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Laparoscopic enhanced imaging modalities for the identification of endometriosis implants a review of the current status

Abstract

Endometriosis is a benign, complex, chronic and progressive gynecologic disorder defined as the presence of viable, estrogen-dependent endometrial-like gland and stroma associated with inflammatory response outside the uterine cavity. Laparoscopy with tissue pathologic biopsy is well accepted as the "gold standard" for the diagnosis of endometriosis and constitute the therapeutic approach of choice when medical treatment produce unsatisfactory results. Accuracy of visual diagnosis at the time of laparoscopy increases with disease severity. Enhanced laparoscopic imaging techniques has been used to improve the detection and diagnostic accuracy of endometriosis implants. In this review, we evaluate current available enhance laparoscopic imaging modalities with emphasis in detection of endometriosis implants.

Keywords: endometriosis, laparoscopy, robotics, imaging

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Introduction

Endometriosis is a benign, complex, chronic and progressive gynecologic disorder defined as the presence of viable, estrogen-dependent endometrial-like gland and stroma associated with inflammatory response outside the uterine cavity.[1] It is estimated that endometriosis is present in 6 to 10% of reproductive age women[2] and has been reported as high as up to 40% in subfertile women.[3] Despite great effort to elucidate the etiology of endometriosis, its pathogenesis remains unclear. Different theories had been proposed to explain the origin of this enigmatic disease, from the initial retrograde menstruation theory proposed by Sampson in 1927 to coelomic pluripotential metaplasia, hematogeneous or lymphatic embolization.[4] In a recent comprehensive manuscript, Laganà et al.,[5] described an interesting hypothesis in which deregulation of genes could lead to aberrations and deregulation within the mesoderm which may cause aberrant implantation of stem cells in addition to alteration in the peritoneal microenvironment creating the conditions for proliferation ectopic endometrial cells. There is three main clinically subtype forms of endometriosis consisting of

i. Superficial endometriotic implants located on the surface of the pelvic peritoneum and ovaries (peritoneal endometriosis),

ii. Ovarian cysts lined by endometrioid mucosa (endometriomas), and

iii. Complex solid masses of endometriosis implants mixed with adipose and fibromuscular tissue infiltrating the rectovaginal septum (Deep infiltrating endometriosis. DIE).[1]

Patients affected by endometriosis often present with a variety of symptoms including dysmenorrhea, dyspareunia, chronic pelvic pain, presence of a pelvic mass and/or subfertility. Comorbid conditions frequently present in patients with endometriosis are fibromyalgia, interstitial cystitis/painful bladder syndrome, irritable bowel syndrome, migraine headache and temporomandibular disorders.[6] Laparoscopy with tissue pathologic biopsy is well accepted as the "gold standard" for the diagnosis of endometriosis and is the therapeutic approach of choice when medical treatment produce unsatisfactory results. Accuracy of visual diagnosis at the time of laparoscopy increases with disease severity.[7] However, as supported by the European Society of Human Reproduction and Embryology (ESHRE), histologic confirmation with biopsy is recommended because visual identification is associated with a high false positive rate.[8,9] Moreover, endometriosis implants are usually found in multiple different location such as the ovaries, fallopian tubes, utero-sacral ligaments, broad ligaments, round ligaments, culd-de-sac, ovarian fossa, bladder serosa, ureters and rectovaginal septum. A thorough inspection of the peritoneal cavity during laparoscopy is mandatory to identify all possible endometriosis implants.

Although infrequent, extrapelvic endometriosis can also be found in the upper abdomen, the appendix, bowel, diaphragm, abdominal wall as well as abdominal scars and umbilicus, pancreas, spleen, pleura and pericardium, respiratory system, and on brain tissue.[10–12] Superficial peritoneal endometriosis can be clinically suspected but unfortunately, cannot be diagnosed by any non-invasive imaging modality. Accurate laparoscopic identification of superficial endometriosis implants is poor. Using conventional laparoscopy with white light the positive predictive value of suspected endometriosis lesions confirmed with pathology was only 66%.[13] Accurate identification and excision of all endometriosis lesions is associated with better surgical outcomes and could possible decrease the recurrence of the disease.[14,15] Enhanced laparoscopic imaging techniques has been used to improve the detection and diagnostic accuracy of endometriosis implants. In this review, we evaluate current available enhance laparoscopic imaging modalities with emphasis in detection of endometriosis implants.

Enhanced imaging techniques in endometriosis

Laparoscopic identification of superficial endometriosis implants represents a challenge for the gynecologic surgeon. Endometriosis lesions may present in a wide spectrum of appearance according to a

"lifecycle" of the implants. The lesions can be flat or vesicular. They can have any combination of color typically red, back/brown and white. Active "red" lesions, large endometriomas, deep infiltrating nodules, and typical "powder-burn" lesions are easier to identify than "white" old fibrotic lesions. The endometriotic implants are hypervascular. The diagnostic accuracy at laparoscopy is also affected by the experience of the surgeon and the laparoscopic equipment.[16] Because of the difficulty in diagnosing endometriosis based on visual appearance, there has been great interest in facilitating laparoscopic recognition of the implants. Surgeons have always depended on white light to illuminate their surgical field. Under white light, tissue color varies in a limited shade of colors mostly red, yellow, white and gray making it difficult to differentiate normal from pathologic tissue.

Enhanced laparoscopic imaging techniques that allow differentiation of normal from pathologically infiltrated tissue is been utilized in different surgical specialties especially in surgical oncology.[17,18] Like malignant process, neovascularization is present in most endometriosis implants and could be used to differentiate endometriosis lesions from normal peritoneum. Due to the diverse visual appearance of the endometriosis implants and the low positive predictive value of performing peritoneal biopsies based on appearance, there is great interest in improving accuracy of the visual diagnosis. Enhanced imaging modalities are used to help the surgeon to identify peritoneal endometriosis lesions.

Fluorescent Laparoscopy techniques:

Autofluorescence imaging (AFI)

Autofluorecence imaging is an advanced technology that exploits the autofluorent nature of tissue and allows the detection of small endometriosis superficial lesions. Although the precise mechanism of autofluorescence of tissue has not been determined, it is accepted that it can change if the epithelial layer thickens or if the concentration of chromophores change second to hypervascularization.[19] This technique relies on blue light excitation and differences in epithelial thickness and neovascularization. It produces different color tones that differentiate endometriosis lesions from normal peritoneum.[20,21] Endogenous fluorophores such as tryotophan, collagen, elastin, Flavin, and co-enzimes of the respiratory chain lead to tissue differentiated autofluorescence. Demco L. described the use of blue light at a frequency of 440Hz to facilitate the visualization of endometriosis implants in 25 patients with suspected endometriosis. He concluded that the use of blue light facilitates the visualization of endometriosis lesions and allow detection of endometriosis implants not visible with the use of white light.[22] Buchweitz et al.,[20] reported a prospective analysis of 83 patients undergoing laparoscopy for suspected endometriosis under white light and autofluorescence for the detection of non-pigmented peritoneal endometriotic lesions. They reported a sensitivity of 65% with the use of white light and 92% with the aid of autofluorescence (1.42 fold increase) concluding that the use of white light and autofluorescence is significantly superior to white light illumination alone for the detection of non-pigmented endometriotic lesions.

5-aminolevulinic acid induced fluorescence (5-ALA)

The principle of fluorescent imaging is the use of a special endoscope that releases light at different wavelength which stimulates a signal released by the biomarker that is captured by the endoscope and is then mapped digitally onto a screen. Fluorescence after administration of 5-ALA is a diagnostic tool used in the early diagnosis of cancerous disorders in urology and pulmonology.[23,24] 5-ALA is a administered as an oral prodrug that increases the level of protoporphyrin IX in epithelial tissue that is then fluorescently illuminated. When blue light is then applied following 5-ALA administration, non-pigmented endometriosis lesions are accentuated. Patients should avoid exposition to direct sunlight for 24hours after administration due to photosensitization. A common reported side effect is nausea and vomiting which occur in up to 10% of the cases.[20] Malik E et al.,+published a series of 37patients with suspected endometriosis who underwent diagnostic laparoscopy after the administration of 30mg of 5-ALA/Kg body weight PO the night before surgery. They reported a sensitivity of fluorescence diagnosis of 100% with a specificity of 75%. The likelihood ratio for a positive test indicating endometriosis was 4.

In contrast, the sensitivity of the visual diagnosis of endometriosis under white illumination is only 69%, with a specificity of 70%. The likelihood ratio is 2.3. This represent a diagnostic increase of 46% compared with white light illumination (sensitivity: 48%, specificity: 60%) The authors concluded that the diagnosis of non-pigmented occult endometriotic implants is feasible and could help the surgeon to differentiate endometriotic lesions from other peritoneal unspecific changes. Buchweitz et al.,[26] found similar sensitivity of fluorescence diagnosis with 20mg/Kg body weight, with the added benefit of reduced cost and decreased incidence of adverse effects. Fluorescence diagnosis should be considered as an additional diagnostic tool that complements the conventional use of white light illumination. However, it has some limitations that should be considered. Fluorescence diagnosis cannot replace the use of white light because the depth of penetration of the blue light is too shallow to detect deep infiltrating endometriosis. Also, the fluorescence fades with increased duration of the laparoscopy which prevent its use for the entire case.

Narrow Band Imaging Techniques (NBI)

Narrow Band Imaging (NBI) is a modality that uses a narrow wavelength of light to change the color contrast of the endoscopic image improving the detection of neovascularization which allows visualization of endometriotic implants. In NBI only the green and blue light of the spectrum are excited. Barrueto et al.,[27] reported the sensitivity and specificity for their clinical impression for the detection of endometriotic peritoneal implants using NBI and white light and found that using NBI the sensitivity was 84% and specificity 24% compare to using WL with a sensitivity of 71% and specificity 36%. It is important to note the low specificity which can result in unnecessary resection of healthy peritoneum, increasing the chance of surgical complications, with potential increase of postoperative pain and adhesion formation.

Near-infrared (NIR) imaging with Indocyanine green (ICG) (FireFly®). Near infrared wavelength is often used in endoscopy as it results in greater depth of penetration. It is used with indygocianine green (ICG) as a non-specific biomarker. ICG is a water-soluble tracer dye that binds to plasma proteins with a peak spectral absorption at 800nm. It is administered intravenously (IV), has a half-life of 3 to 4minutes and is cleared by the liver. This is used with the infrared fluorescence imaging system integrated with the robotic platform. There are 2 conventional laparoscopy endoscopes available to use this technology (Pinpoint, Nvadaq, Canada and D-Light, Storz, Germany) and one for the Da Vinci robotic platform (FireFly Intuitive Surgical,

Inc, Sunnyvale, CA) The FireFLy® mode on the da-Vinci Si platform has been available since 2001 and approved by the Food and Drug Administration (FDA) for imaging use in August 2014. It facilitates identifying endometriosis lesions using infrared technology to identify vascular structures surrounded of fibro-vascular tissue.

It requires the injection of 5mg of ICG into the IV. The endometriotic lesion will fluoresce as a dark green area surrounded by a lighter area of fibrosis. In 2015, Guan et al.,[28] reported that the use of FireFly® technology and ICG facilitated the identification of endometriosis allowing to perform single site laparoscopic excision of endometriosis nodules with complete resolution of symptoms and excellent cosmetic results. The use of Firefly technology has also proven helpful for excision of extragenital endometriosis, in particular for the excision of implants nodules overlying the ureter and rectum.[28] These lesions are often subtle and are not visualized with the use of white light, but when illuminated using Firefly technology, complete resection of the targeted affected area is possible. Precaution should be taken with patients with known iodine allergy, hyperthyroidism or kidney failure are at increased risk of anaphylaxis.

Conclusion

Laparoscopy is the gold standard for diagnosis and treatment of endometriosis. The current clinical approach of endometriosis favors visual inspection and tissue pathologic biopsy diagnosis. Advances is surgical technology specially enhanced imaging techniques show encouraging results to improve the identification of endometriosis implants. Further studies are needed to confirm the clinical benefit of adopting this promising technological modality.

Compliance of ethical standards

This study received no funding.

Conflicts of interest

i. Jose Carugno declare that he has no financial conflicts to disclose.

ii. Fausto Andrade declare that he has no financial conflicts to disclose.

iii. Antonio Laganà declare that he has no financial conflicts to disclose.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Authors contribution

i. J Carugno: Project development and Manuscript writing.

ii. F Andrade: Project development and Manuscript writing.

iii. AS Laganà: Project development and Manuscript writing.

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