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Case series

A case series of triplet anti-hormonal therapy in androgen receptor-positive recurrent adult ovarian granulosa cell tumor☆

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ABSTRACT

Therapeutic options for recurrent adult granulosa cell tumors (AGCT) are limited. After examining the hormonal pathways involved in *FOXL2*-mutated granulosa cell tumor development, a novel treatment regimen was utilized for recurrent AGCT: a combination of an androgen receptor antagonist, a gonadotropin-releasing hormone receptor agonist, and an aromatase inhibitor for hormonal blockade. In this case series, seven patients at our institution were treated with bicalutamide 50 mg orally once daily, Leuprolide acetate 7.5 mg intramuscular (IM) injection every 4 weeks, and a daily oral aromatase inhibitor. These patients had recurrent AGCT with androgen receptor positive tumors and had failed prior aromatase inhibitor therapy. All patients had undergone multiple surgical resections and many cycles of chemotherapy. Patients were monitored for toxicities and for response to treatment. Of the seven patients receiving the triple therapy, six saw clinical benefit. Two patients demonstrated a partial response and four patients had stable disease. One patient had progressive disease on the regimen. For the two patients who had a partial response to the triple therapy, there was strong expression of the androgen receptor (AR) noted on tumor immunohistochemistry. This drug combination was well-tolerated except for severe hot flashes in one patient. In conclusion, the triple therapy combination of an androgen receptor antagonist, aromatase inhibitor, and GnRH agonist demonstrated measurable responses in patients with recurrent AGCTs after multiple previous treatments. A prospective clinical trial is planned to further investigate these findings.

1. Introduction

Adult granulosa cell tumors (AGCT) account for up to 5 % of ovarian malignancies. Survival outcomes in this disease are generally favorable, but disease tends to recur with increasing stage (Schumer and Cannistra, 2003). Approximately 33 % of patients will relapse and 50–80 % of patient with recurrent disease will die of their disease (Färkkilä et al., 2017). There is a large unmet need for therapies for recurrent AGCT that produce measurable tumor response and provide clinical benefit.

Steroidogenesis is dysregulated in AGCT via a *FOXL2* somatic missense mutation (C134W) which is present in nearly all tumors (Fig. 1). *FOXL2* is a transcription factor which is involved in cell proliferation, apoptosis, and steroidogenesis (Leung et al., 2016). $FOXL2^{C402G}$ mutation results in substitution of a tryptophan for a highly conserved cysteine in the fork-head DNA binding region of the protein. This mutation lacks the consistent induction of oncogenes or inactivation of tumor suppressor genes found among other tumor types (Shah et al., 2009).

The $FOXL2^{C402G}$ mutation is thought to disrupt CYP19 (aromatase) and CYP17 gene transcription. Wildtype FOXL2 is thought to bind to steroidogenic factor-1 (SF-1) to negatively regulate the transcriptional activity of SF-1 which acts on CYP17 and CYP 19. $FOXL2^{C402G}$ stimulates CYP19 transcription leading to elevated estrogen synthesis via direct induction of aromatase. Also, CYP17 (a key enzyme involved in androgen production) is no longer repressed leading to increased androgen and estrogen expression (Leung et al., 2016). FOXL2 also plays a role in activating GNRHR as part of an AP1-SMAD3-SMAD4 complex which encodes the GnRH receptor (Ellsworth et al., 2003; Shah et al.,

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2009). Cheng *et al.* suggested that wild-type FOXL2 ectopically expressed in the commercially-grown AGCT cell line, KGN, may alter GnRH-induced apoptosis by increasing GnRH receptor protein expression and mRNA expression (Cheng et al., 2013; Leung et al., 2016; Nishi et al., 2001). Given the consistent *FOXL2* mutation in all AGCT, we proposed a novel treatment regimen for recurrent AGCT: a combination of an androgen receptor antagonist, a gonadotropin-releasing hormone receptor agonist, and an aromatase inhibitor for complete hormonal blockade. The goal of this case series was to retrospectively review the efficacy and tolerability of this multimodal regimen in our institutional cohort of patients with recurrent AGCT tumors positive for AR expression.

2. Methods

This is a retrospective case series of seven patients treated at our institution from August 2020 to August 2022. Publication of this case series was approved through the Institutional Review Board (IRB) at the Medical College of Wisconsin, project number PRO00042018. Informed consent was waived by the IRB. Women had tumors positive for the androgen receptor (AR) (>1% by Leica IHC-AR27 antibody at a dilution of 1:50), estrogen receptor (ER) positive by Leica clone 6F11 (no dilution required). Additional progesterone receptor (PR) staining was also done with Leica clone 16 (no dilution required). The choice of a > 1 % threshold for tumor positivity was extrapolated from institutional protocols for ER and PR staining, as we do not have a current standardized guideline for AR positivity. Staining of these tumor slides was performed at the Wisconsin Diagnostics Lab and reviewed by investigator MM.

The seven patients were each treated with bicalutamide 50 mg by mouth once daily, leuprolide acetate 7.5 mg by intramuscular injection every-four weeks, and an aromatase inhibitor (anastrozole, exemestane or letrozole) by mouth once daily. Medications were prescribed through our pharmacy and billed through insurance. The aromatase inhibitor and bicalutamide were started first in order to decrease estrogen production and block tumor receptors. Leuprolide acetate was then started one week later. All patients were heavily pre-treated with two to seven prior lines of therapy, and had undergone two to seven prior surgical resections. Prior treatment lines consisted of prior chemotherapy (bleomycin, etoposide, cisplatin, carboplatin, paclitaxel, gemcitabine), hormonal therapies including exemestane, letrozole, and anastrozole, and targeted therapies including bevacizumab, everolimus, pembrolizumab, and olaparib. All patients had failed prior aromatase inhibitor therapy.

Patients were monitored for toxicities and for response to treatment via surveillance exams, tumor markers (inhibin B levels or antimullerian hormone), and computed tomography (CT) scans at the discretion of the treating physician.

All patients underwent two to three CT scans between initiation of therapy and the time of clinical review and/or progression. Partial response, stable disease and disease progression were determined by RECIST criteria, version 1.1, as measured by RS and EH, then compared for confirmation. Figures were constructed in R, version 4.2.1, using *ggplot2*, version 3.3.6, *swimplot* version 1.2.0 and *ggbreak*, version 0.1.0. All patients were followed until disease progression or until time of data cut-off for publication.

3. Results

Of the seven patients treated with the combination of bicalutamide, leuprolide acetate and an aromatase inhibitor evaluated over 24 months, one patient developed progressive disease after five months of treatment, two had partial responses and four had stable disease. At time of publication, duration of clinical benefit was not yet reached by the remaining six patients and their disease did not progress for up to 20 months of treatment. The regimen was generally well-tolerated. Subject and tumor characteristics, treatment courses and treatment results are summarized in Table 1. Treatment courses for each patient are depicted in Fig. 2. Inhibin B trends are shown in Fig. 3.

Patient 1 underwent three surgical resections since diagnosis in 2013. She was treated with five lines of therapy prior to the triple therapy regimen, and failed an aromatase inhibitor (letrozole) in a prior line of therapy. Her most recent treatment line prior to initiation of triple therapy was bevacizumab, followed by cytoreductive surgery with rapid recurrence of disease. Her initial CT at four months on the triple therapy regimen showed a partial response, which was sustained on subsequent CT scans. Her disease burden involved multiple intrabdominal implants. After three months on treatment, the patient developed grade 2 adverse event (AE) of hot flashes and venlafaxine was initiated. The patient required a treatment break due to vasomotor side effects, despite attempted mitigation with venlafaxine. She had disease progression by

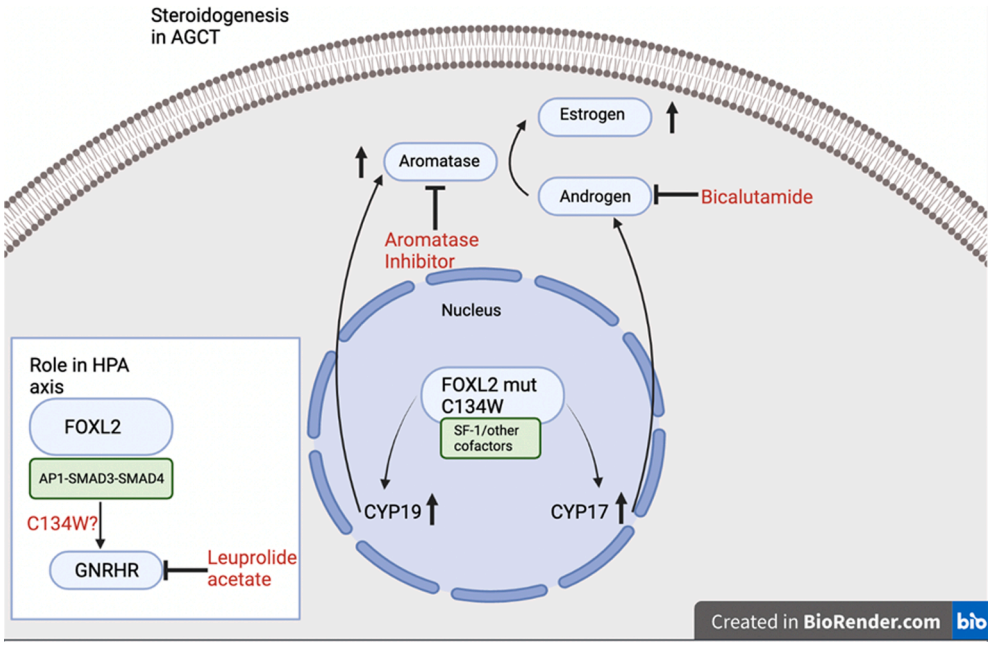

Fig. 1. Steroidogenesis in AGCT. $FOXL2^{C134W}$ is thought to alter FOXL2-SF-1 transcription of CYP19 and CY17 by causing upregulation of CYP19 and loss of repression of CYP17.(Leung et al., 2016) Consequently, there is increased hormonal production. FOXL2 also plays a role in activating GNRHR as part of an AP1-SMAD3-SMAD4 complex which encodes the GnRH receptor.(Ellsworth et al., 2003; Shah et al., 2009) There have been studies looking into the role $FOXL2^{C134W}$ plays in this pathway.[4,7] Utilizing an aromatase inhibitor, androgen receptor blocker, and GnRH agonist would allow for complete hormonal blockade in AGCT as noted in this figure.

Table 1
Patient Summary. Clinical summary of hormone status, mutation status (if known), radiographic monitoring and outcomes in AGCT patients treated with triplet therapy of bicalutamide, aromatase inhibitor and leuprolide acetate. IHC stains to assess hormone status in patient 1 were performed on two biopsies performed 2.5 years apart and reported in chronological order; all other stains were performed on the most recent biopsy or resection specimen. All patients received bicalutamide and leuprolide acetate but aromatase inhibitors varied, and are listed in the table.

Subject	Age (y)	Aromatase inhibior	AR+ (%)	ER+ (%)	PR+ (%)	CT exams (months from treatment initiation)	PFS (months)	Response of target lesion	Toxicity on current regimen (CTCAE v5.0)	Prior treatment lines (n)
1	40	Exemestane	>95	10 50	50 >95	4, 8, 12, 15	13 months	Partial response (treatment break due to side effect profile)	Grade 3 hot flashes	5
2	64	Exemestane	95	30	95	8, 12, 15	> 16 months	Partial response	None	4
3	73	Exemestane	80	50	>50	3, 7, 11, 16	> 20 months	Stable disease	Grade 1 fatigue	7
4	67	Exemestane	50	10	80	3, 11,	> 15 months	Stable disease	Grade 1 arthralgias	2
5	67	Letrozole	95	2–3	60	1, 8	> 13 months	Stable disease	None	3
6	36	Exemestane	50	40	70	5	5 months	Progressive disease	None	5
7	66	Anastrozole	95	60	85	3, 5, 7	> 9 months	Stable disease	Grade 1 nausea	2

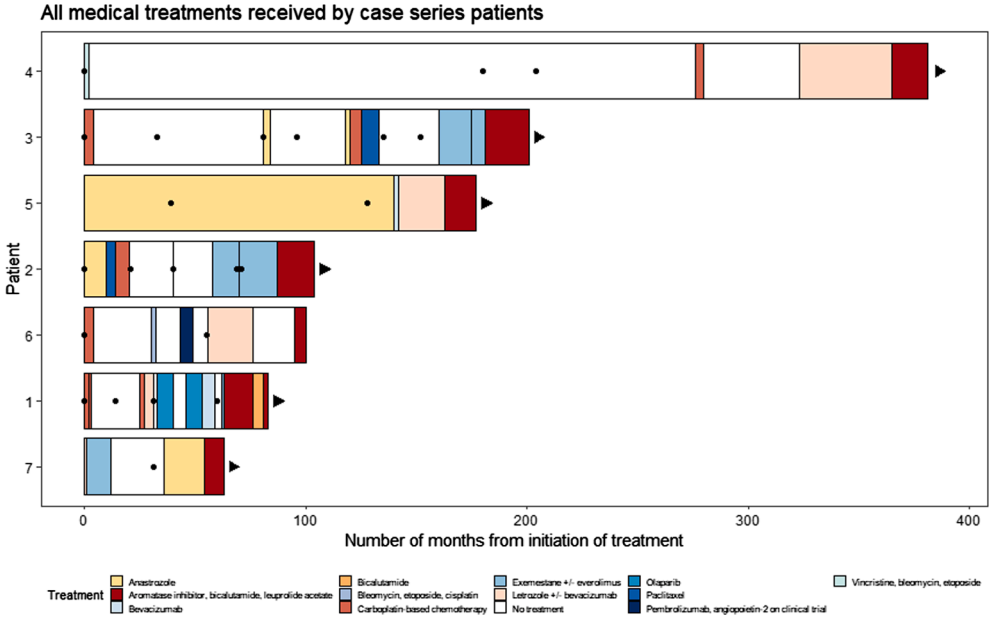

Fig. 2. Treatment courses for case series patients. Swimmer plot of treatments received by each of the seven patients, starting with the initial receipt of medical therapy for AGCT. Instances of initial surgical treatment or surgery for recurrence not requiring medical therapy were excluded for ease of viewing. Dots represent surgical cytoreduction or interventional radiology tumor ablation. Arrows represent ongoing treatment with our triplet regimen. The most recent therapy for each patient is an aromatase inhibitor, bicalutamide and leuprolide acetate.

CT scan two months after starting her treatment break. She restarted the triple therapy regimen using norethindrone, venlafaxine, and gabapentin to mitigate vasomotor symptoms with grade 1 hot flashes noted.

Patient 2 underwent three surgical resections since diagnosis in 2007. She received four lines of systemic therapy, including an aromatase inhibitor (anastrozole) following her first recurrence in 2013. This was followed by systemic chemotherapy regimens. Just prior to initiation of the triple therapy regimen, disease was treated with exemestane/everolimus. Her recurrent disease consisted of a pelvic mass and peritoneal metastases. She had a partial response on her initial CT scan which was sustained for 16 months at time of data cut-off for publication. There were no treatment-related AEs on the triple therapy regimen.

Patient 3 was diagnosed with AGCT in 1991 and underwent seven surgical resections since diagnosis. She received seven lines of treatment including a prior aromatase inhibitor (anastrozole). Just prior to initiation of the triple therapy regimen, disease progressed on exemestane and everolimus. Antimullerian hormone level was a marker for her disease and inhibin B was not. Her current disease (presacral mass) remained stable since initiation of treatment with the triple therapy regimen, 20 months at time of data cut-off for publication. Grade 1 fatigue was noted.

Patient 4 underwent three surgical resections of disease, including initial surgery in 1984. She was treated most recently with letrozole, prior to initiation of the triple therapy regimen. Her disease (a pericolonic nodule and peritoneal metastases) remained radiographically stable for 15 months of treatment at time of data cut-off for publication. Grade 1 arthralgias were noted.

Patient 5 underwent two surgical resections and three lines of treatment since diagnosis in 1991. She was treated with both anastrozole and letrozole in the past, with letrozole being utilized as the most recent treatment prior to initiation of triple therapy regimen. Recurrent disease consisted of para-aortic and gastrohepatic lymphadenopathy. Disease remained radiographically stable and tumor marker decreased after 13 months of study treatment at time of data cut-off for publication. There were no treatment-related AEs on the triple therapy regimen.

Patient 6 had three prior surgical resections and five lines of treatment since diagnosis in 2009. She received chemotherapy, immunotherapy, and a prior aromatase inhibitor (letrozole). Disease progressed within five months on the triple therapy regimen. CT imaging showed carcinomatosis, a pelvic mass, and abdominopelvic lymphadenopathy.

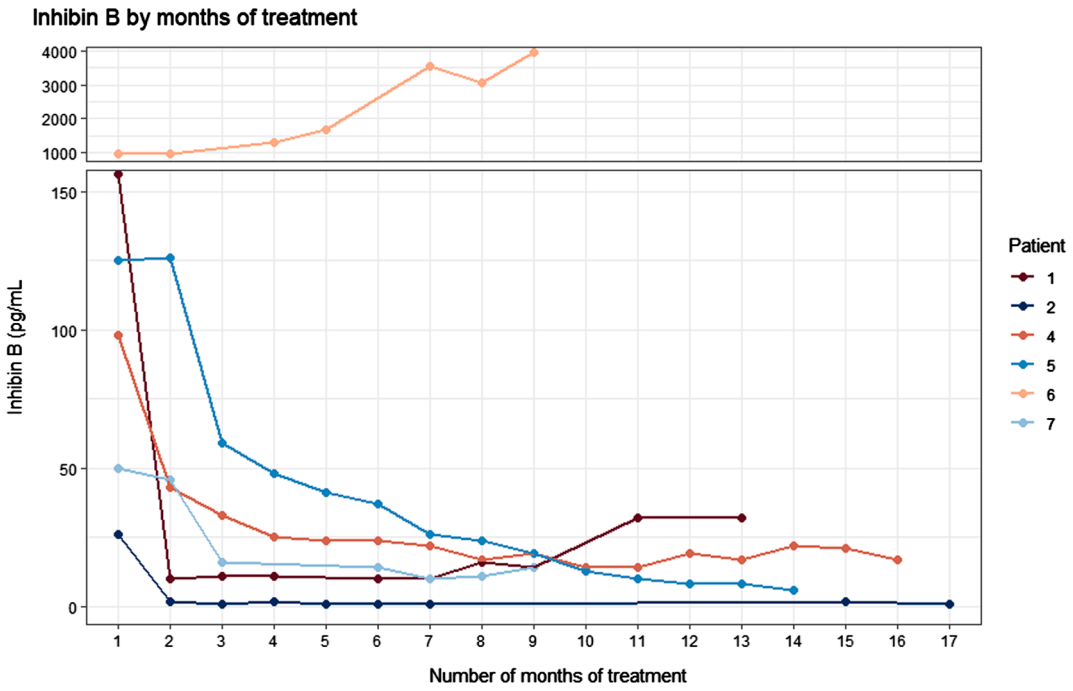

Fig. 3. Inhibin B levels graphed over time. Inhibin B values of patients 1, 2, 4, 5 and 7 are shown on the y axis on the left and number of months since initiation of treatment is depicted on the x-axis. Inhibin B values for patient 6 are graphed on the superior y axis. Inhibin B was not a tumor marker for patient 3.

There were no treatment-related AEs on the triple therapy regimen.

Patient 7 underwent three prior surgical resections and three lines of therapy (exemestane/everolimus, letrozole, anastrozole) since diagnosis in 2004. Her most recent treatment line prior to initiation of triple therapy regimen was anastrozole. Disease (perihepatic implant and a pancreatic implant) remained radiographically stable at nine months on the study regimen at time of data cut-off for publication. Grade 1 arthralgias noted on triple therapy regimen.

The clinical benefit rate of this triple therapy regimen in our institutional cohort was 85.7 %. There were two partial responses correlating with an overall response rate of 28.6 % in our cohort.

4. Discussion

This targeted regimen of an androgen antagonist, aromatase inhibitor, and GnRH agonist combination therapy in recurrent AGCT is a promising therapy based on the responses of this heavily pretreated cohort. In addition, the regimen has been well tolerated.

New treatments for recurrent AGCT are greatly needed. A recent review by Brink *et al* showed an overall response rate and disease control rate of 30 % and 58 %, respectively, when studies evaluating chemotherapy were combined (Brink et al., 2022). This same review identified a disease control rate of 66 % with hormonal therapies (Brink et al., 2022). In a systematic review of case reports of hormonal therapies by van Meurs *et al* in 2014, 3/5 patients had a complete response (CR) and 2/5 patients had a partial response (PR) on anastrozole. Similarly, 2/5 patients had a CR and 2/5 patients had a PR on letrozole. On medroxyprogesterone acetate,1/3 patients had a CR and 2/3 patients had a PR. On megestrol acetate, 2/3 patients had a PR while the other patient progressed. Of two subjects on leuprolide and tamoxifen, one patient had CR and one had progression of disease. On gosrelin, 2/4 patients had a CR while one progressed. On leuprolide alone, 3/10 patients had a PR, 5/10 stable disease and 2/10 progressive disease (van Meurs et al., 2014). An institutional review by van Meurs *et al* in 2015 showed a pooled median PFS of 10 months in 22 patients following treatment with progestins, selective estrogen receptor modulators, aromatase inhibitors or GnRH agonists (van Meurs et al., 2015). Importantly, the only prospective trial published to date evaluating hormonal therapy in this population was PARAGON (ANZGOG-0903), which identified a 2.7 month median progression-free survival (PFS) and favorable quality of life outcomes. The difference between the positive responses reported in these case reports and the lower PFS reported in prospective and retrospective studies highlights the selection bias in case reports as well as the difficulty in investigating treatment of a rare and slow-growing tumor.

Regarding past trials of androgen blockade in AGCT, a case report describing ketoconazole and hydrocortisone for recurrent *FOXL2*^{C134W} reported stable disease after 10 months of therapy (Garcia-Donas et al., 2013). GREKO studies I, II and III have investigated ketoconazole, orteronel and enzalutamide, respectively, in this population. The abstract from GREKO I reports a 14.06 month median PFS; 5/6 patients achieved stable disease $>$ 12 months.(Garcia-Donas et al., 2019) GREKO II was terminated due to slow accrual and the status of GREKO III is unknown (Grupo Español de Tumores Huérfanos e Infrecuentes, 2020; Rodriguez-Moreno et al., 2015).

The benefit of chemotherapy has also been limited in this population. A recent review found an objective response rate and disease control rate of 30 % and 58 %, respectively, when chemotherapy agents were pooled.(Brink et al., 2022) A phase II trial evaluated BEP for recurrent disease and found that 51 % of women with recurrent disease remained progression-free, but a majority had a non-measurable clinical response and stable disease.(Homesley et al., 1999) In the ALIENOR-ENGOT-ov7 randomized clinical trial, the objective response rate was 25 % with paclitaxel alone and increased to 44 % with the addition of bevacizumab.(Ray-Coquard et al., 2020) In a phase II study, 16.7 % of patients with recurrent AGCT had a response (partial) to single-agent bevacizumab (Brown et al., 2014).

The triple therapy combination of an androgen receptor antagonist, aromatase inhibitor, and GnRH agonist demonstrated a high clinical benefit rate in 85.7 % of patients in this case series and a response rate of 28.6 % which was similar to or improved compared to previously studied regimens.(Brink et al., 2022) Importantly, this regimen was tolerable and subjects within our institutional cohort were on this regimen for greater than one year at time of publication.

Strengths of our study included its novel intervention and promising results. This triple therapy intended for complete hormonal blockade may be more effective than a single agent when comparing to historical references. Limitations of our study included the small sample size and retrospective nature. We do not yet know the duration of response and long-term side-effects to treatment as six of seven patients in the case series remained on treatment at time of publication. Also, the relationship of tumor hormone receptors to treatment response is unknown and worthy of further investigation. AGCT are typically slow-growing tumors and since this study was not randomized, it was difficult to determine if lack of progression was due to the indolent nature of the disease or the treatment. As above, our study was also subject to selection bias due to investigator patient selection. Long term follow-up of patients will be needed in additional prospective studies.

Due to the response rate and tolerability of this regimen, we believe that further investigation is warranted via a prospective clinical trial. We would also like to further elucidate the toxicities of this regimen as well as any biomarkers that are predictive of response.

5. Conclusions

This targeted regimen of androgen antagonist, aromatase inhibitor, and GnRH agonist is a promising and well-tolerated therapy for patients with recurrent AGCT.

Author contribution

Elizabeth Hopp: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, supervision, writing - original draft, writing - review & editing

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors do not have any relevant disclosures or conflicts of interest. This project was supported by the Department of OBGYN Women's Health Research Program; we received no outside funding for this project.

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