Fibroids: when should they be removed to improve in vitro fertilization success?

Uterine fibroids are extremely common smooth muscle tumors found in women of reproductive age. Over 75% of women will develop fibroids prior to menopause. A continued challenge is determining when fibroids are problematic and involved in the etiology of infertility, rather than an incidental finding. Fibroids are classified based on their size and location within the uterus (1). Fibroids that are intracavitary (i.e., entirely within the uterine lumen) or that project into the cavity and significantly distort its shape have been clearly associated with infertility. The standard of care is to remove such fibroids as they are often associated not only with infertility, but also with bleeding and increased risk of spontaneous abortion. Subserosal fibroids, remote from the uterine cavity, do not affect fertility and are typically not removed prior to in vitro fertilization (IVF). More controversial are the type 3 fibroids that are in close proximity to the endometrium yet are 100% intramural. These fibroids typically do not distort the cavity when viewed hysteroscopically and yet, their close proximity to the uterine cavity suggests that they may have an impact.

Fibroids have traditionally been thought to exert their adverse effects on pregnancy by primarily mechanical mechanisms. Fibroids distort the endometrial cavity. They may thin the endometrium immediately above the fibroid and distort blood flow to the endometrium. However, mechanical disruption of the endometrium is only one component of fibroid action. The adverse effects of fibroids are also due to their innate ability to biochemically signal their surrounding environment. Fibroids produce abundant extracellular matrix as well as numerous cytokines and growth factors that have a profound impact on adjacent tissues. A remote effect of fibroids on endometrium was first demonstrated by Rackow et al. (2). Directed endometrial biopsies were obtained at the time of the hysteroscopy from well-defined regions within the uterine cavity, including areas overlying fibroids as well as areas that appeared unaffected by fibroids. Surprisingly, areas far removed from any fibroid had similar defects in endometrial receptivity as did areas directly over a fibroid. HOX genes, leukemia inhibitory factor as well as beta 3 integrin were all reduced throughout the entire endometrium, including areas that were visually unaffected by the fibroid. These data implicate a signaling molecule produced by the fibroids that reaches the entire endometrial cavity, regulating the adverse effects of fibroids on endometrial receptivity with obvious implications for IVF success. Removing these fibroids is expected to not only improve local endometrial receptivity immediately overlying the fibroid, but also to have an effect on the entire endometrium. These results are consistent with the well-known significant adverse effects of intracavitary fibroids on implantation, even when the fibroid does not contact the entire endometrial cavity.

In subsequent studies, we identified the signal to endometrium as transforming growth factor β (TGF- β), a diffusible molecule that is produced in abundance by fibroids. Leiomyoma-derived TGF-β impairs the bone morphogenic protein type 1 and 2 receptors that are essential for endometrial receptivity (3). Given this mechanism, fibroids making sufficient quantities of TGF- β and in close enough proximity to the endometrial cavity, allowing this signaling molecule to reach the endometrium, will impact fertility.

In this issue of *Fertility and Sterility,* Yan et al. (4) describe a retrospective study examining the effect of type 3 fibroids on IVF success. These fibroids are in close proximity or contact the endometrium, but are still intramural without evidence of their presence on hysteroscopy. While this study is not a prospective trial and has some limitations, the results are still profound. Patients with type 3 fibroids of at least 2 cm in size had a significantly lower frequency of implantation, biochemical pregnancy, clinical pregnancy and live birth. Perhaps most dramatically, the live birth rate was increased by more than 50%, from 21% to 34%, in women without fibroids. These data suggest a significant impact of fibroids on IVF pregnancy. A review of the baseline characteristics in these women younger than 40 years of age showed very few confounders that would have contributed to these findings, suggesting that the differences in pregnancy rates are likely attributable to the fibroids alone. Interestingly, a trend exists for fibroids even less than 2 cm; live birth was numerically lower in those with small fibroids, although this difference did not reach statistical significance. From this study we can safely conclude that large, intramural fibroids in close proximity to the endometrial cavity do affect IVF success rates by impacting endometrial receptivity and embryo implantation. We should consider removing intramural fibroids when in close proximity to the endometrial cavity. Further clinical trials are needed to determine of myomectomy truly restores optimal endometrial receptivity.

Large fibroids produce more TGF-β3 and those closest to the uterine cavity allow more TGF to reach endometrial cells. One would predict that the size of the fibroid would determine TGF-beta production and that the amount of TGF-β reaching the cavity would vary by the square of the distance from the cavity ($1/X^2$, where X is the distance from the fibroid to the endometrium). In other words, both size and distance matter. Small fibroids remote from the cavity are unlikely to have a significant effect, whereas large fibroids are more likely to affect endometrial receptivity. As the effect would be expected to vary with the square of the distance, even relatively small differences in proximity to the endometrial cavity would result in profound differences in the ability of fibroids to affect the adjacent endometrium. Those close to the endometrial cavity would have a severe effect while those even slightly removed from the cavity are predicted to have a much smaller effect. We can likely ignore fibroids that are a significant distance from the endometrial cavity.

We have previously demonstrated that not only does TGF-β secreted by fibroids affect endometrial receptivity, it also effects the endogenous production of anticoagulants in the endometrium that help to regulate normal menstrual flow (5). TGF-β 3 alters production of plasminogen activator inhibitor-1, antithrombin 3, and thrombomodulin in the

endometrium. These alterations in endometrial hemostatic mechanisms contribute to menorrhagia. While Yan et al. (4) did not report on menorrhagia in this group, it is likely that menorrhagia would have predicted the effect on endometrial receptivity. As endometrial receptivity and endometrial anticoagulant expression are both altered by the same signaling molecules, it is likely that those fibroids that affect bleeding also simultaneously affect endometrial receptivity. It will be interesting to see if this correlation holds true. However, a fibroid in close enough proximity to cause menorrhagia is also likely to be affecting endometrial receptivity.

In summary, large intramural fibroids in close proximity to the endometrial cavity warrant removal prior to IVF. The effect of fibroids on endometrium is global, transmitted through molecular signaling rather than entirely through physical and mechanical disruption. The effect diminishes rapidly with distance from the cavity. Fibroids simultaneously affect endometrial hemostasis and endometrial receptivity. A good proxy for the effect on endometrial receptivity is bleeding. The data provided by Yan et al. (4), along with a large body of literature describing a molecular signal to endometrium, suggest that intramural fibroids in close proximity to the cavity or that cause alterations in menstrual bleeding warrant removal prior IVF.

Hugh S. Taylor, M.D.
Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, Connecticut

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