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Editorial

Pushing the envelope: expanding fertility sparing treatment of endometrial cancer

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Fertility-sparing management of apparent early stage, low grade endometrial cancer is becoming more prevalent as growing evidence reveals acceptable oncologic and reproductive outcomes. Expansion of who can receive conservative therapy is especially relevant as more women delay childbearing and the incidence of endometrial cancer continues to rise, including rates among premenopausal women [1]. Current society guidelines recommend consideration of fertility-sparing management for only complex atypical endometrial hyperplasia and grade 1 (well differentiated) endometrioid endometrial cancers that meet very specific criteria [2,3].

The oncologic safety of a fertility-sparing treatment approach in grade 2 endometrioid endometrial cancers is largely unknown. To date, small retrospective case series have comprised the bulk of the literature including this important patient population. Prior to the current manuscript by Falcone and colleagues, the largest series included 17 patients with grade 2–3 endometrial cancer without myometrial invasion treated with oral medroxyprogesterone. This agent achieved a complete response rate of 76.5% and recurrence rate of 23.1% [4]. Another series included 8 patients with grade 2 endometrial cancer treated with levonorgestrel-releasing intrauterine device (LNG-IUD) alone and demonstrated an overall response rate of 75% [5]. Importantly, these responses are quite similar to outcomes for grade 1 endometrioid tumors [5,6]. Despite reports of reassuring response rates, in one study, grade 2 endometrial cancer treated with medroxyprogesterone and LNG-IUD was associated with a lower live birth rate when compared to grade 1 endometrial cancer [7]. Conversely, a recent study from China included 11 grade 2 endometrial cancer patients treated with oral progestin therapy and reported equivalent response, recurrence, and pregnancy rates compared to grade 1 endometrial cancer [8]. Given the substantial differences in median body mass index across these studies, the impact of obesity on underlying tumor biology, progestin response, and fertility outcomes remains unknown. There is a clear paucity of evidence in the management of these patients.

In this issue of the *Journal of Gynecologic Oncology*, Falcone and colleagues [9] report on the oncologic and reproductive outcomes in 23 patients with grade 2 endometrial cancer from multiple centers. Patients were treated with a combination of hysteroscopic resection plus

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Conflict of Interest

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progestin therapy with LNG-IUD, megestrol acetate or norethisterone acetate. One of the clear strengths of this study is sample size. With a total of 23 patients, it is now the largest reported case series of grade 2 endometrial cancers receiving fertility-sparing management. The reported complete response rate (73.9%) was consistent with previous studies. It is notable, however, that time to complete response was slightly longer (6 v 4.5 months) and duration of response was shorter (21 vs. 58 months) when compared to the largest reported series of conservatively treated grade 1 endometrial cancer patients [6]. The fact that only 58.5% of the complete responders attempted to conceive in this study coupled with refusal of definitive surgery in some patients, highlights the need for a comprehensive counseling approach prior to considering a treatment that strays from standard of care.

The authors mention the potential application of biomarkers, which could prove essential in predicting response to treatment and reducing risk of unfavorable outcomes. However, with very limited data on conservatively treated grade 2 endometrial cancers, biomarker analyses have not yet been reported. Histopathologic evaluation demonstrating absence of exogenous progesterone effect at early time points after progestin therapy initiation has been associated with lack of progestin response [5]. Given the known discordance in grade and histotype between pathologists, analysis of ProMisE classification using p53, MSH6, PMS2, and POLE could be implemented to improve reproducibility in identifying at-risk groups [10]. A preliminary report of this application in 48 patients with endometrial intraepithelial neoplasia or endometrial cancer (two of which were grade 2), revealed that presence of the copy number high/p53 aberrant molecular phenotype was associated with shorter time to progression after treatment with the levonorgestrel IUD [11]. This is certainly interesting but requires validation in larger prospective studies. Prediction of progestin response using other biomarkers in grade 1 endometrioid endometrial cancers has produced conflicting results, but could be used to guide selection of candidate markers for evaluation in grade 2 cancers [12]. Proliferation rate (Ki67) and progesterone receptor (including specific isoforms and glandular or stromal expression patterns) may be candidates for evaluation.

We commend the authors for their contribution to an area in desperate need of evidence-based guidance and we strongly agree with their conclusion that the numbers must be interpreted with caution. While these are encouraging data, in the absence of larger prospective studies, patients should be counseled with a shared decision-making approach. One must clearly understand the lack of high-quality evidence available, potential oncologic perils including risk of a missed underlying histologic diagnosis and/or undetected spread of disease, which could ultimately have a detrimental effect on overall survival. In addition, it is of paramount importance to consider overall health and fertility potential of an individual patient prior to recommending oncologic treatment that deviates from the standard of care. Early evaluation with oncofertility colleagues should be strongly considered. Given the relative rarity of this intervention, all providers should systematically follow these patients and contribute to the literature by reporting oncologic and reproductive outcomes in order to maximize care of this growing patient population.

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