

The use of GnRH-a among women with hepatic endometriosis: therapeutic benefit?

GnRH-a's act on the pituitary glands production of hormones that directly control ovarian synthesis of estrogen.⁽⁴²⁾ The (5) cases of surgically-induced menopausal women do not clarify the purpose of hormone suppressants. It's implied their intent was lesion shrinkage to reduce intraoperative risks, increase probability of full lesion excision and spare liver tissue. The ovaries are no longer present. So what happens after surgically induced menopause? GnRH-a's affect the ovaries. Does the body still produce estrogen? The arrival of menopause is the drastic decline in estrogen produced by the ovaries. Other body tissues partially compensate for these changes.

Without the presence of active ovaries, can GnRH-a's still make an impact on endometriosis lesions? Their mechanism of action aren't directed toward disruption of estrogen synthesis in non-ovarian tissues or endometriosis lesions. There are numerous extragonadal (nonovarian) body tissues that produce very small amounts of estrogen (Liver, Spleen, Intestines, Adrenal Glands, Blood Vessels, Brain, Bone, Skin and Adipose tissue (body fat)).⁽⁴³⁾

“The chemical structure and biological activity of the estrogens synthesized in the extra-gonadal sites are not different from those that are produced by the gonads. However, there are unique features that make the extra-gonadal estrogen synthesis differ from the gonadal synthesis. A major difference is in the biochemical pathway of estrogen synthesis.” - Barakat R. et al. (2016)⁽⁴³⁾

Prior to menopause, the ovaries are the largest producers of estrogen and location of highest amount of Aromatase. Aromatase is vital for the production of endometriosis. After menopause, there is a shift toward other tissues of the body for production of Estrogen but rely on neighboring tissues to create aromatase to each this. Adipose (body fat) is a major producer of aromatase after menopause.

“Although aromatase level per adipose tissue fibroblast may be small, the sum of estrogen arising from all adipose tissue fibroblasts in the entire body makes a physiologic impact.” Attar E, Bulun SE (2005)⁽⁴³⁾

Endometriosis lesions, unlike the endometrium of the uterus, also produce *aromatase*. Unlike endometrium, endometriosis lesions can produce estrogen. The quantity of estrogen is very small, and inadequate to affect systemic circulating levels but adequate to sustain the lesion, acting locally. ⁽⁴⁴⁾

Is use of GnRH-a's, in attempt to shrink endometriosis lesions in surgically induced menopausal women a misapplication? It is important to consider the limited option available in 2002 and 2004. With concern for risks associated with resection of large lesions from the liver, potential loss of healthy liver tissue and risk of residual disease and regrowth, attempts to reduce lesion size conservatively prior to liver resection is strongly encouraged. In 2002 and 2004, a newer hormone suppressant suitable for women postmenopause was in its very early stages of clinical use. The first published report of Aromatase Inhibitor efficacy in a postmenopause women occurred in 1998.⁽⁴⁵⁾ The next two publications did not occur until 2004.⁽⁴⁵⁾ Knowing that GnRH-a's were the only option, despite their use specific to premenopause, it is sensible that some conservative attempt still be placed in attempt to reduce lesion size prior to resection. A smaller lesion increases probability entire lesion is removed, spare healthy liver tissue and reduce operative complications.

What happened w/ postmenopausal cases administered GnRH-a?

One (1) of the two (2) postmenopausal women, the original lesion (11cm x 7cm), was reduced to 2cm diameter but no further during GnRH-a treatment.⁽¹⁵⁾ Over a period of three years, the patient developed right shoulder pain, misdiagnosed as a shoulder injury and immediately prior to reconfirmation of the **regrown** endometrioma, was mistaken for pneumonia. The recurrent lesion was measure 11.7 x 7.3cm. A five month **retrial** of GnRH-a was

readministered. **No impact** of lesion size was observed. The patient underwent liver resection. Given that GnHR-a's do not block estrogen synthesis of endometriosis lesions, or block receptor sites of the lesion to circulating estrogens, and understanding of the pathway for extragonadal estrogen production is incompletely understood, the pharmacological actions of Aromatase Inhibitors for lesion size reduction preoperatively is a consideration. Their use is recommended among postmenopausal women and have a direct action of estrogen production among tissues with aromatase, present in endometriosis lesions and extragonadal sites of estrogen synthesis.⁽⁴⁴⁾ However, these were not an option at the time of these cases.

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Extrapelvic Not Rare