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Review

Endometrial cancer and obesity

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Key content

- Of the 20 most common tumour types, endometrial cancer has the strongest association with obesity.
- Endometrial cancer should be considered in young, obese women with irregular or heavy menstrual bleeding.
- To reduce the risk of postoperative complications, surgery for endometrial cancer should be performed using minimal access techniques whenever possible.
- For women who are unfit for, or who decline, surgery, alternative treatments include progestins or radiotherapy, but these have lower efficacy and are associated with a higher risk of disease relapse.
- Obesity is associated with reduced overall survival following endometrial cancer because of increased cardiovascular mortality; it may also affect disease-specific survival.

Learning objectives

- To further understanding of the mechanisms through which obesity drives endometrial carcinogenesis.
- To improve understanding of the potential difficulties associated with the management of endometrial cancer in obese women.
- To increase knowledge of alternative treatment options for women who are unfit for, or who decline, standard endometrial cancer management.

Ethical issues

- The number of young, premenopausal women with endometrial cancer is increasing – how should these women be managed?
- Should super-obese women with endometrial cancer only be treated in cancer centres?
- After treating a woman's endometrial cancer, how should she be counselled her about her weight and cardiovascular disease risk?

Keywords: cardiovascular disease risk / endometrial cancer / levonorgestrel-releasing intrauterine system (LNG-IUS) / obesity / weight loss

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Introduction

Endometrial cancer is the most common gynaecological cancer in the UK, with over 9000 new diagnoses made every year.[1] The incidence of endometrial cancer is rising year on year (Figure 1) and this trend is set to continue, both in the UK and globally.[2] As a consequence, endometrial cancer is expected to overtake lung and colorectal cancers to become the third most common cancer in women in the USA by 2030.[3] Deaths from endometrial cancer are also climbing, but at a slower rate (Figure 1), most likely because of the preponderance of tumours associated with a good prognosis. This means that more women are now surviving endometrial cancer than ever before.

The rising incidence of endometrial cancer has been blamed on the obesity epidemic. Among all cancers, endometrial cancer has the highest association with obesity.[4] Every 5 kg/m^2 increase in body mass index (BMI) is linked to a 60% increase in endometrial cancer risk.[5] This relationship is even greater at extremely high BMIs: a woman with a BMI of 40 kg/m^2 or more is nearly ten times more likely to be diagnosed with endometrial cancer than is a woman of normal weight, giving her a lifetime risk of disease of 10–15%. Such is the strength of this association that 40% of endometrial cancer diagnoses are directly attributable to obesity and thus are ultimately preventable.[6] Obesity is related to a sedentary lifestyle and low levels of physical activity, which are also independent risk factors for the disease.[7] Obesity is most strongly linked with good-prognosis type 1 (endometrioid) tumours, but its influence is also implicated in the pathogenesis of more biologically aggressive type 2 tumours.[5]

Mechanisms through which obesity drives endometrial carcinogenesis

There are three distinct, but interrelated, mechanisms through which obesity influences endometrial carcinogenesis: excess estrogen exposure, insulin resistance and inflammation (Figure 2).

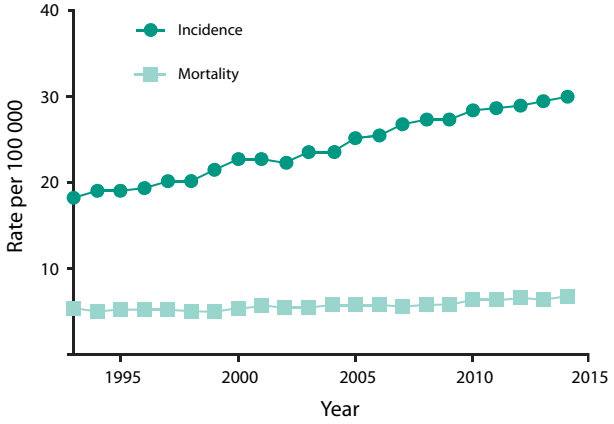

Figure 1. Endometrial cancer incidence and mortality rates in the UK. The incidence of endometrial cancer has risen by over 50% in the last 20 years.

Adipose tissue produces the enzymes aromatase and 17β-hydroxysteroid dehydrogenase (17β-HSD), which are responsible for the conversion of the androgens androstenedione and testosterone to the estrogens estrone and estradiol, respectively.[8] Hyperinsulinaemia leads to a decrease in sex-hormone-binding globulin (SHBG), which increases the bioavailable fraction of estrogen. The net effect is excess estrogen exposure without the natural counterbalance of cyclical progesterone in postmenopausal and anovulatory premenopausal women. Estrogen drives endometrial proliferation while simultaneously inhibiting apoptosis. Estrogen also promotes rapid cellular turnover through local production of insulin-like growth factor-1 (IGF-1) and, in so doing, increases the risk of accumulation of mutations in key proto-oncogenes and tumour suppressor genes.[9]

Obesity is associated with insulin resistance and chronic hyperinsulinaemia. There is now substantial in vitro evidence of a direct effect of insulin and IGF-1 on the endometrium, with activation of the insulin receptor promoting cellular proliferation and survival.[10,11] These effects are mediated through the PI3K-Akt-mTOR and MAPK pathways. Hyperinsulinaemia also increases ovarian androgen production and its peripheral aromatisation to estrogen.

Adipose tissue expansion and its subsequent hypoxia initiates the secretion of proinflammatory cytokines by activated adipocytes and infiltrating macrophages, creating an inflammatory environment.[12] Activation of the NF-kB pathway by inflammatory cytokines inhibits apoptosis, overrides cell cycle arrest and causes the transcription of genes encoding proinflammatory cytokines, leading to a vicious inflammatory cycle and tumourigenesis.[13] Inflammation also promotes insulin resistance and IL-6 stimulates aromatase activity and the conversion of testosterone to estrogen within adipose tissue.[14]

Knowledge of these key drivers of obesity-driven endometrial carcinogenesis can facilitate the development of targeted prevention and treatment strategies.

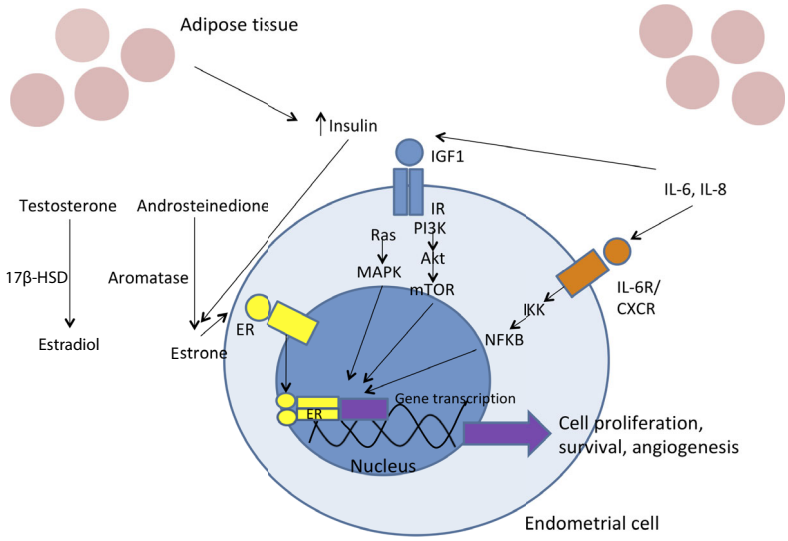

Figure 2. Mechanisms through which obesity drives endometrial carcinogenesis. Excess adipose tissue is responsible for the creation of a state of estrogen excess, hyperinsulinaemia and inflammation, which work in concert to upregulate gene transcription, cell proliferation and the accumulation of cancer-causing mutations within the endometrial cell. Abbreviations: 17β-HSD = 17β-hydroxysteroid dehydrogenase; ER = estrogen receptor; IKK = IkB kinase; CXCR = chemokine receptor; IL-6R = interleukin-6 receptor; IR = insulin receptor.

Preventing obesity-driven endometrial cancer

Tackling obesity is a logical first step to endometrial cancer prevention.[15] Women should be encouraged to attain and maintain a normal weight as key components of living a healthy lifestyle. Obese women who lose weight through dieting have been shown to lower their serum estrone and testosterone levels, while increasing insulin sensitivity and SHBG levels.[16] However, current evidence suggests that endometrial cancer risk is not reduced until weight loss of at least 20 lbs is achieved.[17]

To date, there have been no trials exploring the effects of physical activity on the primary prevention of endometrial cancer, but exercise is likely to be effective because of its beneficial effect on BMI. Women should be advised to undertake at least 20 minutes of moderate-intensity exercise – sufficiently intense to raise their heart rate – five times per week, similar to the recommendations made for breast cancer prevention.[18] Regular physical activity reduces the risk of endometrial cancer by 20–30%, with even greater benefits for those who undertake higher intensity exercise of greater duration.[19]

For morbidly obese women (that is, those with a BMI greater than or equal to 40 kg/m^2), bariatric surgery is an effective means of reducing endometrial cancer risk, resulting in a 70–80% lower disease risk compared with BMI-matched controls.[20,21] While the greatest benefit is seen in women who achieve a normal body mass following surgery, even those who remain obese have a lower risk of endometrial cancer. This suggests that the effect is predominantly mediated through rapid improvements in insulin sensitivity.[21,22] The National Institute for Health and Care Excellence (NICE) does not currently list cancer prevention as an indication for bariatric surgery, but eligible women should be counselled about the additional positive effects of weight loss surgery on endometrial cancer risk.

Young obese women should be advised about contraceptive choices that reduce endometrial cancer risk. Use of the levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®; Bayer, Whippany, NJ, USA) is associated with a 54% reduction in endometrial cancer risk, which increases to 75% if treatment is prolonged.[23] Five or more years of exposure to the combined oral contraceptive pill is effective in reducing the risk of endometrial cancer by 50%, with durable protection up to 30 years post-treatment,[24] although the risks may outweigh the benefits in obese women with multiple cardiovascular risk factors. Indeed, a BMI of >35 kg/m^2 is a relative contraindication for the combined oral contraceptive pill.[25]

Well-designed primary endometrial cancer prevention trials are needed to provide robust evidence for risk-reducing interventions, but these will be very expensive and time consuming. Risk prediction models that refine the population most likely to benefit from targeted prevention strategies are needed to ensure trials are adequately powered and have sufficient follow up to generate clear answers.[26]

Diagnosing endometrial cancer in obese women

The age at which incidence of endometrial cancer peaks is 70–74 years, but since the 1990s there has been a 36% increase in diagnoses among premenopausal women.[1] Endometrial cancer should be considered as a potential underlying cause of persistent irregular or heavy menstrual bleeding, particularly in the context of additional risk factors such as polycystic ovary syndrome (PCOS) or type 2 diabetes.[27] Premenopausal women are not considered in the updated Suspected Cancer guidance from NICE[28] and as such are unlikely to be urgently referred for endometrial biopsy unless general practitioners are aware of the risks.[29]

It can be technically challenging to obtain an endometrial sample for histological assessment from obese women. A Winterton speculum is longer than the average Cusco speculum and enables complete visualisation of the cervix, particularly if used in combination with left lateral position or a colposcopy chair.

The upper weight limit of magnetic resonance imaging (MRI) scanners used in the UK varies, but for very old machines it can be as low as 125 kg, with a maximum diameter of approximately 60 cm.[30] This may prevent some obese women from undergoing an MRI scan for staging purposes. To circumvent this issue, it may be appropriate to refer such women to tertiary units with bariatric or open MRI machines. Alternatively, a computed tomography (CT) scan may be performed, although this is only useful for excluding extrauterine disease because it has lower sensitivity than MRI in determining the depth of myometrial invasion and pelvic lymphadenopathy.[31]

Treating obese women with endometrial cancer

Surgery

Total hysterectomy and bilateral salpingo-oophorectomy is the primary treatment for most women with endometrial cancer and is curative for those with early stage disease that is limited to the uterus.[31] However, gynaecologists undertaking this procedure in obese women are faced with several potential difficulties, including the presence of comorbidities such as cardiovascular disease and obstructive sleep apnoea (OSA), which reduce their fitness for anaesthesia; restricted surgical access caused by intra-abdominal obesity; and an increased risk of postoperative complications, particularly wound infection, if open surgery is required.

To allow time for pre-surgical optimisation, a thorough preoperative assessment should be performed soon after diagnosis of endometrial cancer. This should include at least an electrocardiogram to assess arrhythmias, echocardiography to determine left ventricular function and the presence of valvular abnormalities, and other tests to investigate cardiac function, such as an exercise stress test or cardiac MRI. The STOP-BANG questionnaire is used to screen women for OSA, with formal diagnostic testing using polysomnography (sleep study that involves taking recordings of heart rate, brain and muscle activity, and eye movements) for those identified as being at high risk with a score of 3 or more (Table 1).[32] An anaesthetic review is often required to ensure that the woman will be able to tolerate a Trendelenburg position and to assess the need for postoperative care in a high dependency unit.

Ideally, surgery should involve a minimal access technique because this has been associated with a shorter hospital stay, lower infection rate and less postoperative pain.[33,34] Importantly, the available data show no difference in survival or rates of recurrence between patients with endometrial cancer undergoing a total laparoscopic hysterectomy and those treated by laparotomy.[34,35] Compared with laparoscopy, robotic surgery may have benefits because the operating time, blood loss, hospital stay and rate of conversion to laparotomy are lower, although the cost remains prohibitive for many hospital trusts.[36–38] There are currently insufficient data to inform the safest choice of surgical route in women with a BMI greater than 50 kg/m^2, for whom conversion rates are much higher than for women with a lower BMI.[39,40]

Few studies have compared the yield of pelvic and para-aortic lymph nodes in obese patients with endometrial cancer undergoing different modalities of surgery, although fewer lymphadenectomies appear to have been attempted in women with an extremely high BMI, by any surgical route.[40,41] If open surgery is planned, the procedure may be combined with an apronectomy to remove the excess skin and fat hanging over the pubic area so that access is improved.[42] In the rare instances in which even this is not feasible, vaginal hysterectomy with or without removal of the ovaries may be performed under regional anaesthesia in patients with localised endometrioid endometrial cancer.[31]

The operating theatre set-up is critical to reduce the risk of intraoperative and postoperative complications and requires good multidisciplinary working relationships between surgical, anaesthetic and nursing team members. Considerations include ensuring that the operating table can accommodate the patient's weight, use of a hover mattress to transfer the patient to the operating table, use of a beanbag or shoulder supports to prevent the patient from slipping down the table when in head-down tilt, use of an open entry technique or a long veress needle, availability of an adequate number and length of ports to make the operation as ergonomic as possible, and ensuring that experienced surgeons and assistants are available to undertake the procedure. A steep Trendelenburg position is required to move the bowel as far as possible out of the operative field, and this may be aided with the use of fan retractors. The Trendelenburg position may need to be reduced episodically to avoid respiratory compromise.

Table 1. STOP-BANG questionnaire screening for obstructive sleep apnoea.*

STOP	
S (snore)	Loud snoring
T (tired)	Daytime tiredness
O (observed)	Anyone observed cessation of breathing during sleep
P (blood pressure)	Have been or being treated for high blood pressure
BANG	
B (BMI)	BMI >35 kg/m^2
A (age)	Age >50 years
N (neck)	Neck circumference >40 cm
G (gender)	Male

*Individuals answering yes to three questions or more are considered at high risk of the condition. BMI = body mass index.

Radiotherapy

Adjuvant radiotherapy reduces the rate of pelvic recurrence in women with intermediate- to high-risk endometrial cancer.[43] It is preferentially administered as vaginal brachytherapy for women in whom the risk of lymph node metastases is low; this has been demonstrated to be non-inferior to external beam radiotherapy in achieving locoregional control but is associated with fewer bladder and gastrointestinal side effects.[44] Greater daily shifts and larger errors make planning and delivering radiotherapy more difficult in obese women; consequently, it is harder to accurately target the radiotherapy beam and avoid non-affected tissues.[45] Greater margins are therefore required to achieve optimal control.

Primary radiotherapy is an alternative option for women who are unfit for surgery and for those who are bleeding heavily. Most published data to date suggest that primary radiotherapy is inferior to surgery for primary disease management, being associated with a rate of recurrence of up to 18%.[46] Combined external beam radiotherapy and intracavitary brachytherapy is associated with the best locoregional control and long-term outcomes; however, high-dose brachytherapy alone may prove sufficient in early-stage, low-grade endometrial cancer.[47] The accurate placement of intrauterine applicators to deliver brachytherapy is limited by the patient's fitness for general anaesthesia and is technically

challenging at extremely high BMIs. When placing intrauterine applicators, some centres sedate the patient or use no anaesthesia,[48] but this approach is not widely practiced or available. There are no randomised controlled trials (RCTs) comparing surgery or hormone treatment and primary radiotherapy with curative intent in endometrial cancer.

Chemotherapy

The PORTEC-3 study has provided the necessary evidence on which to base decisions regarding the use of chemotherapy in endometrial cancer.[49] The trial demonstrated that combined chemoradiotherapy using platinum and paclitaxel chemotherapy improved failure-free survival only in women with stage III disease. Adjuvant chemotherapy had no effect on survival in women with high-risk disease confined to the uterus, or on overall survival.

Most morbidly obese women present with low-grade, early-stage disease and do not require adjuvant chemotherapy. For obese women with intermediate- to high-risk disease, it is challenging to ensure that they receive an adequate dose of chemotherapy. The formulae used to estimate glomerular filtration rate and dose carboplatin can potentially result in the delivery of inadequate doses of the drug because they underestimate creatinine clearance in individuals with a large body surface area.[50] Obese women also have larger volumes of distribution, which can reduce target tissue drug levels and can clear chemotherapeutics from the circulation at a different rate to women with lower BMIs, particularly if there is coexisting fatty liver disease or renal dysfunction.[51] There are, however, no clinical trial data available to guide chemotherapy dosing in obese women. Dose capping is often employed to try to prevent toxicity, but this may compromise clinical outcome, including progression-free and overall survival.

Conservative treatment

For women with atypical hyperplasia and low-grade endometrioid endometrial cancer with minimal myoinvasion, who are either medically unfit for surgery or who decline hysterectomy because of a desire to preserve fertility, the LNG-IUS Mirena® (Figure 3) and/or oral progestins are alternative treatment options.[52] Initial success rates of 50% and 65% have been reported for stage Ia low-grade endometrial cancer and atypical hyperplasia, respectively, but recurrence rates may be as high as 25%. Intrauterine progestin may have equivalent clinical efficacy to oral progestins, but fewer systemic side effects.[52,53] There have been no RCTs comparing these treatments with standard care, and the available data on their effectiveness are derived from a small number of observational studies with limited follow up.

Baseline imaging is important if conservative treatment is chosen. Progestin treatment is unlikely to be curative if disease has progressed past stage Ia, but it may stabilise disease progression and alleviate symptoms and, if disease is more advanced, there may be benefits for quality of life. There is a high prevalence of coincident adnexal masses in women treated conservatively for endometrial cancer and serial imaging may be necessary to exclude sinister pathology.[54] Expert review of the index biopsy and a repeat sample taken at the time of LNG-IUS insertion or oral progestin prescription is also important to rule out rapid progression and/or high-grade disease.

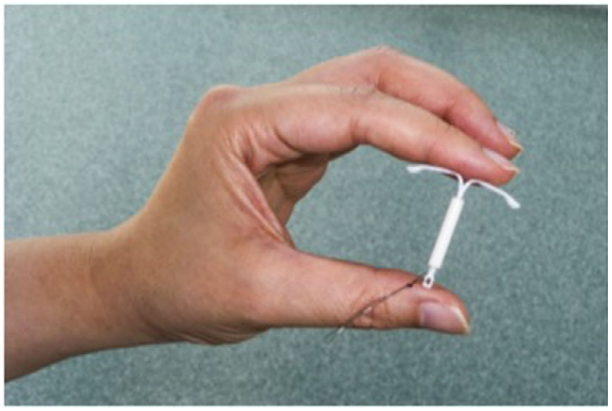

Figure 3. The levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena®). The Mirena® coil releases 20 µg levonorgestrel per day directly into the uterine cavity, ensuring the highest level of the drug is delivered to the endometrial abnormality, while minimising systemic side effects.

The optimal dose and route of progestin therapy for the conservative management of atypical hyperplasia and endometrial cancer is unknown. Doses of medroxyprogesterone acetate (MPA) of 200–400 mg daily, in single or split doses, are commonly used, but this drug is associated with weight gain, headaches and an increased risk of venous thromboembolic events.[55] The LNG-IUS ensures compliance and, crucially, does not cause weight gain. For most women, even those with an extremely high BMI (>60–70 kg/m^2), it can be inserted in clinic if a Winterton speculum and colposcopy chair are available. Around 20–30% of women experience increased bleeding and pain in the first 6 weeks, but this is not of oncological consequence. Single agent LNG-IUS is probably sufficient if the endometrium is thickened but there is no intrauterine mass. Resection of large intrauterine polyps prior to LNG-IUS insertion may improve response rates,[56] but large volume disease may benefit from combined treatment with both oral and intrauterine progestin, particularly if the first endometrial surveillance biopsy at 3 months does not show a marked progestin response (Figure 4). There is no evidence that treatment schedules should differ according to menopausal status.

Using the 6–12 month progestin treatment window to address endometrial cancer risk factors, including obesity and insulin resistance, may improve outcomes for obese

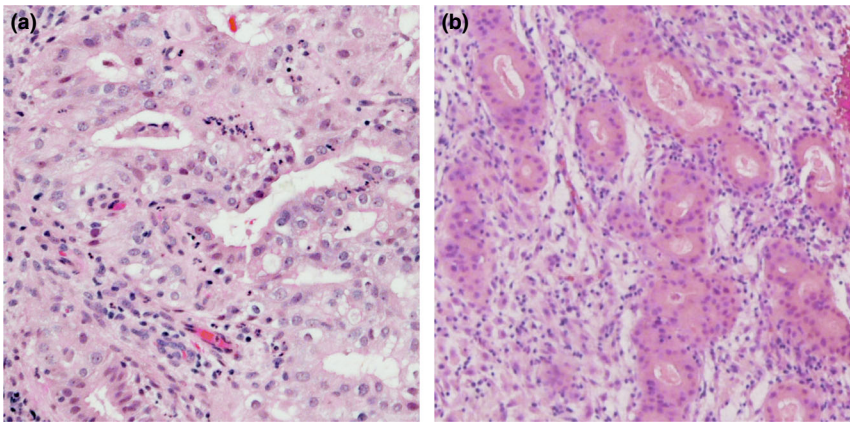

Figure 4. Photomicrographs of intrauterine progestin-treated endometrial cancer. a) shows residual endometrial neoplasia despite progestin treatment; b) shows minor cytological atypia only with marked progestin effect.

endometrial cancer patients. Weight loss may increase pathological complete response rates to progestin treatment,[22] reduce recurrence after treatment cessation, enable minimal access hysterectomy if progestin treatment fails, improve natural fecundity, enable assisted reproduction and/or improve the likelihood of its success, and improve general health and quality of life (Figure 5). The continuing ANZGOG feMME trial aims to be the first RCT to determine the efficacy of treatment with LNG-IUS ± metformin ± weight loss on pathological complete response rate in early-stage endometrial cancer in obese women at 6 months.[57]

Follow up of women using these alternative treatments should include an endometrial biopsy every 3 months in the first year, and twice a year thereafter, to check for disease resolution, progression or recurrence. Interval MRI imaging is also recommended if surgery could be an option. Currently, there are no validated biomarkers to predict treatment response,[58] and most experts opine that hysterectomy should be performed once childbearing is complete, irrespective of disease status, in those who choose to avoid hysterectomy for fertility-sparing reasons.[31]

Long-term outcomes in obese patients with endometrial cancer

Epidemiological studies have suggested that obesity adversely affects prognosis for patients with endometrial cancer,[59] but it is unclear whether this is because of an increased risk of endometrial cancer-specific death or death from other causes.[60] Endometrial cancer management is frequently suboptimal in obese women because of the difficulties described above. This, in itself, adversely affects survival. When obese women do receive standardised treatment consistent with non-obese women, as happened in the MRC ASTEC RCT, there is no difference in endometrial cancer-specific survival between the two groups.[61]

Whether weight loss improves endometrial cancer-specific survival is unknown. Studies in breast cancer have shown that weight loss reduces markers of recurrence, including total and free estradiol, insulin, adiponectin and inflammatory and cancer-promoting proteins.[62,63] Few studies have investigated the benefits of weight loss following treatment for endometrial cancer and all have had limited follow up, been underpowered to examine the effect of the intervention on survival and used diet and exercise regimes that failed to achieve substantial weight loss.[64] Only one RCT reported survival at 24 months and found no improvement in overall survival with a lifestyle and behavioural intervention.

Achieving and maintaining clinically meaningful weight loss is extremely challenging; however, endometrial cancer may be the patient's first obesity 'symptom' and serve as an important 'teachable moment' to underpin their subsequent lifestyle choices.[65] Furthermore, the gynaecologist may be uniquely placed to deliver this teachable moment: one study found that of obese survivors of endometrial cancer who were counselled by their gynaecological oncologist, all attempted weight loss compared with just 56% of those who were counselled by their GP.[66] Successful weight loss was reported more frequently when the intervention was delivered within 6 months of endometrial cancer diagnosis.[66,67]

Besides any potential impact on disease-specific survival, weight loss could improve overall survival in women with a history of endometrial cancer by reducing the risk of death from other causes. Cardiovascular disease remains the most common cause of death in women with early-stage endometrial cancer, with twice as many deaths occurring from myocardial infarction, stroke and heart failure than cancer.[68,69] This is because of an increased prevalence of obesity, hypertension,

Figure 5. Intrauterine progestin plus gastric bypass for grade 1, stage Ia endometrial cancer with no myometrial invasion. Mary (who consents to her photo being shown) a) at baseline, weight 170 kg; b) at 12 months, weight 120 kg. c) MRI pelvis at baseline, showing bulky stage Ia endometrial cancer (arrow); d) MRI pelvis at 12 months, showing complete radiological resolution (arrow), with complete endometrial response confirmed on biopsy.

hypercholesterolaemia and diabetes in survivors of endometrial cancer compared with the general population, and these risk factors are more likely to be undiagnosed and inadequately managed.[70,71] Following primary endometrial cancer treatment, women should have their blood pressure, cholesterol and HbA1C measured and their 10-year cardiovascular disease risk calculated using the online QRISK2 calculator (https://qrisk.org/). Cardiovascular risk factors should be optimised, including through promotion of weight loss, and statin therapy instituted for all women with a QRISK2 score of 10% or more for primary cardiovascular disease prevention, irrespective of cholesterol measurement and in accordance with NICE guidance. Such interventions are likely to reduce the number of cardiovascular events in the following 10 years and potentially improve overall survival in this population.

Conclusion

As well as underpinning its aetiology, obesity adversely affects the diagnosis, management and survivorship of women with endometrial cancer. Abnormal bleeding in morbidly obese, premenopausal women should be taken seriously as a 'red flag' symptom for cancer and investigated appropriately. The management of obese women with endometrial cancer should, whenever possible, include optimising comorbidities, multidisciplinary team input and use of minimal access surgery to provide the best care. Alternative evidence-based treatments for endometrial cancer are urgently needed for premenopausal women and those who are medically unfit for surgery. Weight loss should be encouraged to reduce the risk of endometrial cancer in the prevention setting and to improve overall and cardiovascular-specific survival in the post-treatment setting. Whether weight loss also offers opportunities for the treatment of obese patients with endometrial cancer is an exciting but unexplored area of research.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

SJK and and EJC contributed equally to this article. Both authors read and approved the final version of the manuscript.

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