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ORIGINAL ARTICLE

# Audit of waiting time-to-treatment of atypical endometrial hyperplasia

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**Background:** Atypical endometrial hyperplasia (AEH) is the precursor lesion in endometrial carcinoma, the most common gynaecological malignancy in New Zealand, with inequities in disease burden and outcome for Māori and Pacific women.

**Aims:** In women diagnosed with AEH at two hospitals, to audit five standards of care for surgical management and time-to-treatment, and identify variation in care by ethnicity and other factors.

**Materials and Methods:** Demographic, referral, diagnostic and treatment characteristics were collected for women with a new AEH diagnosis between 1/1/2019 and 31/12/2020. Surgical management and time-to-treatment were audited against Royal College of Obstetricians and Gynaecologists and New Zealand Ministry of Health Faster Cancer Treatment recommendations.

**Results:** Of 124 participants, 60% were Pacific, 86% premenopausal, and 80% had obesity. For 55 women managed surgically, surgical standards of care were met. There were delays between referral, diagnosis and treatment – only 18% and 56% of women met the 62-day (referral to treatment) and 31-day (decision-to-treat to treatment) targets, respectively. Wait times were prolonged for women who had dilation and curettage (vs pipelle), magnetic resonance imaging (MRI) (vs no MRI), and surgery (vs medical management). Ethnic disparities were not identified for any standard.

**Discussion:** Delays to treatment were found throughout women's journeys. Hospital services can streamline their clinical pathways for women referred for abnormal uterine bleeding, flagging obesity as a high suspicion for cancer indicator, increasing access to endometrial sampling in primary care and establishing 'one-stop-shop' outpatient assessment with empiric initiation of intrauterine progestogen.

**KEYWORDS**

atypical endometrial hyperplasia, endometrial carcinoma, faster cancer treatment, surgery, wait time

## INTRODUCTION

Atypical endometrial hyperplasia (AEH) is the premalignant precursor lesion to endometrial cancer (EC) and is reported to coexist with EC in up to 43% of post-hysterectomy specimens.[1,2] AEH is characterised by a focus on endometrial glands which are crowded, with a gland-to-stroma ratio of over 50%, in a focus of over 1 mm in linear dimension, with glands with cytologic demarcation from background glands.[3] Pathogenesis is thought to be mostly from chronic unopposed overexposure to oestrogen.[4] EC was previously considered to be a disease of postmenopausal women, but alongside the global rise in obesity, the incidence of EC has risen, now being diagnosed more commonly in younger premenopausal women.[4] Raised body mass index (BMI) is a consistent and leading risk factor for endometrial hyperplasia, with a dose–response relationship and odds ratio of five for a BMI ≥ 30 kg/m$^2$.[5]

There are no Australasian guidelines for AEH management. The Royal College of Obstetricians and Gynaecologists (RCOG) AEH guideline recommends total hysterectomy, with additional bilateral salpingoophorectomy (BSO) in postmenopausal women, due to the risks of either malignancy progression or coexistence.[2] A laparoscopic approach to hysterectomy is recommended over an abdominal approach as it is associated with a shorter hospital stay, less postoperative pain and quicker recovery.[2] If fertility preservation is desired, or surgical contraindications exist, non-surgical management options consist of the levonorgestrel-releasing intrauterine system (LNG-IUS) as first-line, and high-dose oral progestogens as an alternative.[2] The efficacy of medical therapy on endometrial regression is reported at 85–92% for LNG-IUS and 72% for non-intrauterine progestogens.[6]

In Aotearoa New Zealand (NZ), the burden of EC has significant inequity for Māori and Pacific women, with a relative risk of 2.5 and 5.1 respectively, compared to non-Māori non-Pacific women.[7] While Pacific women have a high prevalence of risk factors, disease-specific survival is worse for Pacific and Māori women.[7] We sought to explore potential contributors to these ethnic disparities, such as delays in diagnosis and treatment of AEH, or suboptimal surgery, by auditing wait times from referral to treatment, and standards of surgical care received, at two NZ hospitals.

## MATERIALS AND METHODS

### Population

The population was women with a new diagnosis of biopsy-proven AEH between 1 January 2019 and 31 December 2021, under the care of gynaecology. The two hospitals are large urban tertiary teaching hospitals, with differences being that one provides the regional gynaecology-oncology service, and the other serves a population with a higher proportion of Māori and Pacific peoples, and of socioeconomic deprivation.[8,9] Women were included if they had a report of 'at least hyperplasia' but did not meet EC diagnostic criteria. Exclusions: AEH or EC diagnosis prior to the study period, non-resident of District Health Boards (DHBs) where study took place, received treatment under a private gynaecologist, or had coexisting EC at time of biopsy.

### Case identification

Potential cases were identified using a pathology database search of pathology reports. At one hospital, the term 'endometrium' was used, and pathology reports were screened by a pathologist to confirm an AEH diagnosis. This list was cross-referenced with a list held by the gynaecology-oncology nurse specialist of women with known AEH. At the other hospital, 'atypical hyperplasia' and equivalent search terms were used. Different search terms were used due to different, unlinked, pathology databases across the two hospitals. Reports were screened by two authors to confirm diagnosis and eligibility.

### Data collection

Electronic clinical records were reviewed to collect the following variables. Demographics: age at biopsy, ethnicity,[10] BMI, menopausal status, parity, neighbourhood deprivation index (based upon address).[11] Referral: indication, date of referral acceptance (or discharge date if acutely admitted, or date of last outpatient clinic appointment if undergoing endometrial sampling for a non-AEH pathology and subsequently diagnosed with AEH), grading of referral (either high suspicion of cancer (HSC) or non-HSC). Diagnostics: location and method of endometrial sampling, date of biopsy report, date the diagnosis was discussed with the patient. Treatment: type (medical vs surgical), date the decision for treatment was made (if no documented date of treatment decision was made, the date of treatment was used), date treatment received, surgery type (total vs subtotal hysterectomy, with or without BSO) and approach (laparoscopy or laparotomy), surgical histology report.

### Audit standards

Standards 1–3 are RCOG AEH treatment recommendations.[2]

1. Women with AEH should undergo total hysterectomy (as opposed to subtotal).[2]

Target: 100%

2. Postmenopausal women should have bilateral salpingoophorectomy together with total hysterectomy.[2]

Target: 100%

Women with previous gynaecological surgery (eg a unilateral salpingectomy), but had the remaining structures removed, were classified as bilateral salpingoophorectomy.

3. A laparoscopic approach is preferable to an abdominal approach.[2]

Target: > 50%.

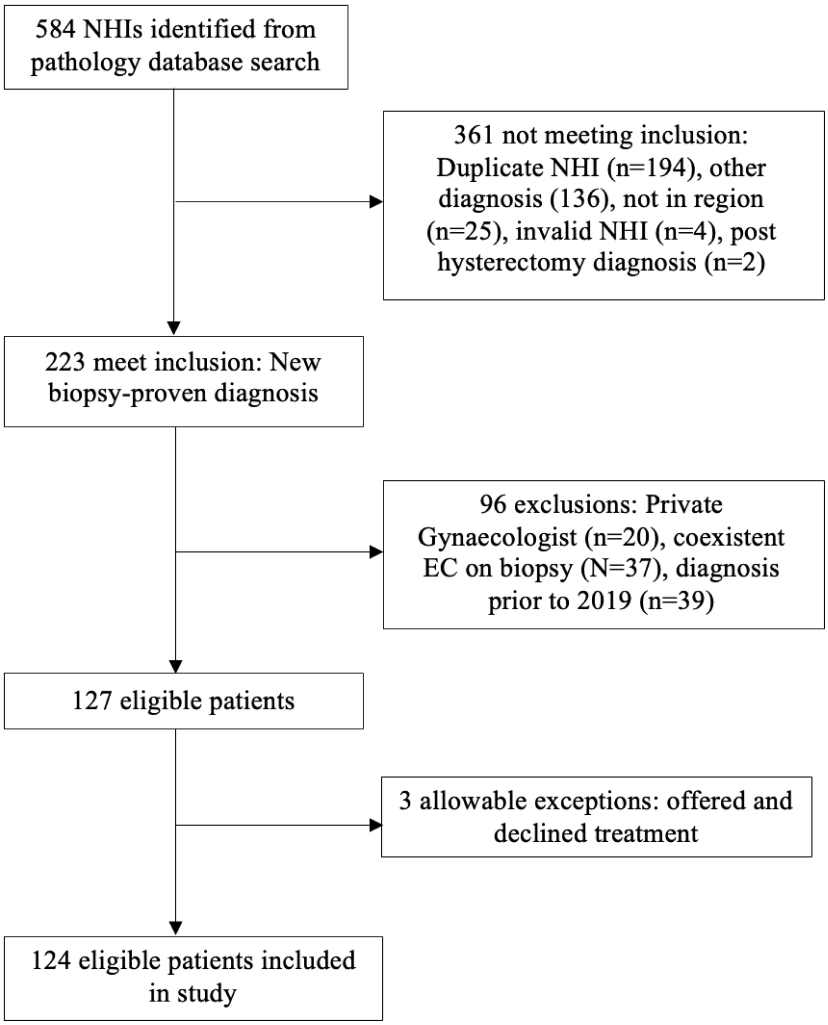


**FIGURE 1** Selection of the study population. EC, endometrial cancer; NHI, national health identifier.

As there are no national or international guidelines for recommended AEH surgical wait times, and given the high rate of coexistent malignancy, we devised wait time standards for AEH treatment based on the NZ Ministry of Health Faster Cancer Treatment (MoH FCT) 62-day (referral to treatment) and 31-day (decision-to-treat to treatment) indicators.[12] Standards 4 and 5 are modified versions of the MoH FCT guidelines.[12] Allowable exceptions for Standards 4 and 5 include women who were offered treatment and declined.

The original MoH 62-day indicator states 'patients referred urgently with a high suspicion of cancer receive their first treatment (or other management) within 62 days of the referral being received by the hospital.'[12] This was adapted to the following.

4. Women receive treatment within 62 days of the referral being accepted by the gynaecology service, regardless of the referral grading.

Target: 90%

The original MoH 31-day indicator states. 'patients with a confirmed cancer diagnosis receive their first cancer treatment (or other management) within 31 days of a decision-to-treat'. [12] This was adapted to the following.

5. Women with a confirmed AEH diagnosis receive treatment within 31 days of a decision-to-treat.

Target: 90%

'Treatment' refers to treatment that was continued long-term. Thus, for women who had surgery who had interim progestogens had their treatment date as 'date of surgery.' Women who had LNG-IUS who had interim oral progestogens had their treatment date as day of LNG-IUS insertion. LNG-IUS or appropriate dose oral progestogen therapy initiated prior to diagnosis, and decided to continue, was classified as zero days from decision-to-treat until treatment (31-day indicator). Oral progestogen was considered treatment at a minimum continual dosage of medroxyprogesterone 10–20 mg/day, norethisterone 10–15 mg/day or megestrol acetate 160 mg/day.[2, 13] Women awaiting surgery as at 15 June 2021 and did not meet the waiting time indicators, had this date entered as 'date of surgery.'

The variables of DHB of residence, ethnicity, grading of referral, biopsy type, and treatment type were further analysed as they had a potential to influence outcome. Wait times were analysed between time points to identify delays within the AEH management pathway.

**TABLE 1** Characteristics of participants

| Characteristic | *N* = 124 |
|---|---|
| Age, years | |
| Mean ± SD | 43 ± 12 |
| Age group, years | |
| <30 | 20 (16%) |
| 31–40 | 35 (28%) |
| 41–50 | 34 (27%) |
| 51–60 | 24 (19%) |
| >60 | 11 (9%) |
| Body mass index, kg/m$^2$ | |
| Mean ± SD | 43 ± 12 |
| Body mass index group | |
| Normal, 18.5–24.9 kg/m$^2$ | 6 (5%) |
| Overweight, 25–29.9 kg/m$^2$ | 10 (8%) |
| Obese, 30 kg/m$^2$ and over | 107 (86%) |
| Class 1–30 to <35 | 9 (8%) |
| Class 2–35 to <40 | 24 (22%) |
| Class 3–40 or higher | 74 (69%) |
| Ethnicity | |
| European | 10 (8%) |
| Māori | 17 (14%) |
| Pacific peoples | 74 (60%) |
| Asian | 21 (17%) |
| Middle Eastern/Latin American/African | 2 (2%) |
| Deprivation group | |
| 1–2, low deprivation | 6 (5%) |
| 3–4 | 11 (9%) |
| 5–6 | 14 (11%) |
| 7–8 | 25 (20%) |
| 9–10, high deprivation | 63 (51%) |
| Unknown | 5 (4%) |
| Parity | |
| Nulliparous | 55 (45%) |
| Multiparous | 68 (55%) |
| Menopausal status | |
| Premenopausal | 93 (75%) |
| Postmenopausal | 30 (24%) |
| District Health Board | |
| Hospital 1 | 75 (60%) |
| Hospital 2 | 49 (40%) |

Data analysis was performed using Prism 9 (GraphPad). Baseline demographic characteristics were tested for normality and were presented as mean (±SD), median (interquartile range (IQR)) as appropriate, or percentages. Audit standards were presented as the number and percentage of women meeting the standard. Comparisons were made using *T*-test, Mann–Whitney or $\chi^2$ test as appropriate. A *P*-value of <0.05 was considered statistically significant.

## Ethics

Ethics approval was obtained from Auckland Health Research Ethics Committee (AH22286). Locality approval was obtained from both hospitals; approvals available on request.

# RESULTS

We identified 124 women to be eligible in this study (Fig. 1). Mean age was 43 years, ranging from 21 to 81 years, and mean BMI was 43 kg/m$^2$. Most women were Pacific (60%), premenopausal (75%), and lived in high deprivation areas (71%) (Table 1).

Initial presentation for 54% (*n* = 67) of women was heavy menstrual bleeding, and 23% (*n* = 29) postmenopausal bleeding. With respect to referrals, 31% (*n* = 38) were flagged as HSC, 44% (*n* = 54) were not, and the remaining 26% (*n* = 32) were not formally referred and missed the opportunity for being flagged. Diagnosis was via dilatation and curettage for 62% (77) and pipelle for 33% (41), with 86% (*n* = 107) completed in an outpatient setting, 12% (*n* = 15) inpatient and 2% (*n* = 2) in primary care. Magnetic resonance imaging (MRI) was completed for 53% (*n* = 66). Treatment for 47% of women was surgery (completed *n* = 55, awaiting *n* = 3), 44% (*n* = 54) had LNG-IUS and 10% (*n* = 12) oral progestogens. Of the surgical candidates, 62% (*n* = 36) were on preoperative progestogen.

Of the 55 women who had surgery completed, postoperative histology was AEH for 38% (*n* = 21), coexisting EC for 38% (*n* = 21) (all International Federation of Gynecology and Obstetrics Stage 1A), and benign for 24% (*n* = 13). For these 13 women, eight were premenopausal and 12 were on preoperative progestogen.

All three surgical audit standards of care were met, with 100% of women having a total hysterectomy (*n* = 55), all postmenopausal women having a bilateral salpingoophorectomy (*n* = 21), and 76% (*n* = 42) of surgeries performed laparoscopically.

The two time-to-treatment standards were not met. For Standard 4, 22 women (18%) had their treatment within 62 days of referral; median wait time (Fig. 2) was 151 days (IQR 76–252 days), with a maximum of 1003 days. For Standard 5, 70 women (56%) had their treatment within 31 days of decision-to-treat; median wait time (Fig. 2) was 22 days (IQR 0–98 days), with a maximum of 506 days.

Further analysis found no difference in time-to-treatment standards by ethnicity when comparing Māori and Pacific women to non-Māori non-Pacific women (62 day indicator: Māori 4 (24%); Pacific 11 (15%) vs Non-Māori non-Pacific 7 (21%); 31 day indicator: Māori 10 (59%); Pacific 44 (59%) vs Non-Māori non-Pacific 16 (48%)). Nor was an effect seen for grading of referral (62 day indicator: HSC 6 (16%) vs non-HSC 6 (11%); 31 day indicator: HSC 17 (45%) vs non-HSC 31 (57%)) or type of biopsy (61 day indicator: dilatation and curettage 12 (16%) vs pipelle 9 (22%); 31 day indicator: dilatation and curettage 46 (60%) vs pipelle 21 (51%)).

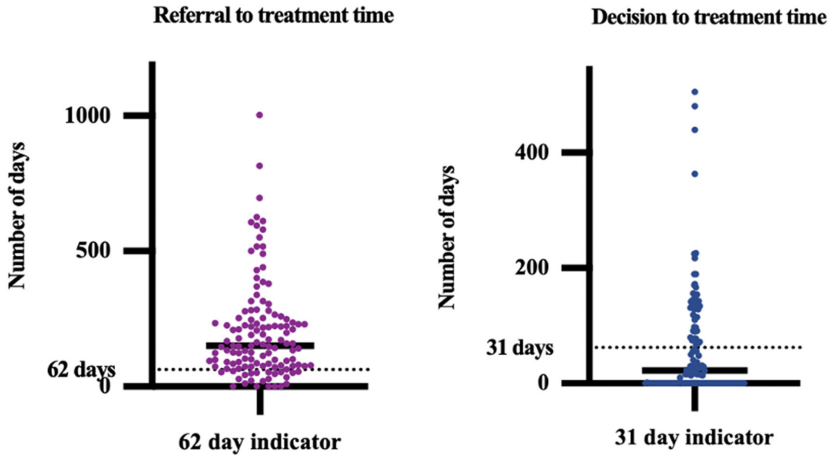


**FIGURE 2** Time to treatment.

Women managed medically were more likely to meet the 62-day (medical 19 (29%) vs surgical 3 (5%); $P = 0.0006$) and 31-day (medical 52 (82%) vs surgical 16 (28%); $P < 0.0001$) indicators. Women at one hospital were less likely than at the other hospital to meet the 62-day (8 (11%) vs 14 (29%); $P = 0.01$) and 31-day (33 (44%) vs 37 (76%); $P = 0.05$) indicators. Women at one hospital were less likely to be managed medically ($P = 0.004$).

Figure 3 breaks down the patient journey from referral to treatment. A prolonged wait time was found from referral acceptance to diagnosis discussion, including a median of 41 days (9–120) from referral to biopsy and 27 days (15–41) from biopsy to diagnosis. Once the diagnosis was discussed, wait times to treatment were not prolonged.

## DISCUSSION

The majority of women diagnosed with AEH in this study were premenopausal and referred for heavy menstrual bleeding, with most having obesity and of Pacific ethnicity. The three audit standards that reflected clinical care were met, suggesting that once under secondary gynaecology services, women were appropriately managed based on international clinical practice guidelines. The two devised audit standards of wait times, which relate to processes and pathways of care, were not met; only 22 out of 124 women received treatment within 62 days of referral being accepted. Ethnic disparities were not found in any audit standard.

We were able to measure elements of the timeline from referral to treatment, and analysis suggests that the shortest timeline occurs where a pipelle biopsy is performed (either in the community or at first attendance to gynaecology clinic), and is not delayed by referral for dilatation and curettage, which had a median delay of 41 days or for additional investigations such as MRI, which had a median delay of 38 days. It is not clear that dilatation and curettage or MRI has additional benefit in the workup of women presenting with abnormal uterine bleeding,[2,14] thus could be made selective rather than routine.

Local hospital clinical guidelines and grading of referrals for abnormal uterine bleeding need to be adapted to the population they serve. The two sites within this study have demographic differences; one has a higher proportion of Māori, Pacific and people living in socioeconomic deprivation.[8,9] Primary Health Pathways reflect this high-risk population, whereby credentialled general practitioners have funding to complete pipelle endometrial sampling in the community.[15] Despite this, only two women in this study had sampling by a general practitioner. As a large proportion of wait time is bypassed with sampling in primary care, collaboration with community providers to assess barriers and enablers to uptake is an area of future research. Moreover, secondary services could consider flagging as HSC those women with obesity at the time of referral, regardless of age or other risk factors.

Alternatively, a shortened timeline can be achieved by empiric initiation of progestogen at the time of biopsy, where a diagnosis of AEH is suspected based on risk factors. Women who had medical treatment started simultaneously met the 31-day indicator. In practice, medical management could be a bridging treatment until surgery, or if appropriate, definitive treatment. If the objective is a shortened timeline, this strategy could be quite easily implemented within secondary gynaecology services, and could save resources. Future directions may include increasing the availability of a hospital-based outpatient 'one-stop-shop' approach to diagnosis and initial treatment, incorporating multi-disciplinary weight loss strategies. The role of weight-loss surgery might be particularly relevant in this population and is yet to be studied.

Ultimately, the diagnosis of AEH was almost exclusively in premenopausal women with obesity. This new demographic is challenging gynaecologists to reconsider medical management as first-line treatment instead of the gold standard of surgery, either as fertility-sparing or as risk avoidance. The evidence in support of progestogen therapy effectiveness in AEH is limited. The 2021 feMMe study, which included women with AEH or early EC and

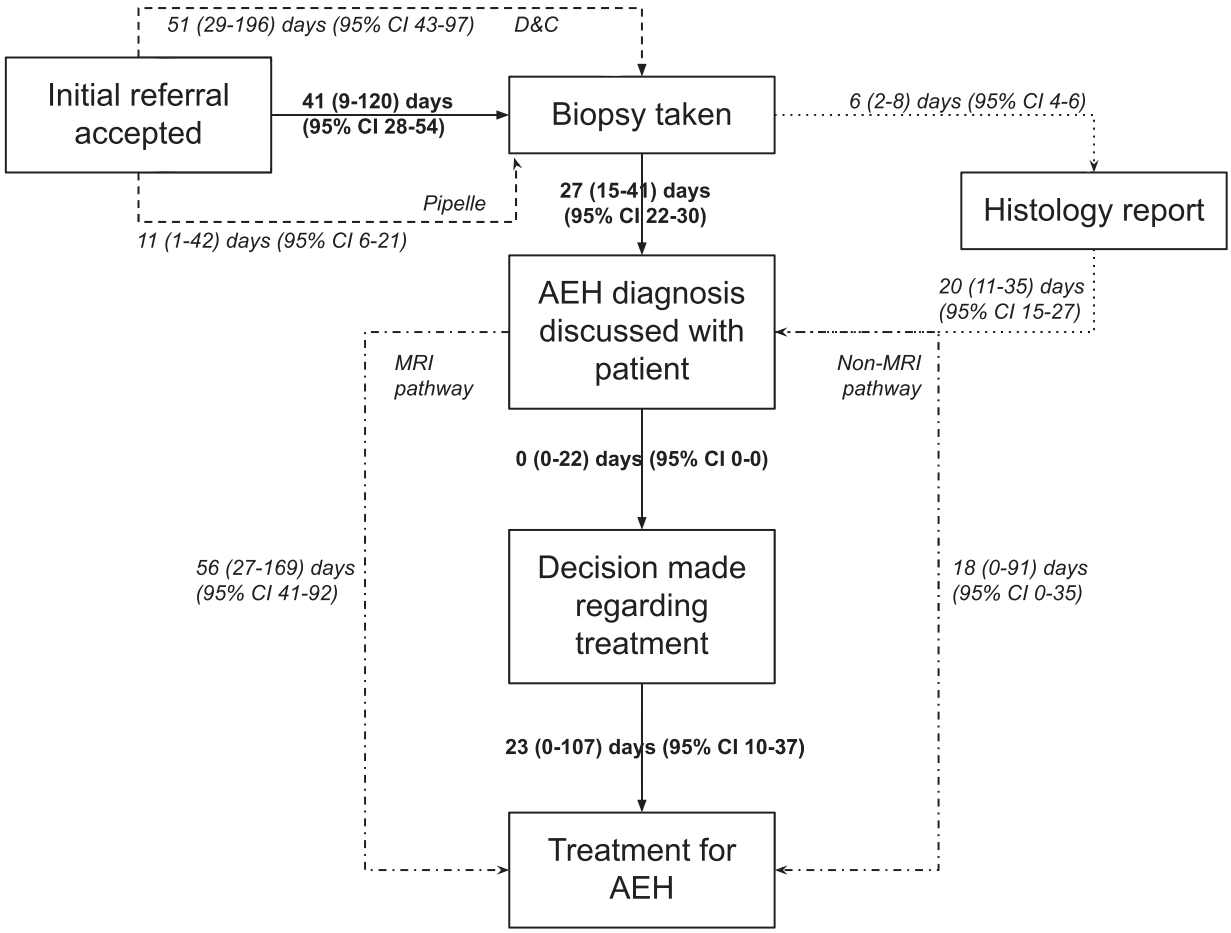


**FIGURE 3** Patient journey from referral to treatment, median wait times. AEH, atypical endometrial hyperplasia; CI, confidence interval; D&C, dilation and curettage; MRI, magnetic resonance imaging

a mean BMI of 48 kg/m$^2$, similar to our population, found a response rate with Mirena IUS treatment of 61%, with no impact of BMI,[16] despite previous literature indicating that obesity may be associated with a higher risk of failure to regress or relapse.[17,18] Alongside this is the requirement for ongoing endometrial surveillance,[2] which may create unintended inequities in a population of women with high socioeconomic deprivation. With the identified wait times for access to endometrial sampling identified in this study, further research into the effectiveness of medical treatment and long-term follow up of women with AEH is warranted. Development of a clinical practice guideline on the management of AEH in the Australasian population is needed.

This study is limited by the absence of NZ specific guidelines for any of our standards. The NZ MoH guidelines were adapted for this audit, but relate to the management of confirmed malignancy. Data were retrospective, thus dependent on accurate coding. COVID-19 restrictions may have affected clinical services during parts of the study period; however, in our region, access to services for the diagnosis and treatment of people with HSC (including AEH) was prioritised and we had minimal disruption. A sensitivity analysis between 2019 and 2020 did not detect a difference in treatment times. Moreover, 'treatment' end-points prioritising surgery over LNG-IUS over oral progestogens means patients on medical therapy having surgery appear to have longer wait times. Women with progestogen prior to diagnosis have a wait time of 'zero days' – although the LNG-IUS may have been for symptom control, making wait times appear shorter. Finally, no information was collected on symptom duration, so we were unable to determine patient and/or clinician delays prior to referral.

In conclusion, surgical standards of care were met; however, wait times to treatment were prolonged, with no variation by ethnicity. The use of progestogens, started at the time of endometrial biopsy, while awaiting surgery or as definitive treatment, was found to reduce wait times. The majority of delay was prior to diagnosis, which may indicate barriers in access to gynaecology clinics and to endometrial sampling in the community.

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