The Use of near Infra-Red Radiation Imaging after Injection of Indocyanine Green (NIR–ICG) during Laparoscopic Treatment of Benign Gynecologic Conditions: Towards Minimalized Surgery. A Systematic Review of Literature

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Abstract: Background and Objectives: To assess the use of near infrared radiation imaging after injection of indocyanine green (NIR–ICG) during laparoscopic treatment of benign gynecologic conditions. Materials and Methods: A systematic review of the literature was performed searching 7 electronic databases from their inception to March 2022 for all studies which assessed the use of NIR–ICG during laparoscopic treatment of benign gynecological conditions. Results: 16 studies (1 randomized within subject clinical trial and 15 observational studies) with 416 women were included. Thirteen studies assessed patients with endometriosis, and 3 studies assessed non-endometriosis patients. In endometriosis patients, NIR–ICG use appeared to be a safe tool for improving the visualization of endometriotic lesions and ureters, the surgical decision-making process with the assessment of ureteral perfusion after conservative surgery and the intraoperative assessment of bowel perfusion during recto-sigmoid endometriosis nodule surgery. In non-endometriosis patients, NIR–ICG use appeared to be a safe tool for evaluating vascular perfusion of the vaginal cuff during total laparoscopic hysterectomy (TLH) and robotic-assisted total laparoscopic hysterectomy (RATLH), and intraoperative assessment of ovarian perfusion in adnexal torsion. Conclusions: NIR–ICG appeared to be a useful tool for enhancing laparoscopic treatment of some benign gynecologic conditions and for moving from minimally invasive surgery to minimalized surgery. However, although preliminary findings appear promising, further investigation with well-designed larger studies is needed.

Keywords: laparoscopy; innovation; technology; gynecology; minimally-invasive; fluorescent dye; fluorescence
1. Introduction

Indocyanine green (ICG) is a fluorescent dye which binds plasma proteins in the vascular system [1–3]. Kodak laboratories invented ICG dye for near infra-red (NIR) photography in 1955 and it was later approved by the FDA for clinical use in 1959 [4]. Once in the blood flow, ICG rapidly binds to lipoproteins and it is almost entirely extracted by the liver appearing visible in the bile 8 min after the injection. When ICG in not injected in the blood stream, it reaches the nearest draining lymph node in approximately 15 min [5,6]. ICG use is safe, with a dose of 0.1–0.5 mg/mL/kg for clinical use [4]. Thanks to its ability to assess tissue vascularity once detected with a specific wavelength of light, NIR imaging with ICG injection (NIR–ICG) has proven a useful, feasible and safe tool during gynecologic, urologic and digestive procedures for both benign and malignant diseases [1,2,7,8]. In particular, NIR–ICG can be used for identifying sentinel lymph nodes during surgical staging for several cancers (melanoma, prostate, rectal or endometrial cancer) [9–11].

On the other hand, for benign conditions, NIR–ICG can be used with several applications. For example, it can be used as a guide during endometriosis surgery facilitating intraoperative diagnosis of occult peritoneal and deep endometriotic lesions at white light [7,12,13]. Furthermore, it has been proven useful in the evaluation for anastomotic perfusion assessment after discoid or segmental resection for rectosigmoid endometriosis (RSE) [14,15]. NIR–ICG dye may also help in the intraoperative assessment of organ perfusion and ischemia after ovarian detorsion and assist the surgeon’s intraoperative decision [16]. Despite the several proposed applications for NIR–ICG in benign gynecologic conditions, to our knowledge, systematic assessment of evidence in this field is lacking in the literature. The aim of this study is to assess the use of NIR–ICG during laparoscopic treatment of benign gynecologic conditions through a systematic review of the literature.

2. Materials and Methods

2.1. Study Protocol

The study followed an a priori designed study protocol, with each review step independently completed by 2 authors. Discussion with senior authors was used as a method to solve disagreements.

The Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement and checklist was used for reporting the whole study (see Supplementary Materials) [17].

2.2. Search Strategy and Study Selection

MEDLINE, Web of Sciences, Google Scholar, Scopus, ClinicalTrials.gov, Cochrane Library, and EMBASE were searched as electronic databases from their inception to March 2022 using different combinations of the following text words: “indocyanine green”, “ICG”, “NIR–ICG”; “near infrared”; “fluorescence”, “firefly”, “arter”, “angiographic”, “vascular”, “ischem*”, “anastomo*”, “perfusion”, “laparoscopy”, “gynecology”, “myom*”, “fibrom*”, “uter*”, “ovar*”, “endometri*”, “adenomyo*”. An example of search strategy (adopted for the MEDLINE) was the following: (indocyanine green OR ICG OR NIR–ICG OR near infrared OR fluorescence OR firefly) AND (arter* OR angiographic OR vascular* OR ischem* OR anastomo* OR perfusion) AND laparoscopy AND (gynecology OR myom* OR fibrom* OR uter* OR ovar* OR endometri* OR adenomyo*).

References from each full-text assessed study were also screened for missed studies. All peer-reviewed studies which assessed the use of NIR–ICG during laparoscopic treatment of benign gynecological conditions were included. We a priori excluded:

- case reports;
- literature reviews;
- studies in languages other than English;
- video articles;
- studies which assessed the use of NIR–ICG in gynecologic malignancies or in non-gynecologic conditions.
2.3. Risk of Bias within Studies Assessment

Two authors independently assessed the risk of bias within the included studies via the Methodological Index for Non-Randomized Studies (MINORS). In detail, the following seven applicable domains were considered for the risk of bias in each study: (1) A clearly stated aim (i.e., if the question addressed is precise and relevant); (2) Inclusion of consecutive patients (i.e., if all patients potentially fit for inclusion were included in the study during the study period); (3) Prospective collection of data (i.e., if data were collected according to a protocol established before the beginning of the study); (4) Endpoints appropriate to the aim of the study (i.e., if explanation of the criteria used to evaluate the outcomes was unambiguous); (5) Unbiased assessment of the study endpoints (i.e., if the assessment of study endpoints was unbiased); (6) Follow-up period appropriate to the aim of the study (i.e., if the follow-up was sufficiently long to allow the assessment of the endpoints); (7) Loss to follow up less than 5% (i.e., if patients lost to follow up were less than 5% of total population).

Authors judged each domain for each included studies as “low risk”, “high risk” or “unclear risk” of bias based on data were “reported and adequate”, “reported but inadequate” or “not reported”, respectively.

2.4. Data Extraction

Data from included study were extracted without modification according to the PICO (Population, Intervention or risk factor, Comparator, Outcomes) items.

“Population” of our study was women with benign gynecological conditions. “Intervention” was the use of NIR–ICG during laparoscopic treatment. “Comparator” was the non-use of NIR–ICG during laparoscopic treatment. “Outcome” was the improvement in surgical laparoscopic outcomes.

Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) was used as a software [18].

3. Results

3.1. Study Selection

After electronic database searches, 345 articles were identified. Sixty articles remained after duplicate removal, 45 after title screening and 38 after abstract screening; these were evaluated for eligibility. Twenty-two articles were then excluded based on the above-reported a priori exclusion criteria. Finally, 16 articles with 416 women were included in our study (Figure 1).

![Flow diagram of studies identified in the systematic review (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).](image-url)
3.2. Studies and Patients’ Characteristics

Of the included studies, one study [19] was a prospective, single-center, randomized within subject clinical trial, while 15 studies were observational: 4 retrospective [14,15,20,21] and 11 prospective [1,2,7,12,16,20,22–27].

Thirteen studies assessed patients with endometriosis [1,2,7,12,14,15,19–25], with the following NIR–ICG applications:

- to localize ureteral course (2 studies [20,23]);
- to assess ureteral perfusion after conservative surgery (1 study [1]);
- to improve visualization of endometriotic lesions (6 studies [7,12,19,21,22,24]);
- to evaluate the different rectosigmoid endometriosis (RSE) vascular patterns and the correlation with clinicopathological data (1 study [2]);
- to assess bowel vascularization after deep infiltrating endometriosis (DIE) surgery to reduce the risk of fistula (2 studies after full-thickness bowel resection [14,15] and 1 study after shaving technique [25]).

The remaining 3 studies [16,26,27] assessed non-endometriosis patients; in particular:

- 2 studies assessed the NIR–ICG capacity to visualize the vascular perfusion of the vaginal cuff after total hysterectomy in order to decrease vaginal cuff dehiscence rate [26,27].
- 1 study assessed if the NIR–ICG was a faceable tool to evaluate intraoperatively ovarian perfusion after detorsion [16] (Table 1).

Table 1.Characteristics of the included studies.

| Field | ICG Application | Study | Country | Study Design | Sample Size | Study Period | Benign Gynecologic Condition Details | Study Outcomes |
|-------|-----------------|-------|---------|--------------|-------------|--------------|--------------------------------------|----------------|
|       |                 | 2015 Park [20] | USA     | Retrospective, observational, cohort study | 10          | 1 July 2014–30 March 2015 | DIE | Iatrogenic ureteral injury, ICG complications, Operative time, Estimated blood loss, Length of hospital stay |
|       |                 | 2019 Mandovra [23] | India  | Prospective, observational, cohort study | 30          | September 2017–December 2017 | DIE | Identification of various ICG complications, Operative time, ICG injection time |
|       | To localize ureteral course | 2020 Raimondo [1] | Italy  | Prospective, observational case series | 26          | May 2018–January 2019 | DIE (Ureteral) | Ureteral perforation grade, NIR-ICG assessment time, Inter-operator agreement regarding ureteral perforation grade, Changes to the surgical plan after NIR-ICG evaluation, Perioperative complications, Clinical-radiologic outcomes at early follow-up |
|       | To assess ureteral perfusion after conservative surgery | 2018 Cosentino [7] | Italy  | Prospective, observational cohort study | 27          | January 2016–February 2017 | PE-DIE ASRM score -Stage I: 0 -Stage II: 3 -Stage III: 10 -Stage IV: 14 | Identified endometriosis lesions |
|       | To improve endometriosis identification | 2018 De Neef [12] | Belgium | Prospective, observational case series | 6           | - | RVDIE | Rejection of RVDIE, Quality of life |
|       |                 | 2019 Jayakumar [12] | USA    | Prospective, observational cohort study | 7           | July 2013–June 201 | DIE | Identified endometriosis lesions, Quality of life |
|       |                 | 2019 Lao [19] | The Netherlands | Prospective, single-center, randomized within subject clinical trial | 20          | February 2016–May 2017 | ASRM stage III–IV | Detection of peritoneal endometriotic lesions |
|       |                 | 2020 Spengler [24] | Switzerland | Prospective, observational, cohort, single-center, single-arm pilot study | 65          | April 2017–December 2018 | PE-DIE ASRM stage 9 (14.3) ASRM stage (%) -Stage I: 12 (19) -Stage II: 15 (5) -Stage III: 11 (17.5) -Stage IV: 20 (31.7) | Identified endometriosis lesions |
|       |                 | 2020 Vezzetti [25] | Italy  | Retrospective, observational cohort case-control study | 20 vs. 27 controls | January 2016–March 2018 | PE-DIE | Visual detection rate of endometriotic lesions |
|       | To evaluate the different RSE vascular patterns and the correlation with clinicopathological data | 2020 Raimondo [2] | Italy  | Prospective, observational cohort pilot study | 30          | June 2019–September 2019 | DIE (RSE) | Perfusion grade of RSE, Preoperative, intraoperative and pathological data |
Table 1. Cont.

| Field | ICG Application | Study | Country | Study Design | Sample Size | Study Period | Benign Gynecologic Condition Details | Study Outcomes |
|-------|-----------------|-------|---------|--------------|-------------|--------------|-------------------------------------|----------------|
| Non-endometriosis | To assess vascular perfusion of the vaginal cuff after total hysterectomy to decrease vaginal cuff dehiscence rate | 2017 Beran [16] USA | Prospective, observational cohort, single-center, pilot study | 20 | 2 months | TLH for benign gynecologic condition | Vaginal cuff fluorescence rate
| | | | | | | Percent of cuff perimeter with adequate perfusion | Length of vaginal cuff adequately perfused |
| | To intraoperatively evaluate ovarian perfusion after adnexal detorsion | 2018 Beran [17] USA | Prospective, observational cohort, single-center, single-arm study | 20 | February 2016-March 2017 | RATLH for benign gynecologic condition | Vaginal cuff perfusion |
| | | | | | | Feasibility of using ICG dye to assess vascular perfusion to the detorsed adnexa | Time to visualized perfusion |
| | | | | | | Ovarian preservation | Post operative follow-up measures |

PE: peritoneal superficial endometriosis; DIE: deep infiltrating endometriosis; ASRM: American Society for Reproductive Medicine; RVDIE: rectovaginal deep infiltrating endometriosis nodules; RSE: rectosigmoid endometriosis; rASRM: revised American Society for Reproductive Medicine; TLH: total laparoscopic hysterectomy; RATLH: robot-assisted total laparoscopic hysterectomy; < not reported.

Details about benign gynecologic conditions were reported in Table 1. Regarding the study population, the mean age ranged from 25 to 36 years, while mean BMI ranged from 22.8 to 35.4 kg/m²; 14.9% of patients had at least one child. The mean intraoperative time ranged from 121 to 163.5 min, with a median estimate of blood loss which ranged from 50 to 150 mL. The follow-up time ranged from 1 to 23 months. Indication for surgery was dysmenorrhea in 43.8% of patients, dyspareunia in 34.5%, dyschezia 27.6%, menorrhagia in 26.7%, rectocarcinoma in 3.1%, ovarian cysts in 30%, infertility in 6.8%, pelvic pain and infertility in 20.63%, renal colic in 6.6%, hydroureter in 20%, hydroureteronephrosis in 13.3%, abnormal uterine bleeding (AUB) in 42.5%, cervical dysplasia in 15%, Lynch syndrome in 5%, postmenopausal bleeding in 5% and pelvic pain in 39.3% (Table 2).

Table 2. Patients’ characteristics.

| Field | ICG Application | Study | Age, Years (Median or Mean ± SD) (Range) | BMI, kg/m² (Median or Mean ± SD) (Range) | Parity | Operative time, Minutes (min) (Median or Mean ± SD) (Range) | Follow up Time (Months) (Median or Mean ± SD) (Range) | Estimated Blood Loss (mL) (Median or Mean ± SD) (Range) | Indication for Surgery |
|-------|-----------------|-------|-----------------------------------------|-----------------------------------------|--------|---------------------------------------------------------------|------------------------------------------------------|----------------------------------------------------------|------------------------|
| To localize uterine course | | 2015 Park [20] | 35 ± ns | 28 ± ns | 1.2 ± ns | 121 ± ns | 5.6 ± ns | 25 ± ns | Dysmenorrhea (5), dyspareunia (4), menorrhagia (7) pelvic pain (6), ovarian cyst (3), infertility (1) |
| | | | | | | | | | |
| | | 2019 Mandova [15] | 46.7 (36–79) | 23.2 (21.6–32.1) | - | 138 (90–240) | - | - | - |
| Endometriosis | To assess uterine perfusion after conservative surgery | 2020 Raimondo [15] | 35.5 ± 6.8 | 24.9 ± 5.85 | 6 patients ≥ 1 | - | - | - | Pelvic pain (13), dysmenorrhea (12), dyspareunia (16), dyschezia (5) |
| | | | | | | | | | |
| | | | | | | | | | |
| | | 2020 Cosentino [7] | 37 (31.5–42.5) | 22 (21–24) | - | - | - | - | Dysmenorrhea (27), dyspareunia (14), dyschezia (5), dyspareunia (25), pelvic pain (22) |
| | | | | | | | | | |
| | | 2015 De Nardo [12] | - | - | 16 (2–23) | - | - | - | Symptomtic RVDIE |
| | | | | | | | | | |
| | | 2019 Jayakumaran [13] | 33 ± 1.8 | 28.6 ± 3 | - | - | - | - | Endometriosis (5) |
| | | | | | | | | | |
| | | 2019 Lier [19] | 34.5 (29.3–39.5) | <25 (12 patients 40%) 25–29 (9 patients 40%) | 0 (0–1) | 30 (30–37.5 min) | - | 50 (IQR: 27.5–100) | Dysmenorrhea (19), dyspareunia (15), dyschezia (16), dyspareunia (10) |
Table 2. Cont.

| Field | ICG Application | Study | Surgical Procedure and Detection System of Fluorescence | Indocyanine Dosage and Injection Method | Time to ICG Visualization in Minutes (Median or Mean ± SD (Range)) | Type of Surgery |
|-------|-----------------|-------|------------------------------------------------------|--------------------------------------|--------------------------------------------------------|-----------------|
| Endometriosis | To localize uterine course | 2019 Mandovra [23] | Laparoscopy | 5 mg ICG diluted in 2 mL of distilled water-cystoscopy and ureteric cannulation | 7 (6–9) | Ventral mesh rectopexy, Paracolpocleisis, Anterior suspension, Sigmoid colpotomy, Right hemicolectomy, Total colectomy, Hysterecomy, Endometriotic cyst excision |
| Non-endometriosis | To assess vascular perfusion of the vaginal cuff after total hysterectomy to decrease vaginal cuff dehiscence rate | 2012 Nicholson [16] | - | - | 73.4 (48–94) | Suspected adnexal torsion |
| | To intraoperatively evaluate ovarian perfusion after adnexal detorsion | 2017 Beran [24] | Robotic-assisted laparoscopy | - | 1.5 (0–4) | - |
| | - | 2018 Beran [27] | Laparoscopy | 5 mg ICG diluted in 2 mL of distilled water | 2 (0–3) | 65.5 (25–400) |
| TOTAL | - | - | - | - | 50–150 (median) | - |

- not reported; PMB: post-menopausal bleeding; AUB: abnormal menstrual bleeding; IQR: interquartile range; ns: not stated.

Laparoscopy was robot-assisted in 5 studies [2,12,20,26,27]. Indocyanine injection was intraurethral in 2 studies [20,23], intravenous in 13 studies and both intraurethral and intravenous in one study [24]. Time to NIR-ICG visualization ranged from 6 to 9 min for intraurethral injection and from 5 s to 30 min for intravenous injection. No complication due to NIR-ICG injection was reported in the included studies.

Details about indocyanine dosage range and type of surgery were reported in Table 3.

Table 3. Details about ICG and surgery.

| Field | ICG Application | Study | Surgical Procedure and Detection System of Fluorescence | Indocyanine Dosage and Injection Method | Time to ICG Visualization in Minutes (Median or Mean ± SD (Range)) | Type of Surgery |
|-------|-----------------|-------|------------------------------------------------------|--------------------------------------|--------------------------------------------------------|-----------------|
| Endometriosis | To localize uterine course | 2019 Mandovra [23] | Laparoscopy | 5 mg ICG diluted in 2 mL of distilled water-cystoscopy and ureteric cannulation | 7 (6–9) | Ventral mesh rectopexy, Paracolpocleisis, Anterior suspension, Sigmoid colpotomy, Right hemicolectomy, Total colectomy, Hysterecomy, Endometriotic cyst excision |
### Table 3. Cont.

| Field | ICG Application | Study | Surgical Procedure and Detection System of Fluorescence | Indocyanine Dosage and Injection Method | Time to ICG Visualization in Minutes [Median or Mean ± SD (Range)] | Type of Surgery |
|-------|-----------------|-------|--------------------------------------------------------|----------------------------------------|---------------------------------------------------------------|-----------------|
| To assess ureteral perfusion after conservative surgery |  | | | | | |
| | | | | | | |
| To improve endometriosis identification |  | | | | | |
| | | | | | | |
| To assess vascular perfusion of the vaginal cuff after total hysterectomy to decrease vaginal cuff dehiscence rate | | | | | | |
| | | | | | | |
| Non-endometriosis | | | | | | |
| | | | | | | |
| To evaluate the different RSE vascular patterns and the correlation with clinicopathological data | | | | | | |
| | | | | | | |
| To assess bowel vascularization after surgery to reduce the risk of fistula | | | | | | |
| | | | | | | |
| | | | | | | |

**ICG**: Indocyanine Green; **NIR**: near infra-red; **DIE**: Deep infiltrating endometriosis; **PE**: peritoneal superficial endometriosis; **RSE**: recto-sigmoid endometriosis; **NPV**: negative predictive value; **PPV**: positive predictive value; **RVDIEN**: rectovaginal DIE nodules.

### 3.3. NIR–ICG Performance

In endometriosis patients, NIR–ICG use appeared to be a safe tool for:

- improving visualization of endometriotic lesions and ureters, preventing iatrogenic injuries after its intraurethral injection [20,23];
- supporting surgeons in surgical decision-making process with the assessment of ureteral perfusion after conservative surgery [1];
- improving endometriosis identification, with particular help in (1) separating the healthy rectal tissue from the rectovaginal DIE nodules (RVDIEN) [22], (2) decision whether to enlarge the resection to the posterior vaginal fornix in case of RVDIEN [22], (3) in the resection of deep infiltrating nodules [22]; such improvement was not found in one study [19];
- intraoperatively assessing bowel perfusion during recto-sigmoid endometriosis nodules (RSE) surgery, with improvement in patient safety, intraoperative decision-making process and surgical outcomes [2,14,15,25].

In non-endometriosis patients, NIR–ICG use appeared to be a safe tool for:

- evaluating vascular perfusion of the vaginal cuff during total laparoscopic hysterectomy (TLH) and robotic-assisted total laparoscopic hysterectomy (RATLH), with help in understanding causes for vaginal cuff dehiscence; however, an improving in
methods for quantification of fluorescence might be needed to utilize it for clinical use [26,27];

- intraoperative assessment of ovarian perfusion in adnexal torsion [16].

3.4. Risk of Bias within Studies Assessment

For the “A clearly stated aim” and “Follow-up period appropriate to the aim of the study” domains, all the included studies were categorized at low risk of bias.

For the domain “Inclusion of consecutive patients”, seven studies did not report if all eligible patients were included in the study during the study period therefore, they were classified at unclear risk of bias [7,12,20–22,26,27]. The other studies were at low risk of bias.

Regarding the “Prospective collection of data”, all studies were considered at low risk of bias except for one study that was at unclear risk of bias because it was not clear if the data were collected according to a protocol established before the beginning of the study [20].

For the “Endpoints appropriate to the aim of the study” and “Unbiased assessment of the study endpoint” domains, 2 studies were considered at unclear risk of bias because they did not clearly state the study outcomes and it was unclear if the assessment of study endpoints was unbiased [20,22].

For “Loss to follow up less than 5%” two studies were considered at unclear risk because it was not clearly stated if all the patients completed their follow up period [1,7]; four studies were evaluated at high risk of bias because more than 5% of the patients were lost during the follow up period [16,23,26,27].

Results about risk of bias within study assessment were graphically shown in Figure 2.

![Figure 2](image-url)
4. Discussion

4.1. Main Findings

This study showed that NIR–ICG might be a safe tool for improving laparoscopic treatment of some benign gynecologic conditions. In particular, it might enhance surgery for endometriosis women, with improvement in: visualization of endometriotic lesions and ureters, surgical decision-making process and assessment of bowel perfusion. Such improvements seem to benefit even more complex laparoscopic surgery for DIE. Regarding other benign gynecologic conditions, NIR–ICG appeared to support TLH and RATLH providing the chance of evaluating vascular perfusion of the vaginal cuff and laparoscopic treatment of adnexal torsion with the assessment of ovarian perfusion.

4.2. NIR–ICG History

Over the last few years, the clinical role of NIR–ICG has clearly increased also due to its capacity to visualize tissue and organ perfusion in real-time. Moreover, it has been proven that it is a nontoxic substance with a short lifetime, allowing for repeated administrations [4].

The first applications of this technique were in the measurement of liver function, the study of cardiac output and in the detection of choroidal vascularization; later, it has been used to estimate vascularization of colorectal anastomoses [28].

4.3. NIR–ICG Application in Gynecological Conditions

Still later, NIR–ICG has been widely studied and employed in laparoscopic treatment of benign gynecological conditions [1,2,7,12,14–16,19–27].

4.3.1. Endometriosis

In particular, the main field of application has been endometriosis, with specific regard to DIE [1,2,7,20–25]. In fact, DIE surgery is challenging and can be associated with major and minor complications, such as hemorrhage, infections, nerve damage, laparotomic conversion, fistula and bladder and bowel dysfunction [29–37]. Therefore, enhancing such surgery with innovative tools able to reduce complications rate appears to be a priority. In detail, in DIE surgical treatment, NIR–ICG has been assessed with several applications.

Localization of Ureteral Course

First, it has been assessed as a tool to localize ureteral course and to prevent iatrogenic injuries during complex laparoscopic surgery [20,23]. In fact, iatrogenic intraoperative ureteral injury is one of the most common avoidable complications of laparoscopic gynecological surgery, with an incidence of 7.6% [23,37]. When compared to methods for intraoperative ureteral identification (i.e., conventional DJ ureteral stents or illuminated ureteral catheters), NIR–ICG shows the advantage of avoiding a complete ureteral catheterization with related complications. Furthermore, it appears cheap and easy to be performed even in the absence of a urologist [23]. However, given the small sample size of the studies assessing NIR–ICG for this application [20,23], further studies are necessary for validating this promising role in supporting endometriosis surgery.
Regarding NIR–ICG application in ureteral assessment, it has been also studied for evaluating ureteral vascularization during endometriotic surgery, concluding that it can be a helpful tool for preventing any useless stent positioning and its related complications after ureterolysis for DIE [1].

Endometriosis Identification and DIE

Later, NIR–ICG has been evaluated as a tool for improving identification of endometriosis based on the known neovascularization of endometriosis lesions [7,12,20–25]. In particular, Cosentino et al. reported that it may be used for an intraoperative endometriosis diagnosis, both confirming visible endometriosis lesions and identifying occult endometriosis lesions that white light evaluation had misinterpreted [7]. In this study, it showed sensitivity of 82.0%, specificity of 97.9%, positive predictive value of 97.8% and negative predictive value of 82.3% in identification of endometriosis lesions; sensitivity even increased to 89% considering DIE alone [7]. However, the fact that 20 pathologic lesions (20.1%) were not confirmed intraoperatively with NIR–ICG implied that it cannot totally replace the white light evaluation but could be used together with it to detect occult lesions. In fact, removing occult disease leads to a decrease in postoperative pain and a risk of persistence and/or relapse of symptoms [7].

The use of NIR–ICG in addition to white light evaluation was also supported by Lier et al. [19] and Vizzielli et al. [21]. Additionally, Jayakumara et al. conclude that NIR–ICG could help surgeons to better visualize, diagnose and treat endometriosis [11]. On the other hand, De Neef et al. found that NIR–ICG may be helpful in achieving a macroscopic resection of RVDIEN, allowing the operators to differentiate peritoneal endometriosis from healthy rectal tissue and thus reduce the risk of rectal perforation [22]. However, additional data are necessary to confirm these preliminary promising results.

Conversely, Siegenthaler et al. described that even though NIR–ICG may be helpful in the resection of deep infiltrating nodules by providing better demarcation from the surrounding healthy tissue, its diagnostic value in detecting and confirming occult endometriosis is minimal, with a reported sensitivity of 14.7% [24]. These contrasting findings might be explained by a different prevalence of some parameters negatively impacting upon the endometriosis detection rate with NIR–ICG, such as a lower ICG exposure time, a higher number of previous abdominal surgery, more advanced-stage endometriosis and a prolonged adhesiolysis [24].

Such a low diagnostic value in detecting and confirming occult endometriosis might regard even more avascular or hypovascular pattern nodules [2]. However, these nodules might be identified thanks to the contrast with the surrounding more vascularized tissue [12]. In any case, as many mechanisms are involved in the vascularization of endometriosis nodules, such as angiogenesis, inosculation of preformed microvascular network and vasculogenesis, ICG might use of several of them to improve endometriosis nodules identification [38–40]. Another NIR–ICG application in endometriosis field has been the assessment of bowel vascularization after DIE surgery to reduce the risk of bowel fistula. In particular, Bourdel et al. assessed this role for NIR–ICG during laparoscopic rectal shaving [25], while Raimondo et al. assessed it through qualitative and quantitative analyses after full-thickness bowel resection for RSE [15]. In fact, bowel fistula shows a pathogenesis related to vascular impairment, and, although difficult, intraoperative estimation of the rectal residual vascularization appears to be a helpful indicator of the risk of postoperative fistula [25,41]. NIR–ICG appears accurate in assessing residual bowel vascularization, with a complementary role to the other available methods to assess bowel after RSE surgery. Indeed, the gas and Blue test methods are effective tools to detect microperforation and real perforation, but are not adequate for vascularization [25]. However, a delayed perfusion or a low blood flow rate is not always easily identifiable even through NIR–ICG assessment.

In the near future, a detailed analysis of perfusion time and intensity (i.e., a quantitative NIR–ICG evaluation) could allow one to overcome this limit. Further studies are
necessary indeed, after the promising findings about quantitative NIR–ICG analysis by Raimondo et al. [14].

4.3.2. Non-Endometriosis Conditions
Evaluation of the Vascular Perfusion of Vaginal Cuff

Regarding benign gynecologic conditions other than endometriosis, NIR–ICG has been used to evaluate the vascular perfusion of vaginal cuff after RATLH or TLH [26,27]. However, although Beran et al. provided a foundation for ICG dose and measurable outcomes for this application, its clinical utility seems uncertain, with a need for developing improved methods for quantification of fluorescence. In the future, assessment of vascular perfusion of vaginal cuff through NIR–ICG might reduce the incidence of vaginal cuff dehiscence [26,27].

Evaluation of Ovarian Perfusion after Adnexal Detorsion

Lastly, in 2022, Nicholson et al. tried to determine the possible use of NIR–ICG in patient with adnexal torsion. In particular, it was used to evaluate tissue viability after detorsion during surgery [16]. Such application tried to overcome limitations related to the current visual assessment of ovarian blood perfusion after detorsion. In fact, the current visual assessment (i.e., tissue color) may not adequately reflect the tissue viability and the real blood supply [16]. However, although NIR–ICG has proven to be safe and inexpensive also for this application, more studies are needed to draw conclusions about the utility and the clinical use of NIR–ICG in this setting [16].

4.4. Strengths and Limitations

To our knowledge, this study may be the first systematic review to assess the use of NIR–ICG during laparoscopic treatment of benign gynecologic conditions in the Literature. In fact, previous studies assessed NIR–ICG role only in endometriosis field [28] or in non-gynecologic diseases [42]. As a limitation, our findings may be affected by a low overall quality of the evidence as shown by the risk of bias within studies assessment. Therefore, although promising, NIR–ICG use in gynecologic conditions requires further investigation by future well-designed larger studies. Furthermore, additional and more comparable studies are necessary to perform comparisons and to provide pooled data.

5. Conclusions

NIR–ICG appeared to be a useful tool for enhancing laparoscopic treatment of some benign gynecologic conditions and for moving from minimally invasive surgery to minimalized surgery. In particular, it might enhance endometriosis surgery by improving visualization of endometriotic lesions and ureters, the surgical decision-making process, and the assessment of bowel perfusion, with major impact on complex surgery for DIE. Furthermore, NIR–ICG might also help surgeons in evaluating vascular perfusion of the vaginal cuff after TLH and RATLH and ovarian perfusion after laparoscopic treatment of adnexal torsion. However, although promising, NIR–ICG’s role in gynecologic conditions requires further investigation by future well-designed larger studies.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/medicina58060792/s1, Figure S1: PRISMA 2020 Checklist.

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