Searching for truth

The Cheshire Cat: Then it doesn’t much matter which way you go.

Alice: ... So long as I get somewhere.

The Cheshire Cat: Oh, you’re sure to do that, if only you walk long enough. (Lewis Carroll, Alice in Wonderland)

Sir,

Hopton and Redwine (2014) dispute the existence of occult microscopic endometriosis (OME), and claim that even the smallest endometriotic implants can be identified intraoperatively, provided that the surgeon keeps the tip of the endoscope very close to the peritoneum. Reviewing the literature, one may notice that Redwine provides as evidence studies where no OME has ever been found (Redwine, 1988; Redwine and Yocom, 1990). Other experienced surgeons (Nisolle et al., 1990; Nezhat et al., 1991; Khan et al., 2014) agree that endometriosis foci could exist beneath visually normal peritoneum, since they identified such foci in biopsies of normal peritoneum. If Hopton and Redwine believe that simply looking closer at the peritoneum allows identification of small implants that have not been previously seen, it would be logical to expect that further increasing endoscope magnification could reveal other, even smaller foci, and this fact would actually correspond to the existence of OME. Whatever the real mechanism of endometriosis occurrence, there is no reason to assume that macroscopic endometriotic implants, whose ultimate units are the cells of endometrial epithelium and stroma, rigorously start their evolution and growth from a baseline macroscopic size. Hopton and Redwine accept that ovarian suppressive therapy may hinder the visual detection of endometriosis implants by inducing considerable regression of their size and for that reason they do not recommend its use. But this is a paradoxical viewpoint: if the peritoneal implants can become invisible, it means that suppressive therapy might decrease the size of peritoneal implants even below the baseline size that is always visible!

It is not surprising that the reported percentages of OME vary from study to study, as they depend on the number of biopsies/case, the site of biopsies and the amount of peritoneum submitted to histological examination. It is likely that increasing the number of biopsies will consequently increase the accuracy of detection, and the most precise estimate would be provided by the removal and examination of the whole pelvic peritoneum.

The approach that more aggressive surgery can definitively cure endometriosis in a patient is highly debatable. The major question is “what is the actual goal of endometriosis management: removing implants or avoiding symptoms?” Depending on specific localization of the disease, accomplishing both objectives could be quite challenging, and the surgeon must try to maintain a balance between endometriosis symptoms and unfavorable outcomes of aggressive surgery (Roman et al., 2013). Most surgeons agree that in patients with widespread endometriotic implants, complete resection is impossible, as extensive peritoneal resection used in stage III ovarian cancer cannot reasonably be recommended in benign diseases such as endometriosis. For patients with Stage I superficial endometriosis responsible for pain, I have performed large resections of peritoneum and pouch of Douglas for years, with the belief that removing all macroscopic implants would improve the clinical pain. Thus, I came to realize that the mid-term improvement of pain after large resections of peritoneum is far from being consistent, and therapeutic amenorrhea provides effects on pain which are at least as good as those of extensive peritoneal resection. To support this observation, a prospective study concerning post-operative outcomes in Stage I endometriosis is in preparation.

Previous trials usually assessed medical treatments administered for a period smaller than the follow-up, thus explaining the apparent lack of advantage of amenorrhea (Somigliana et al., 2013). To shed light on this issue we need a randomized trial enrolling only women with superficial endometriosis and without adenomyosis, in which to compare long-term outcomes of aggressive surgery with those of continuous amenorrhea rigorously extended to the end of the follow-up. If the theory of Hopton and Redwine is correct, the long-term rate of lesion recurrence in the surgical arm would be insignificant, while the rate of pain recurrences significantly lower than that recorded in the medical arm. Based on previously reported series, these outcomes are rather unlikely.

The hypothesis of the absence of OME argues the recommendation for an aggressive surgery for endometriosis and overlooks potential benefits of adjuvant continuous hormonal treatment on cyclic symptoms related to endometriosis. Unfortunately, a large majority of studies previously reported in the literature are retrospective, non-comparative, rarely focused on Stage I endometriosis alone, provide short follow-up and lack information concerning concomitant medical treatments, and have high rates of patients lost to follow-up. I agree with Hopton and Redwine that the data on endometriosis pathophysiology is quite confusing, but I am not sure their therapeutic approach is the most beneficial for the patients.

References


Reply: Searching for truth

Sir,

Accurate identification of endometriosis during surgery is essential. The notion of occult microscopic endometriosis (OME) is at the extreme low end of the visual spectrum, where macroscopic and microscopic features become blurred. The prime importance of the criteria of normal peritoneum is often overlooked in discussions about OME. In order to identify visually normal peritoneum, one must first distinguish peritoneum that is abnormal from peritoneum that is normal. Peritoneum that is thought to be normal is then removed for histology in order to prove how visually ‘normal’ it really is. The studies by Redwine (1988); Redwine and Yocom (1990) were the first to establish and validate simple, comprehensive criteria of normal peritoneum.

Can visual criteria of normal peritoneum be readily applied to larger expanses of peritoneum? Conducting complete peritoneal excision without clinical indication raises ethical considerations. Since the rate of OME is measured in patients visually diagnosed with endometriosis, complete peritoneal excision will necessarily include areas of visually normal peritoneum devoid of OME.

Decreasing the viewing distance of the tip of the laparoscope from the peritoneal surface has been shown to reduce the rate of OME (Redwine, 2003), presumably due to the avoidance of abnormal peritoneum for biopsy. As microscopy has proved (Redwine, 1988; Redwine and Yocom, 1990), decreasing the viewing distance will not increase the rate of OME by finding ever-smaller deposits of ‘microscopic’ endometriosis. Dr Roman’s concern that smaller deposits of OME might exist that could have been missed by laparoscopy had already been dispelled decades before his letter was written. The histologically proven absence of OME in visually normal tissue obtained with a viewing distance of <1 cm instead supports the proposition that endometriosis is a macroscopic entity (Fig. 1) regardless of stage of evolution.

Dr Roman states that Evers’ work (1987) that endometriosis becomes invisible presents a paradox with our assertion that OME does not exist. In that study, however, the observation at surgery of hemorrhage resulting from destabilization of capillaries adjacent to active endometriosis was decreased at the end of ovarian suppressive therapy compared with observation conducted at surgeries performed several months later. Although the hemorrhagic footprint adjacent to endometriosis was decreased, nothing was said about the endometriotic lesions themselves shrinking or disappearing. Biopsies were not

---

Dr Roman’s complaint that since other investigators have found a small incidence of OME therefore OME exists, is tautological; other investigators did not use defined criteria for normal peritoneum and therefore their results cannot be used to nullify the results of Redwine (1988); Redwine and Yocom (1990). Surgical experience is not a proxy for sound experimental methodology in the search for normal peritoneum devoid of OME.

Accurate identification of endometriosis during surgery is essential. The notion of occult microscopic endometriosis (OME) is at the extreme low end of the visual spectrum, where macroscopic and microscopic features become blurred. The prime importance of the criteria of normal peritoneum is often overlooked in discussions about OME. In order to identify visually normal peritoneum, one must first distinguish peritoneum that is abnormal from peritoneum that is normal. Peritoneum that is thought to be normal is then removed for histology in order to prove how visually ‘normal’ it really is. The studies by Redwine (1988); Redwine and Yocom (1990) were the first to establish and validate simple, comprehensive criteria of normal peritoneum.

Can visual criteria of normal peritoneum be readily applied to larger expanses of peritoneum? Conducting complete peritoneal excision without clinical indication raises ethical considerations. Since the rate of OME is measured in patients visually diagnosed with endometriosis, complete peritoneal excision will necessarily include areas of visually detectable disease. The larger the area of tissue removed, the harder the surgeon’s task of ensuring that all areas of biopsied tissue are free of visual abnormalities. Endometriosis has been found to follow predictable patterns in its location of occurrence, with the posterior cul-de-sac the most common location (Redwine, 1987). Biopsying visually normal tissue from this anatomical location would have the greatest chance of confirming the existence of OME. Expanding the search to areas less commonly affected by endometriosis is unlikely to further improve upon results. Given the dozens of biopsies taken in the studies by Redwine (1988); Redwine and Yocom (1990), the selection criteria used have been shown to be highly reproducible.

Approaching the question of OME without criteria of normal peritoneum replaces science with opinion. The ‘science’ resulting from such an opinion-based approach can be imprecise and contradictory.

---


*Correspondence address. Tel: +33-232-888-643; Fax: +33-235-981-149; E-mail: horace.roman@gmail.com

doi:10.1093/humrep/deu100

Advanced Access publication on May 16, 2014

---

Figure 1 Microscope slide with macroscopically identifiable individual endometriotic gland/stroma complexes (arrows) alongside a human hair, which is ~100 μm in diameter. Photo courtesy of DB Redwine.