $p < 0.001$; Vilodre et al., 1997).

An association between endometrial polyps and uterine fibroids has also been documented (Lieng et al., 2009).

Diagnosis

Transvaginal ultrasound

Endometrial polyps are commonly diagnosed at transvaginal ultrasound. In menstruating women, transvaginal ultrasound should be performed during early proliferative phase, when a thin endometrium allows for better accuracy (Nalaboff et al., 2001).

The ultrasonographic appearance of an endometrial polyp is commonly that of an intrauterine echogenic structure which is surrounded by a thin hyper-echoic halo (Martinez-Perez et al., 2003). Sometimes, however, only a non-specific endometrial thickening can be identified at ultrasound (Goldstein SR, 2011). In certain patients tiny hypo-echoic cysts, which can be seen within the context of the polyp, represent the ultrasonographic appearance of dilated glands (Hulka et al., 1994; Baldwin et al., 1999).

Office transvaginal ultrasound is a very convenient diagnostic tool, which, nowadays, represents the most common way to assess uterine pathology. It is simple, well tolerated by the patients, and it successfully combines

low requirements and high availability, being virtually in every outpatient gynecology clinic.

Unfortunately, ultrasound produces a high number of equivocal findings, and its accuracy shows great variability among different studies (Cicinelli et al., 1994; Dueholm et al., 1999; Dueholm et al., 2001).

As a matter of fact, literature data on transvaginal ultrasound compared to hysteroscopy and biopsy for the diagnosis of endometrial polyps, show a sensitivity of 19-96%, specificity of 53-100%, positive predictive value (PPV) of 75-100%, and negative predictive value (NPV) of 87-97% (Salim et al., 2011). This variability in measured accuracy could be explained by the heterogeneity of the published studies, or by a reported low reproducibility of transvaginal ultrasound by means of poor inter-observer agreement particularly among less experienced operators (Dueholm et al., 2002).

A possible bias of studies on the accuracy of ultrasound evaluation of the uterine cavity is represented by the fact that most of them are conducted on selected patient groups, i.e. those presenting with symptoms, such as bleeding, or infertility.

In a recent study by Kasraeian et al. (2011), transvaginal ultrasonography was found to be a moderately accurate test in asymptomatic postmenopausal women. It showed high false-positive rate, and its positive results could not be interpreted (Kasraeian et al., 2011).

The accuracy of transvaginal ultrasound in diagnosing endometrial polyps seems to be improved by the color-doppler identification of a single feeding vessel.

A prospective observational study from Timmerman et al. (2003), shows how the so-called "pedicle artery test" had an apparent sensitivity of 76.4%, specificity of 95.3%, positive predictive value (PPV) of 81.3%, and negative predictive value of 93.8%. Interestingly, the same test showed a PPV of 94.2% for the detection of unspecified focal intracavitary pathology (Timmerman et al., 2003).

Hysterosonography

A sensible improvement to the accuracy of transvaginal ultrasound for the evaluation of abnormalities of the uterine cavity, such as endometrial polyps, came from the introduction of contrast sonography (Kamel et al., 2000; de Kroon et al., 2003). Hysterosonography, i.e. ultrasound of the uterus where the cavity has been filled with a contrast medium, is clearly superior to traditional ultrasound for the diagnosis of intrauterine lesions. The enhanced sonographic contrast of the uterine cavity allows for an easier assessment of an endometrial polyp's features.

Most commonly, a polyp will appear as a hyper-echoic lesion outlined by anechoic fluid. In an early study on transvaginal hysterosonography, Baldwin et al. (1999) described how an hyper-echoic line surrounding the suspected intrauterine lesion, particularly when seen together with cystic areas within the same lesion, allows prediction of focal intrauterine pathology, especially endometrial polyps.

For polypoid lesions, hysterosonography has the same diagnostic accuracy of hysteroscopy, while traditional transvaginal ultrasound shows a sensitivity of only 50% (Soares et al., 2000).

Hysterosonography with saline contrast is significantly more accurate than transvaginal ultrasound for the diagnosis of intracavitary masses (Grimbizis et al., 2010).

Moreover, it is significantly more accurate for the diagnosis of intracavitary fibroids and endometrial polyps if compared with the traditional method (Grimbizis et al., 2010).

Some authors have also found that hysterosonography with saline as a contrast induces significantly less discomfort than hysteroscopy, suggesting that it should be considered the method of choice for the evaluation of the uterine cavity (Rogerson et al., 2002; van Dongen et al., 2008).

Although saline is the most commonly used contrast medium, gel instillation sonography has been reported to be a feasible, accurate alternative, and to have fewer technical failures (Werbrouck et al., 2011).

The use of gel as intrauterine contrast during transvaginal ultrasonography does not seem to affect the examination of endometrial polyps with power Doppler signal (Van Den Bosch et al., 2011).

Hysteroscopy

Hysteroscopy, allowing for direct intrauterine observation and sampling, is still considered the *gold standard* for the diagnosis of polyps and other endometrial pathology.

Similarly to ultrasound, hysteroscopy can be, safely and effectively, performed as outpatient procedure (Nagele et al., 1996). Thanks to the introduction of narrow hysteroscopes, modern entry techniques such as the "no touch" (vaginoscopic) hysteroscopy, and sampling devices such as the *H Pipelle* or micro instruments (5 French), diagnostic hysteroscopy is a method with high compliance, that can be performed in an outpatient setting without any need for anesthesia (Gambadauro and Magos, 2010; Madari et al., 2009; Sagiv et al., 2006).

As for ultrasound, while performing a hysteroscopy in the office setting, patient-doctor interaction is preserved during the procedure, since the awake patient can be informed directly of the findings and might also choose to follow the procedure on a screen (Gambadauro and Magos, 2009).

Another advantage of modern diagnostic hysteroscopy is the possibility of the so-called *see-and-treat* approach for endometrial polyps. A whole

generation of mechanical and electrosurgical micro-instruments is available for use through the hysteroscope's working channel.

Examples of mechanical instruments are represented by microscopic scissors, grasping forceps or biopsy forceps. Advantages of using mechanical instruments are the lack of need of electrosurgical generators and their costs, since these are reusable instruments, albeit relatively fragile (Bettocchi et al., 2004). A potential disadvantage of a purely mechanical tool is represented by the lack of coagulation.

Newer electrosurgical instruments are now widespread, although no major advantages of electrosurgical instruments over mechanical tools have been reported for the hysteroscopic removal of endometrial polyps (Garuti et al., 2008).

Among these, both monopolar and bipolar needle-shaped instruments are available. Monopolar intruments require a non-ionic distension medium, such as glycine or mannitol-sorbitol, while bipolar energy can be used safely in normal saline solutions.

Some authors have reported a possible safer profile of bipolar instruments over the monopolar counterparts, mainly because of the unchanged serum

sodium when operating with normal saline as distension fluid (Berg et al., 2009).

Regardless of the presence of electrosurgical power, and of its nature, all these instruments allow the removal of endometrial polyps in an office setting, turning a diagnostic procedure into a therapeutic one, with obvious advantages also in terms of cost-effectiveness (Bettocchi et al., 2004; Marsh et al., 2006; Saridogan et al., 2010).

A limit in this kind of approach is represented by the restricted time which is usually allocated to outpatient diagnostic procedures in most hospital settings, where tight patient schedules are common. In those settings, it is unlikely to switch to an unscheduled operative procedure since it may result in delays in other following procedures, and unnecessary stress and anxiety in waiting patients.

Moreover, the commonly used 5-French instruments lack the advantageous ergonomics of surgical resectoscopes, like for instance the 90° angle of most cutting loops or an ergonomic handle with spring mechanism. Those advantages are instead still present when using a mini-resectoscope, a promising 16-French device (~5mm in section) which combines the same good ergonomics of a standard resectoscope with the

reduced size of office hysteroscopes (Papalampros et al., 2009). In a prospective, observational study of 30 women undergoing hysteroscopic resection, a prototype of a 16-French, monopolar mini-resectoscope (Karl Storz, Tuttlingen, Germany) was safe and effective for the removal of endometrial polyps (16 cases) and submucous fibroids (4 cases). One third of the procedures (10/30) took place in an outpatient hysteroscopy clinic, while the rest in the conventional operating theatre. Sixteen procedures were carried out without any anesthesia, while fourteen with intracervical block. Intrauterine lesions of a diameter up to 5 cm were completely resected, and all the surgeries took less than 15 minutes operative time.

In spite of some proven advantages, the see-and-treat approach is not yet universally adopted; many patients still undergo a preliminary hysteroscopy for a diagnosis, and a second hysteroscopy for surgical treatment.

In this context, we feel that hysteroscopy as a diagnostic tool cannot be considered suitable for screening, but only as a tool for those cases where first-line investigations, such as ultrasound with contrast, are inconclusive or suspicious, or when there is a persistent symptom such as uterine bleeding in high risk patients (e.g. postmenopausal women).

In case of a clear ultrasonographic diagnosis of intrauterine polypoid mass, and when surgery might be indicated, diagnostic hysteroscopy can be avoided, and an operative procedure can be planned most of the times.

Clinical aspects

Endometrial polyps are often asymptomatic. The clinical significance of endometrial polyps is dependent on two main conditions: abnormal uterine bleeding and subfertility. A relevant third issue relates to the risk of endometrial hyperplasia and cancer in women with endometrial polyps. The latter is a main subject of this thesis and will be reviewed on a specific chapter later on, while the two following sections will review current knowledge on endometrial polyps and, respectively, abnormal uterine bleeding and subfertility.

Abnormal uterine bleeding

Abnormal uterine bleeding is often associated to endometrial polyps. Both pre- and post-menopausal women with polyps commonly have bleeding as presenting symptom. One-fifth of women with post-menopausal bleeding are found to have an endometrial polyp at hysteroscopy (Nagele et al., 1996).

In general, women with endometrial polyps most commonly suffer from heavy periodic bleeding (Lieng et al., 2009), but also other bleeding patterns, such as postcoital bleeding or inter-menstrual bleeding, are possible.

The mechanism for such bleeding is largely unknown, but it has been referred to stromal congestion causing venous stasis and apical necrosis of the endometrial polyps.

Studies have reported increased production of matrix metalloproteinase and cyclooxygenase as well as increased microvascular density in endometrial polyps (Erdemoglu et al., 2008; Tokyol et al., 2009). Those findings support the hypothesis of an abnormal angiogenesis, which might be responsible for dilated and fragile vessels on the surface on endometrial polyps, thus justifying uncontrolled bleeding (Lockwood CJ, 2011).

Despite the epidemiological association between endometrial polyps and abnormal uterine bleeding, a causal relationship is still being debated due to a lack of clear understanding of bleeding pathogenesis.

As a matter of fact, available data indicate that most postmenopausal women with polyps are symptom free and that abnormal bleeding is not

commonly associated with polyps in premenopausal women (Salim et al., 2011).

Abnormal uterine bleeding is not related to number, size or location of the polyps (Hassa et al., 2006).

Interestingly, a study conducted on a population of 686 Danish women between 20 and 74 years old showed that abnormal uterine bleeding is significantly less frequent in women with endometrial polyps compared to women without (Dreisler et al., 2009).

Yet, thanks to the spread of accurate and cheap diagnostic techniques, such as contrast sonography and office hysteroscopy, polyps are often diagnosed accidentally in asymptomatic women.

Moreover, polyp removal is recommended by most gynaecologists in order to treat abnormal bleeding and allow for histology (Clark et al., 2002).

A causal relationship between endometrial polyps and abnormal bleeding could be supported by well-designed trials comparing the clinical results of surgery versus expectancy. A systematic review published in 2006 failed to identify such a study and reported a lack of quality in the available studies on the clinical efficacy of polypectomy (Nathani and Clark, 2006).

The limited available evidence reviewed suggested that hysteroscopic polypectomy leads to improvement in AUB symptoms in the majority of women (75%–100%) in the short- and medium term. The authors concluded with a call for urgently needed randomized controlled trials with the aim of determining the effectiveness and cost-effectiveness of uterine polypectomy, one of the most common procedures in gynaecology.

Since then, a single randomized controlled trial of hysteroscopic removal versus observation has been published (Lieng et al., 2010). One hundred and fifty premenopausal women with an ultrasonographic diagnosis of endometrial polyp were randomized to either hysteroscopic resection with a resectoscope or observation for six months. No difference in periodic blood loss was found between the groups at six months follow-up when using a Pictorial Blood Assessment Chart. However, patients who underwent resection showed better outcomes in terms of mean difference of periodic blood loss measured using a visual analog scale (adjusted difference of 0.7 on a 10-point VAS score; 95%CI 0.11–1.30; p=0.02), and occurrence of gynaecological symptoms at follow-up (7/75 cases vs 28/75 controls; 9.3% vs 37.3%; p=0.001). Interestingly, although the aim of this study was to assess the clinical effectiveness of polyp resection, only a proportion of the patients had gynaecological symptoms (75% in the

resection group and 61% in the control group). Moreover, the main outcomes were subjective, while the patients were not blinded, and a six-month follow-up is relatively short. All these limits have been clearly acknowledged by the authors (Lieng et al., 2010).

We believe that available evidence on the clinical effectiveness of polyp removal is still inadequate and new and well-designed studies would be desirable.

Subfertility

Endometrial polyps are often found in subfertile women. A prevalence of 16-26% has been reported among women with otherwise unexplained infertility (Kim et al., 2003; de Sa Rosa e de Silva et al., 2005).

Endometrial polyps may adversely affect fertility by mechanical interference with sperm transport or embryo implantation, or by functional interference with endometrial receptivity and implantation.

Moreover, polyps have been found in up to 46-68% of infertile patients with endometriosis (Kim et al., 2003; Shen et al., 2011). In these patients,

hysteroscopic resection of polyps and removal of endometriotic foci can increase the chances of conception (Shen et al., 2011).

An association between endometrial polyps and adenomyosis has been recently described (Indraccolo and Barbieri, 2011).

Comparative non-randomized studies show an association between polypectomy and improved spontaneous pregnancy rates (Varasteh et al., 1999; Spiewankiewicz et al., 2003; Shokeir et al., 2004).

A randomized trial from Spain showed that hysteroscopic polypectomy significantly improves pregnancy rates in patients with indication for intrauterine insemination (IUI) (Perez-Medina et al., 2005). The authors randomized 215 infertile women with endometrial polyps, diagnosed at ultrasound, to hysteroscopic polypectomy or diagnostic hysteroscopy and polyp biopsy. The group submitted to polypectomy showed double chance of conceiving following surgery (RR 2.1; 95%CI 1.5-2.9). Interestingly, 65% of the pregnancies in the study group were spontaneous and occurred even before the planned infertility treatment (i.e. intrauterine insemination). The average polyp size in this randomized controlled trial by Perez-Medina et al. (2005) was 16 mm, and available studies suggest that endometrial polyps <2 cm in size appear to have no impact on IVF

outcome (Taylor and Gomel, 2008). Nevertheless, Stamatellos et al. (2008) did not find differences in pregnancy rates after hysteroscopic polypectomy depending on the size or number of the polyps.

At present, no clear evidence supports surgery or expectancy based on polyp size in infertile women, and also a tiny structure with a 1 cm diameter is bulky in the virtual uterine cavity when compared to embryo size or catheters section. Therefore, it is common practice to remove evident intrauterine pathology in the setting of reproductive medicine, regardless of its size.

Recent studies have been trying to identify the factors behind the association between endometrial polyps and subfertility. Endometrial polyps seem to interfere with endometrial receptivity and embryo implantation.

Low *IGFBP-1* and *osteopontin* levels were detected in uterine flushings in mid-luteal phase in patients with endometrial polyps (Ben-Nagi et al., 2009). A significant increase of the same factors was observed following polypectomy (Ben-Nagi et al., 2009).

A decreased expression of PRs has been found in endometrial polyps (Peng et al., 2009). This may result in progesterone resistance and cause

abnormalities in the secretion of progesterone-regulated implantation markers (Peng et al., 2009).

Finally, statistically significantly lower expression of *HOXA10* and *HOXA11* was identified in endometrium from uteri with polyps compared with controls, suggestive of impaired endometrial receptivity (Rackow et al., 2011).

While it seems agreeable that, in fertility patients, polyps should be removed regardless of their symptoms, before embarking in assisted reproductive technology, the management of polyps seen during the course of controlled ovarian hyperstimulation (COH) for in-vitro fertilization (IVF) is controversial (Tiras et al., 2012). Yet, this is not an uncommon circumstance, since women undergoing stimulation with gonadotropins are exposed to a higher level of estrogen, which seems to be a predisposing factor to the development of endometrial polyps (Hinckley and Milki, 2004). Ideally, the strategy to adopt in these cases should be individualized, depending on the number of available embryos, on the reproductive background of the patient and on the success rates of frozen embryo programs of individual clinics (Afifi et al., 2010).

If an endometrial polyp is diagnosed during the COH phase of an IVF cycle, traditional management options include continuation of the cycle and cancellation or total embryo cryopreservation.

Hysteroscopic polypectomy and continuation of the IVF cycle is controversial because of the fear of compromising endometrial integrity and receptivity in view of embryo transfer. Two small series published in literature seem to reassure on the safety of hysteroscopic resection during controlled ovarian hyperstimulation for IVF, both showing good pregnancy rates (Madani et al., 2009; Batioglu et al., 2005).

Introduction

Oncological significance of endometrial polyps

Endometrial polyps are common, and the majority of them are benign. Nevertheless, pathology might sometimes show premalignant or malignant changes in patients with polyps. Unfortunately, while it is relatively easy, nowadays, to diagnose an intrauterine polypoid lesion by means of traditional transvaginal ultrasound or contrast sonography, those techniques are not able to identify cancerous polyps.

Technical improvements in ultrasound technology and the adoption of added tools, such as the use of doppler, might eventually lead to a better assessment of a polyp´s oncologic potential (Lieng et al., 2008; Perez-Medina et al., 2002), but so far tissue sampling and pathology have been the only way of diagnosing or excluding malignant or premalignant changes. Therefore, it is common practice to refer any patient with suspect endometrial polyps to hysteroscopy and hysteroscopic resection, regardless of the symptoms or clinical presentation (Clark et al., 2002).

Prevalence of cancer in patients with endometrial polyps

The estimated prevalence of cancer in endometrial polyps is around 3% (Lieng et al., 2010; Lee et al., 2010), and it is mostly calculated on patients where a polyp diagnosis was often guided by symptoms or, for instance, the use of tamoxifen for breast cancer.

As a matter of fact, a relevant heterogeneity is found in studies assessing the prevalence of malignant changes in endometrial polyps. As a result, the prevalence of malignant changes varies from 0.2 to 23.8% for premalignant changes, and from 0 to 12.9% for cancer (Lieng et al., 2010).

Risk factors

Menopausal status seems to be a risk factor for malignant tissue changes in endometrial polyps. A systematic review and meta-analysis published in 2010 found that endometrial neoplasia was identified in 4.91% (182 of 3,705) of postmenopausal women, compared with 1.30% (46 of 3,544) of premenopausal women (RR 4.29; 95% CI 3.09–5.96; Lee et al., 2010; Lee et al., corrections, 2011).

The same study also identified a significantly higher risk in women with abnormal uterine bleeding. At meta-analysis, the prevalence of malignancy in endometrial polyps resulted 4.09% (192 of 4,694) in women with symptomatic bleeding, compared with 2.13% (84 of 3,940) in asymptomatic (RR 2.00; 95% CI 1.24 –3.23; Lee et al., 2010; Lee et al., corrections, 2011).

A cumulative meta-analysis performed within this study shows that statistical significance for the elevated risk of malignancy associated with postmenopausal status or bleeding symptoms would be achieved even if limiting analysis to studies with low prevalence of malignancy (Lee et al., 2010).

Apart from menopausal status and abnormal uterine bleeding, also other risk factors for the presence of malignant changes in endometrial polyps have been studied.

Patient age is correlated with the oncologic potential of polyps, and various authors have found a higher prevalence of premalignant and malignant changes when endometrial polyps are removed from older women (Baiocchi et al., 2009; Ferrazzi et al., 2009; Savelli et al., 2003; Antunes et al., 2007; Ben-Arie et al., 2004; Machtinger et al., 2005).

However, some of those authors could not confirm statistical significance of age as a risk factor when adjusting for other variables after multivariate analysis (Ferrazzi et al., 2009; Savelli et al., 2003).

The size of endometrial polyps has been addressed as a risk factor, and studies have found malignancy to be more frequent in polyps larger than 15-18 mm in diameter (Ben-Arie et al., 2004; Ferrazzi et al., 2009). A large Italian multi-centric study, including 1152 asymptomatic postmenopausal patients, assessed the association between various factors and malignancy or premalignancy in endometrial polyps. After multivariate analysis, the only variable significantly associated to malignant or premalignant histopathology in asymptomatic women was the diameter of the polyps removed, with an odds ratio of 6.9 for diameters above 18mm (CI 2.2-21.4; Ferrazzi et al., 2009).

Given the known effects of hormones on endometrial growth, and the similarities between normal endometrium and endometrial polyps in terms of hormonal dependence, various authors have studied the association between hormonal treatments and malignancy in polyps.

A significantly higher risk of cancer has been seen in women with endometrial polyps treated with tamoxifen (Martinez et al., 2004).

Malignant polyps have also been associated with the use of hormonal replacement therapy in post-menopause (Orvieto et al., 1999). As pointed out, previous use of oral contraceptives seems to represent a protective factor for the development of endometrial polyps (Dreisler et al., 2009), and no reliable data show an association between contraceptives and malignant polyps (Lee et al., 2010).

Obesity, which has been implicated in the etiopathogenesis of endometrial polyps because of the associated high levels of circulating estrogens (Gredmark et al., 1999), has also been found to be significantly correlated to malignancy in polyps (Gregoriou et al., 2009).

The association between malignancy in endometrial polyps and diabetes is controversial (Gregoriou et al., 2009; Wang et al., 2010; Savelli et al., 2003).

Some authors have reported an association between hypertension and malignant polyps (Savelli et al., 2003; Baiocchi et al., 2009), but this finding has not been confirmed by other studies (Wang et al.,2010; Gregoriou et al., 2009).

Are endometrial polyps premalignant lesions?

Despite the evidence of an association between polyps and endometrial cancer, it is still controversial whether polyps are *true cancer precursors*.

Perri et al. (2010) have recently published an interesting study comparing age standardized incidence ratios (SIR) of endometrial cancer between patients with endometrial polyps and with fibroids. Interestingly, the SIR of cancer in women with polyps resulted significantly lower than in those with fibroids (polyps: OR 8.0; 95% CI, 6.6 –9.5; fibroids: OR 19.1; 95% CI 16.0–22.6). These findings support the existence of a detection bias by which polyps would represent an enhanced detection opportunity rather than a real endometrial cancer precursor (Perri et al., 2010).

As a matter of fact, most of the studies evaluate the association between polyps and endometrial cancer, but lack details on whether the cancer is localized on the polyp or somewhere else in the cavity.

In the setting of a study of the risk of malignancy in symptomatic and asymptomatic women with endometrial polyps, Wethington et al. (2011) have evaluated whether polyp-associated endometrial hyperplasia and cancer were arising in the polyp or the adjacent endometrium. In their experience, the cancer was confined to the polyp in only 3 out of 13 cases

(Wethington et al., 2011). This finding suggests that in many women endometrial cancer arises in the endometrium and spreads to an adjacent polyp, which strengthens the above discussed hypothesis of a detection bias (Wethington et al., 2011).

Other authors have conducted similar studies in order to give insight on the origin of cancer and hyperplasia in patients with endometrial polyps.

Mittal and Da Costa (2008) found that, at hysterectomy, endometrial pathology is present in two thirds of cases with hyperplasia, and in 90% of cases of adenocarcinoma in endometrial polyps.

In a study published in 2009 by Rahimi et al., two biopsies of hysteroscopically normal endometrium were performed at the time of polyp resection in 694 consecutive patients. Among postmenopausal women, the sampled endometrium showed hyperplasia without atypia in 21.6%, atypia 12%, and adenocarcinoma 1.2%. These findings suggest that visual inspection by hysteroscopy is not always reliable and polypectomy should be combined with a biopsy of the background endometrium, particularly in high-risk women (Rahimi et al., 2009).

Finally, Kelly et al. (2007) reported that, in cases of hyperplastic polyps, hyperplasia might often involve the non-polypoid endometrium (52% of the cases).

The scientific relevance of endometrial polyps

A bibliometric study[1]

Background

Endometrial polyps are commonly described as sessile or pedunculated overgrowths of the endometrial layer. The clinical relevance of endometrial polyps is linked to abnormal uterine bleeding, infertility and the risk of endometrial atypia and cancer (Lieng et al., 2009; Afifi et al., 2010; Lee et al., 2010).

Scientific advances during the last decades have contributed to the evidence-based establishment of reliable tools for diagnosis and treatment of endometrial polyps, such as transvaginal ultrasound and hysteroscopy (Salim et al., 2011; Sharma et al., 2004).

Nevertheless, the clinical relevance of endometrial polyps, particularly in asymptomatic and premenopausal women, is debated and expectancy has been advocated, keeping in mind that one out of four polyps can regress

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[1] This study has been published by Gynecological Surgery, official journal of the European Society for Gynecological Endoscopy, the British Society for Gynecological Endoscopy and Arbeitsgemeinschaft Gynecologische Endoskopie, as: Gambadauro P, Torrejón R. The relevance of endometrial polyps: a bibliometric study. Gynecol Surg 2013; DOI: 10.1007/s10397-013-0788-2
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without treatment (American Association of Gynecologic Laparoscopists practice report, 2012).

We have conducted this bibliometric study in order to explore, analyze and describe the current status and past trends of scientific literature on endometrial polyps.

Materials and methods

We have conducted a systematic, electronic search through scientific literature published between 1982 and 2012, with the aim to retrieve publications related to the topic of endometrial polyps. In order to achieve our goal, we searched the Scopus database (http://www.scopus.com) during Autumn 2012 for the terms "endometrial polyps", "endometrial polyp" and "hysteroscopic polypectomy". Our search strategy was based on the following query:

TITLE-ABS-KEY("endometrial polyps" OR "endometrial polyp" OR "hysteroscopic polypectomy") AND SUBJAREA(medi OR nurs OR heal) AND PUBYEAR > 1981 AND (EXCLUDE(SUBJAREA, "VETE"))

This original search was then refined with the additional keywords: "infertility", "bleeding", and "cancer". Data were extracted from the original and refined searches regarding number of retrieved publications,

source journals, the language and the geographical origin of each article. The number of retrieved articles per year was also normalized to the total number of articles indexed by Scopus.

We divided the retrieved articles into two different periods (1982-1996 and 1997-2012) in order to allow for comparative analysis. For source journals analysis, we focused on the period 2007-2012, in order to provide recent data.

All data were initially stored on a custom-made, online electronic database, based on Google Drive spreadsheets (http://drive.google.com). This allowed simultaneous access to both authors (Gambadauro and Magos, 2008).

Descriptive statistics and charts were used to analyze data and provide information on publication trends. Student´s t-test and Fisher's exact test were used were appropriate and differences were considered statistically significant with a p-value <0.05.

The software Numbers '09 v2.2 (Apple Inc.) and SPSS v20 (IBM) for Mac OSX were respectively used for charts and statistical calculations.

The global map on publications was generated on Google Drive.

Results

Our systematic search retrieved 1.144 relevant publications out of a database of 12,125,345 articles published in the past 30 years in the subject area of interest. An overview of descriptive findings is given in Table 1.

Table 1.

	N of articles	%
Total	1144	(0.009 %†)
1982-1996	210	18.36%
1997-2012	934	81.64%
Language		
English	913	79 %
Other	231	21 %
Geographical distribution per country‡		
United States	213	19.0 %
Italy	90	8.0 %
United Kingdom	88	7.8 %
Turkey	79	7.0 %
Spain	63	5.6 %
Others	589	52.6 %
Geographical distribution per continent‡		
Europe	513	45.7 %
Asia	260	23.1 %
North America	236	21 %
South America	68	6 %
Africa	23	2 %
Oceania	22	1.9 %
Refined search:		
"cancer"	431	37 %
"bleeding"	376	33 %
"infertility"	132	11.5 %

Summary of findings. († % of articles retrieved out of the total amount of articles (n 12.125.345) indexed by Scopus in the same period and subject areas. ‡ Calculated on 1122 articles with retrievable information on source country.)

Analysis of the yearly publication trends reveals how the absolute number of articles related to endometrial polyps has been growing since 1982 (Figure 1).

Figure 1.
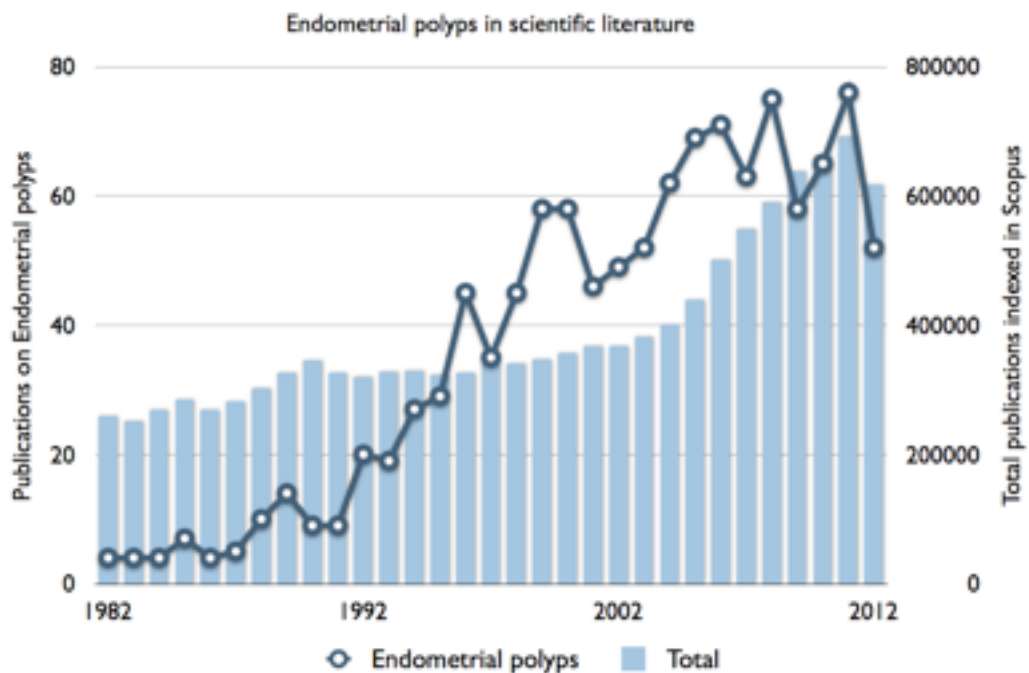
Our systematic search (Autumn 2012, Scopus) shows a growing trend of publications retrieved with the keywords "endometrial polyps", "endometrial polyp" or "hysteroscopic polypectomy" throughout the last 30 years.

Significantly more articles per year have been published after 1997 (1982-1996: 14±11.988; 1997-2012: 58.38±11.506; p<0.0001). A similar statistically significant difference is found when normalizing the yearly amount of retrieved articles to the total of publications indexed by Scopus

(1982-1996: 0.0044%±0.0035; 1997-2012: 0.0127%±0.0025; p<0.0001; Figure 2).

Figure 2.
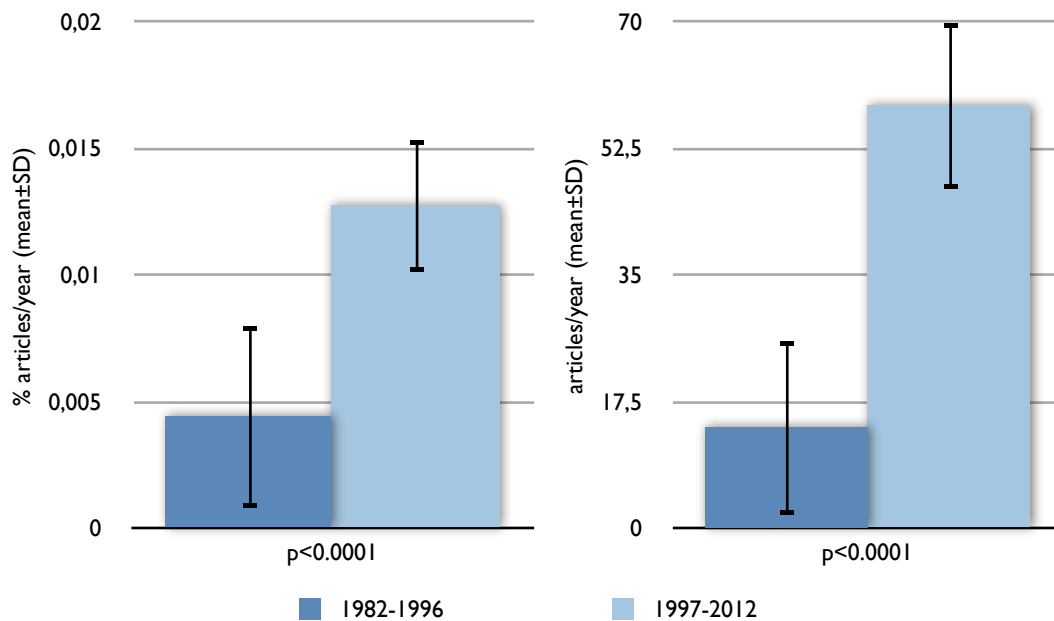
This figure shows a significative increase of mean yearly publications related to endometrial polyps after 1997. The chart to the right shows the yearly publications normalized to the total amount of articles indexed in Scopus.

English was dominant over other languages (913/1144 publications; 79%). The proportion of publications in English has significantly increased from 74.76% in the period 1982-1996, to 80.94% in the period 1997-2012 (157/210 vs 756/934; p 0.046; Figure 3).

Figure 3.
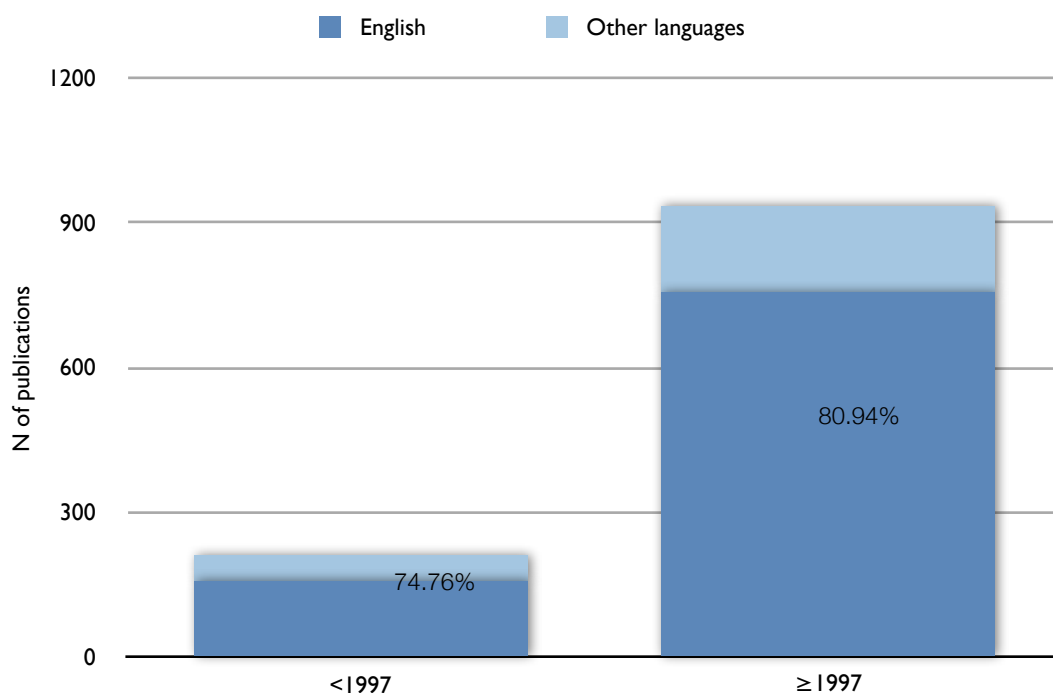
English is the dominant language in this field of research.

The USA is by far the most prolific country (19%), followed by Italy (8%) and the UK (7.8%). While 65 countries contributed with at least one publication, nearly half of all the retrieved articles originated from the five top countries: US, Italy, UK, Turkey and Spain (Table 1).

The global geographic distribution is shown in Figure 4.

Figure 4.
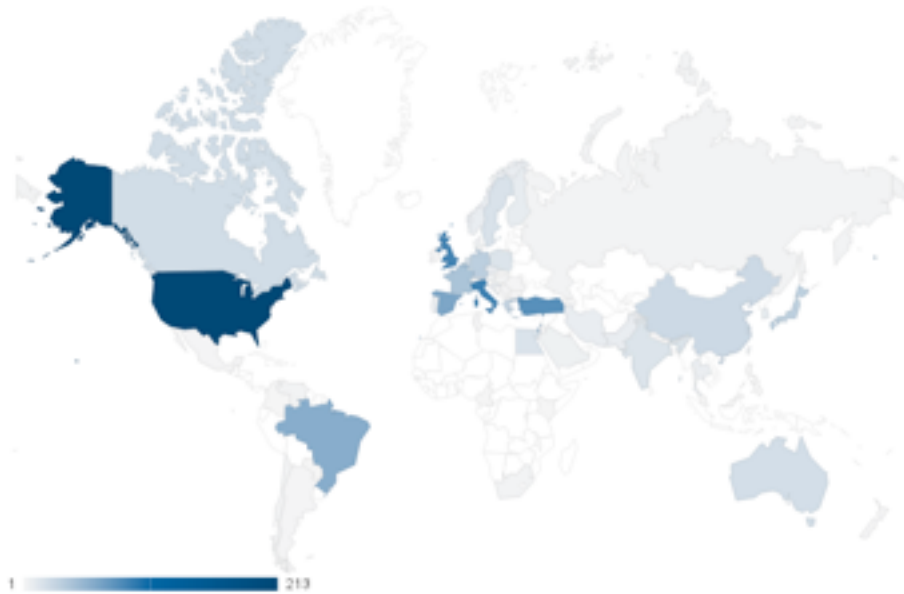
Geographical distribution of publications related to endometrial polyps, by country, 1982-2012
(Autumn 2012, Scopus).

After refining our original search query with three additional keywords, we observed that more articles were retrieved by the keywords "cancer" and "bleeding" (respectively 37% and 33%) respect to "infertility" (11.5%).

A publication trend analysis shows how the proportion of articles related to "infertility" and "bleeding" has been growing more than that of papers related to "cancer" during the last 30 years (Figure 5). Interestingly, the

geographical distribution of publications is more even in the case of papers dealing with "infertility", where Turkey, USA, UK and Italy have got similar shares (respectively 17%, 15%, 10% and 10%).

Figure 5.

Endometrial polyps (EP) and "infertility", "bleeding" and "cancer": publication trends
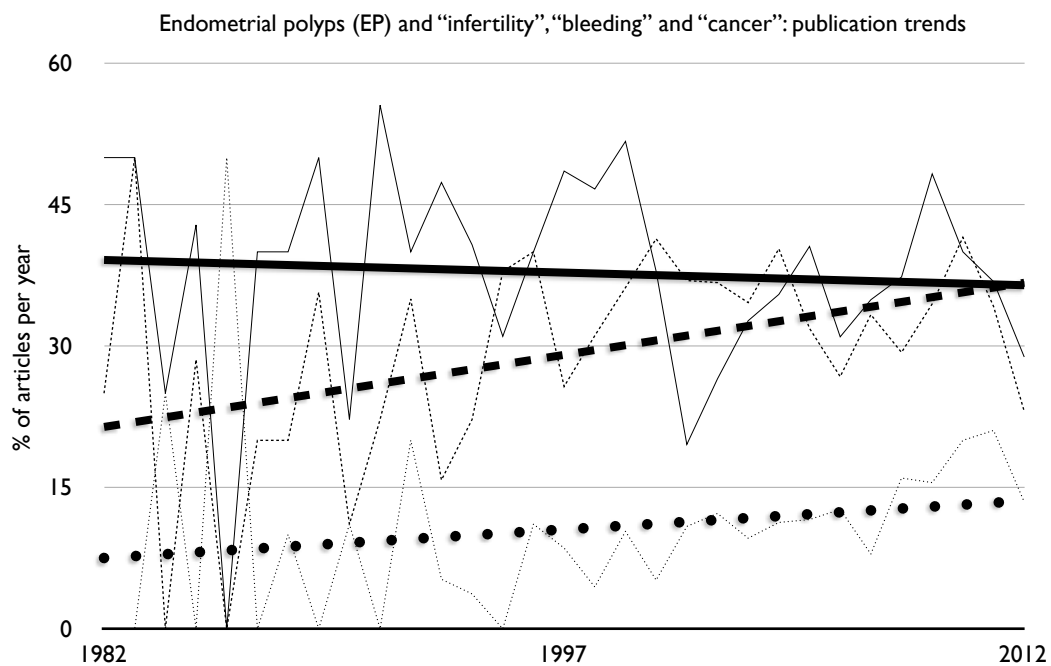
We have refined our main Scopus search with the additional keywords "cancer", "bleeding", and "infertility". This graph shows the publication trends per each one of those additional keyword (Autumn 2012, Scopus).

A total of 160 publishing sources have contributed articles included in this study. The journal mostly represented in our search results is Obstetrics and Gynecology with a total of 37 publications retrieved belonging to the period 1982-2012. When restricting our search to recent literature (from 2007), Fertility and Sterility was the journal with most publications

retrieved (25/389; 6.4%), followed by the Journal of Minimally Invasive Gynecology (18/389; 4.62%) and the European Journal of Gynaecological Oncology (14/389; 3.59%). After normalizing the number of retrieved publications to the total amount of articles indexed for each journal, Gynecological Surgery is the journal with the highest proportion of publications on endometrial polyps (2.1% of all its articles; Table 2).

Table 2.

journal	retrieved	indexed	%
Fertil Steril	25	5716	0,44 %
J Minim Invasive Gynecol	18	1080	1,67 %
Eur J Gynaecol Oncol	14	945	1,48 %
Arch Gynecol Obstet	13	2445	0,53 %
Eur J Obstet Gynecol Reprod Biol	13	2129	0,61 %
Gynecol Surgery	11	519	2,12 %
Menopause	10	1275	0,78 %
Int J Gynec Pathol	10	569	1,76 %
Ultrasound Obstet Gynecol	8	1657	0,48 %
Am J Obstet Gynecol	7	3785	0,18 %
J Obstet Gynaecol	7	1679	0,42 %
Reprod Biomed Online	7	1576	0,44 %

The 12 top publishing journals in the field of "endometrial polyps" (2007-2012).

Discussion

We have conducted this study in order to explore the scientific relevance of endometrial polyps by means of a quantitative bibliometric analysis of scientific literature published from 1982 to 2012.

Our results show that both the absolute and relative number of publications related to endometrial polyps have increased steadily during the last 30 years, testifying growing interest in the subject. During the same period great progress has occurred concerning the development of minimally invasive methods for diagnosis and treatment of intrauterine pathology (Kamel et al., 2000; Di Spiezio et al., 2008). We are now simply better than 30 years ago at looking inside the uterus and operating effectively, and with minimal invasiveness, conditions which in the past required a hysterectomy (Sharma et al., 2005; Gambadauro and Magos, 2010; Papalampros et al., 2009). Endometrial polyps represent just one example of the different abnormalities of the uterine cavity frequently related to abnormal bleeding, infertility or cancer risk (Marbaix and Brun, 2004). We might speculate that the increase in the clinical use of minimally invasive methods for diagnosis and treatment (van Dijk et al., 2012) might

have played a role in the increase of scientific interest on endometrial polyps, but this should be confirmed by other studies.

Another fact emerging from our study is the uneven linguistic and geographical distribution of publications in the field of endometrial polyps. This is certainly not unexpected, but deserves a few comments.

English is the predominant language in this field of research, and its relevance has been increasing throughout the study period. This is in line with common knowledge and several other reports, and might only partially be justified by the fact that two of the 5 top countries in our study have English as official language (USA and UK). English is universally acknowledged as the *lingua franca* in science and the language of most medical literature. As a result, authors and researchers choose to submit the results of their research to journals published in English, since those usually have broader audience and better bibliometric indicators, such as the impact factor (Lenhard et al., 2006). In spite of well grounded criticism (Gambadauro and Torrejón, 2007), the impact factor is still misused to evaluate a researcher's performance, and publishing on high impact factor journals might be as important as publishing "good" research in order to disseminate your own work and get cited by colleagues (Callaham et al., 2002).

We have also analyzed the geographical distribution of research reports in the field of endometrial polyps. While as many as 65 countries, spread throughout the five continents, have contributed to scientific literature on this topic, only few of them have originated the majority of all articles. A geographical bias in publication patterns has been previously reported in other fields of research (Tutarel O, 2002; Boulos MN, 2005; Yeung and Bhandari, 2012). Such circumstance might be related to local interests in this field, or socioeconomic factors such as population, investments in research, or gross domestic product (total and per capita). We cannot speculate on those hypotheses since they fall beyond the goals of this observational study.

Endometrial polyps are commonly associated with abnormal bleeding, infertility and risk of endometrial atypia/cancer. The relevance of those associations is reflected in scientific literature, where more than 1/3 of articles is linked to the keywords "cancer" and "bleeding" . Moreover, the association with "bleeding" and "infertility" is acquiring relevance, as demonstrated by our trend analysis. Interestingly, the USA loses the predominance as source country in the specific subset of articles retrieved by the keyword "infertility".

We would like to point out that several online tools exist to assist us in the search for scientific literature for bibliometrics. The most commonly used are PubMed (by the United States National Library of Medicine, NLM; http://www.pubmed.com), Web of Science (by Thomson Reuters; http://http://wokinfo.com/wok/products_tools/multidisciplinary/webofscience/) and, as in our case, Scopus (by Elsevier B.V.; http://www.scopus.com). The latter was a natural choice for us since we are familiar with its system of queries that, in our opinion, facilitates searching by keywords and result retrieval. Moreover, Scopus covers a wider journal range than the other databases (Falagas et al., 2008). For instance, by searching on PubMed we would have missed the publications of Gynecological Surgery, journal of the European Society for Gynecological Endoscopy (ESGE), which is not currently indexed on MEDLINE. This would have compromised our analysis, since we found that Gynecological Surgery dedicates more of its editorial space than other journals to "endometrial polyps". A logical consequence of this finding would be a strong recommendation for scholars conducting research on endometrial polyps to consider searching for references in more comprehensive databases than PubMed, as already recommended in other research fields (Suarez-Almazor et al., 2000).

Finally, our search strategy was meant to use only electronic queries, and its results are depending on the quality of indexing (Dickersin et al., 1994). It seems reasonable to mention how hand-searching, possibly with the help of desktop search engines (Magos and Gambadauro, 2005), might be the best complement of database searching in order to increase the accuracy of the results particularly when qualitative analysis is the goal.

Conclusions

The relevance of endometrial polyps as a scientific subject is growing, as shown by a positive trend in related publications during the last 30 years. This area of research is dominated by Europe, although the USA is the country publishing most articles.

Several journals contribute articles to endometrial polyps related research, some of them not covered by the most popular database, PubMed. Researchers in this field should adopt comprehensive search strategies in order to retrieve information also from journals not indexed by PubMed.

Original research

Aims of the research

This scientific work was designed to assess the oncological significance of an ultrasonographic diagnosis of endometrial polyp, and is structured into two main parts. The main aims of this original research were as follows:

Part I

- to calculate the frequency of malignant and premalignant changes in the endometrium of women with an ultrasonographic diagnosis of endometrial polyp.

- to describe the characteristics of all the cases of endometrial neoplasia diagnosed in a cohort of women referred to hysteroscopy following the ultrasonographic diagnosis of endometrial polyp.

- to identify possible factors associated to a high-risk endometrial neoplasia in the same patients.

Part II

- to identify possible factors associated with malignancy in women with suspected endometrial polyps at transvaginal ultrasound.

Materials and methods

Patients
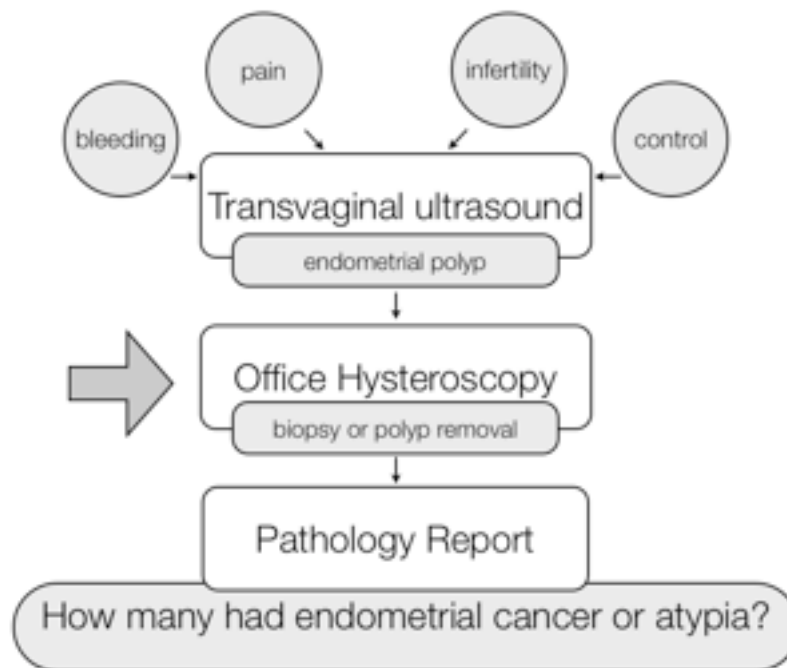
A total population of 1390 women were referred for hysteroscopy between January 2006 and September 2012, following ultrasonographic diagnosis of endometrial polyp, at the Department of Obstetrics and Gynaecology of the Virgen del Rocío University Hospital, Seville, Spain.

Figure 6.

Study flow chart. The arrow indicates the point when the population of 1390 patients was identified.

The ultrasonographic diagnosis was made via transvaginal ultrasound scanning, performed by qualified physicians, and in different settings, including public and private healthcare facilities.

The office hysteroscopies at Virgen del Rocío University Hospital of Seville are performed at a centralized outpatient unit. All patients are met by specialized staff and are thoroughly informed about the procedure. These facilities are equipped with thin double- flow hysteroscopes such as the Bettocchi ® 5mm Hysteroscope (Karl Storz, Tuttlingen, Germany). These hysteroscopes have a working channel allowing for the use of mechanical (scissors, grasping forceps, biopsy forceps) and electrosurgical micro instruments such as the Versapoint ® bipolar 5-french electrodes (Gynecare, Ethicon). This setting allows for purely diagnostic procedures, hysteroscopically-guided biopsies and operative procedures with hysteroscopic removal of polyps, according to a *see-and-treat* principle. Almost all the procedures are performed by a vaginoscopic (no-touch) approach, and do not require cervical dilatation or any sort of anesthesia. The patients are allowed to leave the premises after a very short observation time.

Those patients who, in spite of the confirmed diagnosis of an endometrial polyp or any other intra-cavitary pathology requiring surgical treatment,

are not considered suitable for a *see-and-treat* approach, are scheduled for hysteroscopic resection as a hospital day-surgery procedure. These operative procedures are performed with patients under general anesthesia. Cervical dilatation is required and the resection is carried out by using a monopolar resectoscope. In this case, a non-ionic distension medium is used for the uterine cavity, and an accurate control of the fluid balance is mandatory.

All specimens are routinely sent for histo-pathologic assessment by specialized pathologists.

After each procedure, regardless of the diagnostic or operative nature, the patients' clinical data are introduced in a digital register, together with the report of each procedure. The register might be searched by means of digital queries, using pre-defined filters.

Our study population was identified by means of a digital query based on the search field "indication" for hysteroscopy.

Within this cohort of patients, we have identified all the cases of pathologically confirmed malignant and premalignant changes of the endometrium, including all forms of endometrial carcinoma together with cases of hyperplasia with atypia. The decision to include atypical

hyperplasia in the analysis was taken in view of the relatively high risk of coexistence with endometrial cancer reported in literature. As a matter of fact, a prospective cohort study published on Cancer in 2006 showed a 42.6% prevalence of endometrial carcinoma in women with a preliminary diagnosis of atypical hyperplasia at bioptic sampling (Trimble et al., 2006). Hysterectomy is commonly indicated in women with atypical endometrial hyperplasia who do not have desire to conceive. Moreover, a common terminology has been advocated for endometrial atypias and low-grade adenocarcinomas (Bergeron et al., 1999). For all the above reasons, we considered atypical hyperplasia together with endometrial cancer for the aims of this study, and we will refer to the whole group as "malignancy" or endometrial "neoplasia" throughout the paper, following the example of Lee et al. (2010).

In the second part of our original research, a hospital-based, nested case-control study, the same group of patients with endometrial neoplasia, identified in the first part, was compared to controls from the same cohort who resulted having only benign endometrial polyp at histology.

The choice of the nested case-control design was guided by the low prevalence of the disease under study within the study population (16/1390; 1.15%).

With the aim to improve the power of the study, a ratio of 4:1 between controls and cases was chosen. Increasing the number of controls increases the power of the study. Nevertheless, little improvement is seen beyond a ratio of 4:1. On the contrary, a higher ratio might compromise the precision of the results by affecting the confidence intervals (Grimes and Schulz, 2005).

The controls were unmatched and selected in a random, blind fashion, by choosing the four patients with endometrial polyp preceding each one of the cases of malignancy on our database list, which had been ordered according to the date of hysteroscopy.

The selection of the controls was performed by looking at the dates of hysteroscopy and at the final pathology report, but before the extraction of other data from the clinical notes. In case of lack of four eligible controls between two consecutive cases of endometrial neoplasia, the search was continued among the patients following the second case.

A visual explanation of the selection process is given in Figure 7.

Figure 7.
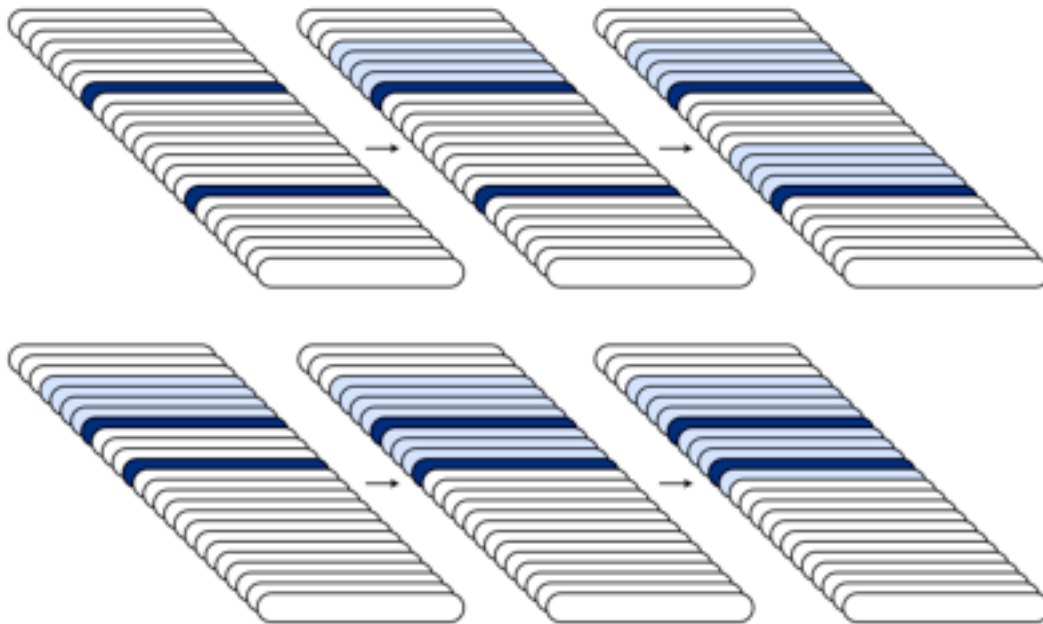
Selection of controls, in a ratio 4:1.

All patients had previously signed written informed consent to the intervention and to the treatment of their personal data. According to local routines, the project was approved and authorized by the Directive Board of the Department of Obstetrics, Gynaecology and Breast Pathology of the Virgen del Rocío University Hospital, Seville, Spain.

Data

For all patients, the hospital notes of all cases and controls were retrieved, and epidemiological and clinical data were extracted and stored anonymously in a pre-defined form.

Epidemiological data included age, body weight, height, body mass index (BMI), parity and menopausal status. Age, body weight, and BMI were treated as continuous variables. Parity was treated as a categorical variable by dividing patients in three groups according to the number of previous deliveries (0; 1; ≥2). Menopausal status was treated as a categorical variable with two alternative values (pre- and post-menopause).

We also collected anamnestic data such as hypertension, diabetes, previous endometrial polyps, use of estro-progestinics, diagnosis of endometriosis, infertility, cancer, and use of tamoxifen.

Concerning clinical data, we focused on the initial indication to vaginal ultrasonography (bleeding, pain or control), hysteroscopic findings,

presence and number of polyps at hysteroscopy, pathology results of a first biopsy or polyp removal, and of a final diagnosis at hysterectomy.

The size of the polyps, as available from ultrasound or pathology measurements, was recorded and treated as a categorical variable by creating two groups, "small" (<20mm) and "large" (≥20mm), depending on the largest diameter. This was decided after taking into account the results of previous studies, namely a large multi-center Italian study where, at multivariate analysis, a polyp diameter above 18mm was the only variable significantly associated with malignant or premalignant histopathology in asymptomatic, postmenopausal women, with an odds ratio of 6.9 (CI 2.2-21.4; Ferrazzi et al., 2009).

The number of endometrial polyps found at hysteroscopy in each patient was recorded and treated as a categorical variable. Two groups were established: single polyp versus multiple polyps (≥2).

The stage of disease according to the FIGO staging system was recorded for all confirmed cases of carcinoma of the endometrium. The FIGO staging system underwent a revision in 2009 (Colombo et al., 2011), while part of our cases had been operated before that date. Those patients had been assigned a stage according to the previous FIGO 1988 classification.

In order to have a homogeneous staging system, allowing for accurate comparison, we thoroughly readall pathological reports and converted the old staging to the new 2009 FIGO system, where needed. In any case of stage IA, which according to the 2009 FIGO classification includes both cancers confined to the endometrium and also those infiltrating <50% of the myometrial layer, we recorded whether the tumor was only confined to the mucosa or not. The grading of the tumor was also recorded according to common standards (G1 well differentiated; G2 moderately differentiated; G3 poorly differentiated). Cases of histotypes other than type I, endometrioid carcinoma, were recorded.

Two groups were established for reciprocal comparison depending on the risk of disease. A lower risk group included cases of atypical hyperplasia and cases of well to moderately differentiated (G1 and G2) adenocarcinomas of stage IA. The higher risk group included the cases of moderate-high grade (G3) endometrial cancer IA and above stages, and other histotypes. This group assignment was based on the knowledge that the prognosis of IA-G1 and G2 endometrial cancer is good (Table 3; Colombo et al., 2011). Survival rates based on the 2009 FIGO staging system are of 89.6% for stage IA versus 77.6% for stage IB (Colombo et al., 2011). Moreover, as already reminded, some authors have previously

proposed the grouping of this stage and grade of disease, together with atypical endometrial hyperplasia, under the term of "endometrial neoplasia" (Bergeron et al. 1999; Trimble et al. 2006).

Table 3.

risk	stage/grade/type
Low risk	stage IA (G1 and G2) of endometrioid type
Intermediate risk	stage IA G3 with endometrioid type stage IB (G1 and G2) with endometrioid type
High risk	stage IB G3 with endometrioid type all stages with non-endometrioid type

Stage I endometrial cancer (FIGO 2009) divided in three risk categories.(Colombo et al., 2011)

Analysis

For the first part of our study, descriptive statistics and charts were initially used to analyze data. Mean, median, range, interquartile range (IQR) and standard deviations (SD) were calculated for continuous variables. Frequencies and percentages were calculated for categorical variables.

We have also looked into possible differences in means and frequencies of all variables between patients with lower and higher risk disease, as previously defined. For this comparative analysis, Student t-test and Mann-Whitney test were respectively used for normally distributed and non-normal variables. Normality of the distribution was assessed using Shapiro-Wilk test. For categorical variables, frequencies were compared with chi-square or Fisher's exact tests as appropriate.

For the second part of our research project, univariate statistics and charts were initially used to analyze data. Mean, median, range, interquartile range (IQR) and standard deviations (SD) were calculated for continuous

variables. Frequencies and percentages were calculated for categorical variables.

To compare cases and controls, Student t-test and Mann-Whitney test were respectively used for normally distributed and non-normal variables. Normality of the distribution was assessed using Shapiro-Wilk test. Frequencies of categorical variables were compared using chi-square or Fisher's exact tests as appropriate: when analyzing a 2x2 contingency table, Fisher's exact test was used when any of the cells contained values below 5.

A logistic regression model was used in order to assess the independent effect of the variables that resulted as being associated to the outcomes at bivariate analysis. The goodness to fit of this logistic regression model was assessed by Hosmer and Lemeshow test.

Differences were considered statistically significant with a two-tailed p-value of less than 0.05. Odds ratio (OR) was used to express the strength of associations, together with 95% confidence intervals (CI).

The statistical analyses were performed on the software SPSS® Statistics v20 (IBM®) for Mac OSX, and manually.

Results

Results

Part I

Malignant and premalignant changes in the endometrium of women with an ultrasonographic diagnosis of endometrial polyp.

Between January 2006 and September 2012, 1390 patients were referred for hysteroscopy because of suspected endometrial polyps at transvaginal ultrasound. As per local routines, all hysteroscopies were performed in an office-setting by a qualified specialist in Obstetrics and Gynaecology with experience of the method.

Out of this large cohort of patients, 16 cases of endometrial neoplasia, as previously defined, were found at final pathology (prevalence 1.15%). Fourteen cases consisted of endometrial cancer (1.01%), and two of atypical hyperplasia (0.14%).

Table 4.

Malignant and premalignant lesions of the endometrium in the cohort of 1390 patients referred to hysteroscopy between 2006 and 2012 because of an ultrasound diagnosis of endometrial polyp.

	N	%
Endometrial polyp at ultrasound	1390	100
Atypical hyperplasia	2	0.14
Endometrial cancer	14	1.01
Total "endometrial neoplasia"	16	1.15

The patients' mean age was 64.19±9.382 (range 49-78), and the mean BMI

was 29.40±5.2 (median 27.66; range 24.21-45.74). Only one patient was

premenopausal (1/16, 6.3%). Most of the patients had given birth to 2 or

more children.

Anamnestic data are presented in Table 5.

Table 5.

		N	%
Number of cases		16	100
Parity	0	1	6.3
	1	1	6.3
	≥2	14	87.5
Menopause	pre	1	6.3
	post	15	93.8
Anamnesis	hypertension	4	25
	diabetes	1	6.3
	polyps	1	6.3
	estro-progestinics	1	6.3
	endometriosis	0	0
	infertility	0	0
	cancer	1	6.3
	tamoxifen	0	0

Anamnestic data

According to the case notes, all the patients had undergone the initial

assessment with transvaginal ultrasonography because of symptoms,

consisting of abnormal uterine bleeding in 15/16 cases (93.8%) and pelvic

pain in one case (6.3%). Interestingly, the only woman who was submitted to ultrasound,mainly because of pelvic pain, also had sporadic bleeding, more precisely post-coital bleeding, that wasn't initially reported to the physicians as it was thought to originate from an atrophic vaginal mucosa. During following assessments, this woman was found to have a cervical stenosis, which might have reduced the probability of frank bleeding.

At office hysteroscopy, 14 patients (87.5%) were found to have an identifiable intrauterine polypoid growth, while the remaining 2 (12.5%) presented with a diffuse hyperplasia of the endometrium. Most patients had a single polyp (10/16, 62.5%).

Figure 8.

How was the specimen obtained at hysteroscopy

- biopsy
- polyp removal with microinstruments
- polyp resection with monopolar resectoscope
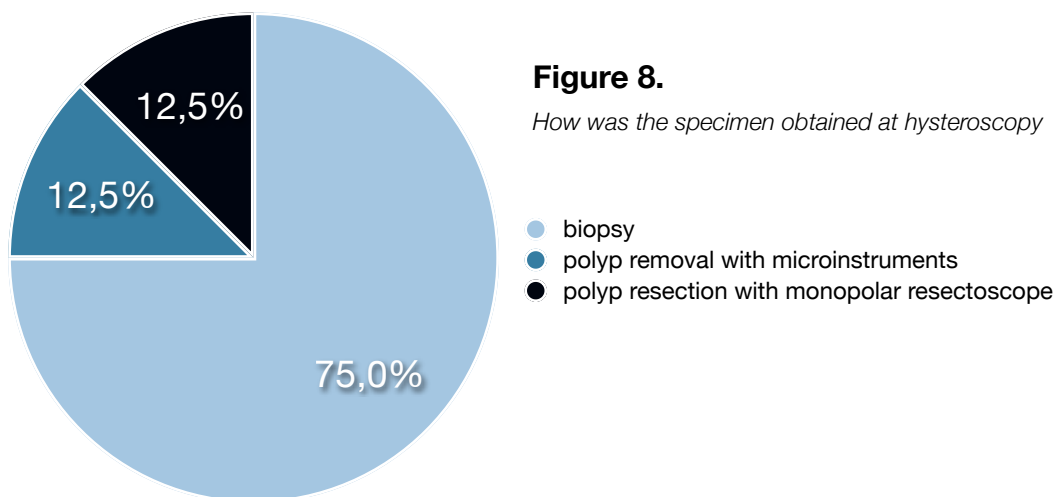
In twelve cases (75%) a biopsy was taken during hysteroscopy, while the four remaining women had undergone polypectomy, two of them directly during office hysteroscopy with microinstruments (12.5%), and the other two at a subsequent operative hysteroscopy by means of resection with a monopolar resectoscope (12.5%).

The histologic assessment of the above-mentioned tissue sampling revealed endometrial cancer in 12 out of 16 cases (75%), and hyperplasia with atypia in the four remaining cases (25%). Following histologic diagnosis, all the patients underwent total hysterectomy with therapeutic and staging intention, as per current practice. At final pathologic evaluation, two out of the four cases previously diagnosed as atypical hyperplasia were found to be endometrial cancer, leading to a total of 14/16 cases of confirmed cancer (87.5%) and 2/16 cases of focal atypia (12.5%) (Figure 9).

Figure 9.

In two out of four (50%) cases of atypia at preliminary histology, endometrial cancer was found at hysterectomy.
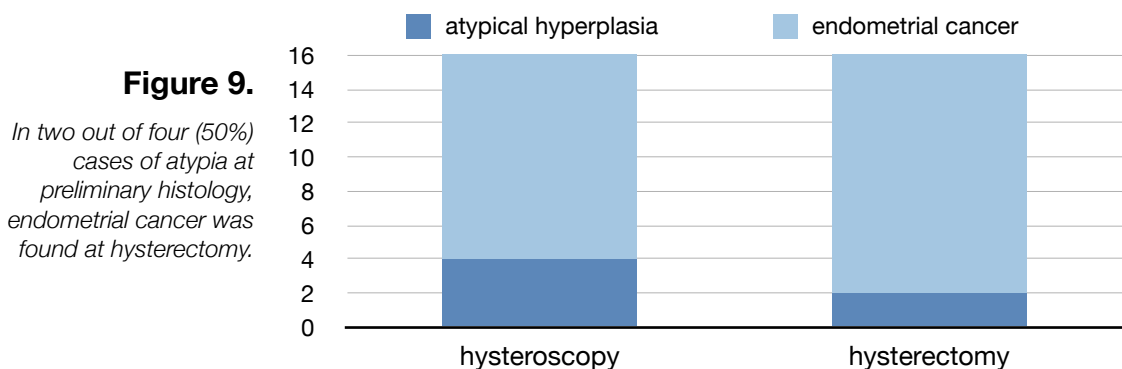
A comprehensive review of the cases is offered by Table 6.

Table 6.

Patient	Age	BMI	Menopause	Main indication	Hysteroscopic findings	N of polyps	First specimen	Pathology at hysteroscopy	Pathology at hysterectomy	Stage (FIGO 2009)	Grade
1	69	24,2	post	bleeding	polyp	1	biopsy	cancer	cancer	IB	G3°
2	77	27,1	post	bleeding	polyp	2	biopsy	atypia	cancer	IA	G1
3	65	30,9	post	bleeding	polyp	1	biopsy	cancer	cancer	II	G2
4	71	27,0	post	bleeding	hyperplasia	-	biopsy	cancer	cancer	IA	G1
5	65	28,9	post	bleeding	polyp	1	biopsy	cancer	cancer	IA	G1
6	68	26,0	post	bleeding	polyp	1	biopsy	cancer	cancer	IA	G2
7	49	27,1	pre	bleeding	polyp	1	biopsy	cancer	cancer	IIIA	G1
8	54	25,1	post	bleeding	hyperplasia	-	biopsy	cancer	cancer	II	G3
9	71	36,2	post	bleeding	polyp	2	resection	atypia	atypia	focal atypia	
10	57	31,6	post	pelvic pain*	polyp	1	biopsy	cancer	cancer	IA	G1
11	56	28,0	post	bleeding	polyp	1	biopsy	atypia	cancer	IB	G2
12	56	29,0	post	bleeding	polyp	1	resection	cancer	cancer	IA	G3°°
13	78	29,4	post	bleeding	polyp	>2	biopsy	cancer	cancer	IA	G1
14	78	27,1	post	bleeding	polyp	2	removal	cancer	cancer	IA	G1
15	58	27,3	post	bleeding	polyp	1	biopsy	cancer	cancer	IB	G2
16	55	45,7	post	bleeding	polyp	1	removal	atypia	atypia	focal atypia	

*This patient initially presented complaining pelvic pain, but she later on, she also reported post-coital bleeding, and had a stenotic cervix
All the cases were endometrioid carcinoma, except for ° (serous) and °° (possible carcinosarcoma)

Table 6.

According to pathology report and related FIGO 2009 staging, nine cases (56.25%) had a low risk disease (2 atypia, 6 Stage IA-G1, 1 Stage IA-G2), while seven had a higher risk neoplasia (≥ IA-G3; 43.75%).

Figure 10
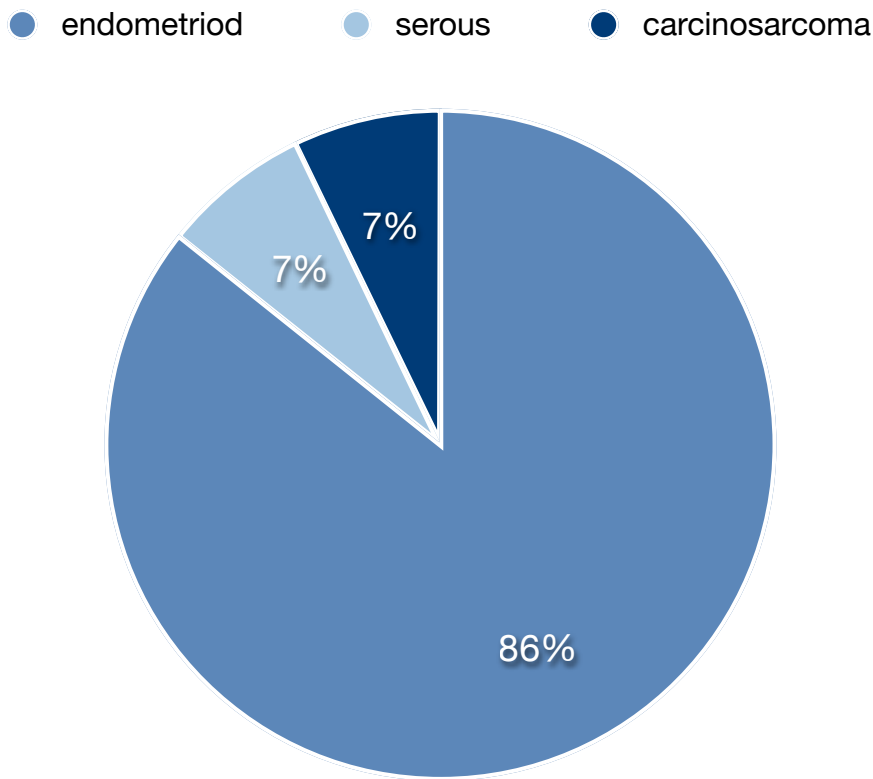

Distribution of cancer histotypes.

Regarding cancer histotypes, 12 out of the 14 cases in this series were of endometrioid type (85.7%). The two remaining cases had a so-called *type II* carcinoma (Albertini et al., 2012). One of them, classified as stage IC according to FIGO 1988 (IB, according to FIGO 2009), was a high-grade

tumor (G3) with dominant features of a serous histotype. Another case, at

stage IA, was a high-grade, undifferentiated tumor (G3) limited to the

endometrium and presenting features suggesting a carcinosarcoma.

Details of the FIGO staging of all cases are provided on Table 6 and Figure

11.

Figure 11.
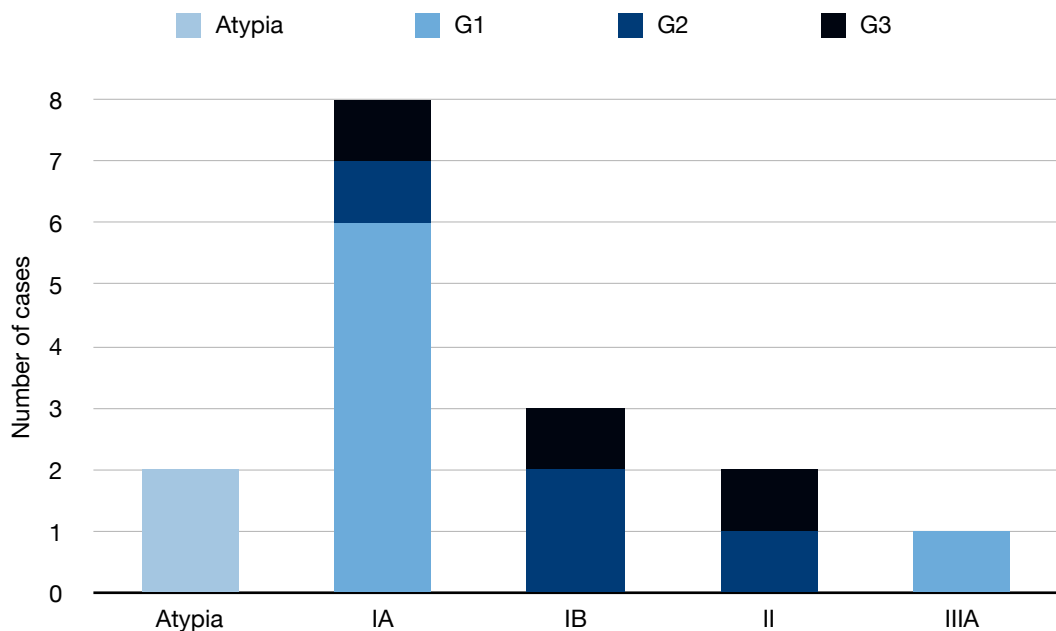
Distribution of stages and grading of the endometrial cancers in this series.

According to pathology reports, the endometrial cancer was confined to

the endometrium only in 2 out of the eight cases of stage IA

Table 7 presents the results of our comparative analysis between lower

and higher risk cases.

At bivariate analysis, higher risk disease was significantly associated (p<0.05) with younger age (58.14±6.768 vs 68.89±8.594; p .017).

Table 7.

		low risk	high risk	p
Number of cases		9	7	
Age (mean±SD)		68.89±8.594	58.14±6.768	.017[a]
Weight (median, kg)		74 IQR 70-83	74.5 IQR 62.7-77	.299[b]
BMI (median)		28.9 IQR 27-33.92	27.28 IQR 25.07-28.95	.408[b]
Parity	0 1 ≥2	1 1 7	0 0 7	.411[c]
Menopause	pre post	0 9	1 6	.438[d]
Indication to US	pain bleeding	1 8	0 7	1.000[d]
Hysteroscopy findings	polyp hyperplasia	7 2	6 1	1.000[d]
N of polyps*	single multiple	5 4	5 0	.221[d]
Size of polyp*	small large	4 4	6 0	.085[d]

[a] *Student's t-test;* [b] *Mann-Whitney U test;* [c] *Chi-square test;* [d] *Fisher's exact test*
*Calculated on the 14 cases where a polypoid lesion was clearly identified at hysteroscopy.

All the patients in the higher risk disease group (6/6; 100%) had smaller polyps (<20mm), while in the lower risk group, 50% of the patients had small polyps (<20mm) and the other 50% had large polyps (≥20 mm). (Table 6). That difference was not statistically significant at Fisher's exact test (p .085)

Multivariate analysis with logistic regression failed to demonstrate the independent association of any variable to the considered outcomes.

Results

Part II

Factors associated with malignancy in women with endometrial polyps at ultrasound: a nested case-control study.

Eighty patients were included in this second part of this research project, with a rate of 4:1 controls to cases.

The case group consisted of 16 patients with atypical hyperplasia or carcinoma of the endometrium identified from a cohort of 1390 women referred to hysteroscopy because of suspected endometrial polyps (16/1390; 1.15%).

Within the same cohort, 64 women with histologically confirmed benign endometrial polyps were identified randomly, according to what described in the previous section.

The mean age of the whole study population was 54.46 ±10.862 (range 28-79). The median BMI was 25.15 (mean 26.05; SD 4.88; range 18.64-47.56; IQR 22.95-27.24).

Other general features of the whole study populations are presented in Table 8.

Table 8.

		N	%
N		80	100
Parity	0	7	8.8
	1	6	7.5
	≥2	67	83.8
Menopause	pre	26	32.5
	post	54	67.5
Indication	bleeding	49	61.3
	pelvic pain	3	3.8
	infertility	1	1.3
	control	26	32.5
Size	small	47	58.8
	large	33	41.3
Number	0	2	2.5
	1	64	80
	≥2	14	17.5

Characteristics of the study population.

At bivariate analysis, patients with endometrial neoplasia resulted significantly older (mean age 64.19 versus 52.03; p .000) and their BMI significantly higher (median 27.66 vs 24.59; p .000) respect to controls with benign polyps.

More post-menopausal women were found among the neoplasia group, and the difference was statistically significant (93.8% vs 60.9%; p .015).

Figure 12.

Menopausal status

Different distribution of menopausal status between cases and controls
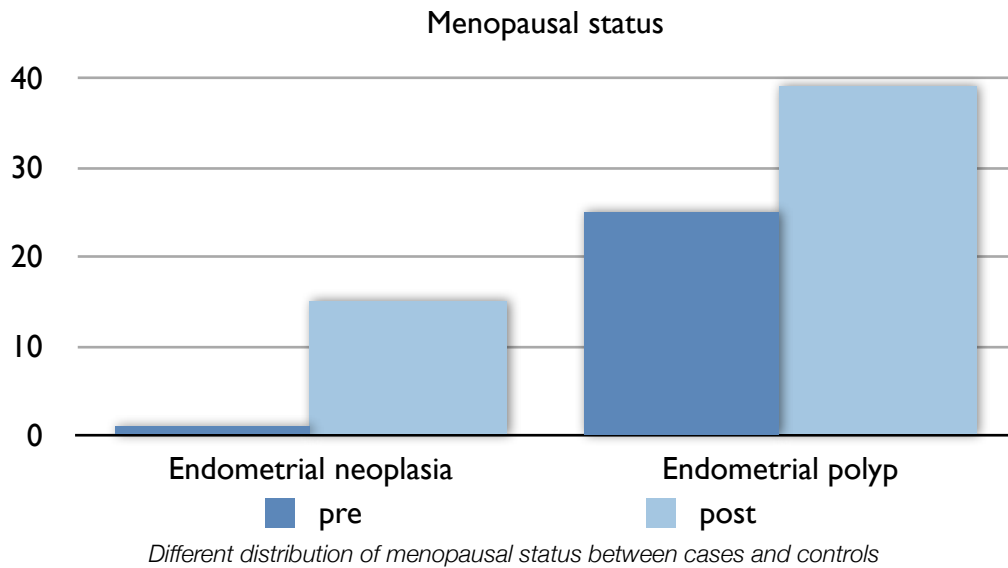
All cases of endometrial neoplasia were found in symptomatic women, while 26 out of 64 women in the control group (40.62%) had been suspected of endometrial polyp at a control transvaginal ultrasound and were asymptomatic.

Figure 13.


Clinical indication or control ultrasound?
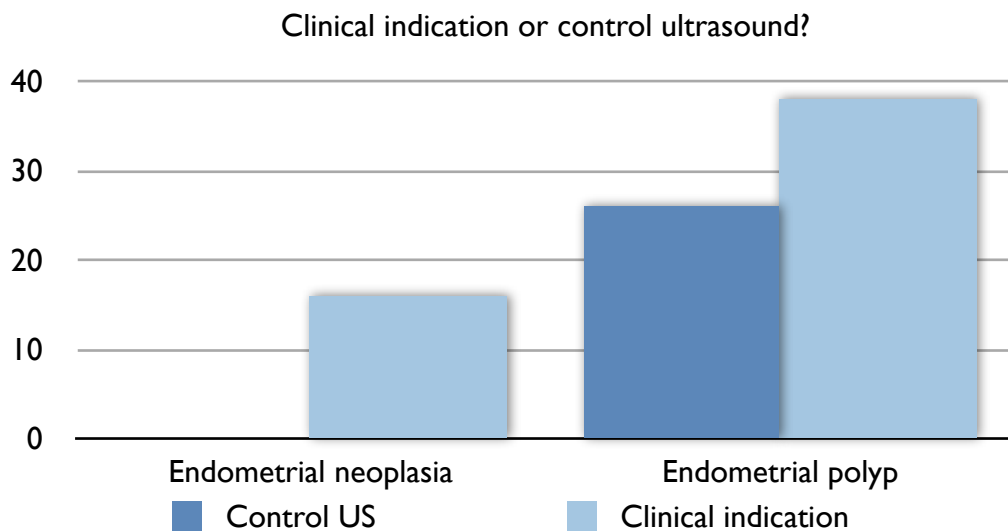
None of the patients in the endometrial neoplasia group had been diagnosed with endometrial polyp at control transvaginal ultrasound. All those patients had a clinical indication for the scan.

Bleeding represented the main indication for transvaginal ultrasound in both groups, but it was significantly more frequent among the cases of neoplasia than among the controls (93.8% versus 54.58%; p .004).

Figure 14.

Bleeding as main indication to ultrasound
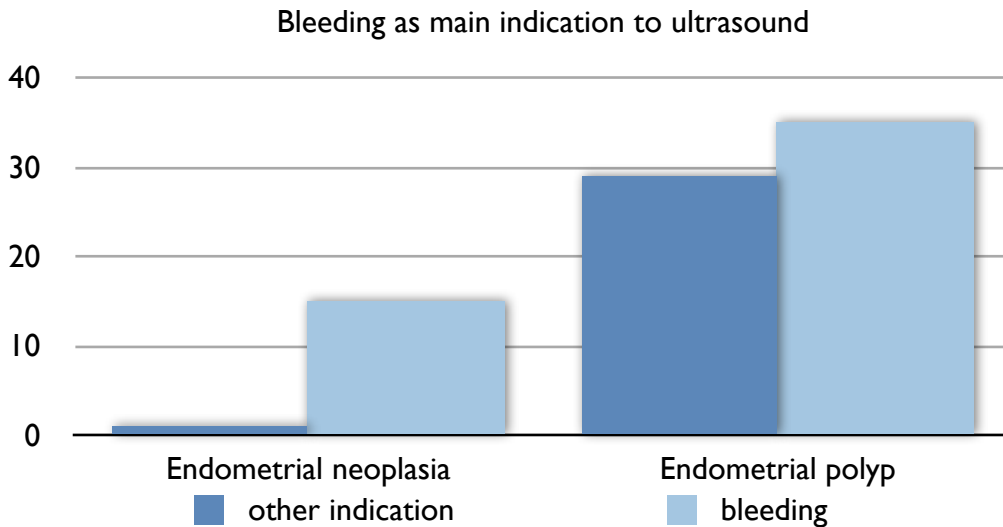
Bleeding was more frequent as main indication among the patients in the endometrial neoplasia group

In one case of the endometrial neoplasia group, the patient had pelvic pain as major complaint, but bleeding emerged as a symptom at further contacts with healthcare providers, and a stenotic cervix was found at hysteroscopy. Therefore, 100% of the patients in the neoplasia group had experienced abnormal bleeding.

Large polyps, ≥20mm in diameter, were more frequent among the control group (cases 28.57% versus controls 43.75%), although the difference did not result statistically significant at Fisher's exact test.

Figure 15.

Size of the polyp
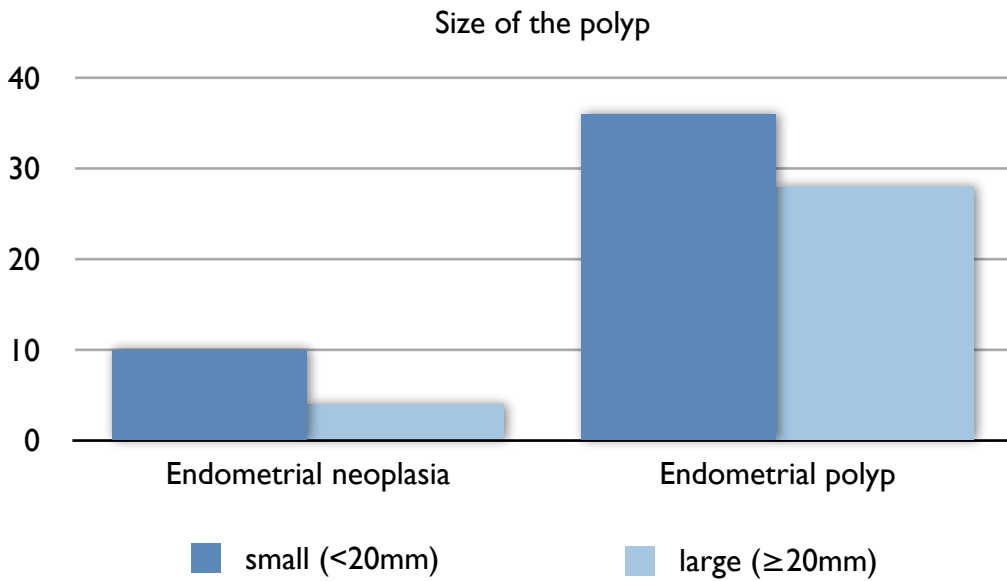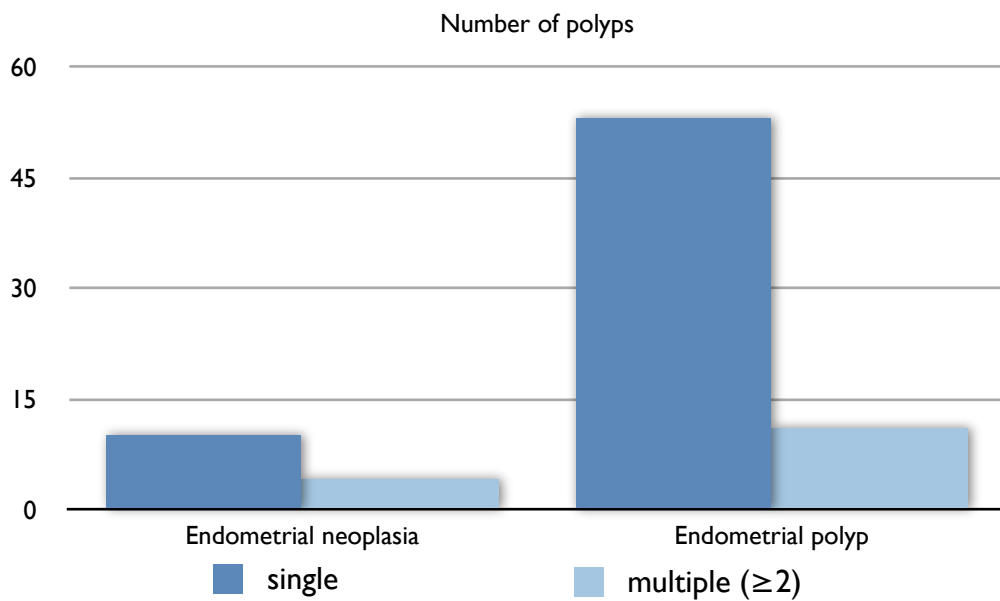

Similar frequency of small (>20mm) and large (≥20mm) polyps between the two groups.

The frequency of multiple polyps (≥2) was similar between the two groups (cases 28.57% versus controls 20.75%; $p > .05$).

Figure 16.

Number of polyps

Similar frequency of multiple polyps between the two groups.

The results of our bivariate analysis are presented in Table 8.

Table 9.

		cases	controls	p
Number of patients		16	64	
Age (mean±SD)		64.19±9.382	52.03±9.846	.000 [a]
BMI (median)		27.66 (IQR 26.97-30.47)	24.59 (IQR 22.7-26.1)	.000 [b]
Parity	0	1	6	ns [c]
	1	1	5	
	≥2	14	53	
Menopause	pre	1	25	.015 [d]
	post	15	39	
Bleeding	no	1	29	.004 [d]
	yes	15	35	
Control US	no	16	38	.001 [d]
	yes	0	26	
Size*	small	10	36	ns [d]
	large	4	28	
Number*	1	10	53	ns [d]
	≥2	4	11	

[a] *Student T-test;* [b] *Mann-Whitney U test;* [c] *Chi-square test;* [d] *Fisher's exact test.*
* Calculated on the 14 cases where a polypoid lesion was clearly identified at hysteroscopy.

We have carried out a bivariate analysis to compare the frequencies of the following anamnestic variables from cases and controls: previous diagnosis of endometrial polyp, diagnosis of endometriosis, use of tamoxifen; use of estro-progestins, hypertension, diabetes, infertility,

cancer of any kind. No significative differences were found between the two groups for anamnestic variables such as hypertension, diabetes, previous endometrial polyps, use of estro-progestinics, endometriosis, infertility, or cancer. No patient in the endometrial neoplasia group had a history of tamoxifen use, versus 3 out of 64 patients in the control group (p >0.99 at Fisher's exact test). Results of this comparative analysis are presented in Table 10.

Table 10.

	cases	controls	p*
Number of patients	16	64	
Previous polyp	1	10	ns
Hypertension	4	13	ns
Diabetes	1	2	ns
Estro-progestinics	0	1	ns
Tamoxifen	0	3	ns
Endometriosis	0	0	ns
Infertility	0	1	ns
Cancer	1	3	ns

Homogenous distribution of anamnestic data between cases and controls.
*all calculations were performed with Fisher's exact test

At logistic regression we examined four variables that had resulted significantly associated (p <0.05) to the outcomes at bivariate analysis: age; BMI; menopausal status; bleeding as a main symptom (Table 11).

Our multivariate analysis showed that patients who are found to have an endometrial neoplasia are more likely to be older than the ones with benign endometrial polyps (OR 1.102; 95% CI 1.015-1.198; p .021).

We also found that bleeding is independently associated with a significantly higher risk of endometrial neoplasia (OR 13.7; 95% CI 1.486-126.278; p .021). The results of the logistic regression analysis are presented in Table 11.

Table 11.

	OR	95% CI	p
Age	1.102	1.015-1.198	.021
BMI	1.019	0.885-1.174	.791
Menopause (post)	2.35	0.179-30.884	.516
Bleeding	13.7	1.486-126.278	.021

Logistic regression analysis showing the independent association of the variables "age" and "bleeding" to the outcome "endometrial neoplasia".

The *goodness to fit* of this logistic regression model was confirmed by Hosmer and Lemeshow test (p .708).

Discussion

Discussion

Endometrial polyps are common and, during the last decades, have increasingly been chosen as a research subject, with a specific focus on their association with endometrial cancer (Gambadauro and Torrejón, 2013).

In spite of the scientific interest in that association, the results of the first part of our study show that endometrial neoplastic or pre-neoplastic changes are rare in patients with a preliminary diagnosis of endometrial polyp at transvaginal ultrasound.

As a matter of fact, only 1.15% of the patients, in our cohort of 1390 consecutive cases, was later on diagnosed with a neoplastic lesion of the endometrium which required further surgical treatment, i.e. hysterectomy ± surgical staging. This is in line with a reported prevalence of cancer in endometrial polyps of around 3% (Lieng et al., 2010; Lee et al., 2010).

Patients in this series had a mean age of 64, and a mean BMI of 29.4 (median 27.66). Both age and BMI have been previously identified as risk

factors for malignancy in patients with endometrial polyps (see chapter "Oncological significance of endometrial polyps").

Also menopause has been found to be associated with a higher risk of cancer in endometrial polyps, and all of the patients in our series except one were indeed postmenopausal (15/16, 93.8%).

Four of the patients were initially diagnosed with atypical hyperplasia, but pathological assessment of the surgical specimen showed endometrial cancer in two of them, one at FIGO 2009 stage IA, and the other at FIGO 2009 stage IB. This finding agrees with published data, since a 42.6% prevalence of endometrial carcinoma in women with a preliminary diagnosis of atypical hyperplasia at bioptic sampling has been reported (Trimble et al., 2006). We therefore believe that our choice to examine these cases together with malignancies was well justified.

It is still matter of debate whether endometrial polyps are real precursors of endometrial cancer, or represent instead an enhanced detection opportunity (Perri et al. 2010). A great element of bias in this subject is given by the various, and variably reliable, methods to diagnose endometrial polyps. We know that not all the polyps are diagnosed by ultrasound, and that many of the "polyps" seen at scan might not be real

polyps. Nevertheless, wishing to adopt a pragmatic approach, we decided to conduct this study by analyzing patients with a preliminary diagnosis at transvaginal ultrasound, since this is the way most cases are classified as "endometrial polyp", and referred for hysteroscopy.

In a series published by Wethington et al. in 2011, cancer was confined to the polyps in only 3 out of 13 cases. Endometrial pathology is extremely frequent (up to 90%) in patients with endometrial malignancy (Mittal and Da Costa 2008), and atypia is often found in non-polypoid endometrium (Kelly et al. 2007; Rahimi et al. 2009).

Interestingly, the standardized incidence ratio of cancer in women with endometrial polyps is significantly lower than in women with uterine fibroids (Perri et al. 2010).In this context, our data support the hypothesis of a detection bias.

In most of our cases, endometrial cancer, when present, was not confined to the polyp. Two patients had a focal atypia, and eight cases of cancer were at stage IA, according to FIGO 2009 staging system. Out of those cases at stage IA, two had had the whole polyp removed at hysteroscopy, but cancer was still present at hysterectomy, meaning that the cancer was not confined to the polyp. Moreover, the cancer was confined to the

endometrium only in 2 out of the eight cases of stage IA. One of them was a suspected carcinosarcoma (G3), apparently confined to the polyp . In the rest of the patients with endometrial cancer with ≥ stage IB (FIGO 2009), the neoplasia was clearly not confined to polyp, and in two of these cases, not even a clear polyp was found at hysteroscopy.

Most of the cases of endometrial cancer in this series were of type I (12/14; 85.7%), endometrioid histotype. This is the most common histotype for endometrial cancer, usually has a better prognosis, and is correlated to hyperestrogenism, a characteristic shared with endometrial polyps (Albertini et al., 2012). The remaining two cases (2/14; 14.3%) were of the so-called type II (one serous carcinoma and one carcinosarcoma). Those histotypes are less common and have a poorer prognosis (Albertini et al., 2012). They most commonly occur on atrophic mucosa, while the type I is thought to have endometrial hyperplasia as precursor lesion (Albertini et al., 2012). Therefore, the type II endometrial carcinomas seem to share fewer similarities with endometrial polyps.

In the first part of this research project, we have also attempted to identify factors associated with the probability of higher risk (stage/grade) neoplasia. The patients with a higher risk disease were significantly younger (mean age 58.14 vs 68.89). The distribution of small and large

polyps was also different between the low and high risk groups. All the polyps in the high risk cases belonged to the small size group (<20mm), versus 50% in the low risk cases. The association of high risk with smaller polyp was nevertheless not statistically significant (p .085 at Fisher's exact test). We failed to demonstrate significancy at multivariate statistical analysis with the two variables associated to higher risk disease (p < 0.1), age and size. This could be related to the relatively small sample, and, considering the low prevalence of endometrial malignancy in patients with endometrial polyps, a multi-centric study would be needed to draw conclusions.

The aim of the second part of our research project was to identify possible predicting factors of endometrial neoplasia among patients with suspected endometrial polyps at transvaginal ultrasound.

We have previously explained why we considered both atypical hyperplasia and endometrial cancer as endometrial neoplasia. Our control group consisted of patients with histologically confirmed endometrial polyps selected randomly within the same cohort, in a ratio of 4 controls to 1 case.

Existing literature on the same topic is highly heterogeneous because of the different ways the study population is selected across the study groups (e.g. ultrasound, hysteroscopy or pathology reports). We have previously motivated our choice of including in this study only patients with a diagnosis at transvaginal ultrasound. We felt that a pragmatic approach to this subject was needed, and we know that, in common practice, women are diagnosed with "endometrial polyps" by means of transvaginal ultrasound.

A review and meta-analysis by Lee et al. has identified postmenopausal status and abnormal bleeding as predictive factors for malignancy and pre-malignancy in patients with endometrial polyps (Lee et al., 2010; Lee et al., corrections, 2011).

Our bivariate analysis confirms those results, since patients with endometrial neoplasia were significantly more likely to be post-menopausal and to have bleeding as their main symptom.

We also found a positive association between age and risk of malignancy. Moreover, our data show that patients with suspected endometrial polyps who are found to have a cancer are significantly less likely to be asymptomatic (OR 0.594; 95% CI 0.485-0.727; p 0.001 at 2-sided Fisher's

exact test). As a matter of fact, none of the patients in the case group was asymptomatic, and this results should raise a question on whether it is acceptable to offer transvaginal ultrasonography to asymptomatic women with no clinical indication.

Another interesting result of our bivariate analysis is the positive association between higher BMI and risk of neoplasia. A similar association has been previously reported (Gregoriou et al., 2009) and might be linked to the higher levels of circulating estrogens, which in turn are implicated in the etiopathogenesis of endometrial polyps (Gredmark et al., 1999).

Because of the risk of bias by confounding factors, we have tried to identify factors independently associated with the risk of endometrial neoplasia in these patients by means of a multivariate analysis with logistic regression. The factors that resulted significantly associated were age and bleeding. Regarding age, controversial results have been previously published. Although various authors have reported an association, two large Italian studies have failed to confirm such association at multivariate analysis (Ferrazzi et al., 2009; Savelli et al., 2003). In our case, age is independently associated to the risk of endometrial neoplasia in patients with suspected endometrial polyps, also

when adjusting for post-menopausal status. On the contrary, according to our multivariate analysis, post-menopausal status does not seem to be independently associated with the risk of neoplasia .

Similarly to what already reported in existing literature, our data support bleeding as a strong predictor of malignancy in patients with a preliminary diagnosis of endometrial polyp. In all the cases and controls of our study, as well as in all the other women in the original cohort, the suspicion of polyp was raised at transvaginal ultrasound. Among our cases, 15 out of 16 presented with bleeding as main indication to the ultrasound scan. Interestingly, the only patient who presented with pelvic pain as main indication, was later found to have had postcoital bleeding, that was thought to depend on atrophic vaginal mucosa, and had a stenotic cervix uteri at hysteroscopy.

Finally, our multivariate analysis failed to confirm the association between endometrial neoplasia and higher BMI.

Conclusions

Conclusions

Conclusions

Endometrial polyps are common and have been increasingly studied as research subject in the last decades. Our bibliometric analysis of scientific literature shows a significative increase in publications on this topic during the last 30 years; as scientific literary topics, endometrial polyps are frequently associated with cancer. The growing scientific interest in endometrial polyps that we have documented seems to be related to the higher diagnostic possibilities and the patient-friendliness offered by transvaginal ultrasound and hysteroscopy rather than to an association with endometrial cancer, with the role of tumor precursor.

In spite of the common practice to refer all women with an ultrasound diagnosis of polyp to hysteroscopy, our data show how the prevalence of endometrial neoplasia in these patients is as low as 1.15%. Moreover, since the malignancy is not confined to a polyp in most of the cases, one cannot assume that the cancer originated from the polyp itself, or exclude that the polyp was secondarily infiltrated by the neoplastic tissue.

Our results show that, among women with an ultrasonographic suspicion of endometrial polyp, those who are later found to have a malignancy , are

more likely to be older, post-menopausal as well as symptomatic. Abnormal uterine bleeding is strongly associated with endometrial neoplasia in these patients, and no case of cancer was found in asymptomatic women. Therefore, in the absence of a clinical indication, the role of ultrasonography for routine controls of the endometrium of asymptomatic women should be questioned.

As a whole, our data support the idea that the hypothesized association between polyps and endometrial cancer depends on a detection bias.

Acknowledgements

In spite of the *one-person show* nature of a doctoral dissertation defense, all of us know that research is team-work. Moreover, people and events surrounding us always interfere with our lives and projects, and our successes, or failures, are never just "ours".

Without a colorful mosaic of events and plenty of people, by my side and on my way, this project would not have been the same. I would like to thank all those who, directly or indirectly, intentionally or unwittingly, have supported me on this journey through research, in particular:

Nicola Maria Gambadauro, my brother, thank you for all your support and patience through the difficulties. I love you.

Lina and Giampietro, my mum and dad, thank you because you make me feel safe and loved, and for everything else. And yes, the kids are fine, and I am eating my fruit and vegetables.

Nicolino, Concetta and Iana, my pole stars.

Vladimir Carli, Giovanni Tinelli and Nino Costabile, the memory of those times is always with me.

Saro Gambera, best friends are best friends, forever.

Cádiz, Andalucía, if you wonder why I thank Her, then you have never seen the sun setting on the ocean at the *Caleta*, nor you have walked through the *callejones* on a rainy Carnival night.

Sicily, no place is more beautiful than You.

Finally, I would like to dedicate this work to those who deserve it the most:

Diego and Evert, the sweetest things I have ever done, and Malin, my Malin, my light that never goes out.

Summary

Background

Endometrial polyps are common benign lesions. The development and spread of accurate and minimally invasive diagnostic tools, such as transvaginal ultrasound or office hysteroscopy, has led to improved diagnosis of endometrial polyps. Endometrial polyps are often clinically irrelevant, but are also commonly found in women with abnormal bleeding or infertility. The risk of endometrial hyperplasia and cancer in women with endometrial polyps is low, but still represents a controversial issue. In spite of growing scientific literature on the subject, it is not clear yet whether polyps represent a cancer precursor or an independent risk factor for endometrial malignancy.

The main objectives of this research were to calculate the frequency of malignant and premalignant changes in the endometrium, and to identify possible factors associated with malignancy in women with suspected endometrial polyps at transvaginal ultrasound.

Materials and methods

Our study population consisted of 1390 consecutive patients that were referred to office hysteroscopy because of the ultrasonographic diagnosis of endometrial polyps.

In the first part of our research, we have identified all cases of atypical hyperplasia and endometrial cancer in the study population. For these cases, we have used descriptive statistics to analyze clinical data and stage of disease. Moreover, we have conducted a comparative analysis between lower and higher risk neoplasia, in order to study possible associations with clinical data.

The second part of our research consisted of a nested case-control study, where the cases of endometrial neoplasia previously identified were compared to controls with benign endometrial polyps. The controls were selected randomly from the same initial cohort of 1390 patients, and in a ratio of 4:1 (controls:cases). Bivariate statistical analysis was initially performed to study the differences of means/medians or frequencies of variables such as age, BMI, menopausal status, bleeding and other symptoms, polyp number and size. A logistic regression model was used to assess the independent association between considered variables and endometrial neoplasia.

Results

Sixteen cases of endometrial neoplasia were found out of the 1390 patients in our population (1.15%). At pathologic assessment of the specimen obtained by hysteroscopy, 4 atypias and 12 endometrial cancers were diagnosed. After final pathology, on hysterectomy specimen, 2 of the aytpia cases were found to be endometrial cancer. Therefore, the frequencies of atypia and cancer in our population were 0.14% and 1.01% respectively.

All patients except one were post-menopausal (93.8%). All of them had undergone the initial ultrasonographic assessment because of symptoms, and 93.8% had reported bleeding as main symptom. Nine cases had a lower risk disease (56.25%; atypical hyperplasia and endometrial cancer stage IA-G1,2), while 7 had a higher risk cancer (43.75%; ≥ stage IA-G3). Patients with a higher risk disease were found to be significantly younger, and their polyps were smaller, albeit non-significantly. None of those variables was found to be significantly different at multivariate analysis.

In our nested case-control study, 64 controls with confirmed benign endometrial polyps were compared to the 16 cases of endometrial neoplasia. At bivariate analysis, the cases were significantly older (mean age 64.19±9.382 vs 52.03±9.846; p<0.001), and had a greater BMI (median 27.66 vs 24.59; p<0.001). Other factors significantly associated with endometrial neoplasia were postmenopausal status and bleeding, as a main symptom. At multivariate analysis with logistic regression, the only factors that showed a statistically significant association with endometrial neoplasia were older age (OR 1.102; 95% CI 1.015-1.198) and bleeding (OR 13.7; 95% CI 1.486-126.278).

Conclusions

In spite of the common practice to refer all women with an ultrasound diagnosis of polyp to hysteroscopy, our data show how the prevalence of endometrial neoplasia in these patients is low (1.15%). Moreover, the malignancy is not confined to a polyp in most of the cases.

Among women with an ultrasonographic suspicion of endometrial polyp, those who are later found to have a malignancy are more likely to be older,

post-menopausal as well as symptomatic. Bleeding is strongly associated with endometrial neoplasia in these patients, and no case of cancer was found in asymptomatic women. Therefore, the role of ultrasonography for routine controls of the endometrium in asymptomatic women should be questioned, as well as the routine indication to polypectomy in the absence of a clinical indication or a reasonable risk of malignancy. As a whole, our data support the idea that the hypothesized association between polyps and endometrial cancer depends on a detection bias.

Resumen en Castellano

Introducción

Los pólipos endometriales representan la tumoración benigna más frecuente de la mucosa endometrial, constituidos por una formación excrecente (sesil o pediculada) de glándulas y estroma endometrial con un eje vascular.

El desarrollo y la difusión de métodos e instrumentos de evaluación de la cavidad uterina mínimamente invasivos, como la ecografía transvaginal y la histeroscópia ambulatoria, ha contribuido al aumento de diagnóstico de pólipos endometriales. Paralelamente, hemos asistido a un aumento de interés científico en este tema, reflejado en un creciente número de publicaciones que hemos documentado en un estudio bibliometrico recién publicado por nuestro grupo.

Los pólipos endometriales no suelen tener consecuencias clínicas y las pacientes muy a menudo son asintomáticas, aunque es más frecuente encontrar pólipos endometriales en mujeres que presentan hemorragias uterinas anormales o infertilidad.

A pesar del importante número de artículos publicados, no se ha establecido claramente si los pólipos endometriales pueden considerarse

precursores de neoplasias endometriales o como un factor de riesgo independiente de carcinoma de endometrio.

El riesgo de hiperplasia con atipias o cáncer endometrial en mujeres con pólipos parece ser bajo. No obstante, la actitud terapéutica con los pólipos endometriales en mujeres asintomáticas es un tema controvertido, siendo habitual indicar la extirpación histeroscópica, a pesar de recientes recomendaciones, como la de la American Association of Gynecological Laparoscopists, que aconsejan evitar la cirugía en casos de bajo riesgo.

Objetivos

Los objetivos principales de este estudio son:

- Valorar la prevalencia de lesiones malignas o premalignas del
  endometrio en mujeres con un diagnostico ultrasonografico de pólipo
  endometrial.

- Describir las características de los casos de neoplasia endometrial que se
  diagnosticaron en un cohorte de mujeres remitidas para realizar
  histeroscopia diagnostica tras la sospecha de pólipo endometrial
  mediante ecografía transvaginal.

- Identificar potenciales factores que estén asociados a neoplasias
  endometriales en estas pacientes.

Material y métodos

Población de estudio: 1390 pacientes consecutivas que habían sido derivadas para la realización de histeroscopia ambulatoria tras el diagnostico de pólipo endometrial mediante ecografía transvaginal.

Todas las pacientes se remitieron a la consulta de histeroscópia del Hospital Universitario Virgen del Rocío de Sevilla, desde 2006 a 2012.

En la primera parte de la investigación, hemos identificado todos los casos de hiperplasia con atipias y cáncer de endometrio diagnosticados en la población de estudio, analizando el estadio de la enfermedad diferenciando entre neoplasias de alto y bajo riesgo para evaluar factores de riesgo relacionados con la severidad de las lesiones.

La segunda parte de nuestro proyecto de investigación consistió en un estudio de casos y control de tipo "nested", donde los casos de neoplasia endometrial previamente identificados se compararon a controles con pólipos endometriales benignos confirmados histopatológicamente.

Los controles se seleccionaron de forma aleatoria de la misma cohorte de 1390 pacientes, y en una proporción de 4 controles para cada caso.

Se ha realizado un análisis estadístico bivariante para evaluar las diferencias entre las medias/medianas de las variables: edad, IMC (índice de masa corporal), status menopausico, hemorragia genital, número y tamaño de los pólipos y otra sintomatología asociada. Así mismo se ha realizado una regresión logística que ha permitido evaluar la asociación de cada variable estudiada de forma independiente con la aparición de neoplasias endometriales.

Resultados

De las 1390 pacientes en nuestra población de estudio, hemos identificado 16 casos de neoplasia endometrial (1.15%). Inicialmente a partir del estudio histopatologico del material obtenido en la histeroscopia se identificaron 4 hiperplasias con atipia y 12 casos de cáncer endometrial. Al diagnóstico definitivo realizado sobre la pieza de histerectomía, dos de los casos de hiperplasias con atipias resultaron ser cánceres de endometrio, por lo cual en la cohorte estudiada hemos encontrado una prevalencia de 0.14% de hiperplasia con atipias (2/1390), y del 1.01% de cáncer endometrial (14/1390).

Las pacientes tenían una edad media de 64.19±9.382 años (rango 49-78), y un IMC medio 29.40±5.2 Kg/m2 (mediana 27.66; rango 24.21-45.74). Todas las pacientes menos una eran postmenopausicas (93.8%). En todos casos, las pacientes se habían remitido para realizarles una ecografia transvaginal por presentar síntomas, concretamente el 93.8% (15/16 pacientes) había referido hemorragias genitales como síntoma principal. Una paciente había referido inicialmente dolor pelviano, pero posteriormente refirió también sangrados, en forma de coitorragias, que se atribuyeron inicialmente a la atrofia genital que presentaba.

Nueve casos correspondieron a neoplasias endometriales de bajo riesgo (56.25%), o sea hiperplasias con atipia y carcinomas endometriales de estadio IA, G1 y G2, tipo histologico endometrioide. Los siete restantes casos fueron de riesgo elevado (43.75%) o sea de un estadio FIGO (2009) igual o superior al IA G3, o tipo histologico diferente al endometrioide.

Mediante análisis estadístico bivariante se ha evidenciado que las pacientes con neoplasia de riesgo mas elevado eran significativamente más jóvenes, y tenían pólipos de tamaño inferior, aunque este aspecto no resultó estadísticamente significativo.

En el estudio de casos y controles "nested", 64 controles con pólipos benignos confirmados mediante estudio histopatologico se compararon a los 16 casos de neoplasia endometrial. Mediante análisis bivariante los casos de neoplasia resultaron ser de mayor edad (edad media 64.19±9.382 versus 52.03±9.846 en los controles; p<.001), y de mayor IMC (mediana 27.66 versus 24.59 en controles; p<.001). Otros factores significativos asociados a la neoplasia endometrial fueron: el estado postmenopáusico, y el sangrado como síntoma principal.

Todas las pacientes con neoplasia tenían síntomas, mientras que entre los controles había un 40.62% de pacientes asintomáticas, que habían sido diagnosticadas de pólipo endometrial mediante una ecografía de control.

Al realizar un análisis multivariante con regresión logística se confirmó la asociación estadísticamente significativa entre neoplasia de endometrio y mayor edad (OR 1.102; 95% CI 1.015-1.198), y sangrado como síntoma principal (OR 13.7; 95% CI1.486-126.278).

Conclusiones

Aunque existe la práctica clínica habitual de remitir a todas las pacientes que presentan un diagnóstico ecográfico de pólipo endometrial independientemente de que existan factores de riesgo o síntomas clínicos,

nuestros datos muestran que la prevalencia de neoplasias endometriales en estas pacientes es baja (1.15%). En la mayoría de los casos la neoplasia no está circunscrita al pólipo endometrial.

En las mujeres a las que se les ha diagnosticado pólipos endometriales mediante ecografía vaginal, la coexistencia con neoplasias endometriales está relacionada con la edad (mayor edad), el estatus postmenopáusico y los síntomas clínicos. El sangrado genital está presente en prácticamente todos los casos. No encontramos ningún caso de cáncer endometrial en mujeres asintomáticas.

Por ello creemos que la realización de ecografías en mujeres asintomáticas, así como la realización rutinaria de histeroscópias /polipectomías en pacientes con pólipos endometriales que no presentan síntomas debería cuestionarse, a menos que existan consistentes factores de riesgo de cáncer.

References

References

Afifi K, Anand S, Nallapeta S, Gelbaya TA. Management of endometrial polyps in subfertile women: a systematic review. Eur J Obstet Gynecol Reprod Biol 2010 Aug;151(2):117-21.

Albertini AF, Devouassoux-Shisheboran M, Genestie C. Pathology of endometrioid carcinoma. Bull Cancer. 2012 Jan;99(1):7-12. doi: 10.1684/bdc.2011.1526.

American Association of Gynecologic Laparoscopists. AAGL practice report: practice guidelines for the diagnosis and management of endometrial polyps. J Minim Invasive Gynecol. 2012;19(1):3-10.

Antunes A Jr, Costa-Paiva L, Arthuso M, Costa JV, Pinto- Neto AM. Endometrial polyps in pre- and postmenopausal women: factors associated with malignancy. Maturitas. 2007;57:415–21.

Baiocchi G, Manci N, Pazzaglia M, Giannone L, Burnelli L, Giannone E, Fratini D, Di Renzo GC. Malignancy in endometrial polyps: a 12-year experience. Am J Obstet Gynecol. 2009 Nov;201(5):462.e1-4.

Baldwin MT, Dudiak KM, Gorman B, Marks CA. Focal intracavitary masses recognized with the hyperechoic line sign at endovaginal US and characterized with hysterosonography. Radiographics. 1999 Jul-Aug;19(4): 927-35.

Batioglu S, Kaymak O. Does hysteroscopic polypectomy without cycle cancellation affect IVF? Reprod Biomed Online. 2005 Jun;10(6):767-9.

Ben-Arie A, Goldchmit C, Laviv Y, Levy R, Caspi B, Huszar M, Dgani R, Hagay Z. The malignant potential of endometrial polyps. Eur J Obstet Gynecol Reprod Biol. 2004;115: 206–10.

Ben-Nagi J, Miell J, Yazbek J, Holland T, Jurkovic D. The effect of hysteroscopic polypectomy on the concentrations of endometrial implantation factors in uterine flushings. Reprod Biomed Online 2009;19:737–744.

Berg A, Sandvik L, Langebrekke A, Istre O. A randomized trial comparing monopolar electrodes using glycine 1.5% with two different types of bipolar electrodes (TCRis, Versapoint) using saline, in hysteroscopic surgery. Fertil Steril. 2009 Apr;91(4):1273-8. doi: 10.1016/ j.fertnstert.2008.01.083. Epub 2008 Apr 18.

Bergeron C, Nogales FF, Masseroli M, Abeler V, Duvillard P, Müller-Holzner E, Pickartz H, Wells M. A multicentric European study testing the reproducibility of the WHO classification of endometrial hyperplasia with a proposal of a simplified working classification for biopsy and curettage specimens. Am J Surg Pathol. 1999 Sep;23(9):1102-8.

Bettocchi S, Ceci O, Nappi L, Di Venere R, Masciopinto V, Pansini V, Pinto L, Santoro A, Cormio G. Operative office hysteroscopy without anesthesia: analysis of 4863 cases performed with mechanical instruments. J Am Assoc Gynecol Laparosc. 2004 Feb;11(1):59-61.

Boulos MN (2005) On geography and medical journalology: a study of the geographical distribution of articles published in a leading medical informatics journal between 1999 and 2004. Int J Health Geogr 4(1):7.

Callaham M, Wears RL, Weber E. Journal prestige, publication bias, and other characteristics associated with citation of published studies in peer-reviewed journals. JAMA 2002;287(21):2847–2850.

Cicinelli E, Romano F, Anastasio PS, Blasi N, Parisi C. Sonohysterography versus hysteroscopy in the diagnosis of endouterine polyps. Gynecol Obstet Invest 1994;38:266–71.

Clark TJ, Khan KS, Gupta JK. Current practice for the treatment of benign intrauterine polyps: a national questionnaire survey of consultant gynaecologists in UK. Eur J Obstet Gynecol Reprod Biol. 2002;103:65– 67.

Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, Sessa C; ESMO Guidelines Working Group. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011 Sep;22 Suppl 6:vi35-9. doi: 10.1093/annonc/mdr374.

de Kroon CD, de Bock GH, Dieben SW, Jansen FW. Saline contrast hysterosonography in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG. 2003 Oct;110(10):938-47.

de Sá Rosa e de Silva AC, Rosa e Silva JC, Cândido dos Reis FJ, Nogueira AA, Ferriani RA. Routine office hysteroscopy in the investigation of infertile couples before assisted reproduction. J Reprod Med 2005;50:501–6.

Dibi RP, Zettler CG, Pessini SA, Ayub AV, de Almeida SB, da Silveira GP. Tamoxifen use and endometrial lesions: hysteroscopic, histological, and immunohistochemical findings in postmenopausal women with breast cancer. Menopause. 2009 Mar-Apr;16(2):293-300.

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ 1994;309:1286–1291.

Di Spiezio Sardo A, Taylor A, Tsirkas P, Mastrogamvrakis G, Sharma M, Magos A. Hysteroscopy: a technique for all? Analysis of 5,000 outpatient hysteroscopies. Fertil Steril. 2008;89(2):438-43.

Dreisler E, Stampe Sorensen S, Ibsen PH, Lose G. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. Ultrasound Obstet Gynecol. 2009;33:102–108.

Dreisler E, Sorensen SS, Lose G. Endometrial polyps and associated factors in Danish women aged 36-74 years. Am J Obstet Gynecol. 2009 Feb; 200(2):147.e1-6.

Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Evaluation of the uterine cavity with magnetic resonance imaging, transvaginal sonography, hysterosonographic examination, and diagnostic hysteroscopy. Fertil Steril. 2001 Aug;76(2):350-7.

Dueholm M, Lundorf E, Sørensen JS, Ledertoug S, Olesen F, Laursen H. Reproducibility of evaluation of the uterus by transvaginal sonography, hysterosonographic examination, hysteroscopy and magnetic resonance imaging. Hum Reprod. 2002 Jan;17(1):195-200.

Dueholm M, Laursen H, Knudsen UB. A simple one-stop menstrual problem clinic with use of hysterosonography for the diagnosis of abnormal uterine bleeding. Acta Obstet Gynecol Scand. 1999 Feb;78(2): 150-4.

Erdemoglu E, Gü̈ney M, Karahan N, Mungan T. Expression of cyclo-oxygenase-2, matrix metalloproteinase-2 and matrix metalloproteinase-9 in premenopausal and postmenopausal endometrial polyps. Maturitas 2008;59:268-274

Exacoustos C, Zupi E, Cangi B, Chiaretti M, Arduini D, Romanini C. Endometrial evaluation in postmenopausal breast cancer patients receiving tamoxifen: an ultrasound, color flow Doppler, hysteroscopic and histological study. Ultrasound Obstet Gynecol. 1995 Dec;6(6):435-42.

Falagas ME, Pitsouni EI, Malietzis GA, Pappas G. Comparison of PubMed, Scopus, Web of Science, and Google Scholar: strengths and weaknesses. FASEB J 2008;22(2):338-342.

Ferrazzi E, Zupi E, Leone FP, Savelli L, Omodei U, Moscarini M, Barbieri M, Cammareri G, Capobianco G, Cicinelli E, Coccia ME, Donarini G, Fiore S, Litta P, Sideri M, Solima E, Spazzini D, Testa AC, Vignali M. How often are endometrial polyps malignant in asymptomatic

postmenopausal women? A multicenter study. Am J Obstet Gynecol. 2009 Mar;200(3):235.e1-6.

Gambadauro P, Magos A. Office 2.0: a web 2.0 tool for international collaborative research. Lancet 2008;371(9627):1837-8.

Gambadauro P, Magos A. Watching the screen during hysteroscopy: a patient choice. BJOG. 2009 Jun;116(7):1006-7

Gambadauro P, Magos A. Pain control in hysteroscopy. Finesse, not local anaesthesia. BMJ. 2010 Apr 20;340:c2097. DOI: 10.1136/bmj.c2097.

Gambadauro P, Torrejón R. Impact factor and the quality of research: What is a rose defined by, its name or its scent? Eur J Obstet Gynecol Reprod Biol 2007;134(2):269-270.

Gambadauro P, Torrejón R. The relevance of endometrial polyps: a bibliometric study. Gynecol Surg 2013; DOI: 10.1007/s10397-013-0788-2

Garuti G, Centinaio G, Luerti M. Outpatient hysteroscopic polypectomy in postmenopausal women: a comparison between mechanical and electrosurgical resection. J Minim Invasive Gynecol. 2008 Sep-Oct;15(5):595-600. doi: 10.1016/j.jmig.2008.07.001.

Goldstein SR. Significance of incidentally thick endometrial echo on transvaginal ultrasound in postmenopausal women. Menopause. 2011 Apr;18(4):434-6. doi: 10.1097/gme.0b013e31820ad00b.

Gredmark T, Kvint S, Havel G, Mattsson LA. Adipose tissue distribution in postmenopausal women with adenomatous hyperplasia of the endometrium. Gynecol Oncol 1999;72:138-42.

Gregoriou O, Konidaris S, Vrachnis N, Bakalianou K, Salakos N, Papadias K, et al. Clinical parameters linked with malignancy in endometrial polyps. Climacteric 2009;12:454–8

Grimbizis GF, Tsolakidis D, Mikos T, Anagnostou E, Asimakopoulos E, Stamatopoulos P, Tarlatzis BC. A prospective comparison of transvaginal ultrasound, saline infusion sonohysterography, and diagnostic hysteroscopy in the evaluation of endometrial pathology. Fertil Steril. 2010 Dec;94(7):2720-5.

Grimes DA, Schulz KF. Compared to what? Finding controls for case-control studies Lancet 2005;365:1429–33

Hassa H, Tekin B, Senses T, Kaya M, Karatas A. Are the site, diameter, and number of endometrial polyps related with symptomatology? Am J Obstet Gynecol. 2006;194:718–721.

Hinckley MD, Milki AA. 1000 office-based hysteroscopies prior to in vitro fertilization: feasibility and findings. JSLS. 2004;8:103–107.

Hulka CA, Hall DA, McCarthy K, Simeone JF. Endometrial polyps, hyperplasia, and carcinoma in postmenopausal women: differentiation with endovaginal sonography. Radiology. 1994;191:755–758.

Indraccolo U, Barbieri F. Relationship between adenomyosis and uterine polyps. Eur J Obstet Gynecol Reprod Biol. 2011 Aug;157(2):185-9.

Kamel HS, Darwish AM, Mohamed SA. Comparison of transvaginal ultrasonography and vaginal sonohysterography in the detection of endometrial polyps. Acta Obstet Gynecol Scand. 2000 Jan;79(1):60-4.

Kasraeian M, Asadi N, Ghaffarpasand F, Karimi AA. Value of transvaginal ultrasonography in endometrial evaluation of non-bleeding postmenopausal women.Climacteric. 2011 Feb;14(1):126-31.

Kelly P, Dobbs SP, McCluggage WG. Endometrial hyperplasia involving endometrial polyps: report of a series and discussion of the significance in an endometrial biopsy specimen. BJOG. 2007 Aug;114(8): 944-50.

Kim KR, Peng R, Ro JY, Robboy SJ. A diagnostically useful histopathologic feature of endometrial polyp: the long axis of endometrial glands arranged parallel to surface epithelium. Am J Surg Pathol. 2004 Aug;28(8):1057-62.

Kim MR, Kim YA, Jo MY, Hwang KJ, Ryu HS. High prevalence of endometrial polyps in endometriosis-associated infertility. J Am Assoc Gynecol Laparosc. 2003 Feb;10(1):46-8.

Lee SC, Kaunitz AM, Sanchez-Ramos L, Rhatigan RM. The oncogenic potential of endometrial polyps: a systematic review and meta-analysis. Obstet Gynecol. 2010 Nov;116(5):1197-205.

Lee et al. Corrections, Obstet Gynecol 2011;118(2):364

Lenhard MS, Johnson TR, Himsl I, Ditsch N, Rueckert S, Friese K, Untch M. Obstetrical and gynecological writing and publishing in Europe. Eur J Obstet Gynecol Reprod Biol 2006;129(2):119-123.

Lieng M, Istre O, Sandvik L, Engh V, Qvigstad E. Clinical effectiveness of transcervical polyp resection in women with endometrial polyps: randomized controlled trial. J Minim Invasive Gynecol. 2010;17:351–357.

Lieng M, Istre O, Sandvik L, Qvigstad E. Prevalence, 1-year regression rate, and clinical significance of asymptomatic endometrial polyps: cross-sectional study. J Minim Invasive Gynecol. 2009 Jul-Aug; 16(4):465-71.

Lieng M, Qvigstad E, Dahl GF, Istre O. Flow differences between endometrial polyps and cancer: a prospective study using intravenous contrast-enhanced transvaginal color flow Doppler and three-dimensional power Doppler ultrasound. Ultrasound Obstet Gynecol. 2008;32:935–40

Lockwood CJ. Mechanisms of normal and abnormal endometrial bleeding. Menopause. 2011 Apr;18(4):408-11.

Lopes RG, Baracat EC, de Albuquerque Neto LC, Ramos JF, Yatabe S, Depesr DB, Lippi UG. Analysis of estrogen- and progesterone-receptor expression in endometrial polyps. J Minim Invasive Gynecol. 2007 May-Jun;14(3):300-3.

Machtinger R, Korach J, Padoa A, Fridman E, Zolti M, Segal J, et al. Transvaginal ultrasound and diagnostic hysteroscopy as a predictor of endometrial polyps: risk factors for premalignancy and malignancy. Int J Gynecol Cancer. 2005;15:325–8.

Madani T, Ghaffari F, Kiani K, Hosseini F. Hysteroscopic polypectomy without cycle cancellation in IVF cycles. Reprod Biomed Online. 2009 Mar;18(3):412-5.

Madari S, Al-Shabibi N, Papalampros P, Papadimitriou A, Magos A. A randomized trial comparing the H Pipelle with the standard Pipelle for endometrial sampling at "no touch" (vaginoscopic) hysteroscopy. Br J Obstet Gynaecol 2009;116:32-7

Magos A, Gambadauro P. Desktop search engines: a modern way to hand search in full text. Lancet 2005;366(9481):203-204.

Maia H Jr, Maltez A, Studart E, Athayde C, Coutinho EM. Ki-67, Bcl-2 and p53 expression in endometrial polyps and in the normal endometrium during the menstrual cycle. Br J Obstet Gynaecol. 2004; 111:1242–1247.

Marbaix E, Brun JL. Concise survey of endometrial pathologies detected at hysteroscopy. Gynecol Surgery 2004;1(3):151-7.

Marsh FA, Rogerson LJ, Duffy SR. A randomised controlled trial comparing outpatient versus daycase endometrial polypectomy. BJOG. 2006 Aug;113(8):896-901. Epub 2006 Jun 2.

Martinez MA, Jou P, Novell R, Cardona M. Endometrial polyps: risk of transformation and clinico-anatomic correlation. Prog Obstet Ginecol 2004;11:506–10.

Martinez-Perez O, Perez-Medina T, Bajo-Arenas J. Ultrasonography of endometrial polyps. Ultrasound Rev Obstet Gynecol. 2003;3:43.

McCluggage WG. My approach to the interpretation of endometrial biopsies and curettings. J Clin Pathol. 2006 Aug;59(8):801-12.

Mittal K, Da Costa D. Endometrial hyperplasia and carcinoma in endometrial polyps: clinicopathologic and follow-up findings. Int J Gynecol Pathol. 2008 Jan;27(1):45-8.

Moritani S, Ichihara S, Hasegawa M, Iwakoshi A, Murakami S, Sato T, Okamoto T, Mori Y, Kuhara H, Silverberg SG. Stromal p16 expression differentiates endometrial polyp from endometrial hyperplasia. Virchows Arch. 2012 Aug;461(2):141-8. doi: 10.1007/s00428-012-1276-1. Epub 2012 Jul 7.

Nagele F, O'Connor H, Davies A, Badawy A, Mohamed H, Magos A. 2500 Outpatient diagnostic hysteroscopies. Obstet Gynecol. 1996;88: 87–92.

Nalaboff KM, Pellerito JS, Ben-Levi E. Imaging the endometrium: disease and normal variants. Radiographics. 2001;21:1409–1424.

Nathani F, Clark TJ. Uterine polypectomy in the management of abnormal uterine bleeding: A systematic review. J Minim Invasive Gynecol. 2006 Jul-Aug;13(4):260-8.

Orvieto R, Bar-Hava I, Dicker D, Bar J, Ben-Rafael Z, Neri A. Endometrial polyps during menopause: characterization and significance. Acta Obstet Gynecol Scand 1999;78:883–6.

Papalampros P, Gambadauro P, Papadopoulos N, Polyzos D, Chapman L, Magos A. The mini-resectoscope: a new instrument for office hysteroscopic surgery. Acta Obstet Gynecol Scand 2009;88(2):227-30

Peng X, Li T, Xia E, Xia C, Liu Y, Yu D. A comparison of oestrogen receptor and progesterone receptor expression in endometrial polyps and endometrium of premenopausal women. J Obstet Gynaecol. 2009 May; 29(4):340-6.

Pérez-Medina T, Bajo-Arenas J, Salazar F, Redondo T, Sanfrutos L, Alvarez P, Engels V. Endometrial polyps and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. Hum Reprod. 2005 Jun;20(6):1632-5.

Perez-Medina T, Bajo J, Huertas MA, Rubio A. Predicting atypia inside endometrial polyps. J Ultrasound Med. 2002;21:125–8.

Perri T, Rahimi K, Ramanakumar AV, Wou K, Pilavdzic D, Franco EL, Gotlieb WH, Ferenczy A. Are endometrial polyps true cancer precursors? Am J Obstet Gynecol. 2010 Sep;203(3):232.e1-6.

Peterson WF, Novak ER. Endometrial polyps. Obstet Gynecol 1956;8:40-9.

Rackow BW, Jorgensen E, Taylor HS. Endometrial polyps affect uterine receptivity. Fertil Steril. 2011 Jun 30;95(8):2690-2.

Rahimi S, Marani C, Renzi C, Natale ME, Giovannini P, Zeloni R. Endometrial polyps and the risk of atypical hyperplasia on biopsies of unremarkable endometrium: a study on 694 patients with benign endometrial polyps. Int J Gynecol Pathol. 2009 Nov;28(6):522-8.

Reslova T, Tosner J, Resl M, Kugler R, Vavrova I. Endometrial polyps: a clinical study of 245 cases. Arch Gynecol Obstet. 1999;262:133–139.

Rogerson L, Bates J, Weston M, Duffy S. A comparison of outpatient hysteroscopy with saline infusion hysterosonography. BJOG. 2002 Jul; 109(7):800-4.

Sagiv R, Sadan O, Boaz M, Dishi M, Schechter E, Golan A. A new approach to office hysteroscopy compared with traditional hysteroscopy: a randomized controlled trial. Obstet Gynecol 2006;108:387-92.

Salim S, Won H, Nesbitt-Hawes E, Campbell N, Abbott J. Diagnosis and management of endometrial polyps: a critical review of the literature. J Minim Invasive Gynecol. 2011 Sep-Oct;18(5):569-81.

Saridogan E, Tilden D, Sykes D, Davis N, Subramanian D. Cost-analysis comparison of outpatient see-and-treat hysteroscopy service with other hysteroscopy service models. J Minim Invasive Gynecol. 2010 Jul-Aug;17(4):518-25.

Savelli L, De Iaco P, Santini D, Rosati F, Ghi T, Pignotti E, et al. Histopathologic features and risk factors for benignity, hyperplasia, and cancer in endometrial polyps. Am J Obstet Gynecol 2003;188:927–31.

Sharma M, Taylor A, Magos A. Management of endometrial polyps: a clinical review. Rev Gynaecol Pract 2004;4(1):1-6

Sharma M, Taylor A, di Spiezio Sardo A, Buck L, Mastrogamvrakis G, Kosmas I, Tsirkas P, Magos A. Outpatient hysteroscopy: traditional versus the 'no-touch' technique. BJOG 2005;112(7):963-7.

Shen L, Wang Q, Huang W, Wang Q, Yuan Q, Huang Y, Lei H. High prevalence of endometrial polyps in endometriosis-associated infertility. Fertil Steril. 2011 Jun 30;95(8):2722-4.e1.

Shokeir et al., Significance of endometrial polyps detected hysteroscopically in eumenorrheic infertile women. J Obstet Gynaecol Res. 2004 Apr;30(2):84-9.

Soares SR, Barbosa dos Reis MM, Camargos AF. Diagnostic accuracy of sonohysterography, transvaginal sonography, and hysterosalpingography in patients with uterine cavity diseases. Fertil Steril. 2000;73:406–411

Spiewankiewicz B, Stelmachów J, Sawicki W, Cendrowski K, Wypych P, Swiderska K. The effectiveness of hysteroscopic polypectomy in cases of female infertility. Clin Exp Obstet Gynecol. 2003;30(1):23-5.

Suarez-Almazor ME, Belseck E, Homik J, Dorgan M, Ramos-Remus C. Identifying clinical trials in the medical literature with electronic databases: MEDLINE alone is not enough. Control Clin Trials 2000;21:476-487.

Taylor E, Gomel V. The uterus and fertility. Fertil Steril 2008;89:1-16

Timmerman D, Verguts J, Konstantinovic ML, et al. The pedicle artery sign based on sonography with color Doppler imaging can replace second-stage tests in women with abnormal vaginal bleeding. Ultrasound Obstet Gynecol. 2003;22:166–171.

Tiras B, Korucuoglu U, Polat M, Zeyneloglu HB, Saltik A, Yarali H. Management of endometrial polyps diagnosed before or during ICSI cycles. Reprod Biomed Online. 2012 Jan;24(1):123-8.

Tokyol C, Aktepe F, Dilek FH, Sahin O, Arioz DT. Expression of cyclooxygenase-2 and matrix metalloproteinase-2 in adenomyosis and endometrial polyps and its correlation with angiogenesis. Int J Gynecol Pathol 2009;28:148-156.

Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ 2nd, Alberts D, Curtin J. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer. 2006 Feb 15;106(4):812-9.

Tutarel O. Geographical distribution of publications in the field of medical education. BMC Med Educ 2002;2:3.

Van Den Bosch T, Van Schoubroeck D, Luts J, Bignardi T, Condous G, Epstein E, Leone FP, Testa AC, Valentin L, Van Huffel S, Bourne T,

Timmerman D.   Effect of gel-instillation sonography on Doppler ultrasound findings in endometrial polyps. Ultrasound Obstet Gynecol. 2011 Sep;38(3):355-9. doi: 10.1002/uog.9043. Epub 2011 Aug 10.

van Dijk LJEW, Breijer MC, Veersema S, Mol BWJ, Timmermans A. Current practice in the removal of benign endometrial polyps: a Dutch survey. Gynecol Surgery 2012;9(2):163-8.

van Dongen H, de Kroon CD, van den Tillaart SA, Louwé LA, Trimbos-Kemper GC, Jansen FW.   A randomized comparison of vaginoscopic office hysteroscopy and saline infusion sonography: a patient compliance study. BJOG. 2008 Sep;115(10):1232-7.

Varasteh NN, Neuwirth RS, Levin B, Keltz MD. Pregnancy rates after hysteroscopic polypectomy and myomectomy in infertile women. Obstet Gynecol. 1999 Aug;94(2):168-71.

Vilodre LC, Bertat R, Petters R, Reis FM. Cervical polyp as risk factor for hysteroscopically diagnosed endometrial polyps. Gynecol Obstet Invest. 1997;44(3):191-5.

Wang JH, Zhao J, Lin J. Opportunities and risk factors for premalignant and malignant transformation of endometrial polyps: management strategies. J Minim Invasive Gynecol 2010;17:53– 8

Werbrouck E, Veldman J, Luts J, Van Huffel S, Van Schoubroeck D, Timmerman D, Van den Bosch T. Detection of endometrial pathology using saline infusion sonography versus gel instillation sonography: a prospective cohort study. Fertil Steril. 2011;95(1):285-8.

Wethington SL, Herzog TJ, Burke WM, Sun X, Lerner JP, Lewin SN, Wright JD. Risk and predictors of malignancy in women with endometrial polyps. Ann Surg Oncol. 2011 Dec;18(13):3819-23.

Winkler B, Alvarez S, Richart RM, Crum CP. Pitfalls in the diagnosis of endometrial neoplasia. Obstet Gynecol. 1984 Aug;64(2):185-94.

Yeung M, Bhandari M. Uneven global distribution of randomized trials in hip fracture surgery. Acta Orthop 2012;83(4):328-333.