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Improving treatment for obese women with early stage cancer of the uterus: Rationale and design of the levonorgestrel intrauterine device ± Metformin ± weight loss in endometrial cancer (feMME) trial

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ABSTRACT

Purpose: Endometrial adenocarcinoma (EC) is the most common gynaecologic cancer. Up to 90% of EC patients are obese which poses a health threat to patients post-treatment. Standard treatment for EC includes hysterectomy, although this has significant side effects for obese women at high risk of surgical complications and for women of childbearing age. This trial investigates the effectiveness of non-surgical or conservative treatment options for obese women with early stage EC. The primary aim is to determine the efficacy of: levonorgestrel intrauterine device (LNG-IUD); with or without metformin (an antidiabetic drug); and with or without a weight loss intervention to achieve a pathological complete response (pCR) in EC at six months from study treatment initiation. The secondary aim is to enhance understanding of the molecular processes and to predict a treatment response by investigating EC biomarkers.
Methods: An open label, three-armed, randomised, phase-II, multi-centre trial of LNG-IUD ± metformin ± weight loss intervention. 165 participants from 28 centres are randomly assigned in a 3:3:5 ratio to the treatment arms. Clinical, quality of life and health behavioural data will be collected at baseline, six weeks, three and six months. EC biomarkers will be assessed at baseline, three and six months.
Conclusions: There is limited prospective evidence for conservative treatment for EC. Trial results could benefit patients and reduce health system costs through a reduction in hospitalisations and through lower incidence of adverse events currently observed with standard treatment.

1. Introduction

Endometrial adenocarcinoma (EC) is the most common gynaecologic malignancy in the developed world [1]. Type 1 EC is often associated with well-differentiated tumours with no or minimal invasion into the surrounding myometrium and carries a good prognosis [2]. Endometrial Hyperplasia with Atypia (EHA) is precancerous and refers to the

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excessive proliferation of endometrial glands that show cytological atypia [3,4]. Trimble et al. reported a 43% incidence of EC in patients with a preoperative diagnosis of EHA [5]. Obesity is the main risk factor for EC with more than 60% of patients reported as obese [2,6,7]. Obesity is associated with more detailed preoperative assessments and intensive postoperative care, and obese patients have an increased risk of premature death due to associated comorbidities [8,9].

Current standard treatment for EC and EHA is total hysterectomy and bilateral salpingo-oophorectomy with or without surgical staging. Five year disease-free survival ranges from 95-80% in stage 1 EC [10]. However, while the relative innocuousness of the tumour and radical surgery offer excellent survival prospects, drivers for change include poor surgical recovery [11], surgical adverse events [12,13], and greater treatment costs [11,14]. Also, surgical treatment of women of childbearing age results in irrevocable infertility [15–18]. As such, conservative treatment is a meaningful quality of life goal for selected cases [5]. The femme trial will investigate the effectiveness of a levonorgestrel intrauterine device (LNG-IUD; Mirena®), metformin and weight loss intervention.

Metformin (dimethylbiguanide) is widely used to treat Type 2 Diabetes Mellitus. There is an association between diabetes and cancer [19,20] and clinical observations have highlighted metformin as a potential anti-cancer therapy [21]. Schuler et al. (2013) conducted a window of opportunity study where 20 women with EC were treated with 850 mg metformin once daily for 1-4 weeks before hysterectomy. The study observed a significantly reduced mean Ki-67 index ($p < 0.008$) from pre- to post-treatment [22]. Soliman and colleagues reported the first window of opportunity study of metformin and found a decrease in post-treatment AKT and s6 expression after metformin treatment. However, in contrast to Schuler et al. they found no significant difference in ki67 and caspase 3 expression between pre- and post-treatment samples [23].

Weight loss interventions are feasible and safe [24], and already in use by gynaecological oncologists to make women eligible for surgery. Weight loss of 7% body weight induces a large biological effect (e.g. reduces incidence of diabetes by 58% [25], and hypertension by 26% [26]). A 6-month weight loss and physical activity intervention trial for overweight/obese EC survivors ($n = 75$) found that 26% of intervention participants lost ≥ 5% of their weight compared with 9% of usual care participants. However, the study was limited by small sample size, biomarkers or tumour responses were not studied, and although promising, the clinical implications are unclear as <7% weight loss was achieved [27].

The primary aim of this phase II, three-arm randomised trial is to determine the efficacy of LNG-IUD ± metformin ±weight loss intervention to achieve a pathological complete response (pCR) at 6 months. Secondary aims are to predict the response to LNG-IUD ± metformin through clinical (body size), blood and tissue predictive biomarkers and to increase our molecular understanding of the biological pathways of "early" EC.

2. Methods

2.1. Design

This trial has been designed as an open label, randomized phase II trial (Fig. 1). The study protocol was approved by the Human Research Ethics Committees of all institutions that enrol patients. Randomisation aims to eliminate selection bias rather than formal comparison of groups. Eligibility and exclusion criteria are detailed in Table 1. To minimise the risk of enrolling patients with aggressive EC, patients are only eligible for enrolment if they have apparent stage 1 disease (absence of lymphadenopathy or pelvic masses), endometrioid cell type and FIGO grade 1 EC and no lymph vascular space invasion on curettings, no or only minimal myometrial invasion on MRI (to exclude deeply invasive cancers), and a serum CA125 of 30 U/ml or less [28].

In addition to the established criteria for low-risk disease (CT and MRI scan, FIGO grade) we will also only offer patients with negative serum CA125 participation in the trial. We previously found that baseline CA125 was the most accurate predictor of extrauterine disease, even outperforming FIGO grade [29]. Considering the strict criteria above, we can expect that we will find advanced or aggressive disease in less than 3% of patients. In addition, all patients will undergo a safety check at 3 months from baseline.

We plan to record medical co-morbidities and use the Charlson index score [30] to document them in a standardised way for comparison purposes.

Randomisation has been programmed via an interactive Voice Response System. Participants will be randomly allocated to LNG-IUD: LNG-IUD + weight loss intervention: LNG-IUD + metformin in a 3:3:5 ratio. Participants will be stratified by body mass index (BMI) categories 30 kg/m2 - 40 kg/m2 and ≥40 kg/m2, menopausal status, treatment centre and diagnosis (EHA versus EC). Patients not eligible for Metformin are still eligible to be randomised to either LNG-IUD or LNG-IUD plus weight loss and patients not eligible for weight loss are still eligible to be randomised to LNG-IUD or LNG-IUD plus metformin.

2.2. Interventions

LNG-IUD is currently approved by the Australian Therapeutic Goods Administration (TGA) for contraception, treatment of idiopathic menorrhagia and prevention of endometrial hyperplasia during oestrogen replacement therapy and will be placed into the uterine cavity releasing 52 mg levonorgestrel at a rate of 20 microgram/24 hours. In addition to LNG-IUD, 75 patients will receive metformin with meals, 1000 mg daily. This dose is similar to clinical trials in the breast cancer adjuvant setting (NCT00909506 and NCT01302002) where doses between 500 mg and 1000 mg daily are given. Metformin is well tolerated by the vast majority of patients without side effects. Its most common adverse effects [31] are gastrointestinal (diarrhoea, cramps, nausea, vomiting, increased flatulence); side effects are dose-dependent. The dose of 1000 mg daily can be reduced to 500 mg daily if required. The investigational products (LNG-IUD and metformin) have been described in Table 2. In addition to LNG-IUD, 45 patients will be assigned to weight loss intervention. They will be provided with a voucher for a comprehensive subscription to a standard weight loss program (Weight Watchers®). The weight loss program is an evidence-based and tested program of dietary intervention, which has produced consistent weight loss success for overweight or obese people [32]. Group meetings are held in locations throughout Australia, and promote a hypo-energetic diet,

physical activity, social networking and support. Online tools feature self-audit and management resources, healthy recipes, and online social networking opportunities. Participants are encouraged to use the face-to-face and online tools, and are called every calendar month (±3 days) by the study manager or coordinator to assess their use of the program and progress with weight loss (the target is 7% weight loss).

We will only provide standardised study information to all patients, but will not specifically inform patients not assigned to the weight loss group about weight loss. Patients my seek support for weight loss on their own terms, and we will monitor how many patients may enrol in weight loss programs in each group. The LNG-IUD group will allow us to assess the effect of hormone treatment without confounding by weight loss.

Treatment Adverse events will be managed by local investigators and documented according to current good clinical practice guidelines [33] (Common Toxicity Criteria V4 [34]).

2.3. Study Assessments and Procedures

A summary of study assessments and procedures at baseline, day 1, week 1, week 6, 3 months and 6 months has been outlined in Table 3.

2.4. Baseline assessments

Baseline assessments will be performed according to the trial standard operating procedures (SOPs), including CT and MRI scans, medical history, concomitant medical co-morbidities documented and scored according to Charlson [30], fasting blood sample, as well as weight, height, waist/hip circumference. According to standard referral pathways, endometrial tissue will be obtained by a hysteroscopy, dilatation and curette (D&C) by the treating gynaecological oncologist. Histopathological tumour board review will confirm cell type and grade of differentiation. Central histopathology review will be facilitated at the end of the trial. Blood samples will be processed for shipping and formalin-fixed D&C blocks will be obtained for molecular biomarker analysis.

We will use the same self-administered questionnaires as in our previous randomised trial with endometrial cancer patients to allow comparison across studies: Functional Assessment of Cancer Therapy Questionnaire, plus endometrial cancer module [35,36]; Hospital Anxiety and Depression Scale [37]; Health Services use questionnaire [38]; Pelvic Floor Distress Inventory [39]; Victorian Cancer Council Food Frequency Questionnaire.

Formalin-fixed samples (FFPE) and serum biomarkers will be assessed at baseline, 3 and 6 months. An initial immunohistochemistry (IHC) study of biomarkers will be performed using markers aimed to develop an IHC- based predictive assay for LNG-IUD and/or metformin. To allow for quantitative determination of protein expression at different time points automated algorithms will be used. Molecular biomarker testing on tumour tissue will be followed by genetic testing for germline mutations to determine the origin of mutation. We will measure levels of IGF1, IGFBP-1 and 3, sex-hormone binding globulin, total and free oestradiol, progesterone, leptin, prolactin, active and total ghrelin, and adiponectin using commercial ELISA kits. Blood samples for germline DNA will be taken to assist future studies. Serum will also be used to investigate the metabolic balances and EC-related endocrine profiles.

Biomarkers will include PTEN and p-S6K as surrogate markers of PI3K-AKT-mTOR activity and LKB1, which will be expected to increase after metformin treatment. ERα, PRα and PRβ will also be assessed with special emphasis placed on individual quantification of stromal and epithelial components as more evidence accrues that stromal HR expression may play an important role in EAC. Finally a number of ER and PR response genes will be assessed to confirm progesterone action as well as the proliferative marker Ki-67. Our hypothesis is that metformin treatment will lead to a prolonged increase in PR even in the presence of progesterone, which will lead to a more durable response to progesterone. DNA will also be extracted from FFPE sections and common somatic mutations in PR, P53, PTEN, PI3KCA, ARID1A, KRAS, CTNNB1 will be assessed

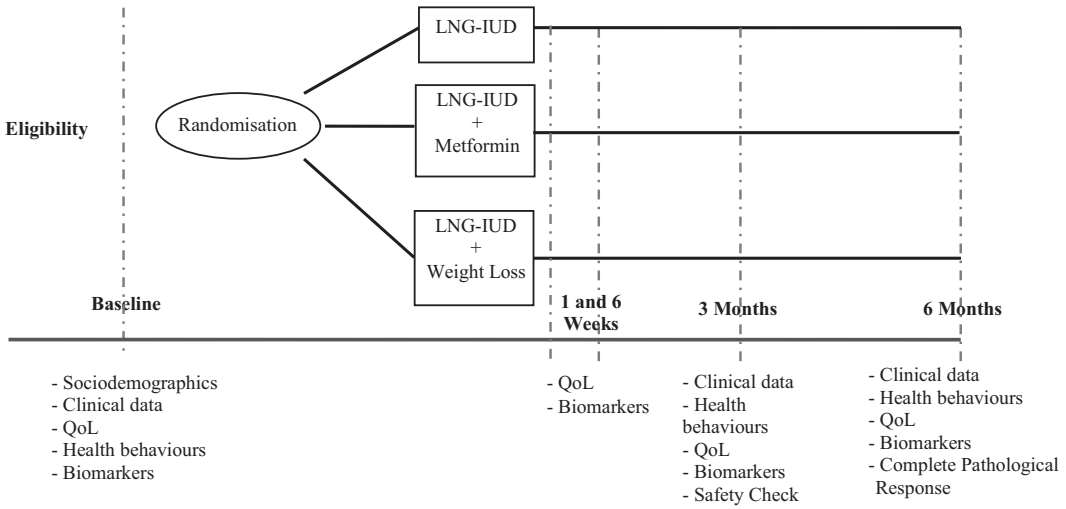

Fig. 1. Study design.

using iPLEX technology on a MassARRAY Compact Analyser (Sequenom Inc., San Diego, USA).

2.5. Efficacy assessments

At 3 months endometrial tissue will be obtained (safety check) to exclude progression of EHA or EC. At this point in time we will not attempt to ascertain a pathological complete response (pCR). If a patient progresses (i.e., patients with EHA progress to Grade 1 EC), develop grade 2 or 3 cancer or develop other histological cell types than endometrial) at 3 months, the patient will be returned to routine clinical care; surgical treatment (including a hysterectomy if appropriate) will be offered.

At 6 months endometrial tissue will be obtained and pCR will be assessed (primary study endpoint). After 6 months, women will be returned into the care of their usual clinician and will make a decision about the most appropriate treatment with their clinician on an individual basis.

The primary aim of this trial is to determine the efficacy of LNG-IUD ± metformin ± weight loss to achieve a pCR at 6 months from randomization, defined as absence of invasive EC or EHA at 6-month [dilation and curette (D&C)]. Secondary aims include to predict the response to LNG-IUD ± metformin through clinical (body size), blood and tissue predictive biomarkers and to increase our molecular understanding of the biological pathways of "early" EC.

2.5.1. Physical activity

Exercise level (sedentary, moderately active, and sufficiently active) will be measured using the Active Australia Survey [40], while the Hospital Anxiety and Depression Scale (HADS) [37] will briefly measure current anxiety and depressive symptomatology [41].

2.5.2. Quality of life

The FACIT (Functional Assessment of Chronic Illness Therapy) Measurement System is a 43-item questionnaire with 5 domain-specific subscales: physical well-being; social/family wellbeing; emotional well-being, functional well-being and EC specific additional concerns [42].

Table 1
Study Schedule of Event.

	Baseline	Day 1	Week 1	Week 6	3 Months	6 Months
	(within 30 days of Day 1)				(±14 Days)	(±14 Days)
Assessment						
Informed Consent	√					
CT Scan of Pelvis / Abdomen	√					
CT Scan of Chest (or chest X-ray)	√					
MRI of Pelvis	√†					
CA125	√				√	√
FBC	√				√	√
ELFT	√				√	√
Serum or Urine Pregnancy Test	√ [1]	√ (Urine) [1]				
Fasting Blood Sugar	√					
HbA1c	√				√	√
HE4	√				√	√
Blood collection for Biomarkers and Genetic Testing	√				√	√
Medical History	√					
Concomitant Medications	√				√	√
ECOG	√				√	√
Height	√					
Weight	√				√	√
Waist and Hip Circumference	√				√	√
Surgical, Medical, Gynaecological and Family History	√					
Current Self Reported Weight and Weight History	√					√
Current Physical Activity Questionnaire	√			√	√	√
Physical Activity History	√					
Anxiety and Depression Scale	√				√	√
Demographics Questionnaire	√					
FACT – EN	√		√	√	√	√
Health Services Questionnaire	√		√	√	√	√
Pelvic Floor Distress Inventory	√				√	√
Dietary recall Interview	√				√	√
Self Efficacy and Social Support Questionnaire	√			√	√	√
Insertion of LNG-IUD		√ [2]			√ [2]	√ [2]
Dispensing of Metformin		√ [2]			√ [2]	
Adverse Events					√	√
Provision of weight watchers voucher		√				
Phone call by study personnel to check on weight watcher use and weight loss progress		√ [3]			√ [3]	√ [3]
Return of used Metformin packets					√	√
D&C or Pipelle					√	√
Intervention adherence [4]				√	√	√

1. If clinically indicated 2. If required 3. To be completed monthly 4. Intervention participants only.

2.5.3. Health services use

Seven items assessing health care utilization during the past 6 months were adapted from Health Care Utilization items developed by the Stanford Patient Education Research Centre [43], which have excellent test-retest reliability ranging from 0.76 - 0.97 and validly assess use of such services [43].

2.5.4. Pelvic floor distress

The Pelvic Floor Distress Inventory (PFDI) provides a standardized, reproducible assessment of the patient's symptoms and their effect on daily life [44].

2.5.5. Diet

The Cancer Council Victoria Food Frequency Questionnaire will be used to assess diet as it has acceptable levels of reliability and validity when compared with seven-day weighted food records, and has been successfully used over the telephone with cancer survivors [45].

Further questionnaires will measure self-efficacy [46] and social support [47].

2.6. Sample Size

Our published meta-analysis [48] suggests that the average pCR rate, based on 12 studies, was 68% (95% CI: 45%-86%). We

Table 2
Description of investigational products.

	Levonorgestrel intrauterine device (LNG-IUD)	Metformin
Description	LNG-IUD (consists of a total of 52 mg levonorgestrel releasing it at a rate of 20 microgram/24 hours) is approved by the Therapeutic Goods Administration (TGA) for contraception, treatment of idiopathic menorrhagia and prevention of endometrial hyperplasia during oestrogen replacement therapy. The LNG-IUD is placed into the uterine cavity (releasing 52 mg levonorgestrel at a rate of 20 microgram/24 hours) by a trained medical professional. LNG-IUD is approved by the Therapeutic Goods Administration (TGA) for contraception, treatment of idiopathic menorrhagia and prevention of endometrial hyperplasia during oestrogen replacement therapy.	Metformin will be self-administered with meals, 500 mg twice daily. This dose is similar to clinical trials in the breast cancer adjuvant setting (NCT00909506 and NCT01302002) where doses between 500 mg and 1000 mg daily are given. Metformin is well tolerated by the vast majority of patients without side effects. Its most common adverse effects are gastrointestinal (diarrhoea, cramps, nausea, vomiting, increased flatulence); side effects are dose-dependent. The most serious potential side effect of metformin is lactic acidosis; this complication is very rare, and the vast majority of these cases seem to be related to co-morbid conditions, such as impaired liver or kidney function, rather than to the metformin itself. The side effects of metformin are similar in diabetic and non-diabetic women. The dose of 500 mg twice daily can be reduced to 250 mg twice daily if required at the Investigators discretion.
Formulation	LNG-IUD is a levonorgestrel-releasing intrauterine system consisting of a T-shaped polyethylene frame with a steroid reservoir containing a total of 52 mg levonorgestrel.	Each tablet contains 500 mg of metformin hydrochloride.
Storage	Store below 25 °C. Protect from direct sunlight and moisture[56].	Store below 25 °C[57]
Supplier	Bayer Healthcare	
Dose	LNG-IUD contains 52 mg of levonorgestrel. Initially, levonorgestrel is released at a rate of approximately 20 mcg/day. This rate decreases progressively to half that value after 5 years.	500 mg twice daily (can be reduced to 250 mg twice daily starting dose is not tolerated at the Investigators discretion) with meals
Metabolism	Following absorption, levonorgestrel is conjugated at the 17β-OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in serum. Significant amounts of conjugated and unconjugated 3α, 5β- tetrahydrolevonorgestrel are also present in serum, along with much smaller amounts of 3α, 5α-tetrahydrolevonorgestrel and 16βhydroxylevonorgestrel. Levonorgestrel and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in levonorgestrel concentrations seen in individuals using levonorgestrel–containing contraceptive products.	Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.
Adverse Effects	The most common adverse reactions are uterine/vaginal bleeding alterations, amenorrhea, intermenstrual bleeding and spotting, abdominal/pelvic pain and ovarian cysts.	The most common adverse reactions are taste disturbance, gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may improve gastrointestinal tolerability.
Contraindications	LNG-IUD is contraindicated in women with known or suspected: pregnancy; congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity; breast carcinoma; uterine or cervical neoplasia; unresolved, abnormal Pap smear; liver disease including tumours; untreated acute cervicitis or vaginitis, including lower genital tract infections (e.g., bacterial vaginosis) until infection is controlled; postpartum endometritis or infected abortion in past 3 months; unexplained vaginal bleeding; current IUD; acute pelvic inflammatory disease (PID) or history of PID (except with later intrauterine pregnancy); or conditions increasing susceptibility to pelvic infections.	Metformin is contraindicated in people with known or suspected: hypersensitivity to metformin hydrochloride or to any of the excipients, diabetic ketoacidosis, diabetic pre-coma, renal failure or renal dysfunction (creatinine clearance < 60 mL/min), acute conditions with the potential to alter renal function, acute or chronic disease which may cause tissue hypoxia, major surgery, severe hepatic insufficiency, acute alcohol intoxication, alcoholism, lactation.

Table 3
Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
1. Females with a BMI >30 kg/m^2 wishing to retain fertility or who are at high risk of surgical complications due to co-morbidities or obesity.	1. ECOG performance status >3.
2. Over 18 years of age at time of randomisation.	2. Grade 1 EC with myometrial invasion deeper than 50% on MRI or any patients with grade 2 or grade 3 EC.
3. Histologically confirmed complex EHA with atypia or grade 1 EC on a curette or endometrial biopsy.	3. Histological (cell) type other than EC (sarcomas or high risk endometrial e.g. papillary serous, clear cell).
4. CT scan of pelvis, abdomen and chest (or chest X-Ray) suggesting the absence of extrauterine disease.	4. Pregnant or planning to become pregnant during trial period.
5. Myometrial invasion on MRI of not more than 50%, for women with suspected EC only.	5. Prior treatment for EC or EHA.
6. No lymph vascular invasion on curetting.	6. Patients with a history of pelvic or abdominal radiotherapy.
7. Serum CA 125 ≤ 30 U/mL.	7. Renal impairment (Creatinine levels over 150 μmol/l (1.7 mg/dL), acute pulmonary oedema or liver failure at investigator discretion.
8. No hyper-sensitivity or contraindications for LNG-IUD or metformin.	8. Unwilling to have additional endometrial biopsies or curettes or unable to attend three monthly clinical assessments.
9. Ability to comply with endometrial biopsies at specified intervals.	9. Unable to provide informed consent or complete questionnaires.
10. Negative serum or urine pregnancy test in pre-menopausal women and women <2 years after the onset of menopause.	10. Evidence of extrauterine spread on medical imaging.
11. No use of metformin for at least 2 years prior to enrolment.	11. Congenital or acquired uterine anomaly which distorts the uterine cavity.
12. No LNG-IUD or LNG-IUD inserted <6 weeks prior to enrolment.	12. Acute pelvic inflammatory disease.
	13. Conditions associated with increased susceptibility to infections with microorganisms (e.g., AIDS, leukaemia IV drug abuse) according to the patient's medical history.
	14. Genital actinomycosis.
	15. Current other cancer.
	16. Breastfeeding mothers.

anticipate that the true pCR rate will be closer to the lower confidence limit of 45%. Using this as the basis and a 3 (LNG-IUD): 3 (LNG-IUD + metformin): 5 (LNG-IUD + weight loss intervention) randomisation (to minimise selection bias), a 60% or higher pCR rate with any combination treatment would provide strong evidence for informing a subsequent phase III trial. Additionally, in the event that the pCR within the LNG-IUD only group is better than 45%, the study would also have more than 80% power with 95% confidence to rule out a 60% LNG-IUD only pCR in favour of a 75% in the LNG-IUD plus metformin or LNG-IUD plus weight loss groups; or alternatively also >80% power to rule out a 65% pCR in favour of 80% pCR rate.

2.7. Statistical Analyses

We will calculate the proportion (+95% confidence intervals (CI)) of patients with pCR of the EHA or EC at 6 months within the LNG-IUD ± metformin ± weight loss groups. We will measure quality of life at baseline week 1, week 6, month 3 and at 6 months for explorative purposes. Descriptive analysis will calculate the mean or median change in molecular markers in each group. In particular, this study will investigate changes in molecular biomarker expression to increase our understanding of molecular mechanisms leading to pCR, persistence or progression. Additionally, appropriate regression methods will be used to explore for potential predictors of pCR at 6 months. Estimations from this trial will form the basis of designing subsequent phase III trials based on level of activity observed.

3. Discussion

Our feMMe trial (NCT01686126) is innovative as it will test the efficacy of three interventions (LNG-IUD, LNG-IUD + metformin, LNG-IUD + weight loss intervention) in the setting of a phase II randomised design. We will enrol obese patients with low-grade and "early" EC or EHA because the prognosis of these patients is excellent and even non-responders will likely not be harmed by having been withheld treatment for 6 months.

We have chosen LNG-IUD as the standard treatment arm, being well aware that the evidence for LNG-IUD to treat EC and EHA is based on case series and a meta-analysis including a total of 20 patients. However, while the efficacy of LNG-IUD is poorly documented, it is currently offered to many young women with early EC or EHA who wish to retain fertility or to women in poor general health who are at high risk of developing surgical complications by undergoing a hysterectomy.

A meta-analysis of outcomes after progestin treatments found oral and intrauterine treatments were similarly effective, although there are only 12 high quality studies in total that included at least 10+ eligible patients with EHA or endometrioid adenocarcinoma (EC) in either the oral or intrauterine treatment arm; patients 6+ months of treatment; not receiving other treatments, were available [48]. In patients with stage 1 EC treated with intrauterine progestins, the weighted mean pCR rate was 68% (95% CI 45-86%), but was only based on one published and one unpublished series [48]. The use of oral progestins for EC is problematic, as side effects include thromboembolic complications (DVT, PE, stroke), weight gain, and the onset or worsening of Type 2 diabetes mellitus [48]. Currently, oral progestins are mainly used to treat EC recurrence. In contrast, LNG-IUD is not known to cause systemic side effects. However, recurrences are common after removal of LNG-IUD [49,50].

The current study is innovative as it will test combinations of pharmaceutical and behavioural interventions with the hope

to reverse the hormonal and metabolic imbalances associated with obesity and insulin resistance leading to EC [51]. Metformin, an oral anti-diabetic, was chosen as evidence is accumulating for its potential as an anti-cancer drug and epidemiological studies suggest that metformin use is associated with improved prognosis in patients with various types of cancers [21]. Several reports have established a direct action of metformin on cancer cells [19]. Metformin activates adenosine monophosphate (AMP)-activated protein kinase (AMPK) via its upstream kinase LKB1. Activation of AMPK effects cellular metabolism and intracellular signalling. The overall effects of AMPK activation on mammalian metabolism are compatible with the hypothesis that it is a tumour suppressor that promotes the oxidative metabolism that is typical of quiescent cells, rather than the glycolytic metabolism typical of tumour cells. AMPK activation also causes inhibition of mTOR [52,53]. mTOR is frequently activated in EC cells [54] and associated with resistance to progestins [55,56]. Metformin has been shown to induce cell cycle arrest and apoptosis and causes up-regulation of PR and reverses resistance to progesterone in vitro in an mTOR dependent manner [52,53,57].

Previous investigators recently completed a nude mouse endometrial cancer xenograft study in which mice were inoculated with EC cells and then treated with oral metformin. Mice treated with metformin were found to have significant reductions in mean tumour volume at necropsy compared to control treated mice. In a window of opportunity study 20 women with EC were treated with 850 mg metformin once daily for 1-4 weeks before hysterectomy, and a strong reduction in the mean Ki-67 index was observed [22].

We chose a weight loss intervention because obesity is undeniably the biggest risk factor for the development of EC. Recurrences after conservative treatment for EC are common and reversal of the main risk factor seems a plausible necessity to maintain a response to LNG-IUD. Weight loss interventions are feasible and safe, and already being implemented by gynaecologic oncologists to make women eligible for surgery, as well, as in the post-treatment setting [25,26,58,27]. The standard weight loss program used in this study is widely available and effective [32].

Retrospective case series and meta-analyses are available on the use of LNG-IUD for the reversal of EHA and EC. In addition, several prospective, randomised and non-randomised clinical trials of LNG-IUD are underway. Trial NCT01594879 is registered on clinical trial.gov as is a single-arm, non-randomised clinical trial examining the efficacy of LNG-IUD and Medroxyprogesterone acetate (MPA) to treat patients with endometrial hyperplasia with atypia and endometrial adenocarcinoma. The study outcome is pathological response at 24 months and a total of 39 patients are planned to be enrolled. In 2008 the MD Anderson Cancer Center commenced enrolment into a non-randomised phase 2 clinical trial on LNG-IUD in patients with EHA and EC. The main study endpoint pCR will be assessed in 50 patients enrolled by 2015 (clinicaltrial.gov NCT00788671). The USC/Norris Comprehensive Cancer Center will commence enrolment of a phase 2 RCT enrolling 130 patients to receive either megestrol acetate or LNG-IUD for 18 months (NCT01943058).

There are also a number of trials of metformin in women with EC that are currently underway or in the planning phase. For example, the Gynaecologic Oncology Group (GOG) is testing paclitaxel, carboplatin, and metformin hydrochloride and comparing it to paclitaxel, carboplatin, and placebo in stage 3 or 4 or recurrent EC (NCT02065687). Whilst investigators from the MD Anderson Cancer Center are conducting an efficacy trial of the molecular effects of metformin, including physiologic changes in insulin/glucose metabolism and the mTOR pathway (NCT01205672), and they are investigating whether metformin and/or a lifestyle intervention can prevent EC in obese post-menopausal women (NCT01697566).

We hope that the current study will extend the low-level evidence for the effectiveness of LNG-IUD in the treatment of low-grade, "early" EC and EHA. The feMMe trial will confirm or readjust pCR rates following treatment with LNG-IUD with or without metformin and a weight loss intervention. We hope that LNG-IUD can be confirmed as an alternative treatment of EC and EHA in obese women with multiple medical comorbidities and in young women who would lose fertility irrevocably through surgery. In Australia, treatment is streamlined with almost all EC cases and an increasing number of women with EHA routinely referred to gynaecological oncologists. Compared to the United States and Europe, Australia has a competitive advantage to contribute to the knowledge about this growing health issue.

4. Conclusion

If successful, the results of this trial could significantly reduce the adverse event rate currently observed when women receive standard surgical care and thus greatly benefit patients and reduce costs for the health care system.

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