Eyes wide shut: the illusory tale of ‘occult’ microscopic endometriosis

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In this issue of Human Reproduction, Khan et al. (2013) revive the debate on the existence and clinical relevance of invisible microscopic endometriosis (IME)—now renamed by them as occult microscopic endometriosis (OME). They report new evidence for immunoreactive microscopic endometriosis in visually normal peritoneum during laparoscopy, as well as an incidence of OME, which is higher than that reported in previous laparoscopic studies of visually normal peritoneum (Redwine, 1988a; Redwine and Yocom, 1990; Nezhat et al., 1991). It is important to outline the concepts central to any discussion on OME—namely, the definition of OME, the criteria and methodology employed to identify visually normal peritoneum, and the definition of endometriosis applied in judging the presence or absence of disease in the biopsied tissue.

In defining OME an important distinction must be drawn between failure to recognize visually detectable areas of disease and the presence of microscopic disease that truly cannot be visually detected by the laparoscope. Recognition of the complete morphological repertoire of endometriosis, in all its protean presentations, and the utilization of well-defined criteria and methodology to detect all areas of visually abnormal peritoneum are paramount. Doing so ensures that contributions to the IME/OME literature are internally valid, reproducible and can be critically evaluated within the context of the existing body of research. Moreover, consensus is needed as to the histological definition of endometriosis. If different authors apply ever-broader definitions of disease, there is a risk of defining endometriosis into existence from any histologic appearance.

The concept of OME is of importance not only in predicting the outcomes and clinical utility of the complete surgical excision of endometriosis but also has far-reaching implications regarding disease phenomenology, pathogenesis and prognosis as indicated in the historical quote introduced in this editorial (Redwine, 1990). How confused has the endometriosis literature become by virtue of incomplete identification of disease?

Murphy et al. (1986) introduced the concept of OME in, reporting microscopic disease in visually normal peritoneum in 25% of a series of 20 patients undergoing laparotomy for endometriosis. This prevalence of OME remains to this day the highest rate ever reported. No formal criteria for normal peritoneum were used in that study, however, and the peritoneal surfaces were viewed at arm’s length and with the limited illumination attendant to laparotomy. Subsequent studies conducted via laparoscopy found ever-smaller rates of OME (Nisolle et al., 1990; Balasch et al., 1996), which seemed to correlate directly with the distance between the tip of the laparoscope and the peritoneal surface being examined (Redwine, 2003). With sufficient magnification, OME virtually ceases to exist (Redwine, 1988a; Redwine and Yocom, 1990; Nezhat et al., 1991). Khan et al. (2013) dispute this thesis in their current publication. We will now turn to examine whether this challenge is valid.

To support or reject the previously published findings, authors must use substantially the same methodology. The methodology of Khan et al. (2013) differs significantly from the methodology of Redwine (1988a) and Redwine and Yocom (1990) in four critical ways: (i) viewing distance, (ii) adherence to criteria of normal peritoneum, (iii) size and location of biopsies and (iv) histologic definition of endometriosis.

The viewing distance of Khan et al. (2013) was stated to be ~4 cm from the peritoneal surface, which differs markedly both from the near-contact laparoscopy used by Redwine (1988a), and Redwine and Yocom (1990), in which the viewing distance was typically ~1 cm, and the viewing distance of Nezhat et al. (1991), which was ~2 cm. If Fig. 1 of Khan et al.’s article represents their viewing distance, it is clear that their methodology differs from the aforementioned studies, since a panoramic view of the pelvis is shown. The incidence of OME at the authors’ viewing distance is predictable from the graph in Fig. 1—their findings are not new.

Khan et al.’s (2013) criteria of normal peritoneum roughly follow that of Redwine (1988a) and Redwine and Yocom (1990) but their surgical stills show a clear departure from these criteria as shown in our annotations of the same photos (Fig. 2). These subtle peritoneal changes are more obvious on the high-definition image, which was supplied with the authors’ submission. If the viewing distance was decreased, even more abnormalities might be obvious. The two surgical stills presented in Fig. 2 of this commentary undermine Khan et al.’s methodology and results.
In searching for normal peritoneum, Redwine (1988a) and Redwine and Yocom (1990) used direct visualization by looking down the laparoscope. Since resolution of morphologic details by video-assisted laparoscopy has not been compared with direct-vision laparoscopy, the use of a video monitor may introduce some undefined margin of error based on differences in resolution of details between the two viewing methods. The size of peritoneal biopsies taken in a search for OME could also have a direct impact on results. Critical visual examination of a larger area of peritoneum may be more prone to error than examination of smaller areas. The surgeon may more readily overlook signs of visually abnormal peritoneum when a larger expanse of peritoneum has to be inspected. Furthermore, there is the possibility that the aforementioned methodological weakness in accurately differentiating the visually normal from abnormal peritoneum will be amplified as a function of the total surface area of tissue biopsied (size × number of specimens biopsied), resulting in a spuriously elevated rate of OME. The biopsies examined by Khan et al. (2013) were several centimeters in dimension, while the biopsies examined by Redwine (1988a) and Redwine and Yocom (1990) were <5 mm in dimension.

The anatomical locations of biopsied peritoneum may also influence results. Khan et al. (2013) suggested that their elevated rate of OME might have resulted from their biopsying multiple anatomical locations in the pelvis, while Redwine (1988a,b) and Redwine and Yocom (1990) specifically obtained biopsies from the posterior cul-de-sac. Given endometriosis is most prevalent in the posterior cul-de-sac (Redwine, 1987) and therefore the location most likely to deliver

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**Figure 1** Incidence of OME according to the distance of the observing lens from the observed surface in papers describing this information. The distance for laparotomy was estimated by the senior author of Murphy et al. (1986). After Redwine (2003), with permission of S. Karger A.G. Basel.

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**Figure 2** Annotated version of Khan et al.’s (2013) surgical stills depicting their example of ‘visually normal peritoneum’. This surgical photo is taken from a distance of >4 cm from the peritoneum and therefore is farther from the peritoneal surface than the authors stated was used in their methodology. Even from this distance there are areas suspicious for retroperitoneal glands (arrows) and specular light reflections (circled), both signs of abnormal peritoneum according to the criteria the authors mentioned. Both frames of this figure show abnormal peritoneum.
biopsies positive for OME, biopsying multiple anatomical locations would not necessarily have contributed to an increased OME rate.

Although Khan et al.’s (2013) histologic Types I and III categories of endometriosis include glandular structures, their Type II does not. Thus they have expanded the definition of endometriosis to include endometriosis without glands. All previous studies on OME have required the presence of both glands and stroma to define endometriosis. This expansion of the classic definition of endometriosis augments the incidence of OME that was found. Moreover, while the authors found that evidence of biologic activity exists in their three types of OME, they do not answer the question of whether such lesions ever become clinically significant or progress to a larger size. Thus, post-operative medical therapy based on the fear that OME might be present despite aggressive excision seems to be unwarranted.

It also appears that some patients in Khan et al.’s (2013) paper may have been undergoing ovarian suppressive therapy at the time of study, which can decrease the visibility of endometriosis (Evers, 1987), although there is no evidence that such therapy eliminates the disease.

For the above reasons, Khan et al.’s (2013) criticism of previously published low prevalence rates of OME is not supported by the methodology they used.

Conclusion

For readers of this journal, what can be learned from Khan et al.’s (2013) paper?

Although their different methodologies do not support a valid rejection of Nezhat et al. (1991), Redwine’s (1988a) and Redwine and Yocom’s (1990) findings, the authors have nonetheless provided even more evidence of a very important point: most women with endometriosis do not have OME. Thus, patients and surgeons alike can be encouraged that proper identification of subtle forms of endometriosis combined with aggressive excision of disease will not leave behind a great burden of overlooked foci of OME of uncertain clinical significance.

Readers should also be encouraged that the editorial review process is alive and functioning. The senior author (D.B.R.) of this commentary was one of the original reviewers of the paper of Khan et al. (2013). The initial inclination was to recommend rejection of this article because of the methodological differences, which do not support their conclusion that OME exists in a significant portion of women with endometriosis. However, rejection of the manuscript would have allowed the possibility that the paper might eventually appear in another journal after a less stringent review—the importance of differing methodologies might have gone overlooked, and an unchallenged paper might have been published adding confusion to the already confused literature on endometriosis.

As one ponders the long history of endometriosis (Redwine, 2012), it is apparent that one form of the disease is truly invisible to the surgeon, but not because it is too small to see. Small deposits of endometriosis laid down within the ovarian stroma are completely hidden, which may contribute to an increased likelihood of recurrence of ovarian endometriosis after excision when compared with recurrence rates following excision of peritoneal and deeply fibrotic disease.

Future directions

Despite its methodological limitations, the elegant study by Khan et al. (2013) raises several important unstated questions for future study.

(1) What is the relationship between pre/peri-operative hormone therapy on the rate of OME? Given the potential for hormone suppression to hinder the visual detection of endometriosis (Evers, 1987), it would be of interest to examine the relationship between hormone therapy and detected rates of OME, so that this potential confounder can be quantified.

(2) What is the relationship between pain and infertility and reported rates of OME? While Khan et al. (2013) make the leap of faith between OME immunoreactivity and the clinical relevance of OME as a potential source of pelvic pain, one way of elucidating this relationship would be by examining differential rates of OME in patients with pelvic pain compared with those presenting without pelvic pain.

(3) Do the 3D viewing capacities provided by robotic surgery really present an improvement in identification of subtle endometriosis over the well-confirmed results of traditional laparoscopy, or is this just marketing hype? Evidence from the OME literature suggests that the use of close-contact laparoscopy as well as stringent criteria for the visual diagnosis of peritoneal abnormality is sufficient for optimal detection and removal of endometriosis. There is no reason to suggest that supposedly superior visualization afforded by robotics has anything to add, and in the absence of comparative studies of visualization of subtle endometriosis between traditional and robotic laparoscopy, statements to the contrary should be treated with caution.

Where do such subtle lesions come from? No paper on OME has shown evidence of initial attachment or secondary proliferation and invasion of peritoneum by refluxed endometrium. Does this mean that established endometriosis has already been laid down during embryogenesis as suggested by Redwine’s concept of Mülleriosis (Redwine, 1988b), supported by the recent findings of Signorile et al. (2009, 2010, 2012)?

Is the term ‘endometriosis’ too confining? It is clear that endometriosis can have protean visual and histologic appearances, as well as dozens, if not hundreds, of differences from eutopic endometrium (Redwine, 2002). Yet endometriosis seems to be only a subset of a larger set of related Müllerian-based syndromes including, among others, adenomyosis, fibroids and abnormalities of hormone receptor distribution and function. In this biologic universe of overlapping Müllerian possibilities, Khan et al.’s (2013) use of their Type II pattern may be a sign that classic definitions of endometriosis are too limiting and lack overarching contextual significance. Their findings cannot all be comfortably accommodated by the term ‘endometriosis’ alone but are easily contained within Mülleriosist.

References


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