

Therapeutic Implications of Progesterone Receptor Status in Endometriotic Lesions: Pathogenic and Pragmatic Considerations

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THERAPEUTIC IMPLICATIONS OF PROGESTERONE RECEPTOR STATUS IN ENDOMETRIOTIC LESIONS: PATHOGENIC AND PRAGMATIC CONSIDERATIONS

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Flores and co-workers observed a correlation between presence of progesterone receptor (PR) in endometriotic lesions removed at surgery and pre-operative response to estrogen-progestins and progestins (1). Thus, PR status assessment in excised specimens might discourage the post-operative use of these hormonal drugs in women with low/absent PR expression.

Most patients with endometriosis undergo surgery because of large cysts, infertility or, precisely, pelvic pain not responding to medical treatment.

Considering the strict correlation between persistent ovulation and the risk of post-operative endometrioma recurrence (2), any ovulation-inhibiting medication can be used after endometrioma excision independently of PR status. In infertile women, no post-operative medical therapy should be used, thus PR status is irrelevant. In case of pelvic pain not responding to estrogen-progestins or progestins, these compounds appear of limited usefulness irrespective of PR status. When estrogen-progestins and progestins are not tolerated, PR evaluation is superfluous because the only alternatives are GnRH agonists and antagonists anyway.

As the authors maintain, in women with pain presumably originating from endometriosis, estrogen-progestins and progestins should be tried before surgery. Indeed, Taylor *et al.*, based on a review of the available evidence, suggest that the non-surgical diagnosis of symptomatic endometriosis is more reliable than previously recognized (3). In these conditions, the likelihood of non-response and the need to step-up to GnRH agonists or antagonists is very limited (4).

More in general, response and non-response should be precisely defined, but Flores *et al.* could not do this, probably owing to the retrospective study design (1). The most frequent pain symptoms in women with endometriosis are dysmenorrhea and deep dyspareunia.

Abolishing menstrual flows is the easiest modality to relieve dysmenorrhea, and this can be achieved with estrogen-progestins and progestins independently of PR status. When amenorrhoeic, patients may not be classified as non-responders by definition.

Deep dyspareunia is more difficult to relieve with medical treatments, because pain at intercourse is frequently caused by infiltrating lesions, fibrotic tissue, chronic peri-lesional inflammation, and secondary hyperalgesia. However, oral nor-ethindrone acetate has been used successfully specifically in patients with endometriosis-associated severe deep dyspareunia (5). The progestin effect was gradual, but progressive over time, and the maximum benefit was observed after 1 year of therapy. Therefore, caution should be used before defining as non-responder a woman still experiencing some degree of pain at intercourse after a few months of treatment.

Hormonal therapies for endometriosis may work via two different mechanism: 1) a systemic mechanism implying anovulation, amenorrhea, and induction of a steady hormonal state generally characterized by low-moderate circulating estrogen levels; 2) a local mechanism, i.e., a direct effect on endometriotic lesions with decidualization and atrophy induced by a targeted interaction with endometriotic cell hormone receptors. Progesterone resistance would determine the degree of response to therapy only in case the local mechanism prevails over the systemic mechanism. However, this should be verified in prospective studies, and limiting the potential effect of selection bias and confounding. This effort toward precision medicine is laudable, but more data seems warranted before implementing PR status assessment in endometriosis management.

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