Effect of bariatric surgery on endometrial cancer regression as part of fertility sparing treatment: A case series and literature review

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Abstract

Introduction: Obesity is a major risk factor in the development of endometrial cancer (EC) in young patients of reproductive age. Fertility sparing treatment is a viable option for a select group of patients with early EC, and involves systemic and intra-uterine hormonal therapy. Weight loss has been associated with improved outcomes in this group. Bariatric surgery (BS) has been shown to be the most efficient and durable method of weight loss in obese patients. However, there is a paucity of data studying the benefit of BS as part of fertility sparing treatment. **Methods:** We present a retrospective case series of five patients who are undergoing fertility sparing treatment for early EC, who also underwent BS for treatment of obesity and related comorbidities. We aim to show early regression of EC for all the patients and also report on the other health benefits of BS. **Results:** All five patients in the series achieved regression of EC within six months of undergoing BS. They also achieved significant weight loss consistent with previous studies, and three patients who had comorbidities related to obesity had remission of these conditions. One of the patients with EC regression also managed to conceive with IVF. **Conclusion:** Patients on fertility sparing treatment for early EC who underwent BS was associated with early regression within 6 months, significant weight loss and resolution of comorbidities. BS could be a promising component of fertility sparing treatment. Long term, prospective studies are required to confirm the benefits reported in this case series.

Effect of bariatric surgery on endometrial cancer regression as part of fertility sparing treatment: A case series and literature review

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Abstract and Keywords

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Conclusion: Patients on fertility sparing treatment for early EC who underwent BS was associated with early regression within 6 months, significant weight loss and resolution of comorbidities. BS could be a promising component of fertility sparing treatment. Long term, prospective studies are required to confirm the benefits reported in this case series.

Keywords: Endometrial cancer, fertility sparing, bariatric surgery.

Introduction

Endometrial cancer (EC) is the second most common gynaecological cancer worldwide with 417,367 cases diagnosed globally in 2020[(1)]. Global estimates showing rising incidence rates in both developed and developing countries [(2)]. EC can be divided into 2 subtypes: type 1, the oestrogen-dependent endometrioid type associated with obesity that accounts for up to 85% of ECs, and type 2, the non-endometrioid subtypes that include serous, clear-cell, undifferentiated carcinomas and malignant mixed Mullerian tumours and are typically not associated with obesity [(3, 4)]. Although the majority of patients with EC are diagnosed when they are postmenopausal, about 20% of patients are diagnosed when they are still of reproductive age. The majority of these patients tend to present with low-grade early stage tumours of the endometrioid subtype that are confined to the endometrium [(5)].

The standard treatment for early EC is total hysterectomy, bilateral salpingo-oopherectomy (THBSO) with or without lymphadenectomy[(6, 7)]. Following current standard surgical treatment, the 5-year survival for EC is good, ranging from 74% to 91%, particularly for women diagnosed with low-grade endometrioid tumours without lymph node involvement [(8)]. However, given the current trends of women of reproductive age delaying childbearing[(9)] and the rising incidence of EC amongst nulliparous women, an alternative treatment is necessary for patients who desire preservation of childbearing potential. Fertility sparing treatment for EC can be considered for a select group of patients who have FIGO grade 1 tumour of the endometrioid subtype, without myometrial invasion, lymph node involvement or distant metastasis. This treatment approach mainly involves endocrine therapy with oral progestins, gonadotropin-releasing hormone (GnRH) agonists or levonorgestrel-releasing intra-uterine devices. Patients on this treatment protocol require regular surveillance

with endometrial biopsy until tumour regression[10]. However, medical treatment alone for EC has the problems of long response time, unpredictable response and high recurrence rates.

Obesity is an established risk factor for EC, mainly due to the endogenous hyper-estrogenic state it creates in a patient's body. The worldwide epidemic of obesity is likely to be a key factor in the increasing incidence of EC [11]. Despite this clear link between obesity and EC, there is a paucity of data studying the effect of weight loss induced by bariatric surgery (BS) as part of the fertility sparing treatment. BS has been shown to be an effective treatment of obesity, producing sustained and significant weight loss, along with improvement in multiple obesity-related co-morbidities[12]. At the tissue level, BS is associated with downregulation of pro-proliferative signalling pathways, reduced endometrial growth, and spontaneous clearance of both latent and precursor endometrial neoplastic lesions [13]. BS is also associated with reducing the odds of developing EC in obese women[14]. Based on these factors, there is a strong biological rationale that weight loss induced from BS is an important factor that could contribute to successful regression of EC in patients on fertility sparing treatment. Additional benefits of BS for this group of patients include improvement in overall health from weight loss and improvement in fertility rates (from both natural conception and assisted reproduction) after fertility sparing treatment. In the event that these patients require surgical resection for EC in the future, weight loss also reduces peri-operative risks and improves success rates for minimally invasive techniques.

The aim of this study is to provide a case series of patients on fertility sparing treatment who underwent BS for the treatment of morbid obesity. The primary outcome of the study is to report on the early regression of EC (within six months) with successful weight loss after BS. The secondary outcome of the study is to report outcomes from BS including weight loss and improvement in related medical co-morbidities. In addition, we aim to review the literature on the relationship between morbid obesity and EC, as well as the role of BS in the fertility sparing treatment of obese patients with early EC.

Methods

All patients undergoing BS in Changi General Hospital (CGH) have their data collected prospectively in the hospital database for audit purposes. The patients who undergo BS are selected based on national healthcare guidelines (BMI greater than 37.5 kg/m^2 or BMI greater than 32.5 kg/m^2, with co-morbidities related to obesity) and are treated by a multidisciplinary team (comprising medical, nursing and allied health professionals) under a standard pathway. The study was approved by the Institutional Review Board (CIRB no: 2022/2195). Starting from January 2021 to December 2022, from the database, we identified a group of five patients who have early EC on fertility sparing treatment who also underwent BS for treatment of morbid obesity. The patients who are on fertility sparing treatment for EC are treated in a specialist gynecological oncology unit in KK Women's and Children's Hospital (KKWCH) by a multidisciplinary team under a standard pathway.

This is a retrospective case series. After consent was taken from patients, we collected data from electronic medical records (EMR). The data consisted of baseline patient characteristics, EC disease characteristics, fertility sparing treatment details, BS details and treatment outcome (in terms of EC regression, weight loss and improvement in metabolic conditions) after BS. The descriptive analysis of the data is show in the section below.

Results

Five patients with confirmed EC were included in this case series. All of them were females at reproductive age who opted for fertility sparing treatment. Their age ranged between 27 and 37; the median patient age was 32. Three patients (60%) had co-morbidities which were related to obesity. The mean pre-op weight was 109.54kg and the mean pre-op BMI was 40.73 kg/m^2. Table 1 summarizes the patient characteristics.

Table 1: Patient Characteristics

Patient	Age	Co-morbidities	Pre-op Weight (kg)	Pre-op BMI (kg/M^2)
1	32	Asthma, DM	106.5	40.65
2	37	Hypertension, Hyperlipidemia, DM	113.1	40.10
3	27	None	89.8	38.80
4	35	Hyperlipidemia	106.4	40.00
5	29	None	131.9	44.10

DM = Diabetes Mellitus.

The patients included in the study were diagnosed between 2020 and 2022. Notably, there were two cases (Patients 4 and 5), where the endometrial cancer had previously regressed with hormonal treatment but subsequently recurred. In addition, Patient 1 had been treated with hormonal therapy for twelve months without regression. This could be because the underlying primary risk factor of obesity had not been addressed. Four patients (80%) were diagnosed with hysteroscopy, dilatation and endometrial curettage (HDC), and one (20%) was diagnosed using with endometrial sampling with the Explora Device. All patients had low grade, early-stage cancer, with endometroid as the tumor subtype. All patients had standard staging investigations after diagnosis with CT scan of the thorax and abdomen, as well as MRI scan of the pelvis. No evidence of myometrial invasion, lymph node or distant metastases were found after staging scans were performed for all patients. Patients 4 and 5 had repeat staging investigations before they were considered for fertility sparing treatment again, after EC recurrence. Before fertility sparing treatment was offered to all the patients, the cases were discussed in a multidisciplinary tumor board meeting, with concurrence from all treating specialists. All patients underwent hormonal therapy with oral Megestrol, gonadotropin-releasing hormone agonists (Triptorelin and Leuprolide) as well as levonorgestrel-releasing intra-uterine device (Mirena), in accordance to the standard treatment pathway. After starting on treatment, patients underwent HDC on three monthly interval for surveillance. Table 2 summarizes EC disease characteristics and hormonal therapy received.

Table 2: EC disease characteristics and hormonal therapy received.

Patient	Date of EC Diagnosis	Method of Diagnosis	Tumor Grade	Tumor Subtyp
1	June 2020	HDC	G1-G2	Endometroid
2	December 2020	HDC	G1	Endometroid
3	August 2021	Explora	G1	Endometroid
4	March 2016 (regressed July 2018, recurred October 2021)	HDC	G1	Endometroid
5	March 2019 (regressed May 2020, recurred March 2022)	HDC	G1	Endometroid

HDC = Hysteroscopy, dilatation and endometrial curettage.

All the patients were referred to undergo BS as their BMI fulfilled criteria based on national healthcare guidelines. Pre-operative preparation was done for all patients based on a standard pathway, including review by members of a multidisciplinary team, blood tests, upper gastro-intestinal endoscopy and two weeks of meal replacement with a very low-calorie diet (VLCD). All patients underwent laparoscopic sleeve gastrectomy (LSG) and there were no complications from BS. After BS, all patients had EC regression within six months based on histology on HDC (Table 3). After BS, the mean time taken for EC regression was 3.2 months. For three patients (1, 3 and 4), there was normalization of endometrial cells. The other two patients (2 and 5) had regression to complex hyperplasia. Patient 2 still had simple endometrial hyperplasia 10 months after BS, while follow-up duration for patient 5 is still very short. Patients are instructed about contraception and to avoid conceiving for at least twelve months after BS. Two patients (1 and 3) underwent

IVF 12 months after BS, with patient 1 successfully conceiving. There are no maternal or fetal complications during the gestation period up to the end of the follow-up period.

Table 3: EC regression after BS.

Patient	Type of BS	Date of BS	Length of follow-up (months)	Time to EC regression (months)	Histology at ti
1	LSG	July 2021	19	1	Progesterone e
2	LSG	July 2021	19	2	Complex hype
3	LSG	December 2021	14	6	Progesterone e
4	LSG	April 2022	10	5	Progesterone e
5	LSG	November 2022	3	2	Complex hype

IVF = in-vitro fertilization.

After BS, all patients were followed-up at three monthly intervals for the first twelve months, with regular blood tests to check for resolution of obesity-related comorbidities and nutritional deficiency. All the patients were placed on vitamin, calcium and iron supplement as part of the standard treatment pathway. The weight loss and comorbidity resolution outcome are reported in Table 4. The mean total weight loss was 27.24kg and mean percentage total weight loss was 25.28%. Patient 5 had lower weight loss compared to the rest of the patients due to the short follow-up, and patients undergoing BS usually achieve maximal weight loss about 9 to 12 months post-op. We expect her weight loss to continue. Besides the regression of endometrial cancer after BS, patients' (1, 2 and 4) comorbidities related to obesity went into remission, and they did not have to take medications to control these conditions anymore.

Table 4: Weight loss and comorbidity resolution results after BS.

Patient	Type of BS	Date of BS	Pre-op Weight (kg)	Length of follow-up (months)	Weight loss at end of follow
1	LSG	July 2021	106.5	19	28.4
2	LSG	July 2021	113.1	19	30.4
3	LSG	December 2021	89.8	14	23.8
4	LSG	April 2022	106.4	10	32.2
5	LSG	November 2022	131.9	3	21.4

BS = bariatric surgery. DM = diabetes Mellitus. LSG = Laparoscopic Sleeve Gastrectomy.

Literature Review

Effect of obesity on EC tumorigenesis

With advances in tissue molecular research, we are now becoming increasingly aware that visceral fat functions as a complex endocrine organ. It is made up of adipocytes, macrophages, stromal, nerve and stem cells. The array of adipokines they secrete exerts a wide range of effects on endometrial cells, leading to increased proliferation, genetic mutations and eventually carcinogenesis [11, 15, 16].

Adipocytes, preadipocytes and mesenchymal stem cells within visceral fat are the main source of endogenous aromatase, which converts androgens to estrogen [17]. In addition, sex hormone-binding globulin levels decrease with increasing adiposity, leading to an increase in the pool of bioactive estrogen [18]. These factors contributes to estrogen-induced proliferation of endometrial cells, via the activation of the various signaling pathways. Estrogen metabolites are also thought to be mutagenic, causing DNA breaks and contributing to genetic instability, increasing the chance of carcinogenesis [19].

EC is strongly associated with metabolic syndrome and hyperinsulinemia, which in turn are strongly associated with obesity [20, 21]. There is increased expression of insulin and IGF1 receptors observed in endometrial

cells when there is endometrial hyperplasia, which increases the responsiveness of the cells to elevated levels of insulin and insulin-like growth factor 1 (IGF1) [22]. This in turn leads to hyperactivity of MAPK and AKT signaling frequently seen in endometrial hyperplasia and EC. Hyperglycemia also serves to fuel the growth of metabolically tissues, including endometrial hyperplastic and cancer cells [23].

It is an increasingly well-established fact that obesity and metabolic syndrome is associated with a chronic inflammatory state. This is modulated by pro-inflammatory adipokines, such as leptin, tumor necrosis factor α and interleukin-6. Together with worsening insulin resistance and hyperinsulinemia, these inflammatory mediators increase the release of IGF1, leading to endometrial cellular proliferation[24]. Because of the chronic inflammatory state, there is also increased cellular stress, leading to genetic instability and DNA damage. When endometrial cells with DNA mismatch repair defects accumulate deleterious genetic mutations, this leads to endometrial hyperplasia, atypia and eventually EC.

The interplay and synergistic effect of a hyper-estrogenic state, hyperinsulinemia and chronic inflammatory state predisposes obese women to an increased risk of developing EC much earlier, when they are of reproductive age.

Bariatric Surgery and Endometrial Cancer

BS has been shown to be the most durable and effective treatment for obesity [12] while improving the life expectancy and quality of life of obese patients [25]. In addition, BS has also been shown to improve multiple aspects of metabolic health of obese patients, including diabetes control (decreased glycated hemoglobin levels, better glycemic control, decreased requirement for glucose-lowering medications), lipid control (decreased triglyceride levels, increased HDL levels) and microvascular complications (decreased urine albumin to creatinine ratio) [26, 27].

Patients who undergo BS have reduced overall cancer risk compared with controls [14, 28 – 30]. There is also good evidence that obese patients who had BS have a reduced risk of developing endometrial cancer [14, 31 – 33]. This is most likely from the improvement in the metabolic and insulin-resistance state from weight loss and other beneficial effects of BS. These common factors and pathways are also involved in the development of EC. Weight loss is associated with spontaneous clearance of serum and endometrial tissue biomarkers of endometrial cancer risks [34].

There is a paucity of data for using BS as part of the fertility sparing treatment. A prospective nonrandomized study conducted by Barr et. al. observed that weight loss improves the response rates in women with obesity and atypical hyperplasia or early EC undergoing fertility sparing treatment with intrauterine progestin. Patients who lost more than 10% of total body weight were nearly 4 times more likely to respond to intrauterine progestin than those who did not (OR 3.95 p=0.02). In this study, BS was offered as a treatment for obese patients and resulted in a greater and more sustainable weight loss compared to nonsurgical treatment [35].

Reproductive outcomes in patients undergoing fertility sparing treatment are promising, especially when Assisted Reproductive Techniques (ART) are used [36]. However, obesity negatively affects fertility rates and lowers the chances of achieving a successful pregnancy, one of the long-term goals of fertility sparing treatment[37]. Studies have indicated that BS improves fertility rates in obese female patients [38]. Pregnancy is safe after BS and evidence shows lower risk of maternal complications like gestational diabetes and pre-eclampsia, compared to patients who are morbidly obese. There is mixed evidence regarding perinatal outcomes in patients who had undergone BS, with some studies showing possible association with reduced birth weight that may be due to nutritional growth restriction [39]. As such, patients who have undergone BS should be advised to avoid conceiving for at least 12 months post-op, with adequate contraception during this period. When patients who have undergone BS conceive, they should have nutritional surveillance and be screened for macro- and micro-nutrient deficiencies regularly. They should also be instructed on strict compliance with nutritional supplementation during pregnancy[40].

Discussion

This study describes BS as a promising component in the fertility sparing treatment for patients who have early EC. This is the first study discussing this topic in the local setting, and one of the few studies worldwide describing using BS in this context.

Morbid obesity is the underlying biological factor that drives the development of endometroid EC in young patients in the reproductive age group. Addressing this underlying factor with BS is a logical treatment strategy that can potentially improve the regression rates and reduce recurrence rates of EC. Indeed, we see two patients who had EC previously and had cancer regression with hormonal therapy. They had recurrence a few years after treatment. Another patient had a long treatment period with hormonal therapy, without regression of EC. This could possibly be because obesity, as the underlying driving factor for cellular proliferation and carcinogenesis, had not been addressed. Long term follow-up and data is necessary to demonstrate if weight loss induced by BS results in reduced EC recurrence and survival benefit.

In addition, weight loss induced by BS improves the chances of fertility, both via natural conception or via ART, reduces maternal and fetal complications antenatally and reduces risks in the peri-partum period. We see that one of the patients had successfully conceived with IVF and had no maternal or fetal complications during the antenatal follow up period. Once the other patients pass the first 12 months after BS, where weight loss is rapid and extensive, they would be counselled to undergo ART to aid in conception.

The improvement in physical and psychological health after BS provides additional benefit to this group of patients. Total weight loss is between 25 to 30%, which is consistent with other large-scale studies. We also saw resolution of obesity related comorbidities, which could lead to improved health outcomes and reduced complications from cardiovascular diseases in the long term [12, 27].

The limitations of this case series include the retrospective nature of the study design, the lack of a control group, the short follow-up time and the small number of patients in the study group. The retrospective nature of the study design makes it prone to selection and measurement bias. The patients included in this study are only those that are treated in the centers in which the authors are based. In addition, the early cancer regression in this group of patient who chose to undergo BS may be due to other factors like higher compliance to the fertility sparing treatment or increased health seeking behavior. Measurement bias can also result from incomplete or heterogeneous data from a lack of standard study protocol. This is partially mitigated by the fact that all the treatment received by the patient (both fertility sparing treatment for EC and BS) were according to a standard pathway, and all data collected were from the same comprehensive EMR system used in both public healthcare institutions. The outcomes measured were also objective in nature e.g. histology proving that EC has regressed and weight loss measured in the outpatient clinic during follow-up appointments. The lack of a control group prevents us from inferring a causal relationship between EC regression and BS. We are also unable to draw any conclusions about the longevity of the cancer regression due to the short follow-up period.

Conclusion

In this retrospective case series, patients on fertility sparing treatment for early EC who underwent BS were associated with early cancer regression within six months. In addition, patients had significant weight loss and resolution of comorbidities. BS could be a promising component of fertility sparing treatment for early EC. The overall and metabolic health benefits from weight loss induced by BS in this study is consistent with current literature. Larger scale, prospective case controlled studies with longer follow-up period is required to confirm the oncological benefit of BS for this purpose. This study could add to the body of evidence and raise awareness for this promising treatment strategy, while forming the background data for future prospective studies.

References

1. Sung H, Ferlay J, Siegel RL et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.

2. Yi et al. Epidemiological trends of women's cancers from 1990 to 2019 at the global, regional, and national levels: a population-based study. Biomarker Research 2021 9:55.
3. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 1983;15:10-7.
4. Setiawan VW, Yang HP, Pike MC et al. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol 2013;31:2607-18.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
6. A. Oaknin, T. J. Bosse, C. L. Creutzberg et. al. Endometrial cancer : ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022 09;33(9):860-877.
7. PDQ Adult Treatment Editorial Board. PDQ Endometrial Cancer Treatment. Bethesda, MD: National Cancer Institute. Updated Feb 24 2022. https://www.cancer.gov/types/uterine/treatment-pdq. PMID: 26389270
8. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet 2016;387:1094-108.
9. Matthews TJ, Hamilton BE. Delayed childbearing: more women are having their first child later in life. NCHS Data Brief 2009:1-8.
10. Andreas Obermair et. al. Fertility-sparing treatment in early endometrial cancer: current state and future strategies. Obstet Gynecol Sci 2020;63(4):417-431.
11. Michaela A. Onstad et. al. Addressing the role of obesity in endometrial cancer risk, prevention and treatment. J Clin Oncol 2016 34:4225-4230.
12. Colquitt J.L. et. al. Surgery for weight loss in adults. Cochrane Review. The Cochrane Library 2014, Issue 8. http://www.chochranelibrary.com
13. MacKintosh ML, Derbyshire AE, McVey RJ et al. The impact of obesity and bariatric surgery on circulating and tissue biomarkers of endometrial cancer risk. Int J Cancer 2019;144:641–50.
14. Syed I. Khalid et. al Association of Bariatric Surgery and Risk of Cancer in Patients With Morbid Obesity. Ann Surg 2022;275:1–6.
15. Renehan AG, Zwahlen M, Egger M: Adiposity and cancer risk: New mechanistic insights from epidemiology. Nat Rev Cancer 2015;15:484-498.
16. Park J, Morley TS, Kim M, et al: Obesity and cancer: Mechanisms underlying tumour progression and recurrence. Nat Rev Endocrinol 2014;10:455-465.
17. Blakemore J, Naftolin F: Aromatase: Contributions to physiology and disease in women and men. Physiology (Bethesda) 2016;31:258-269.
18. Simo R, Saez-Lopez C, Barbosa-Desongles A, et al: Novel insights in SHBG regulation and clinical implications. Trends Endocrinol Metab 2015; 26:376-383.
19. Cavalieri E, Rogan E: The molecular etiology and prevention of estrogen-initiated cancers: Ockham's Razor: Pluralitas non est ponenda sine necessitate. Plurality should not be posited without necessity. Mol Aspects Med 2014;36:1-55.
20. Nead KT, Sharp SJ, Thompson DJ, et al: Evidence of a causal association between insulinemia and endometrial cancer: A Mendelian randomization analysis. J Natl Cancer Inst 2015; 107-178.
21. Mu N, Zhu Y, Wang Y, et al: Insulin resistance: A significant risk factor of endometrial cancer. Gynecol Oncol 2012;125:751-757.
22. McCampbell AS, Broaddus RR, Loose DS, et al: Overexpression of the insulin-like growth factor I receptor and activation of the AKT pathway in hyperplastic endometrium. Clin Cancer Res 2006;12: 6373-6378.
23. Ryu TY, Park J, Scherer PE: Hyperglycemia as a risk factor for cancer progression. Diabetes Metab J 2014;38:330-336.
24. Kwon H, Pessin JE: Adipokines mediate inflammation and insulin resistance. Front Endocrinol (Lausanne) 2013;4:71.
25. Syn NL, Cummings DE, Wang LZ et al. Association of metabolic–bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174 772 participants. Lancet. 2021;397:1830–41.
26. Ghiassi S, Morton JM. Safety and efficacy of bariatric and metabolic surgery. Curr Obes Rep.

2020;9:159–64.
27. Arterburn DE, Telem DA, Kushner RF, Courcoulas AP. Benefits and risks of bariatric surgery in adults. JAMA. 2020;324:879–87.
28. Sjöholm K, Carlsson LMS, Peltonen M et al. Association of bariatric surgery with cancer incidence in patients with obesity and diabetes: long-term results from the Swedish obese subjects study. Diabetes Care. 2022;45:444–450.
29. Wiggins T, Antonowicz SS, Markar SR. Cancer risk following bariatric surgery—systematic review and meta-analysis of national population based cohort studies. Obes Surg. 2019;29:1031–9.
30. Schauer DP, Feigelson HS, Koebnick C et al. Bariatric surgery and the risk of cancer in a large multisite cohort. Ann Surg. 2019; 269:95–101.
31. Ishihara BP, Farah D, Fonseca MCM, Nazario A. The risk of developing breast, ovarian, and endometrial cancer in obese women submitted to bariatric surgery: a meta-analysis. Surg Obes Relat Dis. 2020;16:1596–602.
32. Upala S, Sanguankeo A. Bariatric surgery and risk of postoperative endometrial cancer: a systematic review and meta-analysis. Surg Obes Relat Dis. 2015;11:949–55.
33. Winder AA, Kularatna M, MacCormick AD. Does bariatric surgery affect the incidence of endometrial cancer development? A systematic review. Obes Surg. 2018;28:1433–40.
34. MacKintosh ML, Derbyshire AE, McVey RJ et al. The impact of obesity and bariatric surgery on circulating and tissue biomarkers of endometrial cancer risk. Int J Cancer 2019;144:641–50.
35. Barr CE, Ryan NAJ, Crosbie EJ et. al. Weight loss during intrauterine progestin treatment for obesity-associated atypical hyperplasia and early-stage cancer of the endometrium. Cancer Prev Res 2021;14:1041-1050.
36. Chae SH, Shim SH, Lee SJ et. al. Pregnancy and oncologic outcomes after fertility sparing management for early stage endometrioid endometrial cancer. Int J Gynecol Cancer 2019;29:77-85.
37. Gonthier C, Walker F, Luton D et. at. Impact of obesity on the results of fertility-sparing management for atypical hyperplasia and grade 1 endometrial cancer. Gynecol Oncol 2014;133:33-7.
38. Moxthe LC, Sauls R, Ruiz M et. al. Effects of Bariatric Surgeries on Male and Female Fertility: A Systematic Review. J Reprod Infertil. 2020;21(2):71-86.
39. Khan R, Dawlatly B, Chappatte O. Pregnancy outcome following bariatric surgery. The Obstetrician & Gynaecologist 2013;15:37–43.
40. Denison FC, Aedla NR, Keag O, Hor K, Reynolds RM, Milne A, Diamond A, on behalf of the Royal College of Obstetricians and Gynaecologists. Care of Women with Obesity in Pregnancy. Green-top Guideline No. 72. BJOG 2018.