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A.R.E. is employed by the American Board of Family Medicine. The remaining authors report no conflict of interest.

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REPLY

Check for updates

We thank Eden et al for their letter regarding an oversimplification of the medical specialties categorized as primary care in our analysis. We agree that family medicine physicians, certified nurse midwives, and advanced practice providers are important providers of maternity care services, especially in rural settings, and play a critical role closing both the maternity and substance use treatment gap for pregnant and postpartum women.

The proportion of family medicine providers providing maternity care has declined steadily over the past decade, and we were unable to account for the provision of maternity care services beyond provider specialty in our analysis.[1,2] Because of the limitations inherent in our claims dataset, we choose to categorize family medicine providers as primary care providers.

Certified nurse midwives and other advanced practice providers (eg, nurse practitioners) are also important providers of both maternity care and substance use treatment services, including opioid pharmacotherapy. However, nurse practitioners and physician assistants have only been able to prescribe buprenorphine through the Comprehensive Addiction and Recovery Act since early 2017, and our analysis was limited to data from 2013−2016.[3] Thus, we were unable to include the important contribution from advance practice providers in our analysis.

Given that many pregnant women with opioid use disorder continue to lack access to evidence-based medication-assisted treatment, future research is needed to further understand the gaps in the substance use treatment provider workforce including the type, frequency, and quality of clinical care services beyond pharmacotherapy provided by prescribing providers. ■

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Should we absolutely reject the hypothesis that epithelium-based *Candida* biofilms contribute to the pathogenesis of human vulvovaginal candidiasis?

Check for updates

TO THE EDITORS: We read the article by Swidsinski et al[1] with great interest. The authors used fluorescent in situ hybridization of human vaginal tissue biopsies to demonstrate the absence of *Candida* biofilms in patients with vulvovaginal candidiasis (VVC). This is a very important finding because it might reset the treatment target for recurrent VVC (RVVC) from biotic biofilms to invasive fungi.

However; from the microbiologic aspect, it is reasonable to assume the involvement of *Candida* biofilms in VVC and their resistance to antifungals. Although most clinical isolates

from patients with RVVC/VVC remain sensitive to conventional antifungal agents, the ineffectiveness of these drugs in curing RVVC is reported frequently. This suggests that microbial strategies other than intrinsic resistance might be involved. Such possible strategies include biofilm formation and production of persister cells (a small population of "transiently resistant" cells). Supporting this suggestion is the observation that the recurrence pattern of RVVC coincides with the model of relapsing biofilm infections proposed by Lewis[2] (2010), in which persister cell are major culprits.

Harriot et al[3] (2010) successfully demonstrated vaginal epithelium-based *Candida* biofilms using a mouse VVC model and raised the hypothesis that formation of such biofilms may be an initiating event in VVC. Using the same model, Zhang et al[4] (2013) found a dynamic change of *Candida* growth on vaginal epithelia along with VVC progression. *Candida* pseudohyphae and yeast cells were found on mouse vaginal epithelia 3 days after the infection; these adherent biofilms were replaced gradually by the endocytosed hyphae, which is a unique growth mode also reported by Swidsinski et al.[1] The possibility of the presence of such transient biofilms in patients whose infections have progressed to a later stage should not be excluded. Furthermore, although the endocytosed yeast/hyphal cells in vaginal epithelia do not present any structural characteristics of typical multilayer biofilms, such as the presence of self-producing polymeric matrix or 3-dimensional mushroom structures, they might resemble monolayer biofilms and share some important traits that drive the recurrence of infections, which includes harboring antifungal-tolerant persister cells. We have found that dense growth of monolayer biofilms in a confined space stimulated persister cell production and led to antimicrobial tolerance in vitro.[5] The further clarification of the possible dynamic change of *Candida* growth in the human vagina VVC and whether the endocytosed hyphal cell growth mode promotes persister cell production needs collaborative efforts from experimental microbiologists and clinical investigators.

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REPLY

Phantom limb sensations are obviously very strong in the *Candida*-biofilm research community. It is striking that this and previous letters to the editor with regard to our publication,[1] cite Harriott et al[2] as work that definitively demonstrated the vaginal candida biofilm in rodents. That is not true. We likewise cite the same author in our article and state that "The only publication claiming *Candida albicans* forms biofilms on the vaginal mucosa exclusively includes pictures of smears from vagina without vaginal epithelium."

Neither Harriott nor anybody else have ever presented microscopic proof of candida biofilm on the vaginal wall. In addition, there are major differences between the experimental model of rodent *Candida* vaginal infection and human vaginal candidiasis, for example, microbiota, pH, and the enormous inoculum of yeast organisms that is used in the animal model, which alone may simulate biofilm-similar discharge. Until the visual proof of biofilm on the surface of intact human vaginal epithelium is available, all speculations about the existence of vaginal candida biofilms will remain scientifically unsound.

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