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Complete pathological response following levonorgestrel intrauterine device in clinically stage 1 endometrial adenocarcinoma: Results of a randomized clinical trial

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HIGHLIGHTS

- LNG-IUD is commonly used to treat patients with EHA or EAC.
- Complete response rates were 43% and 82%, for EAC and EHA, respectively.
- Pathological complete response was 61% for LNG-IUD alone.
- Pathological complete response was 67% for LNG-IUD plus weight loss.
- Pathological complete response was 57% for LNG-IUD plus metformin.

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ABSTRACT

Purpose. Intrauterine levonorgestrel (LNG-IUD) is used to treat patients with endometrial adenocarcinoma (EAC) and endometrial hyperplasia with atypia (EHA) but limited evidence is available on its effectiveness. The study determined the extent to which LNG-IUD with or without metformin (M) or weight loss (WL) achieves a pathological complete response (pCR) in patients with EAC or EHA.

Patients and methods. This phase II randomized controlled clinical trial enrolled patients with histologically confirmed, clinically stage 1 FIGO grade 1 EAC or EHA; a body mass index > 30 kg/m2; a depth of myometrial invasion of less than 50% on MRI; a serum CA125 ≤ 30 U/mL. All patients received LNG-IUD and were randomized

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Progestin/progesterone
Levonorgestrel intrauterine device
Metformin
Fertility preservation
Weight loss
Physical activity

to observation (OBS), M (500 mg orally twice daily), or WL (pooled analysis). The primary outcome measure was the proportion of patients developing a pCR (defined as absence of any evidence of EAC or EHA) after 6 months.

Results. From December 2012 to October 2019, 165 patients were enrolled and 154 completed the 6-months follow up. Women had a mean age of 53 years, and a mean BMI of 48 kg/m^2. Ninety-six patients were diagnosed with EAC (58%) and 69 patients with EHA (42%). Thirty-five participants were randomized to OBS, 36 to WL and 47 to M (10 patients were withdrawn). After 6 months the rate of pCR was 61% (95% CI 42% to 77%) for OBS, 67% (95% CI 48% to 82%) for WL and 57% (95% CI 41% to 72%) for M. Across the three treatment groups, the pCR was 82% and 43% for EHA and EAC, respectively.

Conclusion. Complete response rates at 6 months were encouraging for patients with EAC and EHA across the three groups.

Trial registration. U.S. National Library of Medicine, NCT01686126.

1. Introduction

Endometrial adenocarcinoma (EAC) is common, with an estimated global incidence of 382,069 new cases each year [1]. The growing incidence of EAC is likely due to ageing populations, and the increasing prevalence of obesity, which is a recognized risk factor for EAC and is estimated to cause at least 41% of new EACs [2–5]. Obesity is associated with low-grade EAC developing through endometrial hyperplasia with atypia (EHA).

Current standard treatment for EAC is total hysterectomy and bilateral salpingo-oophorectomy (THBSO) with or without surgical staging [6]. While surgical treatment is generally safe and effective, two groups of patients are poorly served by this strategy. Firstly, young women who wish to preserve childbearing capacity [7–9]. For these women, a THBSO will result in irrevocable loss of fertility [10]. Secondly, elderly, morbidly obese women and those with multiple medical comorbidities significantly increasing their risk for procedure-related adverse events, prolonged hospital stay, protracted recovery and high cost, even with enhanced postoperative care [11–13]. Therefore, professional societies, clinicians, and patients identified the development of effective, non-surgical treatments a research priority [14,15].

With the availability of intrauterine levonorgestrel (LNG-IUD), delivering progestins directly into the endometrial cavity without the adverse effects from systemic progestins became feasible [16]. Despite a lack of high-level evidence on the effectiveness of LNG-IUD, it is offered to EAC patients as a primary treatment option [17,18].

Metformin, has shown antiproliferative activity to reduce endometrial cancer cell growth in vitro [19–22]. Epidemiological evidence suggested it is associated with improved survival in women diagnosed with EAC [23–25]. Ongoing trials will determine the effectiveness of metformin in window of opportunity studies in EAC [26–28].

Obesity is potentially reversible through behavior-based weight loss interventions with or without weight loss medications [29] and while it reduces the risk of EAC [30] and increases overall survival in EAC patients [31], evidence that weight loss improves the likelihood of response to LNG-IUD is lacking.

The present trial investigated the effectiveness of LNG-IUD and whether metformin (M) or a weight loss (WL) intervention in addition to LNG-IUD improves the response rate in patients with EAC or EHA.

2. Methods

2.1. Trial design

The feMMe trial was an open label, three-arm randomized phase II clinical trial (NCT01686126). The initial and most recent trial protocol version are provided in Supplement 1. Ethics approvals were obtained from six Human Research Ethics Committees (HREC) in Australia and New Zealand and informed consent was obtained prior to randomization.

2.2. Participants

FeMMe trial methodology was reported previously [32,33]. In brief, the feMMe trial enrolled females over the age of 18 years with histologically confirmed EHA or FIGO grade 1 endometrioid EAC apparently confined to the uterus and with a BMI >30 kg/m2, who wished to maintain fertility or who were at high risk of surgical complications due to severe medical co-morbidities. A BMI of >30 kg/m2 was selected as previous data showed that these patients had increased risk of surgical complications when undergoing total hysterectomy [34]. Patients had to have a computed tomography or magnetic resonance imaging scan of the pelvis, abdomen and chest (chest X-ray was permitted) to confirm the absence of extrauterine disease. Patients with EAC had an MRI scan showing myometrial invasion of not more than 50%. Patients had to have a serum CA125 ≤ 30 U/mL at baseline [32,33]. Patients were considered ineligible if they had: ECOG score > 3; FIGO grade 2 or 3 endometrial cancer; histological cell type other than endometrioid; evidence of extrauterine disease on medical imaging; or received oral or intrauterine progestins prior to 12 weeks before planned randomization.

2.3. Interventions

All participants had a LNG-IUD inserted into the uterine cavity, releasing 52 mg of levonorgestrel at a rate of 20 microgram/24 h. Patients were randomly assigned to (i) Observation (OBS); (ii) weight loss intervention (WL); or (iii) oral metformin (M). Participants in the WL arm were provided with a voucher for a comprehensive six months subscription to Weight Watchers®, providing unlimited use of face-to-face and online support standardized dietary intervention [35]. Patients were encouraged to lose 7% body weight by 6 months and called monthly to assess adherence to the WL program, and encouragement to increase its active use. This was selected based on results from the Diabetes Intervention trial, which provided evidence that weight loss of 7% body weight induces a large biological effect (e.g. reduces incidence of diabetes by 58% [36], and incidence of hypertension by 26%) [37]. Participants assigned to the M arm had 500 mg of metformin orally, twice daily with meals (self-administered). This could be reduced to 250 mg tablets twice daily if the starting dose was not tolerated.

Patients had a HD&C or endometrial sampling at 3 and 6 months after randomization. Patients who developed progressive disease at 3 months were removed from the trial and treated as clinically appropriate. The endometrial sample taken at 6 months was used to assess the response to intervention. Other data collected at baseline included a detailed medical history including Charlson comorbidity score; sociodemographic characteristics; questionnaires on health-related quality of life, health services use, pelvic floor symptoms and dietary intake. These were repeated at 3 and 6 months.

2.4. Outcomes

The primary outcome measure was the proportion of patients with pathological complete response pCR at six months from randomization. A pCR was defined as the absence of any evidence of EAC or EHA. Partial response was defined for EAC patients as a remission to EHA. For patients with EAC or EHA, stable disease was defined as no change from the histological diagnosis at baseline. Progressive disease was defined for patients with EHA if they progressed to EAC from baseline at three or six months. For EAC patients, progressive disease was defined if they progressed to FIGO grade 2 or 3 EAC or to high-risk cell type. Central histopathology review was performed by two gynecological pathologists, blinded to treatment arm. The pathologists recorded presence of EHA, EAC, simple endometrial hyperplasia or absence of any pathology. Discordances between the pathologists were resolved by discussion until consensus was achieved. This histopathological information was then de-identified and submitted to two gynecological oncologists who adjudicated whether the patient developed a pCR, partial response, stable disease or progressive disease at 3 and 6 months, respectively.

Secondary outcomes included compliance with the interventions, body composition (body weight, body mass index, waist and hip circumference); adverse events, and factors predictive of pCR. Compliance with the intervention was determined at 3 and 6 months. Definitions of compliance are detailed in Supplement 1.0. Patients who expelled the LNG-IUD were withdrawn from the study. Data on adverse events (AEs) were recorded at three and six months using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). Causality of AEs was assessed by the sites and classified as not/unlikely/possibly/probably/definitely related to the intervention.

2.5. Sample size

A meta-analysis, based on 12 studies, suggested that the average pCR rate was 68% (95% CI: 45%–86%) [38] and response rates ranged from 50% to 100% although the majority of the studies in the review were small (ranging from 10 to 20 patients) and non-randomized. Based on this data, the anticipated pCR rate was estimated to be closer to the lower confidence limit of 45%. Based on this assumption, an OBS:WL:M randomization of 3:3:5 was chosen for pragmatic considerations (i.e., recruitment) and to increase the numbers of patients in the M group in the event of high non-adherence in the WL cohort with the randomization minimizing selection bias. Additionally, in the event of a pCR within the observation group higher than 45%, the study sample size would also have at least 80% power (95% confidence) to rule out a 60% observation only pCR in favor of a 75% in the M or WL groups; or alternatively also >80% power to rule out a 65% pCR in favor of 80% pCR rate [39].

2.6. Changes to protocol

Protocol version 2.0 (September 2012) randomized participants into two arms (OBS vs. M) was submitted prior to initial HREC approval being granted. Only 1 patient was enrolled before approval for Version 3, which introduced the WL intervention when funding was granted, and increased planned sample size from 111 to 165. Subsequent protocol changes removed practical barriers for enrolment: screening window extended from 30 to 60 days (version 4, May 2013); 90 days (version 5, August 2013); patients allowed to have LNG-IUD inserted 6 weeks (version 5, August 2013); 8 weeks (version 7, March 2016); 12 weeks (version 8, February 2017) prior to randomization. Version 8 (February 2017) allowed use of oral progestins within 12 weeks before randomization to control heavy vaginal bleeding.

2.7. Randomization

Patients who met all eligibility criteria and provided written informed consent were centrally randomized through interactive Voice Response System (NHMRC Clinical Trials Centre, Sydney, Australia). All participants received LNG-IUD and were additionally allocated to either i) OBS; ii) WL; or iii) M in 3:3:5 ratio. Randomization was stratified by diagnosis (EAC versus EHA); BMI (30 kg/m^2, 40 kg/m^2, ≥40 kg/m^2); menopausal status; and treatment site. Women with contraindications to M were randomized to OBS versus WL on 1:1 ratio. Similarly, women not eligible for WL were randomized into OBS versus M on 3:5 ratio. The same stratification factors were used as in the three-arm study.

2.8. Statistical methods

Given the pragmatic randomization scheme, the primary analysis population was pre-specified in the statistical analysis plan to comprise of participants randomized into the three-arm trial, as well as participants who were randomized into each of the two-arm trials because they were contraindicated to take M or WL treatment. Participants who were already taking M prior to screening for the trial were not considered part of primary analysis (see Fig. 1).

Sensitivity analysis combined the three studies into a four-arm comparison: OBS, OBS + WL, OBS + M, and OBS + WL + M (see supplementary Fig. 1).

The proportion of participants with pCR at 6 months was calculated with 95% confidence intervals (CI) from the centrally adjudicated data. Logistic regression analyses explored associations pCR rate with covariates: treatment (as randomized); whether the participant was eligible for randomization to M treatment (yes, no); and whether the participant was eligible for randomization to WL treatment (yes, no); patient's age; baseline BMI (<40 kg/m3 vs ≥40 kg/m^2); ethnicity (Caucasian vs other); diagnosis (EHA vs EAC); menopausal status. Reporting of AEs was conducted by treatment received. Analyses were performed in SAS version 9.4 (Cary, USA) and R version 4.0.2 [40]. All primary and secondary analyses except where stated, were performed according to the intention-to-treat principle. As this study allowed for optional randomization (patients receiving metformin or undertaking a weight loss program were allowed to be randomized to one of the other groups), the purpose of randomization was aimed at reducing bias due to patient selection. The results would be of a pragmatic signal finding nature and not necessarily to determine whether the intervention is better or worse than the control or necessarily obtaining objective comparisons in the usual sense of a phase III comparison.

3. Results

Between December 2012 and November 2019, 912 participants were screened, and 165 randomized at gynecological cancer centers in Australia (12 sites) and New Zealand (4 sites) (Fig. 1). The most common reasons for screening failure included suitable for THBSO (21%, 156/747) or patient declined participation (20%, 153/747). Of 165 randomized patients, 91 were randomized into the 3-arm main trial, while 11 participants were ineligible for WL and randomized into the two-arm OBS:M trial. The remaining 63 patients were ineligible for the M arm and consequently randomized into the two-arm OBS:WL trial.

Baseline characteristics are presented in Table 1. Briefly, women had a mean age of 53 years and a mean BMI of 48 kg/m^2, and 94 patients (57%) were post-menopausal. Ninety-six patients were diagnosed with EAC (58%) and 69/165 patients with EHA (42%).

Three of 165 patients expelled the LNG-IUD between either baseline and 3 months (2 patients), or 3 and 6 months (1 patient) and were withdrawn at those time points (Table S1). Of 58 patients randomized to WL, 50 (86%) registered for Weight Watchers, and at 6 months 23

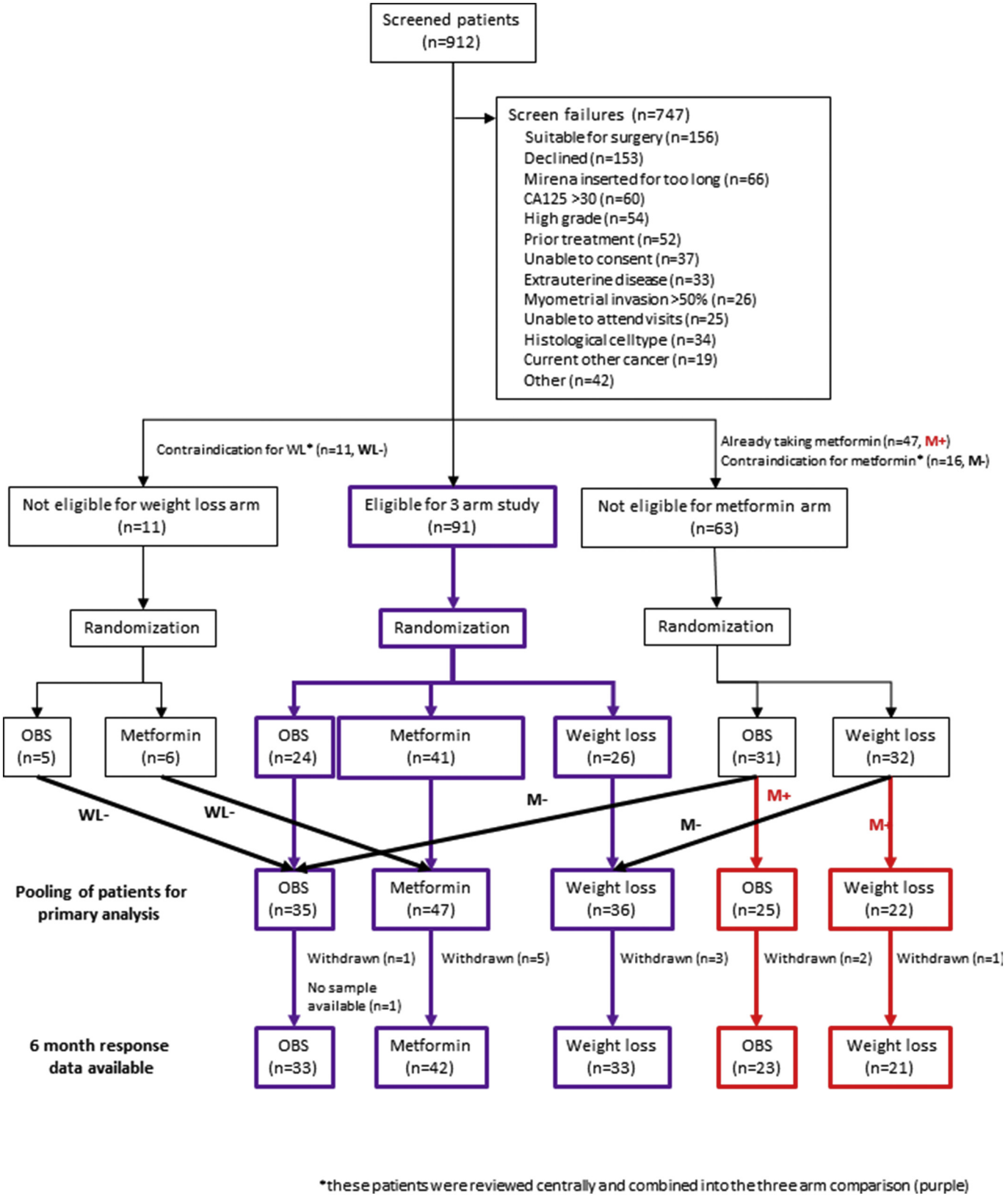

Fig. 1. Consort flow chart for the feMMe trial.

of 39 patients (60%) attended. For participants randomized to M, 43 of 47 patients (91%) commencing M with 14 days of baseline and 30 of 38 patients (79%) were compliant at 6 months.

After pooling for primary analysis, 35 participants were randomized to OBS, 36 to WL and 47 to M. Of these, 33, 33, and 42 patients had an endometrial biopsy available at 6 months, respectively. For 15 patients,

Table 1
Baseline characteristics by study and overall.

	3 arm study	2-arm: LNG-IUD vs LNG-IUD + WL	2-arm: LNG-IUD vs LNG-IUD + M	All patients
Randomized patients	91	63	11	165
EHA	44/91 (48%)	23/63 (37%)	2/11 (18%)	69/165 (42%)
EAC	47/91 (52%)	40/63 (63%)	9/11 (82%)	96/165 (58%)
Pre-menopausal	42/91 (46%)	24/63 (38%)	5/11 (45%)	71/165 (43%)
Post-menopausal	49/91 (54%)	39/63 (62%)	6/11 (55%)	94/165 (57%)
Age in years, mean (SD)	(n = 91) 51.5 (14.1)	(n = 63) 53.9 (13.4)	(n = 11) 60.6 (13.8)	(n = 165) 53.0 (13.9)
Height in meters, mean (SD)	(n = 91) 1.6 (0.1)	(n = 63) 1.6 (0.1)	(n = 11) 1.6 (0.1)	(n = 165) 1.6 (0.1)
Weight in kgs, mean (SD)	(n = 91) 128.8 (25.5)	(n = 63) 128.5 (25.6)	(n = 11) 113.0 (28.6)	(n = 165) 127.6 (25.9)
BMI, mean (SD)	(n = 91) 48.0 (9.7)	(n = 63) 48.3 (9.0)	(n = 11) 43.1 (9.6)	(n = 165) 47.7 (9.4)
CCI, median (Q1-Q3)	(n = 91) 1.0 (0.0–2.0)	(n = 63) 2.0 (1.0–3.0)	(n = 11) 2.0 (1.0–4.0)	(n = 165) 1.0 (0.0–2.0)
CCI 0	34/91 (37%)	11/63 (17%)	2/11 (18%)	47/165 (28%)
CCI 1	25/91 (27%)	17/63 (27%)	3/11 (27%)	45/165 (27%)
CCI 2	22/91 (24%)	15/63 (24%)	1/11 (9%)	38/165 (23%)
CCI 3	7/91 (8%)	13/63 (21%)	1/11 (9%)	21/165 (13%)
CCI 4	2/91 (2%)	6/63 (10%)	2/11 (18%)	10/165 (6%)
CCI 5	1/91 (1%)	1/63 (2%)	2/11 (18%)	4/165 (2%)
Months diagnosis to randomization, median (Q1-Q3)	(n = 91) 1.8 (1.1–2.4)	(n = 63) 1.7 (1.3–2.5)	(n = 11) 1.3 (0.7–2.2)	(n = 165) 1.7 (1.2–2.4)
Currently taking metformin		47/63 (75%)		47/163 (28%)
ECOG				
ECOG 0	63/91 (69%)	38/63 (60%)	3/11 (27%)	104/165 (63%)
ECOG 1	26/91 (29%)	20/63 (32%)	5/11 (45%)	51/165 (31%)
ECOG 2	2/91 (2%)	4/63 (6%)	2/11 (18%)	8/165 (5%)
ECOG 3		1/63 (2%)	1/11 (9%)	2/165 (1%)
Ethnicity				
European	55/91 (60%)	39/63 (62%)	5/11 (45%)	99/165 (60%)
Indigenous Australian	2/91 (2%)	5/63 (8%)	1/11 (9%)	8/165 (5%)
Asian	3/91 (3%)	2/63 (3%)	1/11 (9%)	6/165 (4%)
Pacific Islander	11/91 (12%)	4/63 (6%)	1/11 (9%)	16/165 (10%)
Other	13/91 (14%)	8/63 (13%)	1/11 (9%)	22/165 (13%)
Not answered	7/91 (8%)	5/63 (8%)	2/11 (18%)	14/165 (8%)
Highest level of education				
Primary/High school	38/91 (42%)	32/63 (51%)	6/11 (55%)	76/165 (46%)
Tertiary/Trade	41/91 (45%)	20/63 (32%)	4/11 (36%)	65/165 (39%)
Other	8/91 (9%)	8/63 (13%)	1/11 (9%)	17/165 (10%)
Not answered	4/91 (4%)	3/63 (5%)		7/165 (4%)
Income				
<$40,000	34/91 (37%)	32/63 (51%)	8/11 (73%)	74/165 (45%)
$40,001 to $80,000	30/91 (33%)	17/63 (27%)	1/11 (9%)	48/165 (29%)
>$80,000	21/91 (23%)	9/63 (14%)	1/11 (9%)	31/165 (19%)
Not answered	6/91 (7%)	5/63 (8%)	1/11 (9%)	12/165 (7%)
CA125 in kU/L, mean (SD)	(n = 90) 14.5 (5.5)	(n = 62) 12.7 (4.8)	(n = 11) 13.7 (6.3)	(n = 163) 13.8 (5.3)
HE4 in pmol/L, mean (SD)	(n = 62) 61.5 (42.0)	(n = 40) 63.8 (28.1)	(n = 9) 89.6 (51.3)	(n = 111) 64.6 (38.8)

Data are presented as n/N (%), (n) mean (SD) or (n) median (IQR).
Abbreviations: LNG-IUD, levonorgestrel intrauterine device; WL, weight loss; M, metformin; EHA, endometrial hyperplasia; EAC, endometrioid adenocarcinoma; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CCI, Charlson Comobidity Index; ECOG, Eastern Cooperative Oncology Group.

slides were not available for central histopathology review. For those cases the site-reported pathology result was used to inform adjudication of response to intervention.

After 6 months of treatment, the rate of pCR was 61% (20/33, 95% CI: 42–77%) for OBS, 67% (22/33, 95% CI: 48–82%) for WL, and 57% (24/42, 95% CI: 41–72%) for M (Fig. 2). Results in the sensitivity population were 61% for OBS, 67% for WL, 62% for M and 48% for M + WL. Across the three treatment groups, the pCR was 82% (41/50, 95% CI: 69–91%) for EHA and 43% (25/58, 95% CI: 30–57%) for EAC (Table S2).

A breakdown of response status at 3 months and 6 months is given in Table S3 for the primary population and Table S4 for the sensitivity population. Briefly, partial and complete response rates were generally higher at 6 months than 3 months, and in the pooled 3-arm study, progression rates at 6 months appeared higher in those randomized to the M arm (17%, 7/42).

Patients in all intervention groups lost weight from baseline (Table 2), with those randomized to the WL arm losing the most (8.2 kg). Weight loss of 7% body weight or more was achieved by 6/32 (19%), 8/32 (25%), and 6/38 (16%) of patients in the OBS, WL, and M groups, respectively. Body composition by the sensitivity population is given in Table S5.

The incidence of AEs was similar between the treatment arms. Between baseline and 3 months, 5/165 (3%) patients developed an AE Grade 3 and between 3 and 6 months, 7/165 (4.2%) developed an AE Grade 3 (Table S6). The types of events seen over the trial are given in Table S7. Overall, a total of 19 SAEs were recorded for 165 patients over 6 months.

None of the clinical parameters presented in Fig. 3, apart from EAC vs EHA, were identified to predict pCR.

4. Discussion

In this phase II randomized trial, the pCR for OBS and WL were encouragingly high at 61% and 67%, while M achieved the lowest pCR with 57%. The interventions caused minimal toxicity. While patients with EHA were more likely to respond than EAC patients, no other clinical parameters were identified to predict pCR.

A growing number of patients diagnosed with EAC are not optimally served by THBSO. In young women, it leads to irrevocable loss of

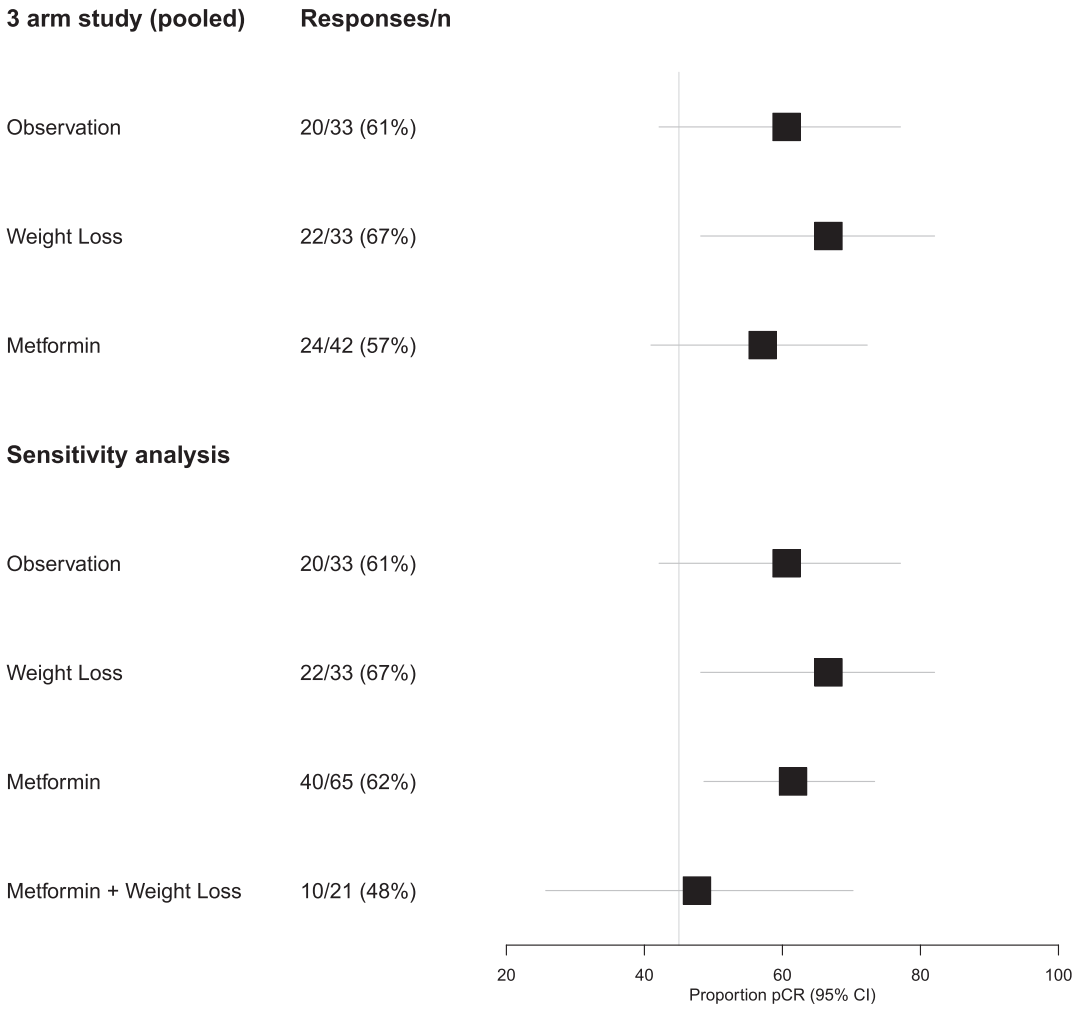

Fig. 2. Forest plot for the pathological complete response rate (pCR) and 95% CI by treatment for the primary and sensitivity analysis.

Table 2
Summary of body composition over time by primary population.

	3 arm study (pooled)			2-arm: LNG-IUD vs LNG-IUD + WL	
	LNG-IUD	LNG-IUD + WL	LNG-IUD + M	LNG-IUD	LNG-IUD + WL
Randomized patients	**35**	**36**	**47**	**25**	**22**
Weight					
Baseline	(n = 35) 126.5 (31.6)	(n = 36) 127.1 (22.1)	(n = 47) 126.9 (23.5)	(n = 25) 124.1 (21.2)	(n = 22) 135.9 (31.6)
Three months	(n = 34) 124.6 (28.2)	(n = 33) 122.4 (19.4)	(n = 44) 125.4 (24.1)	(n = 24) 121.6 (22.5)	(n = 20) 132.8 (33.6)
Six months	(n = 32) 121.2 (29.4)	(n = 32) 118.9 (18.4)	(n = 38) 123.1 (23.4)	(n = 23) 120.6 (22.7)	(n = 20) 130.2 (34.1)
Change at 6 m from baseline	(n = 32) -4.7 (5.9)	(n = 32) -8.2 (11.5)	(n = 38) -3.4 (7.7)	(n = 23) -2.2 (4.6)	(n = 20) -6.3 (5.6)
BMI					
Baseline	(n = 35) 47.2 (10.5)	(n = 36) 47.4 (9.3)	(n = 47) 47.4 (8.7)	(n = 25) 47.0 (8.5)	(n = 22) 50.7 (10.8)
Three months	(n = 34) 46.4 (9.5)	(n = 33) 45.6 (8.1)	(n = 44) 46.9 (8.8)	(n = 24) 46.1 (8.7)	(n = 19) 49.9 (11.6)
Six months	(n = 32) 45.1 (9.5)	(n = 32) 44.3 (7.7)	(n = 38) 46.1 (8.3)	(n = 23) 46.0 (9.1)	(n = 20) 48.8 (11.3)
Change at 6 m from baseline	(n = 32) -1.7 (2.2)	(n = 32) -3.1 (4.5)	(n = 38) -1.2 (2.5)	(n = 23) -0.7 (1.7)	(n = 20) -2.4 (2.3)
Waist circumference					
Baseline	(n = 35) 128.2 (19.4)	(n = 30) 128.0 (15.6)	(n = 46) 128.4 (17.6)	(n = 24) 132.3 (17.1)	(n = 21) 135.2 (12.7)
Three months	(n = 34) 127.5 (16.8)	(n = 28) 126.7 (13.9)	(n = 42) 127.6 (16.7)	(n = 23) 129.6 (17.5)	(n = 20) 131.4 (15.5)
Six months	(n = 32) 124.9 (18.1)	(n = 27) 124.2 (13.0)	(n = 38) 127.4 (16.5)	(n = 23) 128.2 (17.9)	(n = 20) 130.8 (17.6)
Change at 6 m from baseline	(n = 32) -3.1 (6.8)	(n = 26) -5.3 (7.1)	(n = 37) -1.9 (6.0)	(n = 22) -2.8 (8.2)	(n = 19) -4.0 (9.0)
Hip circumference					
Baseline	(n = 35) 143.9 (22.0)	(n = 30) 143.2 (17.3)	(n = 46) 143.2 (15.5)	(n = 24) 144.6 (17.1)	(n = 21) 150.3 (22.8)
Three months	(n = 34) 142.9 (20.4)	(n = 28) 143.2 (15.9)	(n = 43) 143.8 (16.7)	(n = 23) 142.3 (16.2)	(n = 20) 149.0 (23.4)
Six months	(n = 32) 141.2 (20.8)	(n = 27) 140.6 (14.8)	(n = 38) 144.8 (16.8)	(n = 23) 142.8 (17.7)	(n = 20) 146.5 (23.8)
Change at 6 m from baseline	(n = 32) -2.9 (4.5)	(n = 26) -4.3 (6.5)	(n = 37) -0.0 (7.3)	(n = 22) -0.0 (7.4)	(n = 19) -3.6 (10.7)

Data are given as (n = x) mean (SD).
Abbreviations: LNG-IUD, levonorgestrel intrauterine device; WL, weight loss; M, metformin.

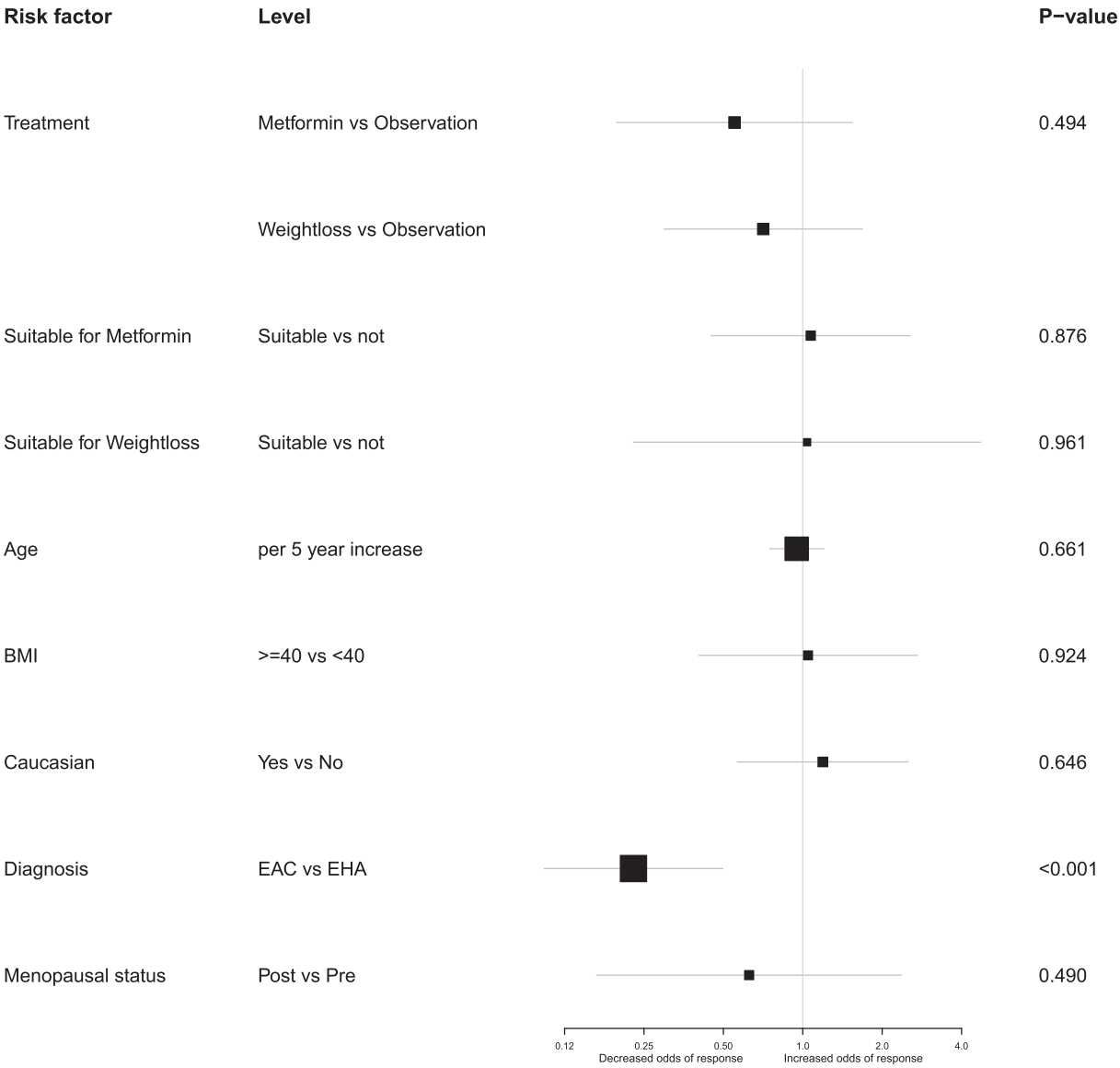

Fig. 3. Forest plot of the Odds Ratios and 95% CI for the effect of risk factors in the adjusted analysis.

childbearing capacity; in elderly, morbidly obese and multimorbid women, it is associated with a high risk of conversion to open surgery, procedure-related AEs and high use of health care services [12]. The search for non-surgical treatments of EAC has been declared a priority by stakeholders, payers and healthcare consumers [41–43].

Despite the regular use of LNG to treat EAC, no randomized evaluation on its effectiveness was available until recently. The feMMe trial was designed to determine the utility of LNG-IUD alone or in combination with WL or M, with randomization important to minimize patient selection bias into the study and provide unbiased estimates of response rates.

Most evidence on the effectiveness of LNG-IUD to treat EAC comes from retrospective series [38,44] whereas only two prospective, clinical trials are available [45,46]. One was a non-randomized phase II multicenter trial of 44 patients with grade 1 EAC who were treated with LNG-IUD plus oral medroxyprogesteroneacetate (500 mg per day). Of 35 assessable patients, only 13 (37%) developed a complete response at 6 months [45]. In a second non-randomized, phase II clinical trial of 21 patients with grade 1 EAC and 36 patients with EHA, the overall response rate was 83% at 12 months (66.7% for EAC and 90.6% for EHA) in 47 evaluable patients [46]. This rate was higher than in the feMMe trial, possibly because it included partial responses (feMMe trial – complete response) and was assessed at 12 months (feMMe trial – 6 months). Similar to feMMe, BMI was not predictive of response. While both of these trials, and another prospective observational study that investigated LNG-IUD in combination with oral hormonal treatment by Minig and colleagues [47] assessed response at 12 months, the feMMe trial protocol's six months main endpoint was more conservative in its intent.

Compared to the above trials, the feMMe trial is novel in its inclusion of a WL intervention arm. A previous prospective cohort study enrolled 72 women (BMI >40 kg/m^2) planning to undergo bariatric surgery [48]. Endometrial sampling revealed an unexpectedly high prevalence of EAC ($n = 4$) or EHA ($n = 6$). After bariatric surgery, 5 of 6 women with EAH achieved a pCR; in 3 of these women due to WL alone, and in 2 due to WL plus LNG-IUD. Other studies that enrolled women at risk of EAC were either small pilot studies or reported low recruitment rates [49–52].

The feMMe trial adds to the sparse evidence on the effectiveness of metformin in EAC [53]. A recent RCT [54] compared the effectiveness of oral megestrol acetate (160 mg/day) versus megestrol acetate plus metformin. Of 125 eligible patients, only 23 had EAC and only 26% had

a BMI > 28 kg/m^2. In the megestrol acetate versus megestrol acetate plus metformin groups the rates of pCR were 20% versus 39% (EHA) and 14% versus 22% (EAC), respectively. Kitson and colleagues [28] examined the antiproliferative effectiveness in a multicenter RCT comparing metformin ($n = 45$) with placebo ($n = 43$). Ki-67 expression was not different between the groups. Sivalingam and colleagues [55] suggested hypoxia and hyperglycemia may cause failure to respond to metformin in EAC.

The feMMe trial applied robust methodology to determine precise estimates of the effectiveness of LNG-IUD. Interestingly, the estimates from previously published meta-analyses, albeit limited to small, retrospective studies, were similar to the pCR rates detected here [38,44].

As a phase 2 RCT, the feMMe trial was not formally powered to compare the outcomes of treatment groups. While we designed the feMMe trial originally as a three-arm trial, we realized that a considerable number of patients who we thought would benefit from it, were ineligible. Some patients were taking M already; others were ineligible for the WL intervention; and some young women who desired fertility did not meet the criteria because their BMI was lower than the required 30 kg/m^2. For those reasons, we amended the protocol so that patients who were ineligible for one of the three arms could still be enrolled. Future trials should consider that concomitant medication may equally impact on trial outcomes. Central histopathology review was valuable and a distinct strength of the feMMe trial.

5. Conclusion

In summary, the feMMe trial demonstrates encouraging response rates for EHA and EAC to both, LNG + WL (67%) and LNG alone (61%). Future research is warranted to identify molecular predictors of response to LNG [56].

Contributors

MJ, VG and AO: Conceptualization. MJ, KPR, VG, JEA, JLN, and AO: Funding acquisition; Investigation; Methodlogy; Project administration; Supervision. Funding Writing - original draft. KPR, VG: Formal analysis. All authors: Data curation; Writing - review &editing.

Data access, responsibility and analysis

KPR had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

After de-identification, data, including de-identified individual participant data that underline the results reported in this article, will be available. The study protocol will also be available. The data will become available beginning 9 months and ending 36 months following article publication to investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") and who propose to use the individual participant data for meta-analyses or methods studies. Proposals should be directed to ao@surgicalperformance.com. To gain access, data requestors will need to sign a data access agreement.

Disclosures

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Previous presentations

The study results were presented at a virtual consumer forum on September 12, 2020 organised by the Queensland Centre for Gynaecological Cancer- Research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.01.029.

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