Clinical diagnosis of endometriosis and optimal medical therapy

Endometriosis is a common estrogen responsive inflammatory disease that continues to represent a diagnostic and therapeutic challenge. Pain is subjective and it is difficult to discern normal from abnormal, except in the extremes. The manifestations of the disease are diffuse and may involve multiple organ systems, often leading to a prolonged and distracting evaluation. There are currently no clear guidelines that allow clinical diagnosis. Yet physicians frequently do make a clinical diagnosis of endometriosis and treat with first line therapies. Most commonly, oral contraceptives are used prior to surgery or more definitive medical therapies.

Similarly, there are no clear guidelines dictating the optimal therapy for endometriosis. An oral contraceptive is routinely used first, yet many patients will fail this therapy due to progestin resistance or the aggressive nature of some forms of endometriosis. Appropriate therapy may require use of a gonadotropin-releasing hormone (GnRH) analog or other more definitive therapies. Can we better identify those who would benefit from a change in therapy or who are failing first line treatment?

Harada et al. (1) report a randomized clinical trial that compared placebo to a novel regiment that allowed the subject to determine when to start a placebo induced menstrual bleed. In the flexible regiment, subjects were instructed to stop a continuous 120 day active pill regiment in response to unscheduled bleeding. After withdrawal the patient would automatically restart the oral contraceptive regiment without needing physician supervision. The authors are to be commended for developing this regiment which empowers patients and creates a protocol to easily handle the most common side effect of a continuous oral contraceptive regiment. Subjects were also randomized to a third group receiving treatment with dienogest.

Interestingly, in this study (2) the diagnosis of endometriosis did not require surgery. A clinical diagnosis of endometriosis was sufficient to identify patients who would respond to endometriosis therapies. Do we really need to use laparoscopy to identify endometriosis? Cyclic and progressive pelvic pain in reproductive aged women is most commonly due to endometriosis. The so called "gold standard," laparoscopy, has a very high false-positive and false-negative rate (2). Currently there is a delay of 7–10 years in the diagnosis of endometriosis in part due to lack of awareness and because of barriers to making the diagnosis (3). Optimal therapy is often delayed. Women with the disease endure pain that can be debilitating during the most formative years of life. A clinical diagnosis of endometriosis will identify women needing therapy as well as allow earlier diagnosis and more rapid adoption of effective therapies.

In the Harada et al. study (1) the scores of most severe pain were similar in all groups at baseline. Not surprisingly pain scores dropped more in the group treated with an oral contraceptive than the group treated with placebo. While statistical comparison to the dienogest group was not performed, the mean pain reduction score was far lower than either the placebo group or the oral contraceptive group. This suggests that many endometriosis patients on a fist line oral contraceptive regiment are not getting adequate pain relief and could be offered more complete therapy. The goal of endometriosis therapy should always be absence of pain; if this end point is not achieved with oral contraceptives, the patient should be offered more definitive therapy.

Many patients fail to adequately respond to oral contraceptives while others develop progestin resistance with disease progression despite using a progestin based therapy. Surgical therapy may provide relief but the disease has a high recurrence rate. Second line therapies for endometriosis are limited and geographically restricted. Dienogest is not available in the United States. GnRH agonist therapy is a very effective treatment that can be offered to those failing first line therapies. As this class of drugs work by estrogen depravation rather than by a progestin mediated pathway, GnRH agonists are usually effective in the setting of initial treatment failure. With add back hormone therapy side effects are minimized or eliminated with no loss of efficacy.

New GnRH antagonists promise to improve treatment options and provide the ability to titrate estradiol levels. GnRH agonists suppress the GnRH receptor and desensitize the pituitary to GnRH, creating a profound reduction in gonadotropins and loss of estradiol. Unlike agonists, GnRH antagonists bind competitively to the receptor allowing titration to a desired estradiol level. With the availability of GnRH antagonists we will be able to partially suppress estrogens, allowing individualized treatment with fewer menopausal side effects. This paradigm has been clearly demonstrated in recent phase III clinical trials using the oral GnRH antagonist elagolix (4). Other GnRH antagonists are under development. We anticipate that broader choices of highly effective therapies which are superior to oral contraceptives will provide better pain relief to endometriosis patients.

Interestingly in the Harada et al. study pain scores improved with therapy despite no reduction in the number of bleeding days. The treatments used were likely modifying disease rather than simply reducing bleeding days or providing symptomatic relief. Clinical diagnosis does identify those with disease and allows selection of patients who will benefit from disease modifying therapy. Dienogest treatment resulted in the greatest average pain reduction score despite also having the greatest number of bleeding days, further suggesting that the therapy was modifying disease, inflammation and pain rather than simply reducing bleeding days. The use of clinical diagnosis can identify those most likely to benefit from therapy and identify those in need of second line therapy.

Women with endometriosis have a real reason to be hopeful. New non-invasive diagnostics (5) and increased awareness of the power of clinical diagnosis will undoubtedly

allow earlier diagnosis. The realization that all therapies have different efficacy and the availability of new endometriosis drugs will allow more rapid progression to definitive therapy. The rapid clinical diagnosis of endometriosis and complete elimination of pain should be our clinical goal.

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REFERENCES

1. Harada T, Kosaka S, Elliesen J, Yasuda M, Ito M, Momoeda M. Ethinylestrdiol 20 μg/drospirenone 3 mg in a flexible extended regiment for the management of endometriosis-associted pelvic pan: a randomized, controlled trial. Fertil Steril 2017;108:798–805.
2. Hsu AL, Khachikan I, Stratton P. Invasive and non-invasive methods for the diagnosis of endometriosis. Clin Obstet Gynecol 2010;53:413–9.
3. Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril 2011;96:366–73.
4. Taylor HS, Guidice L, Lessey B, Abrao M, Kotarski J, Archer D, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. N Engl J Med 2017;377:28–40.
5. Cosar E, Mamillapalli R, Ersoy GS, Cho S, Seifer B, Taylor HS. Serum microRNAs as diagnostic markers of endometriosis: a comprehensive array-based analysis. Fertil Steril 2016;106:402–9.