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REVIEW ARTICLE

Novel diagnostic approaches to intrauterine neoplasm in fertile age: sonography and hysteroscopy

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ABSTRACT

Endometrial carcinoma (EC) is the most common gynecological malignancy in the world. It is mostly detected in postmenopausal women, but it can also occur in women of fertile age who need fertility-sparing therapy. An early diagnosis is the main objective for the correct management of these patients, making it possible to use a fertility-sparing treatment approach without exposing the patients to the risk of cancer progression. In this review, we discuss the role of sonography and hysteroscopy in the detection of intrauterine neoplasm in women of childbearing age.

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Endometrial carcinoma; sonography; hysteroscopy; fertile age

Introduction

Endometrial cancer (EC) is the leading gynecologic cancer in developed countries. In recent years, with the increase in global obesity rates, the incidence of EC has also increased, with an incidence of 65,620 new cases and 12,590 deaths registered in the United States in 2020 [1].

According to the Bokhman classical dualistic model, EC can be classified into two basic types considering clinical, endocrine and histopathological features [2]:

- Type I, the most common type, is more frequent in obese postmenopausal women and includes about 80% of all endometrial cancers. Type I EC is often estrogen-dependent, low-grade and minimally invasive, which is the reason why it is linked to a better prognosis. It is often preceded by endometrial hyperplasia.
- Type II, often diagnosed in younger women, is typically an aggressive, estrogen-independent neoplasm with a poorer prognosis.

Nevertheless, it sometimes does not reflect the full heterogeneity of EC.

New molecular evidence, supported by clinical diversity of cancer, led in 2013 to a new molecular classification presented by The Cancer Genome Atlas Research Network (TGCA) [3].

TCGA Research Network described four novel prognostic subgroups of endometrial carcinoma: POLE/ultramutated (POLE, good prognosis), microsatellite-instable/hypermutated (MSI, intermediate prognosis), copy-number-low/TP53-wild-type (CNL, variable prognosis), and copy-number-highTP53-mutant (CNH, poor prognosis) [4].

However, the prevalence of the TCGA subgroups is not in accordance with the prognostic value of Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) grade, indicating that the current risk stratification of EC will be heavily affected by the molecular signature [4].

A novel molecular classifier, the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), has been developed based on immunohistochemistry as a surrogate of sequencing, trying to overcome technical difficulties and costs of sequencing analysis. ProMisE classifies ECs in the following four prognostic groups: POLE-mutated (POLE-mt),

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mismatch repair-deficient (MMR-d), p53-abnormal (p53-abn), p53-wild-type (p53-wt) [5].

The etiology and pathogenesis of EC have not yet been fully understood [6]. Early menarche, nulliparity, late age at menopause, increased levels of estrogen caused by obesity, diabetes, high-fat diet, advanced age, and tamoxifen use are the most quoted risk factors for EC [7]. In most cases, EC is caused by sporadic mutations, and only 5% of EC patients present genetic mutations. The average age of this latter group of patients is ten to 20 years lower than that of the patients with sporadic cancer [8].

Even though most cases of EC are diagnosed in post-menopausal patients (on average 75 years old) [9], EC can also be detected in reproductive age women (12–51 years old) [10]. In a recent analysis conducted by Van Den Bosch et al., it was shown that 1% of women of reproductive age had endometrial malignancy compared with 11% of postmenopausal women [11]. Moreover, considering that a great number of reproductive-age women are delaying childbearing, the rate of EC diagnosis in nulliparous women has been growing as well, leading to an increase in the number of women diagnosed with EC before the desired completion of childbearing [12].

Whereas the standard treatment for this malignancy results in permanent sterility, new options for the selection of young women who desire to preserve fertility are arising [13]. In selected cases of EC, such as those with locally restricted uterine lesions and no signs of metastasis or infiltration, a combined minimally-invasive approach and adjuvant treatment, may offer the possibility of a less aggressive and fertility-sparing treatment [14]. Uterine preservation may be acceptable along with adequate counseling and close follow-up, always considering the risk of late recurrence. However, to make this option viable, it is important to detect EC at an early stage. Unfortunately, as compared with postmenopausal women in whom EC is relatively easy to detect, especially based on the presence of postmenopausal bleeding, the diagnosis is more difficult in younger women who are still menstruating regularly [15,16]. For this reason, a huge effort has been made to identify all the diagnostic approaches that may facilitate the early detection of EC.

Nowadays, transvaginal ultrasonography, with the measure of endometrial thickness [17], and hysteroscopy [17], with the evaluation of endometrial patterns and the related possibilities of performing endometrial sampling [18,19], are the most valued approaches [20].

Here, we discuss the role of sonography and hysteroscopy in the detection of intrauterine neoplasm in women of childbearing age.

Methods

The data search was conducted using the following databases MEDLINE, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID and Cochrane Library, querying for all articles related to novel approaches to the diagnosis of intrauterine neoplasm in fertile age, with particular attention to sonography and hysteroscopy, from the inception of the database up to March 2021. The following Medical Subject Headings (MeSH) terms were used to screen and identify studies: 'uterine neoplasm', 'hysteroscopy', 'ultrasonography'. Articles were excluded according to the following criteria: (a) articles were not written in English, (b) were published as conference papers or abstracts only, and (c) studies including information that overlapped other publications. In our search, only articles concerning uterine neoplasm were included.

The selection criteria for this narrative review included original articles (randomized and non-randomized clinical trials, including prospective observational studies, retrospective cohort studies, and case-control studies) and review articles regarding the novel approaches for diagnosis of intrauterine neoplasm in fertile age. Articles that met the inclusion criteria were carefully read, and, when appropriate, further articles retrieved from their references were also reviewed with the aim to include other critical studies that might have been missed in the initial search.

A narrative synthesis of the available evidence on this topic is presented.

Results and discussion

Diagnostic cornerstones in intrauterine neoplasm in fertile age

The most controversial debate focuses on which is the best technique to investigate the uterine cavity with a heated debate between supporters of ultrasound and those of hysteroscopy. However, the concept of hysteroscopy and ultrasonography as competing tests may be misplaced, and perhaps they should rather be viewed as complementary diagnostic tools. In this way, a more rational approach to investigating women for endometrial cancer is possible based on the clinical and economic performance of hysteroscopy and

ultrasonography. Moreover, in the presence of a suspected uterine neoplasm, ultrasonography should be always followed by hysteroscopy in order to obtain adequate tissue samples for histological diagnosis.

Ultrasonography

When a woman of childbearing age presents with symptoms suggesting an intrauterine neoplasm, ultrasound-based techniques are usually the first diagnostic choice. The use of ultrasound in the diagnosis of intrauterine pathology was introduced in the late 1980s and early 1990s [21,22]. However, the criterion of 'thick endometrium', one of the most important sonographic features of endometrial neoplasm, has limited importance in women of fertile age. In 2010, the International Endometrial Tumor Analysis (IETA) group published a consensus opinion paper on terms, definitions and measurements to describe the sonographic features of the endometrium and intrauterine lesions [23]. Based on these IETA recommendations, the ultrasound examination should start with the acquisition of a proper midsagittal section of the uterus, followed by the measurement of the endometrium. In the fertile age, this examination should be performed early in the menstrual cycle just after the menstrual bleeding. In addition to the endometrial thickness, the echogenicity of the endometrium (uniform or not uniform), the aspect of the endometrial midline, and the endometrial-myometrial junction should also be examined.

When the results of the standard ultrasound examination are inconclusive, higher-resolution techniques, including power Doppler imaging, 3D ultrasound, and fluid instillation sonography (FIS), can be used [11,24]. The use of 3D ultrasound can help the sonographer to achieve the correct section in cases in which the uterus is twisted laterally. Power Doppler allows for the evaluation of the vascularization pattern of pathological formations, such as polyps and submucosal fibroids. FIS improves the detection and localization of focal lesions protruding into the uterine cavity [24].

A new modification of FIS, using the same technique of uterine cavity distension by fluid installation but employing a specific type of vaginal probes and software, called virtual sonographic hysteroscopy (VSH), is capable of reconstructing virtual 3D images of the uterine cavity similar to those generated by conventional hysteroscopy [25]. As compared with conventional hysteroscopy, VSH is completely noninvasive, without physical penetration of the uterine cavity, and more versatile as to the precise identification and localization of intracavitary pathological formations [25]. In addition to its value for EC diagnosis, a recent cost-effectiveness analysis has also shown that VSH, when performed before the first assisted reproduction attempt, reduces the cost per live birth in different clinical scenarios including *in vitro* fertilization (IVF) with the patient's oocytes, IVF with donor oocytes, and frozen embryo transfer [26].

Though useful as the first-line approach, none of the above sonographic methods is sufficient to distinguish reliably between benign and malignant neoplasms. On the other hand, the sonographic appearance of intrauterine neoplasms, mainly fibroids and polyps, is a valuable guide as to the current risk of their malignization and thus the degree of emergency to proceed with further diagnostic and therapeutic measures. Uterine fibroids (leiomyomas) are the most frequent benign tumors in women of reproductive age [27]. Uterine fibroids can be symptomatic or asymptomatic. Because fibroids may be associated with infertility, especially if they have a submucosal component, they are often discovered during the basic infertility diagnostic workup [28]. Transvaginal sonography is 90–99% sensitive for detecting uterine fibroids, even though it may miss subserosal and small fibroids [29,30]. There is minimal concern for malignancy in women with asymptomatic fibroids [27]. Endometrial polyps (EPs) are sessile or pedunculated focal endometrial protrusions. According to the WHO classification of tumors of female reproductive organs (2014) [31], they arise as monoclonal overgrowths of genetically altered stromal cells, supplied by a thick vascular stalk and covered by secondarily induced surface epithelium and glands. Though less frequent in the general population of women in fertile age, they can be found in up to 30% of infertile women [32] and one randomized controlled trial demonstrated a causal relationship between EPs and infertility [33].

EPs can easily be missed during the conventional sonographic examination when they can be misinterpreted as local areas of thick endometrium. In doubtful cases, FIS in combination with color Doppler can reliably detect EPs, in addition to determining their structure (sessile versus pedunculated), size and vascularization pattern. In its initial stages, EC can be easily mistaken as a benign EP [34]. Given the fact that there is a high rate of regression in EPs <1 cm [35] and those detected in asymptomatic premenopausal women [34], a 'wait-and-see' approach is sometimes chosen. In a meta-analysis exploring the

risk of malignancy within EPs, the prevalence of malignancy was 1.30% in reproductive-age women [36]. In other cases, especially in EPs >1.5 cm and causing abnormal uterine bleeding, hysteroscopic polypectomy is the treatment of choice. In addition to making it possible to perform targeted biopsy so as to obtain an endometrial sample for histological analysis, it also facilitates pregnancy in women who are seeking it [36].

A recent large prospective multicenter study [37] evaluated the ultrasound characteristics of EC and other malignant endometrial neoplasms with the use of the IETA consensus nomenclature. Out of 1,538 women included in the final analysis, 25 had a final diagnosis other than the suspected EC, including uterine carcinosarcoma, synchronous ovarian cancer, synchronous tubal cancer, endometrial stromal sarcoma, adenosarcoma, leiomyosarcoma, ovarian sex cord tumor, and perivascular epithelioid cell tumor [37]. Even so, the diagnosis of EC, suggested by ultrasound, was confirmed in a vast majority (98.4%) of the patients. In the same study, sonographic characteristics of EC were also related with the cancer grade, higher grades of EC being associated with thicker endometrium, higher tumor volume, less regular endometrial-myometrial junction and echogenicity, multiple vessels of focal and multifocal origin and higher Doppler Color score [37]. Ultrasound is also useful for the prediction of myometrial invasion in women with EC [38].

Hysteroscopy

Modern office hysteroscopy offers the clinician the possibility of an accurate evaluation of endometrial morphology and with the advances in miniature instruments. Office hysteroscopy on conscious patients has become the standard to explore the intrauterine cavity, with the ability to perform some minor procedures concomitantly, such as targeted endometrial biopsy under direct visualization allowing the selective sampling of targeted areas of the endometrium [39–42].

Even though there is no screening protocol for the early detection of EC, either in women of postmenopausal age or those in fertile age, the symptomatology of abnormal uterine bleeding is the most important element [43]. Indeed, postmenopausal bleeding represents the commonest symptom defining the onset of EC, while in women of childbearing age, EC is associated with menstrual irregularities, intermenstrual bleeding, or sometimes, menorrhagia of recent onset [44]. Office hysteroscopy is considered the 'gold standard' in the diagnosis of malignant endometrial pathology, considering the possibility of having a direct panoramic view of the uterine cavity and cervical canal, with an assessment of the site, size and macroscopical characteristics of heteroplastic lesions. Overall, the major advantage is obtained from the possibility of taking an accurate biopsy sample, with a subsequent microscopical pathological examination [45].

At hysteroscopic inspection, it is important to observe the characteristics of the endometrium, such as thickening (focal or diffuse, homogeneous or inhomogeneous), vascularization (focal or diffuse, regular or atypical), color and texture considering that some morphological criteria can help to differentiate what can be defined as either normal endometrium or Endometrial Hyperplasia (EH) or EC [46]. Hysteroscopic findings are classified as normal if they were proliferative, secretory, atrophic and hypotrophic, and as abnormal in cases of endometrial polyps, submucous myomas, endometritis, adenomyosis, EH and EC [46].

Generally, EH is considered as a precursor to type 1 EC, with which it shares the condition of hyperestrogenism [47]. As for EC, EH is also more common in women in post-menopausal age (prevalence of 15%), even though it is not rare to find also in women of fertile age (prevalence of 1.3%) [48].

Detecting only endometrial thickening in fertile age is, therefore, an unspecific criterion of EH, and the concomitant presence of other elementary morphological abnormalities, such as architectural distortion of glandular outlets or coexisting cystic dilatations of the mucosa, is the only way to improve the diagnostic accuracy of a standard hysteroscopic examination [49,50]. Indeed, it is necessary to underline that inhomogeneous endometrial thickening may be common to many physiopathologic conditions in women of reproductive age, such as the proliferative glandular stromal stimulus exerted by estrogen or the aspects of endometrium in the luteal phase, capable of mimicking hyperplasia. This is the reason for which an assessment in this phase of the cycle is highly problematic [51]. On the other hand, in menopause, which induces a state of non-evolving hypo-endometrial atrophy, the finding of an inhomogeneous thickened endometrium improves the predictive value of hysteroscopic findings [42,51]. At a macroscopic level, it is quite difficult to differentiate EH without atypia from EH with atypia [52]. For this reason, it is necessary to perform differential diagnosis through a biopsy sample obtained from a representative

diagnostic target site: the diagnostic accuracy of hysteroscopy with targeted endometrial biopsy sampling achieves a sensitivity of 97.5% and a specificity of 100% [53].

As to the method of performing the biopsy, Bettocchi et al. introduced a new biopsy technique to replace the traditional hysteroscopic 'punch biopsy', defined as 'grasp biopsy', proposing a new method to obtain a larger amount of endometrial tissue so as to facilitate adequate histological evaluation [54]. Some evidence underlines the importance of performing not only targeted biopsies at suspicious areas but also 'random endometrial biopsies' to improve the sensitivity and specificity of the diagnostic evaluation [55].

The major hysteroscopic features giving rise to the suspicion of EC are whitish or grayish-white endometrial color, areas of necrosis, hemorrhage and microcalcification, atypical vascularization (diffuse vascular patterns with irregular ramifications or blurred outlines), irregular or ulcerated surface with a soft- friable consistency, susceptible to bleeding on contact with the hysteroscope. EC can appear in a circumscribed form, such as a polypoid lesion, or a diffuse form [56,57].

In fertile women, hysteroscopy has a crucial role not only in the diagnosis but also in the follow-up and treatment of patients with EH with atypia (AH) and EC in the early stage (EEC) [58]. Even though the standard treatment option is a surgical modality with the permanent loss of fertility, the conservative treatment is a therapeutic option that can be offered to patients with a desire for preserving fertility, with the responsibility of strict monitoring performed by an integrated clinical follow-up including periodically scheduled hysteroscopic controls and ultrasound examinations. It is fundamental for the patient to be extremely motivated and correctly informed about the risks of conservative treatment, such as understaging a more advanced cancer, as well as a failed conservative treatment, the persistence or progression of the disease, and initial response to treatment with subsequent recurrence or metastasis [13].

Recent research highlights the role of immunohistochemical markers in predicting the response to conservative treatment of AH and EEC on pretreatment specimens. The most studied predictive markers in the pretreatment phase were progesterone and estrogen receptors and their isoforms (in particular progesterone receptor B), and some mismatch repair proteins combined with other molecules such as phospho-AKT or phospho-mTOR [59]. According to Raffone et al., a weak stromal of the progesterone receptor expression is a highly sensitive predictive marker of both no response and recurrence of AEH and EEC conservatively treated [60], and a deficient expression of mismatch repair proteins (MMR) appears as a highly specific predictor of recurrence of AEH/EEC after initial regression [61].

The conservative treatment for AH can be performed using a combination of medical therapy (antiestrogen or local progestin) with a conservative surgical approach consisting of an endometrial resection that spares the basal endometrial layer if the patient is seeking fertility preservation [58].

Also, young patients with a desire of offspring, who suffer from focal neoplasia of the endometrium at stage IA-G1 (FIGO - International Federation of Gynecology and Obstetrics system 2009), may yet benefit from a combined conservative medical-surgical treatment, which represents an emerging therapeutic option.

According to recent evidence, the combination of hysteroscopic resection with an LNG-IUD as fertility-sparing treatment of EEC and AEH showed a similar response and live birth rates compared with those reported in the literature for progestins alone, but with considerably lower relapse rates [62].

The hysteroscopic technique for conservative treatment of endometrial carcinoma was first described by Mazzon et al. in 2009 [63], a technique that requires the gradual removal of the neoplastic lesion through three steps (removal of the focal neoplastic lesion; removal of the endometrium surrounding the focal malignancy; removal of the myometrium surrounding the neoplastic lesion). Nevertheless, it is mandatory to perform larger prospective studies to establish standard guidelines on the proper selection of patients, medical and surgical management, and follow-up in the short and long term.

Conclusions

Sonography is the first-line approach to examine women of childbearing age with suspected intrauterine neoplasm. Results obtained can suggest the probability of malignant neoplasm and thus the degree of urgency to perform additional diagnostic and/or therapeutic interventions. The office hysteroscopy represents the next step: it can not only confirm the diagnosis but also perform minor surgical procedures to eliminate the suspected lesions and let them be evaluated by histologic examination.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper

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References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA A Cancer J Clin. 2020;70(1):7–30.
[2] Amant F, Moerman P, Neven P, et al. Endometrial cancer. Lancet. 2005;366(9484):491–505.
[3] Wilczyński M, Danielska J, Wilczyński J. An update of the classical Bokhman's dualistic model of endometrial cancer. Prz Menopauzalny. 2016;15:63–68.
[4] Travaglino A, Raffone A, Mollo A, et al. TCGA molecular subgroups and FIGO grade in endometrial endometrioid carcinoma. Arch Gynecol Obstet. 2020;301(5):1117–1125.
[5] Raffone A, Travaglino A, Gabrielli O, et al. Clinical features of ProMisE groups identify different phenotypes of patients with endometrial cancer. Arch Gynecol Obstet. 2021;303(6):1393–1400.
[6] Passarello K, Kurian S, Villanueva V. Endometrial cancer: an overview of pathophysiology, management, and care. Semin Oncol Nurs. 2019;35(2):157–165.
[7] Koh WJ, Abu-Rustum NR, Bean S, et al. Uterine Neoplasms, Version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16(2):170–199.
[8] Resnick KE, Hampel H, Fishel R, et al. Current and emerging trends in Lynch syndrome identification in women with endometrial cancer. Gynecol Oncol. 2009;114(1):128–134.
[9] Tabor A, Watt HC, Wald NJ. Endometrial thickness as a test for endometrial cancer in women with postmenopausal vaginal bleeding. Obstet Gynecol. 2002;99(4):663–670.
[10] Son J, Carr C, Yao M, et al. Endometrial cancer in young women: prognostic factors and treatment outcomes in women aged 40 years. Int J Gynecol Cancer. 2020;30(5):631–639.
[11] Van Den Bosch T, Verbakel JY, Valentin L, et al. Typical ultrasound features of various endometrial pathologies described using International Endometrial Tumor Analysis (IETA) terminology in women with abnormal uterine bleeding. Ultrasound Obstet Gynecol. 2021;57(1):164–172.
[12] Trojano G, Olivieri C, Tinelli R, et al. Conservative treatment in early stage endometrial cancer: a review. Acta Biomed. 2019;90:405–410.
[13] Taylan E, Oktay K. Fertility preservation in gynecologic cancers. Gynecol Oncol. 2019;155(3):522–529.
[14] Yu M, Wang Y, Yuan Z, et al. Fertility-sparing treatment in young patients with grade 2 presumed stage IA endometrioid endometrial adenocarcinoma. Front Oncol. 2020;10:1437.
[15] Braun MM, Overbeek-Wager EA, Grumbo RJ. Diagnosis and management of endometrial cancer. Am Fam Physician. 2016;93(6):468–474.
[16] Clark TJ, Voit D, Gupta JK, et al. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. JAMA. 2002;288(13):1610–1621.
[17] Bakour SH, Dwarakanath LS, Khan KS, et al. The diagnostic accuracy of ultrasound scan in predicting endometrial hyperplasia and cancer in postmenopausal bleeding. Acta Obstet Gynecol Scand. 1999;78:447–451.
[18] Torrejon R, Fernandez-Alba JJ, Carnicer I, et al. The value of hysteroscopic exploration for abnormal uterine bleeding. J Am Assoc Gynecol Laparosc. 1997;4(4):453–456.
[19] van Hanegem N, Prins MM, Bongers MY, et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2016;197:147–155.
[20] Clark TJ. Hysteroscopy and ultrasonography in the diagnosis of endometrial cancer. Gynäkol Geburtshilfliche Rundsch. 2006;46(1–2):3–12.
[21] Osmers R, Völksen M, Schauer A. Vaginosonography for early detection of endometrial carcinoma? Lancet. 1990;335(8705):1569–1571.
[22] Goldstein SR, Nachtigall M, Snyder JR, et al. Endometrial assessment by vaginal ultrasonography before endometrial sampling in patients with postmenopausal bleeding. Am J Obstet Gynecol. 1990;163(1 Pt 1):119–123.
[23] Leone FP, Timmerman D, Bourne T, et al. Terms, definitions and measurements to describe the sonographic features of the endometrium and intrauterine lesions: a consensus opinion from the International Endometrial Tumor Analysis (IETA) group. Ultrasound Obstet Gynecol. 2010;35(1):103–112.
[24] Van den Bosch T. Ultrasound in the diagnosis of endometrial and intracavitary pathology: an update. Australas J Ultrasound Med. 2012;15(1):7–12.
[25] Tesarik J, Mendoza-Tesarik R, Mendoza N. Virtual ultrasonographic hysteroscopy followed by conventional operative hysteroscopy, enabling pregnancy. Am J Obstet Gynecol. 2017;216(2):188.e1.
[26] Vitale SG, Laganà AS, Török P, et al. Virtual sonographic hysteroscopy in assisted reproduction: a retrospective cost-effectiveness analysis. Int J Gynaecol Obstet. 2021 Feb 22. doi: 10.1002/ijgo.13651. Epub ahead of print. PMID: 33615469.
[27] Wallach EE, Vlahos NF. Uterine myomas: an overview of development, clinical features, and management. Obstet Gynecol. 2004;104(2):393–406.
[28] Carranza-Mamane B, Havelock J, Hemmings R, et al. Hemmings R; reproductive endocrinology and

infertility committee; special contributor. The management of uterine fibroids in women with otherwise unexplained infertility. J Obstet Gynaecol Can. 2015;37(3):277–285.,
[29] Cicinelli E, Romano F, Anastasio PS, et al. Transabdominal sonohysterography, transvaginal sonography, and hysteroscopy in the evaluation of submucous myomas. Obstet Gynecol. 1995;85(1): 42–47.
[30] Dueholm M, Lundorf E, Hansen ES, et al. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. Am J Obstet Gynecol. 2002;186(3):409–415.
[31] Kurman RJ, Carcangiu ML, Herrington CS, et al. WHO classification of tumours of female reproductive organs. WHO Classification of Tumours, 4th ed., Vol. 6. Lyon: IARC; 2006.
[32] Hinckley MD, Milki AA. 1000 office-based hysteroscopies prior to *in vitro* fertilization: feasibility and findings. JSLS. 2004;8(2):103–107.
[33] Pérez-Medina T, Bajo-Arenas J, Salazar F, et al. Endometrial polyps and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. Hum Reprod. 2005;20(6):1632–1635.
[34] Ben-Arie A, Goldchmit C, Laviv Y, et al. The malignant potential of endometrial polyps. Eur J Obstet Gynecol Reprod Biol. 2004;115(2):206–210.
[35] DeWaay DJ, Syrop CH, Nygaard IE, et al. Natural history of uterine polyps and leiomyomata. Obstet Gynecol. 2002;100(1):3–7.
[36] Stamenov GS, Vitale SG, Della Corte L, et al. Hysteroscopy and female infertility: a fresh look to a busy corner. Hum Fertil. 2020;2:1–29.
[37] Epstein E, Fischerova D, Valentin L, et al. Ultrasound characteristics of endometrial cancer as defined by International Endometrial Tumor Analysis (IETA) consensus nomenclature: prospective multicenter study. Ultrasound Obstet Gynecol. 2018;51(6):818–828. Erratum in: Ultrasound Obstet Gynecol. 2018;52:684.
[38] Frühauf F, Zikan M, Semeradova I, et al. The diagnostic accuracy of ultrasound in assessment of myometrial invasion in endometrial cancer: subjective assessment versus objective techniques. Biomed Res Int. 2017;2017:1–10.
[39] Bettocchi S, Nappi L, Ceci O, et al. Office hysteroscopy. Obstet Gynecol Clin North Am. 2004;31(3): 641–654.
[40] Vitale SG. The Biopsy Snake Grasper Sec. VITALE: a new tool for office hysteroscopy. J Minim Invasive Gynecol. 2020;27(6):1414–1416.
[41] Vitale SG, Laganà AS, Caruso S, et al. Comparison of three biopsy forceps for hysteroscopic endometrial biopsy in postmenopausal patients (HYGREB-1): a multicenter, single-blind randomized clinical trial. Int J Gynaecol Obstet. 2021 Mar 8. doi: 10.1002/ijgo.13669. Epub ahead of print. PMID: 33686708.
[42] Giampaolino P, Della Corte L, Di Filippo C, et al. Office hysteroscopy in the management of women with postmenopausal bleeding. Climacteric. 2020; 23(4):369–375.
[43] Marchet M, Litta P, Lanza P, et al. The role of hysteroscopy in early diagnosis of endometrial cancer. Euro J Gynaecol Oncol. 2002;23:151–153.
[44] Iram S, Musonda P, Ewies AA. Premenopausal bleeding: when should the endometrium be investigated? A retrospective non comparative study of 3006 women. Eur J Obstet Gynecol Reprod Biol. 2010;148(1):86–89.
[45] Bedner R, Rzepka-Gorska I. Hysteroscopy with directed biopsy versus dilatation and curettage for the diagnosis of endometrial hyperplasia and cancer in perimenopausal women. Eur J Gynaecol Oncol. 2007;28:400–402.
[46] Garuti G, Sambruni I, Colonnelli M, et al. Accuracy of hysteroscopy in predicting histopathology of endometrium in 1500 women. J Am Assoc Gynecol Laparosc. 2001;8(2):207–213.
[47] Tabata T, Yamawaki T, Yabana T, et al. Natural history of endometrial hyperplasia. Study of 77 patients. Arch Gynecol Obstet. 2001;265(2):85–88.
[48] Reed SD, Newton KM, Clinton WL, et al. Incidence of endometrial hyperplasia. Am J Obstet Gynecol. 2009;200:678 e1–6.
[49] Allison KH, Reed SD, Voigt LF, et al. Diagnosing endometrial hyperplasia: why is it so difficult to agree? Am J Surg Pathol. 2008;32(5):691–698.
[50] Uno LH, Sugimoto O, Carvalho FM, et al. Morphologic hysteroscopic criteria suggestive of endometrial hyperplasia. Int J Gynaecol Obstet. 1995;49(1):35–40.
[51] Garuti G, Cellani F, Garzia D, et al. Accuracy of hysteroscopic diagnosis of endometrial hyperplasia: a retrospective study of 323 patients. J Minim Invas Gynecol. 2005;12(3):247–253.
[52] Garuti G, Mirra M, Luerti M. Hysteroscopic view in atypical endometrial hyperplasias: a correlation with pathologic findings on hysterectomy specimens. J Minim Invas Gynecol. 2006;13(4):325–330.
[53] Dijkhuizen FPHLJ, Mol BWJ, Brölmann HAM, et al. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia, a meta-analysis. Cancer. 2000;89(8): 1765–1772.
[54] Bettocchi S, Di Venere R, Pansini N, et al. Endometrial biopsies using small diameter hysteroscopes and 5Fr instruments: how can we obtain enough material for correct histologic diagnosis? J Am Assoc Gynecol Laparosc. 2002;9(3):290–292.
[55] Martinelli F, Ditto A, Bogani G, et al. Accuracy of pre-operative hysteroscopic guided biopsy for predicting final pathology in uterine malignancies. J Cancer Res Clin Oncol. 2017;143(7):1275–1279.
[56] Di Spiezio Sardo A, De Angelis MC, Della Corte L, et al. Should endometrial biopsy under direct hysteroscopic visualization using the grasp technique become the new gold standard for the preoperative evaluation of the patient with endometrial cancer? Gynecol Oncol. 2020;158(2):347–353.
[57] Miyamoto T, Abiko K, Murakami R, et al. Hysteroscopic morphological pattern reflects

histological grade of endometrial cancer. J Obstet Gynaecol Res. 2019;45(8):1479–1487.

[58] Cicinelli E, Comi N, Scorcia P, et al. Hysteroscopy for diagnosis and treatment of endometrial carcinoma precursor. Eur J Gynecol Oncol. 1993;14:425–436.

[59] Travaglino A, Raffone A, Saccone G, et al. Immunohistochemical predictive markers of response to conservative treatment of endometrial hyperplasia and early endometrial cancer: a systematic review. Acta Obstet Gynecol Scand. 2019;98(9): 1086–1099.

[60] Raffone A, Travaglino A, Zullo FM, et al. Predictive accuracy of progesterone receptor B in young women with atypical endometrial hyperplasia and early endometrial cancer treated with hysteroscopic resection plus LNG-IUD insertion. J Minim Invasive Gynecol. 2020;26:S1553-4650(20)31097-9.

[61] Raffone A, Catena U, Travaglino A, et al. Mismatch repair-deficiency specifically predicts recurrence of atypical endometrial hyperplasia and early endometrial carcinoma after conservative treatment: a multicenter study. Gynecol Oncol. 2021;161(3):795–801.

[62] Giampaolino P, Di Spiezio Sardo A, Mollo A, et al. Hysteroscopic endometrial focal resection followed by levonorgestrel intrauterine device insertion as a fertility-sparing treatment of atypical endometrial hyperplasia and early endometrial cancer: a retrospective study. J Minim Invasive Gynecol. 2019; 26(4):648–656.

[63] Mazzon I, Corrado G, Masciullo V, et al. Conservative surgical management of stage IA endometrial carcinoma for fertility preservation. Fertil Steril. 2010;93(4):1286–1289.