Case series

Conservative management of endometrial hyperplasia or carcinoma with the levonorgestrel intrauterine system may be less effective in morbidly obese patients

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https://doi.org/10.1016/j.gore.2018.09.001

Received 18 June 2018; Received in revised form 4 September 2018; Accepted 5 September 2018

Available online 12 September 2018

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undergo or decline surgical management and are using a LNG-IUS for treatment or a means to allow time to medically optimize patients.

Continuous variables were summarized using means, medians, SDs, and IQRs where appropriate, while frequencies were used to describe categorical variables. Univariate associations of continuous variables and BMI groups were assessed using one-way ANOVA or Kruskall-Wallis tests. Pearson Chi-square and Fisher’s exact tests were used to test associations between BMI groups and categorical variables. Differences were considered significant when p ≤ 0.05. Linear regression was used to assess the relationship between BMI and follow up results. Multivariable logistic regression was used to assess risk of progression and adjust for covariates of interest. Statistical analysis was performed using Stata 14.2 software.

3. Results

Sixty women were identified who met the inclusion criteria. Demographic characterization of the cohort is presented in Table 1. The average age of the cohort was 47.4 ± 12.7 years. The majority of patients were Caucasian (63.3%), non-smokers (66.7%), and 48.3% (n = 29) were nulliparous. Notably, the mean BMI of the patients being treated with LNG-IUS was 42.5 kg/m² ± 13.5 kg/m² (254.9 lb. ± 80.9 lb). Twelve patients (20%) in the study population had a BMI < 30 kg/m², 17 patients (28.3%) had a BMI between 30 kg/m² and 30 kg/m², 17 patients (28.3%) had a BMI between 30 kg/m² and 34.6 kg/m², and 31 patients (51.7%) had a BMI > 40 kg/m². The most prevalent medical comorbidities included hypertension (45%) and diabetes (26.7%).

The most common indication for LNG-IUS treatment was poor surgical candidate (n = 26), followed by a desire for preservation of fertility (n = 17) and a desire for conservative medical treatment (n = 17). Twenty-four patients were diagnosed with EH (40%). The median time from LNG-IUS insertion to repeat endometrial biopsy was 4.1 months (IQR 3.2–6.4).

Repeat endometrial biopsy resulted in regression in 41 patients (68.3%). Twelve patients (20%) had persistent disease on repeat sampling, and 7 patients (11.7%) experienced progression. Of the patients with the initial diagnosis of EH (n = 24), 83.3 (n = 20) experienced regression or persistent disease. Similarly those with the initial diagnosis of EHA (n = 18) had 50% regression rate (n = 9) but maintained high rates of regression or persistent disease in 83.3% (n = 15). Similarly those with the initial diagnosis of EC (n = 18) had 50% regression rate (n = 9) but regression or persistent disease in 88.9% (n = 16). Initial diagnosis was not statistically associated with follow-up diagnosis (p = 0.123) (Table 2).

Treatment response was then stratified by BMI. Of the BMI < 30 kg/m² cohort, 10 patients (83.3%) had regression and the remaining patients had persistent disease (n = 2). No patients

| Table 1 | Demographics. Baseline demographics of all patients using the LNG-IUS for treatment of EH/EHA/EC stratified by BMI. |
|---------|---------------------------------------------------------------------------------------------------------------|
|         | n = 60 n (%) | n = 12 n (%) | n = 17 n (%) | n = 31 n (%) | p-value |
| Age (years) | 47.4 (± 12.7) | 46.8 (± 10.0) | 46.4 (± 14.4) | 48.1 (± 13.0) | 0.899 |
| BMI (kg/m²) | 42.5 (± 13.5) | 25.9 (± 2.4) | 34.6 (± 2.6) | 33.2 (± 9.3) | < 0.001 |
| Nulliparous | 29 (48.3) | 5 (41.7) | 9 (52.9) | 15 (48.4) | 0.998 |
| Endometrial strip (mm) | 10 (7–14) | 8.5 (4–13) | 8 (5.5–16) | 10 (8–15) | 0.456 |
| Smoking history | None | 40 (66.7) | 7 (58.3) | 12 (70.6) | 21 (67.7) | 0.923 |
| History | 17 (28.3) | 4 (33.3) | 4 (23.5) | 9 (29.0) | |
| Current | 5 (8) | 1 (8.3) | 1 (5.8) | 1 (3.2) | |
| Other | 4 (6.7) | 0 | 2 (11.7) | 2 (6.4) | |
| White | 38 (63.3) | 9 (75.0) | 10 (58.8) | 19 (61.3) | 0.476 |
| Black | 14 (23.3) | 1 (8.3) | 1 (5.8) | 9 (29.0) | |
| Asian | 4 (6.7) | 2 (16.7) | 1 (5.8) | 1 (3.2) | |
| Other | 4 (6.7) | 0 | 2 (11.7) | 2 (6.4) | |
| Comorbidities | HTN | 27 (45) | 1 (8.3) | 7 (41.2) | 19 (61.3) | 0.006 |
| DM | 16 (26.7) | 2 (16.7) | 6 (35.3) | 8 (25.8) | 0.543 |
| Arthritis | 8 (13.3) | 1 (8.3) | 2 (11.8) | 5 (16.1) | 0.786 |
| Depression | 13 (21.7) | 4 (33.3) | 2 (11.8) | 7 (22.6) | 0.388 |
| HLD | 11 (18.3) | 1 (8.3) | 4 (23.5) | 6 (19.4) | 0.581 |
| Thyroid disease | 8 (13.3) | 2 (16.7) | 1 (5.9) | 5 (16.1) | 0.578 |
| Sleep apnea | 5 (8.3) | 0 (0) | 0 (0) | 5 (16.1) | 0.079 |
| Asthma | 7 (11.7) | 0 (0) | 2 (11.8) | 5 (16.1) | 0.348 |
| Pathology | EH | 24 (40) | 8 (66.7) | 7 (41.2) | 9 (29.0) | 0.057 |
| EHA | 18 (30) | 1 (8.3) | 3 (17.7) | 14 (45.2) | |
| EC | 18 (30) | 3 (25.0) | 7 (41.2) | 8 (25.8) | |
| IUD reason | Desires expectant management | 17 (28.3) | 7 (58.3) | 4 (23.5) | 6 (19.4) | 0.032 |
| Desires fertility | 17 (28.3) | 4 (33.3) | 6 (35.3) | 7 (22.6) | 0.032 |
| Not surgical candidate | 26 (43.3) | 1 (8.3) | 7 (41.2) | 18 (58.1) | 0.032 |
| Concurrent Progesterone based therapy | 22 (36.7) | 4 (33.3) | 6 (35.3) | 12 (38.7) | 0.941 |
| Initial follow up EMB time | 4.1 months (3.2–6.3) | 5.8 months (4.5–6.7) | 4.1 months (3.0–6.3) | 3.6 months (3.2–5.9) | 0.112 |

| Table 2 | Follow up endometrial sampling stratified by initial diagnosis (p = 0.129). |
|---------|---------------------------------------------------------------------------------------------------------------|
| Initial diagnosis | Follow up result | EH | EHA | EC |
| n = 24 n (%) | n = 18 n (%) | n = 18 n (%) |
| Regression | 20 (83.3) | 12 (66.6) | 9 (50) |
| Persistent | 2 (8.3) | 3 (16.6) | 7 (38.9) |
| Progression | 2 (8.3) | 3 (16.6) | 2 (11.1) |

Abbreviations: EH, endometrial hyperplasia; EHA, endometrial hyperplasia with atypia; EC, endometrial carcinoma.
experienced progression of their disease. Within the BMI 30 kg/m² to 40 kg/m² cohort, 13 patients (76.5%) experienced regression and the remaining 4 patients (23.5%) had persistent disease. Again, no patient experienced progression. In the BMI > 40 kg/m² cohort, 18 patients (76.5%) experienced regression and the remaining 4 patients (23.5%) had persistent disease. Again, no patient experienced progression. In the BMI > 40 kg/m² cohort, 18 patients (76.5%) experienced regression and the remaining 4 patients (23.5%) had persistent disease. Again, no patient experienced progression. In the BMI > 40 kg/m² cohort, 18 patients (76.5%) experienced regression and the remaining 4 patients (23.5%) had persistent disease. Again, no patient experienced progression. In the BMI > 40 kg/m² cohort, 18 patients (76.5%) experienced regression and the remaining 4 patients (23.5%) had persistent disease. Again, no patient experienced progression.

As expected, higher BMI was associated with worse initial pathology. The mean BMI of those with EH was 38.2 ± 5.4 kg/m² while that did not progress (p = 0.026).

Table 3
Follow up endometrial sampling stratified by BMI (p = 0.03). Graphical representation of results of repeat endometrial sampling following the use of LNG-IUS stratified by BMI and initial endometrial sampling.

| BMI <30 kg/m² | BMI 30-40 kg/m² | BMI>40 kg/m² |
|--------------|----------------|-------------|
| **EH**       | **EHA**        | **EC**      |
| n=8          | n=1            | n=3         |
| Regression   | 0              | 1 (100)     |
| Persistent   | 0              | 1 (100)     |
| Progression  | 8 (100)        | 6 (85.7)    |
| **EH**       | **EHA**        | **EC**      |
| n=7          | n=3            | n=7         |
| Regression   | 1 (14.3)       | 0           |
| Persistent   | 0              | 3 (42.9)    |
| Progression  | 6 (85.7)       | 4 (57.1)    |
| **EH**       | **EHA**        | **EC**      |
| n=9          | n=14           | n=8         |
| Regression   | 2              | 3 (21.4)    |
| Persistent   | 2 (22.2)       | 2 (25)      |
| Progression  | 6 (66.6)       | 3 (37.5)    |

Abbreviations: EH, endometrial hyperplasia; EHA, endometrial hyperplasia with atypia; EC, endometrial carcinoma.

4. Discussion

The preservation of fertility among women with EH/EHA/EC has been extensively studied. This includes using progesterone and/or LNG-IUS for treatment until desired fertility has been attained and hysterectomy can be performed. Response rates have varied between 58% and 100% (Gotlieb et al., 2003; Gallos et al., 2012).

Although the majority of the literature available has reported response rates following LNG-IUS without addressing stratification of BMI, a small amount of literature has looked at the treatment of EH/EHA/EC specifically in the obese population. Currently in the United States, 75.1% of adults have a BMI ≥ 25 kg/m², 35.7% have a BMI > 30 kg/m² and 6.3% have a BMI > 40 kg/m² (Jensen et al., 2014). Our series mimics these attributes with the average BMI being 42.5 ± 13.5 kg/m². As weight increases, not only are medical comorbidities more prevalent (Arem & Irwin, 2013), but surgical morbidity and mortality increase as well (Walker et al., 2009). Patients often have diabetes, cardiac disease, and other processes that affect intra-operative difficulty and post-operative recovery. Further, Calle et al. have shown that women with a BMI of at least 40 kg/m² were 6.25 (CI 3.75-10.42) times more likely to die from uterine cancer (Calle et al., 2003). Several studies have shown an increased risk of EH/EHA/EC in the obese population, as well as their increased risk of morbidity and mortality from standard treatment (Calle et al., 2003; Renehan et al., 2008). Our series shows that higher BMI was associated with a higher likelihood of EHA/EC compared to EH and further, higher BMI was associated with an increased risk of progression.

In this series, the use of LNG-IUS therapy in place of hysterectomy was performed predominantly because of poor surgical candidacy. Given the importance in lack of progression during medical optimization prior to surgery or during treatment in those that cannot undergo surgery, no progression compared to progression was compared. We found that the use of LNG-IUS resulted in no progression in 88.3% of all patients. Stratifying by BMI, no progression was found in 100% of patients with BMI < 30 kg/m² and BMI 30–40 kg/m² groups. Alternatively, in the BMI > 40 kg/m² group, 77.4% experienced no progression. Progression occurred only in the BMI > 40 kg/m² group. This data suggests that LNG-IUS therapy may not be as effective at preventing progression with increasing BMI, particularly in patients with class III obesity.

The use of exogenous progesterone compared to LNG-IUS in the treatment of EH/EHA/EC has also been studied with varying regression rates (Hubbs et al., 2013; Gallos et al., 2013; Kim et al., 2011). Some data suggests that LNG-IUS achieves higher regression rates compared to exogenous progesterone (66% compared to 92%) (Gallos et al., 2013). Few studies have looked at concurrent progesterone and LNG-IUS. In our study, 36.2% of patients received concurrent progesterone and was distributed equally in each BMI sub-category. Adjusting for concurrent progesterone, BMI remained associated with progression, therefore suggesting that combined systemic plus local progesterone may remain less effective in patients with higher BMI.

We acknowledge that there are limitations to this study, however, it was meant predominantly as exploratory using a small number of retrospectively collected cases. Even though from a single institution, there are multiple centers with different practice patterns. Further, this enabled consistent pathology reporting between initial and follow-up specimens. We also acknowledge that the median re-sampling time for this cohort was 4 months (IQR 3.2-6.4) and that there is evidence to suggest that optimal response time may be 6–12 months. Therefore,
these patients may still respond if they were to be re-sampled further from placement of LNG-IUS. In 2009, there was not an accepted standard for the length of time between LNG-IUS and follow-up endometrial biopsy and these results reflect this deviation from today’s standard.

In the future, we will await the results of the current clinical trial studying the result of oral progesterone versus oral progesterone and LNG-IUG. Further, a randomized clinical trial of LNG-IUS versus LNG-IUS with oral progesterone would be most beneficial at further elucidating the role of LNG-IUS therapy specifically in obese patients. Alternately, given more progression in the most obese patients, additional therapies or therapy combinations should be investigated. It may also be pertinent to study serial endometrial sampling in this subgroup to further elucidate the role of BMI on disease progression.

In conclusion, this study was meant to be a descriptive case series analysis of the role of LNG-IUS in obese women with EH/EHA/EC. The results reveal that in patients with BMIs 40+ kg/m², treatment outcomes using LNG-IUS were more varied, and were more likely to experience disease progression compared to patients with lower BMI. We further suggest that regardless of initial diagnosis or concurrent progesterone therapy with LNG-IUS, higher BMI is associated with progression of disease.

Author contribution

Ashley Graul was the primary researcher who was responsible for the final manuscript, data collection oversight, initial data analysis and submission with the oversight of Sarah Kim as the Principal Investigator. Elise Wilson contributed to a majority of the data collection as well as initial drafts of the manuscript. Emily Ko contributed to the development of the clinical question as well as manuscript revisions and critique. Ashley Haggerty was also involved in assisting in data collection technique as well as manuscript revision and critique. Helen Reed contributed to initial data collection. Nathanael Koelper is a statistician who confirmed appropriate statistical analysis was used. All authors have approved the final manuscript.

Disclosures

All authors listed have approved the final manuscript.

Dr. Graul reports a T32 grant from NIH Reproductive Epidemiology during the conduct of the study. There is no conflict of interest for all other authors in this study.

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