International Journal of Clinical Therapeutics and Diagnosis (IJCTD)
ISSN 2332-2926

The Role of Hysteroscopy In Endometrial Cancer

Review Article

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Abstract

Endometrial cancer (EC) is the most frequent gynecological malignancy. Hysteroscopy is a minimally invasive diagnostic and operative technique mainly deployed in cases presented with abnormal uterine bleeding (AUB) or infertility. During the last decades, diagnostic hysteroscopy tends to be at least equally important as the Dilatation & Curretage (D&C), in investigating AUB. By using this diagnostic method, the uterine cavity can be thoroughly visualized and an endometrial biopsy specimen can be taken under hysteroscopic view. An EC can be detected in 7-10% of postmenopausal patients and 2-3% of premenopausal patients submitted to hysteroscopy. Hysteroscopy has been recently confirmed to be an accurate diagnostic method in the diagnosis of endometrial carcinoma. Hysteroscopic examination before surgery in patients with endometrial cancer may increase the risk of dissemination of malignant cells into the peritoneal cavity. The risk was statistically significantly associated with the use of a liquid medium for uterine cavity distention but not with early-stage disease. There is no evidence to support an association between preoperative hysteroscopic examination and a worse prognosis. There is no reason to avoid diagnostic hysteroscopy before to surgery in patients with endometrial cancer, especially in early stages.

Keywords: Hysteroscopy; Endometrial Cancer; Abnormal Uterine Bleeding (AUB).

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Received: January 31, 2015
Accepted: March 30, 2015
Published: April 01, 2015

Citation: Georgios L. Adonakis, Georgios Androutsopoulos, Minas Paschopoulos (2015) The Role of Hysteroscopy In Endometrial Cancer. *Int J Clin Ther Diagn.* S1:004 12-16. **doi: http://dx.doi.org/10.19070/2332-2926-SI01004**

Introduction

Endometrial cancer (EC) is the most frequent gynecological malignancy. Twenty-five percent of EC are diagnosed in premenopausal women and almost 5% in women up to 40 years aged with a history of estrogen- or hormone-related disorders, such as ovarian dysfunction, chronic anovulation, infertility, obesity, and polycystic ovary syndrome [1].

Hysteroscopy is a minimally invasive diagnostic and operative technique mainly deployed in cases presented with abnormal uterine bleeding (AUB) or infertility. In the case of AUB, investigation aims to exclude or identify pathologies that would need further treatment such as cancer, endometrial hyperplasia, submucous myomas or endometrial polyps. In the past, AUB was assessed by dilation and cutterage (D&C). However, during the last decades, diagnostic hysteroscopy tends to be at least equally important in investigating AUB. By using this diagnostic method, the uterine cavity can be thoroughly visualized and an endometrial biopsy specimen can be taken under hysteroscopic view. An EC can be detected in 7-10% of postmenopausal patients and 2-3% of premenopausal patients submitted to hysteroscopy. Hysteroscopy has been recently confirmed to be an accurate diagnostic method in the diagnosis of endometrial carcinoma [2]. But the concerns regarding safety issues of the method, especially the possibility of spreading cancer cells throughout the tubes into the peritoneal cavity have prevented the universal use of hysteroscopy in these cases [3]. No definitive conclusion has been drawn about this issue till now.

Despite the fact that hysteroscopy is widely applied in clinical practice, there is a continuous debate about its diagnostic value. This debate is mainly driven by the fact that the most individual studies on histopathologic validation of the endoscopic visual interpretation are small, leading to imprecise and heterogeneous diagnostic accuracy estimations. Furthermore, the diagnostic accuracy of hysteroscopy may vary according to the menopausal status and the experience of the physician performing the examination. Hysteroscopy is a subjective diagnostic test; its result depends on the experience, the knowledge and the capability of the

performing physician [4].

Diagnostic Accuracy

Abnormal Uterine Bleeding

In a very recent meta-analysis from the Department of Obstetrics & Gynecology of the University of Ioannina Greece [4], the authors found that the sensitivity as calculated by the HSROC model was satisfactory [82.6 % with 95% CI (66.9–91.7%)]. Specificity on the other hand showed much better performance [99.7 % with 95% CI (98.1–99.9%)]. These estimates changed to 81.1 % [95% CI (75.9–85.6%)] and 99.4% [95% CI (99.2–99.6%)] for sensitivity and specificity, respectively, using the Moses–Littenberg method. The divergence was considerable in the case of sensitivity but not for specificity. As far as specificity is concerned, a random-effects approach was comparable to that of a fixed effect leading to a more solid conclusion of the clarity of the information provided. Hysteroscopy appeared to be a very useful means of ruling out the possibility of cancer in women with AUB. Furthermore, results remained unaffected by the study design (retrospective or prospective) or by the menopausal state (postmenopausal or mixed).

For endometrial hyperplasia, sensitivity was 75.2% (95% CR 55.4–88.1%), while specificity was 91.5% (95% CR 85.7–95.0 %). For endometrial polyps, sensitivity was 95.4% (95% CR 87.4–98.4 %) and specificity was 96.4% (95% CR 93.7–98.0%). Finally, for submucous myomas, sensitivity was estimated to 97.0% (95% CR 89.8–99.2%) and specificity to 98.9% (95% CR 93.3–99.8%).

Endometrial Polyps

Hysteroscopic polypectomy is safe and effective, with rapid recovery, and enables sampling of material for histopathology; however, it is restricted to specialized centers for endoscopic treatment. Use of blind endometrial biopsy has been questioned in the diagnosis of focal endometrial lesions because of high rates of inappropriate or insufficient material. In a very recent study in Brazilian population demonstrated that the sensitivity of hysteroscopy was 100% for the diagnosis of endometrial polyps, and 36.4% for the diagnosis of endometrial adenocarcinoma. Among women with endometrial adenocarcinoma who underwent office hysteroscopy, endometrial polyps were diagnosed in 72.7%. These women demonstrated signs suggestive of hyperplasia, in particular, diffuse endometrial hypervascularization associated with vascular atypia. Postoperative histopathologic analysis confirmed the diagnosis of endometrial polyps in 98.8% of the women who underwent polypectomy, with 25% of endometrial adenocarcinomas associated with endometrial polyps [5].

Endometrial Thickness

A very recent study in Italian population of asymptomatic postmenopausal women proved that the best endometrial thickness cut-off value for the detection of all intra-uterine pathologies was >8 mm. An endometrial thickness cut-off value >10 mm did not miss any cases of endometrial cancer. The success rate of diagnostic hysteroscopy was 89%, but 97% of these revealed a benign intra-uterine pathology. The diagnostic accuracy of hysteroscopy was optimal for all intra-uterine pathologies, except endometrial hyperplasia [6].

Safety

Hysteroscopy is a diagnostic procedure with a high accuracy in diagnosing endometrial cancer. Because of the increase of intrauterine pressure during distention media inflation, several retrospective studies postulated that it may result in cancer cell dissemination within the peritoneal cavity through the fallopian tubes. Therefore there is a discussion whether hysteroscopy increases the risk for intraperitoneal cancer cell dissemination in patients with endometrial cancer and the risk of disease upstaging in patients with clinically early-stage disease.

In a meta-analysis published on 2010, from the Department of Obstetrics & Gynecology of the University of Thessalia, Greece, nine trials were included. One thousand fifteen patients with histologically proven endometrial carcinoma were allocated to hysteroscopy or no hysteroscopy before surgery. Hysteroscopy resulted in a significantly higher rate of malignant peritoneal cytology (odds ratio [OR], 1.78; 95% confidence interval [CI], 1.13-2.79; P = 0.013) and significantly higher disease upstaging owing solely to the presence of malignant cells in the peritoneal cavity (OR, 2.61; 95% CI, 1.47-4.63; P = 0.001) compared with no hysteroscopy. When isotonic sodium chloride was used as distention medium, hysteroscopy resulted in a statistically significant higher rate of malignant peritoneal cytology (OR, 2.89; 95% CI, 1.48-5.64; P = 0.002), whereas a non significant trend for higher malignant cells was observed in patients allocated to the hysteroscopy group (OR, 3.23; 95% CI, 0.94-11.09; P = 0.062) when inflated media pressure reached or exceeded 100 mm Hg [7].

Another parameter regarding the safety is the duration of hysteroscopy and there is a question if the longer duration is correlated with higher rate of positive peritoneal cells and the duration of recurrence-free survival. In a retrospective multi-centre study by Tempfer et al [8], the records of 552 patients with endometrial cancer were investigated. Duration of hysteroscopy was correlated with clinicopathological parameters and patient survival data. The mean [standard deviation (SD)] duration of hysteroscopy was 18.2 (10.5) min in the study population and 17.9 (10.1) min and 17.9 (10.2) min in patients with positive (n=109) and negative peritoneal cytology (n=443), respectively (p=0.9). There were no statistically significant correlations between duration of hysteroscopy and positive peritoneal cytology (p=0.6; rho=-0.028), FIGO stage (p=0.2; rho=-0.080), lymph node involvement (p=0.2; rho=0.106) and patient age (p=0.5; rho=0.033). Longer dura¬tion of hysteroscopy (>15 min) was not associated with positive peritoneal cytology (yes vs. no, p=0.8), advanced tumour stage (FIGO I vs. II, III and IV, p=0.3), lymph node involvement (yes vs. no, p=0.1) and patient age (≤65 vs. >65 years, p=0.4). In a multivariate analysis, FIGO stage [p<0.0001; hazard ratio (HR)=5.1, 95% confidence interval (CI) 2.5-10.2], lymph node involvement (p=0.02; HR=3.2, 95% CI 1.2-8.8) and patient age (p=0.003; HR=2.4, 95% CI 1.3-4.2), but not duration of hysteroscopy (p=0.4; HR=1.2, 95% CI 0.7-2.2), were associated with recurrence-free survival [8].

In a more recent meta-analysis from Chang et al [9], they examined whether preoperative hysteroscopic examination increases the risk for peritoneal dissemination of endometrial cancer cells and the effect of hysteroscopy on disease prognosis. Nineteen studies were included in the meta-analysis. The meta-analysis demonstrat-

ed that hysteroscopy resulted in a statistically significantly higher rate of positive peritoneal cytology results compared with no hysteroscopy. In addition, when a liquid medium was used for uterine distention during hysteroscopy, the difference between the two groups remained statistically significant. However, no statistically significant differences were seen when inflation pressure reached or exceeded 100 mm Hg or when the cancer stage was early. Trials that examined long-term outcomes reported no statistically significant differences in disease prognosis between the two groups.

Conservative Treatment

In premenopausal women EC usually presents with favorable prognostic features, that is, as a focal, well-differentiated lesion, with minimal or absent myometrial invasion [10]. This profile corresponds to the type-1 EC, which correlates with the estrogen/progesterone receptor positive (ER+/PR+) pattern. Primary progestin therapy has been demonstrated to be effective in early well-differentiated tumors and in poor operative candidates with response rates ranging from 58% to 100% (ACOG) [11].

Currently the therapeutic approach to an early-stage EC consists of a staging laparotomy/laparoscopy, including a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO), pelvic washings, and lymphadenectomy (pelvic and aortic), depending on pathological risk profile pre and intraoperatively determined [12, 13]. Therefore, the current standard of surgical approach is preclusive of fertility. So far, conservative management has been experimented anedoctically or in very small series of selected young patients with early EC [14]. Progestin therapies, mostly medroxyprogesterone acetate (MPA) and megestrol acetate (MA) sometimes combined with local surgical excision by hysteroscopy (HSC) or repeated dilation and curettage (D&C), have been used as conservative treatments. The worldwide experience and data concerning hysteroscopic treatment are, however, still limited due to the small numbers of cases, potential methodological bias, and the use of different therapeutic regimes.

Conservative management of early-stage endometrial cancer in young patients desiring future fertility is a feasible management option[15]. A recent systematic review by Gunderson et al [16] showed that progestin therapy was the most common method of management for early-stage endometrial carcinoma in patients who desire to preserve fertility. Among 391 women with both atypical hyperplasia (111 women, 28.4%) and grade 1 adenocarcinoma of the endometrium (280 women, 71.6%) in 45 studies included in the review, 49% were treated with MPA, 25% with megestrol acetate, and 19% with the LNG-IUS. The remaining patients received progestins of unspecified or miscellaneous types. Although the response rate for hyperplasia and carcinoma combined was 77%, in the endometrial carcinoma group, this systematic review showed a 48.2% complete response rate with a median time to response of 6.0 months. Of the women who responded to treatment, 53.2% had a durable response for the 39 months of follow-up; however, 34.5% of women had recurrence within 4 to 72 months after the initial response. Similar results were noted in a 2014 meta-analysis, which reported 78% remission probability at 12 months in combined cases of atypical hyperplasia and endometrial cancer but did not provide a rate for cancer alone [17]. When it comes to pregnancy data, 315 subjects were included in Gunderson et al analysis, and 34.8% of women treated for early-stage endometrial cancer became pregnant after progestin therapy [16]. In the meta-analysis, a 31.6% pregnancy rate was reported, with the majority of successful pregnancies occurring after assisted reproductive technology [17]. Another review reported a 60% pregnancy rate after complete remission of endometrial cancer. The percentage of patients who conceived in the assisted reproductive technology group was higher (80%) than those in the spontaneous pregnancy group (43%) [18]. Many women require assisted reproductive therapies after conservative management of endometrial cancer, which could be caused by coexisting conditions such as obesity, polycystic ovarian syndrome, and chronic anovulation [15]. Although there is currently not enough evidence regarding which patients would benefit from immediate assisted reproductive technology after the completion of hormonal treatment of endometrial cancer, it is recommended that this intervention be strongly considered, especially in women with a previous history of infertility and older age [17]. Although several protocols are used for conservative management of endometrial cancer, not one has been proven to be superior. A combination of hysteroscopic resection and oral progestin therapy has recently been suggested as a novel management option [15]. Hysteroscopy in the management of endometrial premalignant and malignant conditions has previously been described [15]. Based on a prospective cohort study of over 3400 women undergoing hysteroscopic endometrial resection, Edris et al [19] concluded that skillful hysteroscopic resection may be an alternative to hysterectomy in women with endometrial hyperplasia. Vilos et al [20] reported a case of endometrioid adenocarcinoma treated with hysteroscopic resection in a 53-year-old woman who denied hysterectomy. The patient had an excellent outcome with no evidence of clinical recurrence at 5 years. Two case series exist in the current literature reporting a combined hysteroscopic and oral progestin approach for the treatment of early-stage endometrial cancer in women wishing future fertility. Mazzon et al [21] treated 6 patients conservatively by hysteroscopic resection using a 3-step technique: resection of the tumor, resection of the endometrium adjacent to the tumor, and resection of the myometrium below the tumor. All women received postoperative treatment with megestrol acetate 160 mg/d for 6 months. Follow-up diagnostic hysteroscopy and targeted biopsy at 3, 6, 9, and 12 months were negative for atypia or malignancy in all women, and 4 of the 6 patients (66%) achieved childbearing. In the most recent prospective study, Laurelli et al [12] treated 14 women with FIGO stage IA endometrial cancer desiring future fertility with hysteroscopic resection of the lesion and the underlying myometrial tissue followed by oral megestrol acetate 160 mg/d for 6 months or LNG-IUS for 12 months. In this series, one patient had a local recurrence (7%), and another developed endometrial hyperplasia without atypia (7%). Although 3 patients (33.3%) attempted to conceive, only one became pregnant and delivered a healthy baby at term.

Discussion

In the meta-analysis from Gkrozou et al, hysteroscopy was found to have higher specificity than sensitivity when diagnosing endometrial cancer [4]. The 95 % CI was also wider for sensitivity than specificity. The hysteroscopical sensitivity for identifying endometrial cancer was considered adequate. Hysteroscopy performed even better, when evaluated as a diagnostic tool for endometrial cancer, in terms of specificity. Despite a previous report demonstrating that hysteroscopy performs better in diagnosing rather than excluding endometrial cancer [22] in women with AUB, Gkrozou et al showed rather the contrary [4]. In their analysis, hys-

teroscopy is more efficient in excluding rather than diagnosing endometrial cancer cases. This could be justified by the different inclusion criteria employed in their study compared to the publication of Clark et al [22]. A certain degree of variability—implying heterogeneity—was, however, observed. This in part may be justified based on the differences in individual studies included in this meta-analysis. For example, the study of Epstein et al. involved women with an endometrial thickness of more than 5 mm [23]. Such a parameter may influence test results, since the population becomes more specific.

The meta-analysis from Polyzos et al suggests that hysteroscopy in patients with endometrial cancer results in statistically significant higher endometrial cancer cell seeding within the peritoneal cavity and statistically significant higher tumor upstaging in patients with disease limited to the uterus, compared with no hysteroscopy [7]. This effect might be attributed to the transtubal reflux of endometrial cancer cells inside the peritoneal cavity during diagnostic hysteroscopy. Moreover, according to this analysis, a higher degree of cancer cell dissemination may be facilitated when using isotonic sodium chloride as distention medium and when high levels of inflated media pressure are reached. Distention media selection in diagnostic hysteroscopy may indeed influence the potential of intraperitoneal cancer cell spreading. The results of this meta-analysis agree with the principles of fluid dynamics, according to which the carrying capacity is directly proportional to the density of matter. Even if a crossover randomized trial [24] failed to detect any difference regarding transtubal reflux of endometrial cells between liquid or gaseous distention media, the use of different distention media might result in diverse cancer cell seeding potential. Distention medium inflation pressure is another factor that may affect the degree of dissemination. In 4 of 5 of the trials of Polyzos' et al meta-analysis that reported inflation pressure, the pressure reached or exceeded 100 mm Hg [7]. Even these results did not reach statistical significance, there was a clear trend for higher malignant cytology when high pressures were adopted. Previous reports suggested that the risk of transtubal fluid leakage during hysteroscopy is absent when hysteroscopy is performed with intrauterine pressure less than 40 mm Hg [2], notably reduced with pressure lower than 70 mm Hg, whereas it is notably increased at 100 mm Hg [25]. Consequently, it seems very logical a recommendation for the use of hysteroscopy with low inflation pressure. Despite the relationship between hysteroscopy and endometrial cancer cell dissemination, the prognostic significance of positive peritoneal cytologic feature after diagnostic hysteroscopy is unclear. Early experimental data suggested that hysteroscopy can cause dissemination of malignant cells into the abdominal cavity from uteri containing endometrial carcinoma and that these cells can be functionally viable [26]. Nonetheless, 4 of the eligible trials included in Polyzos' et al meta-analysis, that provided data regarding survival or recurrence of the disease did not manage to observe any statistically significant difference among hysteroscopy and non-hysteroscopy treated patients. The lack of adequate number of events (deaths or recurrences) in these trials prevented authors from performing a meta-analysis powered enough to drive solid conclusions in survival and recurrence settings. Hence, future trials may need to focus in these outcomes and not in surrogates such as positive malignant cytologic features.

Tempfer et al who examined the correlation between duration of hysteroscopy and the rate of positive peritoneal cells and the duration of recurrence-free survival, concluded that longer duration of hysteroscopy does not increase the risk of positive peritoneal cytology and it is not an adverse prognostic factor for recurrence-free survival in patients with endometrial cancer [8].

Chang et al concluded from their meta-analysis that, hysteroscopic examination before surgery in patients with endometrial cancer may increase the risk of dissemination of malignant cells into the peritoneal cavity [9]. The risk was statistically significantly associated with the use of a liquid medium for uterine cavity distention but not with early-stage disease.

There is no evidence to support an association between preoperative hysteroscopic examination and a worse prognosis in patients with endometrial cancer. There is no reason to avoid diagnostic hysteroscopy before to surgery in patients with endometrial cancer, especially in early stages.

References

[1]. Valli E, Zupi E, Marconi D, Solima E, Nagar G, et al. (1998) Outpatient diagnostic hysteroscopy. The Journal of the American Association of Gynecologic Laparoscopists 5(4):397-402.

[2]. Solima E, Brusati V, Ditto A, Kusamura S, Martinelli F,et al. (2008) Hysteroscopy in endometrial cancer: new methods to evaluate transtubal leakage of saline distension medium. American journal of obstetrics and gynecology 198(2):214-e1.

[3]. Revel A, Tsafrir A, Anteby S, Shushan A (2004) Does hysteroscopy produce intraperitoneal spread of endometrial cancer cells? Obstet Gynecol Surv 59:280-4.

[4]. Gkrozou F, Dimakopoulos G, Vrekoussis T, Lavasidis L, Koutlas A, et al. (2014) Hysteroscopy in women with abnormal uterine bleeding: a meta-analysis on four major endometrial pathologies. Archives of gynecology and obstetrics 1-8.

[5]. Dias D. S, Bueloni-Dias F. N, Dias R, Nahás-Neto J, Nahás E. A. P, et al. (2014) Usefulness of Clinical, Ultrasonographic, Hysteroscopic, and Immunohistochemical Parameters in Differentiating Endometrial Polyps From Endometrial Cancer. Journal of minimally invasive gynecology 21(2):296-302.

[6]. Giannella L, Mfuta K, Setti T, Boselli F, Bergamini E, et al. (2014) Diagnostic accuracy of endometrial thickness for the detection of intra-uterine pathologies and appropriateness of performed hysteroscopies among asymptomatic postmenopausal women. European Journal of Obstetrics & Gynecology and Reproductive Biology 177:29-33.

[7]. Polyzos N. P, Mauri D, Tsioras S, Messini C. I, Valachis A, et al. (2010) Intraperitoneal dissemination of endometrial cancer cells after hysteroscopy: a systematic review and meta-analysis. International Journal of Gynecological Cancer 20(2):261-267.

[8]. Tempfer C. B, Froese G, Buerkle B, Polterauer S, Grimm C, et al. (2011). Does duration of hysteroscopy increase the risk of disease recurrence in patients with endometrial cancer? A multi-centre trial.Experimental and therapeutic medicine 2(5):991-995.

[9]. Chang Y. N, Zhang Y, Wang Y. J, Wang L. P, Duan H (2011) Effect of hysteroscopy on the peritoneal dissemination of endometrial cancer cells: a meta-analysis. Fertility and sterility 96(4):957-961.

[10]. Benshushan A (2004) Endometrial adenocarcinoma in young patients: evaluation and fertility-preserving treatment. Eur J Obstet Gynecol Reprod Biol 117:132–7.

[11]. American College of Obstetricians and Gynecologists (2005) ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists: management of endometrial cancer. Obstet Gynecol106:413–25.

[12]. Laurelli G, Di Vagno G, Scaffa C, Losito S, Del Giudice M, et al. (2011). Conservative treatment of early endometrial cancer: preliminary results of a pilot study. Gynecologic oncology 120(1) 43-46.

[13]. Leitao MM (2008) Current and future surgical approaches in the management of endometrial carcinoma. Future Oncol 4:389–401.

[14]. Chiva L, Lapuente F, González-Cortijo L, Carballo N, García J. F, et al. (2008). Sparing fertility in young patients with endometrial cancer. Gynecologic oncology 111(2):S101-S104.

[15]. Arendas K, Aldossary M, Cipolla A, Leader A, Leyland N. A (2015) Hysteroscopic Resection in the Management of Early-stage Endometrial Cancer: Report of 2 Cases and Review of the Literature. Journal of minimally invasive gynecology 22(1):34-39.

[16]. Gunderson C. C, Fader A. N, Carson K. A, Bristow R. E (2012) Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review.Gynecologic oncology 125(2):477-482.

[17]. Koskas M, Uzan J, Luton D, Rouzier R, Daraï E (2014) Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. Fertility and sterility 101(3):785-794.

[18]. Tong X. M, Lin X. N, Jiang H. F, Jiang L. Y, Zhang S. Y, et al. (2012). Fertility-preserving treatment and pregnancy outcomes in the early stage of endometrial carcinoma. Chinese medical journal 126(15):2965-2971.

[19]. Edris F, Vilos G. A, Awatif A. M, Ettler H. C, Hollett-Caines J, et al. (2007). Resectoscopic surgery may be an alternative to hysterectomy in high-risk women with atypical endometrial hyperplasia. Journal of minimally invasive gynecology 14(1):68-73.

[20]. Vilos G. A, Ettler H. C, Edris F, Hollett-Caines J, Abu-Rafea B (2007) Endometrioid adenocarcinoma treated by hysteroscopic endomyometrial resection. Journal of minimally invasive gynecology 14(1):119-122.

[21]. Mazzon I, Corrado G, Masciullo V, Morricone D, Ferrandina G, et al. (2010) Conservative surgical management of stage IA endometrial carcinoma for fertility preservation. Fertility and sterility, 93(4), 1286-1289.

[22]. Clark T. J, Voit D, Gupta J. K, Hyde C, Song F, et al. (2002) Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. Jama 288(13):1610-1621.

[23]. Epstein E, Ramirez A, Skoog L, Valentin L (2001) Transvaginal sonography, saline contrast sonohysterography and hysteroscopy for the investigation of women with postmenopausal bleeding and endometrium>5 mm. Ultrasound Obstet Gynecol 18:157–162

[24]. Nagele F, Wieser F, Deery A, Hart R, Magos A (1999) Endometrial cell dissemination at diagnostic hysteroscopy: a prospective randomized cross-over comparison of normal saline and carbon dioxide uterine distension. Human Reproduction 14(11):2739-2742.

[25]. Baker VL, Adamson GD (1995) Threshold intrauterine perfusion pressures for intraperitoneal spill during hydrotubation and correlation with tubal adhesive disease. Fertil Steril 64:1066-1069.

[26]. Arikan G, Reich O, Weiss U, Hahn T, Reinisch S, et al. (2001) Are endometrial carcinoma cells disseminated at hysteroscopy functionally viable?. Gynecologic oncology 83(2):221-226.