

# Using location, color, size, and depth to characterize and identify endometriosis lesions in a cohort of 133 women

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**Objective:** To correlate histology with endometriosis characteristics.

**Design:** Secondary data analysis.

**Setting:** Government research hospital.

**Patient(s):** One hundred thirty-three women with chronic pelvic pain and endometriosis who underwent laparoscopic surgery between 1999 and 2004.

**Intervention(s):** Laparoscopic excision of lesions, including recording of lesion characteristics and surgical impression of the lesions.

**Main Outcome Measure(s):** All biopsies were sent for histological examination for endometriosis, and surgical and histological findings were compared.

**Result(s):** Three hundred fifty-seven of 544 lesions believed to be endometriosis by the surgeon had positive histology. Mixed-color lesions most commonly contained endometriosis (76%), with the percentage of positive lesions being similar between single-color groups. Among subtle (red or white) lesions, 58% (164/283) were positive for endometriosis. Thirty women had only red or white lesions, and 18 (60%) had at least one lesion positive for endometriosis. Lesions were most commonly located in the cul-de-sac (64%), utero-sacral ligaments (68%), and ovarian fossa (70%).

**Conclusion(s):** Wide, deep, mixed-color lesions in the cul-de-sac, the ovarian fossa, or the utero-sacral ligaments had the highest frequency of endometriosis. More than half of subtle lesions had endometriosis. These results should be considered when diagnosing endometriosis. (*Fertil Steril*® 2008;89:1632–6. ©2008 by American Society for Reproductive Medicine.)

**Key Words:** Endometriosis, lesion characteristics, lesion color, prediction of endometriosis, laparoscopy, surgical diagnosis

The 2005 guidelines on endometriosis of the European Society of Human Reproduction and Embryology state that laparoscopic visualization of suspicious lesions is the gold standard for the definitive diagnosis of endometriosis (1). The typical appearance of endometriosis is described as a superficial, so-called powder-burn or gunshot lesion that is black, dark-brown, or blue; but subtle lesions that are red or clear, small cysts with hemorrhage or white areas of fibrosis may also be endometriosis (1). We have found elsewhere that white and mixed-color lesions had a higher percentage of histology-confirmed endometriosis than did black lesions (2). Nisolle and Donnez (3) attributed the color of the endometriosis lesions

to changes as the lesions age, starting as a red lesion and progressing to black and finally to white (2, 4–7). Thus, endometriosis is not limited to a single color and may be confirmed more frequently in a multicolored lesion. At present, it is unclear which color is most frequently associated with endometriosis.

Considering additional lesion characteristics, such as lesion location and size, may improve the ability to predict endometriosis. Locations reported to have a high rate of endometriosis include the cul-de-sac, ovarian fossa, and the uterosacral ligaments (2, 5). In addition, wide and deep lesions have been more strongly correlated with positive histology (2, 5). Other methods for diagnosing endometriosis before surgery, such as detailed history and physical examination, magnetic resonance imaging, or ultrasound (1, 8–12), have shown poor correlation between presurgical prediction and postsurgical findings. To date, surgical findings continue to provide the most accurate and reliable means of diagnosing endometriosis (1).

Defining the characteristics of endometriosis lesions and validating these findings with biopsy results has been one of our long-term objectives. Since we reported our analysis of lesion characteristics in a group of 77 women (2), we

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have operated on 56 additional subjects. Here, we report the findings of the entire cohort of women undergoing surgery from 1999 to 2004.

## MATERIALS AND METHODS

Women between the ages of 18 and 45 years were enrolled from 1999 to 2004 in a National Institutes of Health research protocol evaluating the use of raloxifene for the treatment of endometriosis. All women were healthy, with the exception of pelvic pain that had lasted  $\geq 3$  months; none had received hormonal or surgical treatment during the 6-month study entry. Subjects used a reliable nonhormonal form of contraception, and pregnant women or those attempting to become pregnant were excluded. Patients were excluded if their pelvic pain was due to an infectious, gastrointestinal, musculoskeletal, neurologic, or psychiatric cause. The Institutional Review Board of the National Institute of Child Health and Human Development approved this study.

All participants underwent laparoscopy, during which lesions suspicious for endometriosis were excised with the contact neodymium:yttrium-aluminum-garnet laser (Surgical Laser Technologies, The Oaks, PA). Some lesions were removed that were not believed to be endometriosis, such as adhesions, paratubal cysts, or other peritoneal surface lesions. Normal-appearing peritoneum was not biopsied. All excised lesions were sent for pathologic diagnosis, regardless of the surgeon's impression of the lesion; no lesions were ablated. Peritoneal defects were excised in toto, and endometriomas were removed by stripping the cyst wall from the ovary or peritoneal structures. The appendix was removed if it was chronically inflamed or appeared to contain endometriosis. If an implant was deep in the recto-vaginal septum, obliterated the cul-de-sac, appeared to be transmural to the bowel wall or ureter, or was adherent to a blood vessel, it was not resected because removal of these lesions represented unreasonable risks.

At the time of surgical excision, the following information was collected on all lesions. The surgeon's impression of the type of lesion (endometriotic lesion vs. non-endometriotic lesion) was recorded. Lesion location was listed in categories that included the bladder peritoneum, colon or appendix, cul-de-sac, ovarian fossa, ovary, sidewall, utero-sacral ligament, and uterus or fallopian tube. Width was recorded as the average of two measured diameters and was placed in categories of  $<5$  mm, 5–10 mm, 11–20 mm, and  $>20$  mm. If more than one implant was noted within 5 mm of another one, a single distance across both lesions was measured. Depth was based on one measurement and was then categorized as  $<2$  mm, 2–4 mm, 5–10 mm, and  $>10$  mm. Color categories included red (red or clear), white, black (black, brown, blue, yellow), and mixed (any two of the color categories). The stage of the disease was assigned by using the standards described in the revised American Society for Reproductive Medicine classification system (13).

Once excised, all lesions were sent for histologic examination. A pathologist reviewed hematoxylin and eosin-stained slides from formalin-fixed, paraffin-embedded specimens

for evidence of endometriosis. If no endometriosis was seen on the initial slide, the examination was repeated by using samples from three different levels of the paraffin block, and CD10 staining was performed to aid in identifying glands and stroma (14). Both endometrial glands and stroma were present for the lesion to be labeled as containing endometriosis.

Univariate and bivariate results were calculated by using Stata 8.2 (Stata Corporation, College Station, TX). Statistical testing ( $t$  tests and  $\chi^2$  tests) was performed as appropriate. By using the surgeon's impression as a test for disease, positive predictive value, negative predictive value, sensitivity, and specificity were calculated. A  $P$  value of  $<.05$  was considered statistically significant.

## RESULTS

The mean age of women undergoing surgery was  $31.5 \pm 7.2$  years. Seventy-nine percent reported their race as white; 16%, as black; and 4%, as "other" race. Twenty-one percent (23 of 133) of women had no evidence of endometriosis at the time of surgery despite having clinical symptoms that were highly suggestive for the disease. Of the remaining 110 women, 11 (10%) had lesions that appeared to be endometriosis but lacked histologic confirmation. Eight of these women had stage I disease, two women had stage II disease, and one woman who was believed to have stage IV endometriosis had four biopsies that were negative for endometriosis.

A total of 611 lesions were excised from the remaining 110 women. Surgeon's impression and histologic diagnosis were available on 603 of these lesions. Five hundred forty-four lesions were thought to be endometriosis, and 59 lesions were judged to be non-endometriotic. Of the 544 so-called endometriosis lesions, 350, or 65.0%, met the pathology criteria for endometriosis (true-positive results). In the remaining 194 lesions, endometriosis could not be confirmed with histology (false-positive results). Of the 59 lesions thought to be negative, 52, or 88%, had no evidence of endometriosis (true-negative results). However, 7 lesions (11.9%) in this group had histology confirmed endometriosis despite the surgeon's impression (false-negative results). Of these 7 lesions, 4 were found on the uterus or fallopian tubes, 1 was in the ovarian fossa, and 2 were removed from the ovary.

The positive predictive value of using only an experienced surgeon's impression to identify histologically positive lesions was 64.0%, and the negative predictive value was 88%. The sensitivity and specificity of using this method was 98% and 21%, respectively.

One hundred fifty of these lesions were black (28%), 161 (30%) were red, 123 (23%) were white, and 104 (19%) were of mixed color. Overall, single-color lesions had similar frequencies of biopsy-confirmed endometriosis (62%, 57%, and 59%, respectively), and only lesions with multiple colors had a significantly higher percentage of positive biopsies (76%;  $P=.015$ ; Fig. 1). When lesion width was  $>10$  mm (59% for width  $<10$  mm vs. 82% for width  $>10$  mm) or depth

was >5 mm, there was a higher frequency of biopsy-confirmed endometriosis (41% vs. 78% for <5 vs >5 mm, respectively; Fig. 2). A higher percentage of lesions were positive for endometriosis when they were found in the cul-de-sac (77%), utero-sacral ligaments (77%), and ovarian fossa (76%;  $P < .05$  for all groups; Table 1).

More than half (283 of 544) of all lesions were red or white (subtle) lesions. Of these subtle lesions, 58% (164 of 283) contained histologic evidence of endometriosis, compared with 68% (254 of 536) of black or multicolored lesions. In 30 women, the only lesions identified were either red or white; positive histology was found in 18 (60%) of these women. Even when we restricted the definition of subtle lesions to subtle color (red or white lesions), small size (a width of <10 mm and a depth of <5 mm), and atypical location (other than the cul-de-sac, ovarian fossa, or utero-sacral ligaments), 20 (37%) of these 54 lesions (18 of 42 red and 2 of 12 white ones, respectively) were confirmed by histology as endometriosis. Of five subjects who only had this type of lesion, two women (40%) had lesions that contained positive histology for endometriosis.

## DISCUSSION

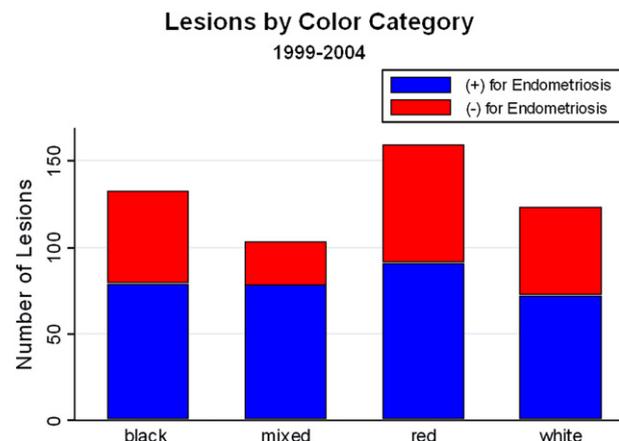
Our results indicate that  $\geq 75\%$  of lesions that have a mixture of colors; have a depth of >5 mm or a width of >10 mm; and that were located in the cul-de-sac, in the ovarian fossa, or on the utero-sacral ligament contain histological evidence for endometriosis. In addition, we found that most endometriosis lesions were subtle in color rather than the traditionally described black, powder-burned appearance (1, 2). Furthermore, all single-color lesions contained biopsy-confirmed endometriosis at about 60%. Therefore, no single color had a high association with endometriosis, and any lesion containing a single color should be considered equally suspicious for containing endometriosis.

Overall, subtle lesions were nearly as likely to contain endometriosis as those that were black or had mixed color (58% vs. 68%, respectively). Of those women ( $n = 30$ ) who only had subtle lesions, 60% ( $n = 18$ ) were confirmed to have endometriosis on biopsy. Had the diagnosis of endometriosis been based solely on the appearance of these lesions, 16% of our subjects would have been excluded. When the definition of a subtle lesion excluded large, deep lesions that were located in the cul-de-sac, ovarian fossa, or on the utero-sacral ligament, 20 (37%) of 54 lesions contained histologically confirmed endometriosis, and a similar proportion of women who only had this type of lesion (2 of 5) were found to have biopsy-proven endometriosis. Thus, when subtle lesions are found, it may be beneficial to confirm the diagnosis of endometriosis by biopsy.

We were able to corroborate the diagnosis of endometriosis with positive histology in most subjects because we performed multiple biopsies on each woman with surgical findings. However, 11 (8%) of the women did not have any biopsy-containing endometriosis despite having clinical

**FIGURE 1**

Distribution of lesions by color category.



Stegmann. Features of endometriosis lesions. *Fertil Steril* 2008.

symptoms that were highly suggestive of the disease. It is possible that these women were misclassified as being disease free because their endometriosis lesions were missed during surgery, despite our systematic approach to identification and excision of lesions.

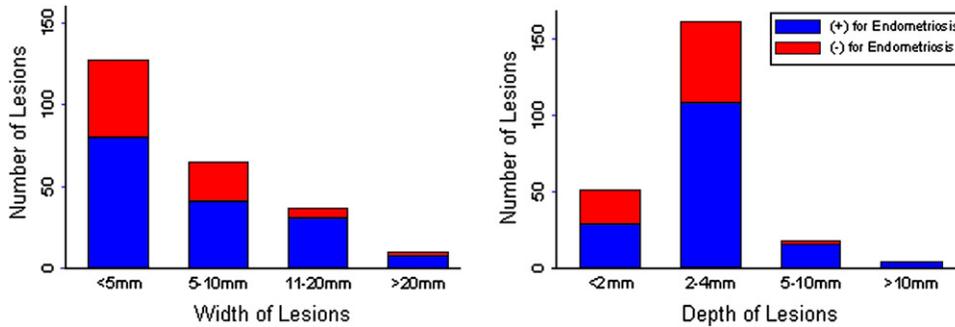
While we attempted to include only women with chronic pelvic pain that was associated with endometriosis, 20% of women had no evidence of any endometriosis lesions at laparoscopy. Other etiologies for chronic pain, such as pelvic adhesions or evidence of previous pelvic infections (2), could not be eliminated by our screening procedures. The ability to diagnose endometriosis by noninvasive means may have prevented these women from undergoing this procedure and would be enhanced with the development of more sensitive screening tests and better serologic markers (1, 9, 15, 16).

This study has significant strengths. A large number of women were enrolled, from whom a large number of samples was obtained. Also, although the primary study objective of the clinical trial was not to describe lesion characteristics, this was a secondary objective, thus allowing for prospective data collection.

The study design may have caused limitations in our analysis. First, the goal of the clinical trial was to evaluate the effects of raloxifene for chronic pain associated with endometriosis. Therefore, patients selected were likely to have endometriosis and thus were not representative of reproductive-aged women. Because of these strict entry criteria, these findings may not apply to the general population. Second, the study was not specifically designed to characterize the color and location of endometriosis lesions; non-endometriotic lesions were not routinely excised and may not have been fully characterized. A third, expected limitation is that as our surgical experience increased, our ability to identify endometriosis correctly improved, as other

**FIGURE 2**

Distribution of lesions by width (*left panel*) and depth (*right panel*).



*Stegmann. Features of endometriosis lesions. Fertil Steril 2008.*

investigators also have reported (6). However, this illustrates the importance of each surgeon comparing her or his surgical findings with histologic reports.

In conclusion, the lesions most likely to be positive for endometriosis were those >10 mm in width and >5 mm in depth; mixed in color; and located in the cul-de-sac, ovarian fossa, or on the utero-sacral ligaments. However, even surgeons knowledgeable and experienced in the characteristics of endometriosis lesions were able to correctly identify lesions with confirmed endometriosis only 64% of the time. The diagnosis of endometriosis is highly dependent on the surgeon's ability to recognize lesions, both so-called typical and subtle lesions. Subtle lesions frequently contained endo-

metriosis and, at times, were the only positive lesions found in the pelvis. This study suggests that lesion characteristics such as color do not reliably identify endometriosis.

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**TABLE 1**

Location of lesions by surgeon's impression and histology.

| Location                 | Presumed positive lesions, n (%) | Presumed positive lesions with (+) histology, n (%) | Presumed negative lesions, n (%) | Presumed negative lesions with (+) histology, n (%) |
|--------------------------|----------------------------------|---|----------------------------------|---|
| Ovarian fossa            | 132 (24)                         | 96 (73)   | 6 (9)                            | 1 (17)  |
| Cul-de-sac               | 133 (24)                         | 92 (69)   | 10 (16)                          | 0   |
| Utero-sacral ligament    | 76 (14)                          | 52 (68)   | 1 (2)                            | 0   |
| Bladder or peritoneum    | 73 (13)                          | 40 (55)   | 4 (6)                            | 0   |
| Ovary                    | 53 (10)                          | 31 (58)   | 17 (27)                          | 2 (12)  |
| Uterus or fallopian tube | 29 (5)                           | 15 (52)   | 16 (25)                          | 4 (25)  |
| Sidewall                 | 32 (6)                           | 16 (50)   | 4 (6)                            | 0   |
| Colon or appendix        | 9 (2)                            | 6 (67)  | 5 (8)                            | 1 (20)  |
| Round or broad ligament  | 5 (1)                            | 2 (40)  | 0                                | 0   |
| Total                    | 542 <sup>a</sup>                 | 350 (65) <sup>b</sup>                               | 63 <sup>c</sup>                  | 8 (12.7) <sup>d</sup>                               |

<sup>a</sup> Seven lesions were missing location data.

<sup>b</sup> Six lesions were missing location data.

<sup>c</sup> Thirty lesions were missing location data.

<sup>d</sup> One lesion was missing location data.

*Stegmann. Features of endometriosis lesions. Fertil Steril 2008.*

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