

THE EFFECTS OF OBESITY ON SURGICAL OUTCOMES IN ENDOMETRIAL CANCER

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List of Abbreviations

HTAR	: Hospital Tengku Ampuan Rahimah
BMI	: Body Mass Index (BMI)
ASA	: American Society of Anaesthesiology (ASA)
TAH	: Total Abdominal Hysterectomy
TAHBSO	: Total Abdominal Hysterectomy and Bilateral Salphingo-oophorectomy
BSO	: Bilateral salphingo-oophorectomy
PLND	: Pelvic lymph nodes dissection
Hb	: Haemoglobin
EBL	: Estimated blood loss
PE	: Pulmonary embolism
DVT	: Deep vein thrombosis
FIGO	: International Federation of Gynecology and Obstetrics
SPSS	: Statistical Package for Social Sciences
EC	: Endometrial cancer
OR	: Operating time
PCOS	: Polycystic ovarian syndrome

ABSTRAK

OBJEKTIF: Masalah kegemukan/obesiti telah menjadi masalah serius diseluruh pelusuk dunia. Ia dikaitkan dengan pelbagai masalah kesihatan termasuk kanser endometrium. Kajian ini dijalankan untuk melihat kesan obesiti terhadap hasil pembedahan pesakit-pesakit kanser endometrium di Hospital Tengku Ampuan Rahimah.

KAEDAH KAJIAN: Kajian retrospektif ini dijalankan di Jabatan Obstetrik dan Ginekologi Hospital Tengku Ampuan Rahimah selama enam tahun (Januari 2014 sehingga Disember 2019). Pesakit-pesakit ini telah disahkan menghidapi kanser endometrium berdasarkan ujian patologi. Rekod perubatan mereka dikaji and maklumat-maklumat tersebut diisi dalam borang informasi. Data yang diperolehi, dipindah masuk ke dalam perisian SPSS versi 26 untuk analisis.

KEPUTUSAN: Seramai 81 pesakit telah dimasukkan ke dalam kajian ini. Purata BMI pesakit adalah 25.99kg/m^2 dengan SD 4.04. Kebanyakan pesakit, (n=41, 50.6%) adalah obes kelas 1 ($\text{BMI} \geq 30\text{-}35.5\text{ kg/m}^2$) diikuti oleh berat badan berlebihan ($\text{BMI } 25\text{-}29.9\text{kg/m}^2$, n=14, 17.3 %) dan pesakit berat badan normal (n=13, 16.0%). Kebanyakan pesakit adalah obes dengan jumlah keseluruhan 54(66.7%) manakala 27(33.3%) pesakit berada dalam kategori bukan obes. Kajian kami mendapati bahawa pesakit obes mempunyai lebih banyak komplikasi intraoperative, termasuk masa pembedahan yang lebih lama (186 min vs. 155min, $p = 0.014$) dan jumlah kehilangan darah yang lebih banyak (701 ml vs. 544 ml, $p = 0.006$). Walau bagaimanapun, tidak ada hubungkait yang ketara antara obesiti dan masalah selepas pembedahan, sama-ada komplikasi jangka pendek atau jangka panjang (30 hari selepas pembedahan).

KESIMPULAN: Obesiti adalah faktor risiko yang besar kepada hasil perioperatif dan pembedahan pesakit dengan kanser endometrium. Oleh kerana masalah obesiti semakin meningkat, usaha untuk mengurangkan kelazimannya dapat memberikan kesan yang baik terhadap hasil pembedahan barah endometrium. Selain itu, kami mencadangkan program pemulihan, yang merangkumi mengenal-pasti pesakit yang obes dan mempersiapkan pesakit dalam keadaan yang optimum sebelum rawatan pembedahan, pengurangan berat badan dan program senaman untuk mengurangkan morbiditi dan menambah baik hasil pembedahan di kalangan pesakit barah endometrium.

ABSTRACT

INTRODUCTION AND OBJECTIVE:

The prevalence of obesity is increasing and it causes significant morbidity and mortality. Obesity is closely related to endometrial cancer. This retrospective study evaluated the effects of obesity on the surgical outcomes among patients with endometrial cancer in Hospital Tengku Ampuan Rahimah.

STUDY METHOD: This retrospective study was performed at Hospital Tengku Ampuan Rahimah over 6 years between 1st January 2014 and 31st December 2019. Patients who were diagnosed histologically with endometrial carcinoma were identified through the cancer registry. Patient's information which included BMI, pre-operative, intra-operative, and post-operative complications was obtained. Data analysis was carried out with SPSS version 26.0.

RESULTS: A total of 81 patients were included in this study. The mean BMI of the patients was 25.99kg/m² with the SD of 4.04. Most of the patients, were obese class 1(n=41, 50.6%) followed by overweight (n=14, 17.3%) and the rest were normal BMI patients(n=13,16.0%). This study found that obese patients had more intraoperative complications, including longer operative time (186 min vs. 155 min, $p = 0.014$), and more blood loss (701 ml vs. 544 ml, $p = 0.006$). However, there is no relationship between obesity and postoperative problems, both short-term and long-term complications (30 days postoperative).

CONCLUSION: Obesity is a significant risk to perioperative and surgical outcomes of patients with endometrial cancer. As the prevalence of obesity is increasing, efforts to reduce its prevalence may provide beneficial effects on the surgical outcome of endometrial cancer. Furthermore, we propose rehabilitation programs, which include patient optimization before surgical treatment, weight reduction and exercise programs to reduce morbidity and improve endometrial cancer patient outcomes.

1.0 INTRODUCTION

Obesity is a major health concern all over the world including in Malaysia. The prevalence of obesity had shown an increment over the last 20 years. In the global context, alongside rapid economic development and prosperity in many countries especially in Asia, obesity has become an alarming health issue. In Malaysia, there is a dramatic increment in the prevalence of obesity over the past decade from 5.5% in 1996, to 12.2 % in 2003 and 14.0% in 2006(Khambalia & Seen, 2010). National Health and Morbidity Survey (NHMS) 2019 found that 50.1% of Malaysian adults are either overweight (30.4%) or obese (19.7%). The prevalence of obesity was high in women, Indian ethnicity and age between 55 to 59 years (NHMS,2019).

It has been well established that obesity and the excess amount of unopposed oestrogen are associated with endometrial cancer. Excessive fat consumption and obesity are important risk factors present in almost 50% of women with endometrial cancer. This is particularly true for the type 1, oestrogen-dependent tumour which is classically associated with anovulation and obesity.

Endometrial cancer is one of the most common gynaecologic malignancies in western countries, with an estimated 60,050 new cases US and 10,170 deaths in 2015. In the UK, 8617 new cases of endometrial cancer were reported in 2012. In Malaysia, the National Cancer Registry (2012-2016) reported that endometrial cancer contributed 4.5% to all cancer cases in women. It is the third most common gynaecological malignancy after cervical and ovarian cancer.

Endometrial cancer is broadly classified into 2 broad histologic types:

- 1) Type I (endometrioid)
- 2) Type II (non-endometrioid)

Type I Endometrioid cancer is made up of cells in the gland that look much like the normal uterine lining (endometrium), are more common, and represent 80-85% of all endometrial cancer.

Type II (non-endometrioid) endometrial cancer such as clear cell carcinoma, mucinous adenocarcinoma and papillary serous adenocarcinoma are less common types of endometrial carcinoma. They tend to grow quickly and often have spread outside the uterus during diagnosis with poor prognosis.

Surgery at diagnosis is the standard treatment for women with endometrial carcinoma. Traditionally surgery for endometrial cancer consists of laparotomy total abdominal hysterectomy and bilateral salphingo-oophorectomy with or without concurrent lymphadenectomy. Laparoscopic surgery for women with early-stage endometrial cancer also gained widespread acceptance as the laparoscopic surgery was found to reduce hospital stay and postoperative complications with similar intraoperative complications.

Surgery in obese patients can be challenging and thus potentially affects the anaesthesiologic parameters, perioperative complications and surgical performance when patients have to be operated on. Although obese women are predisposed to have Type 1, low grade, well-differentiated carcinoma and better prognosis in comparison to women of normal weight, they are ironically seen to have higher mortality with endometrial cancer (Everett E, Tamimi H, Greer B., et al 2003). However, the degree and type of morbidity associated with the surgical staging of endometrial cancer which is attributable to obesity are uncertain. Obesity's effect on endometrial cancer survivors' mortality, both disease-specific and overall survival is remained debatable.

This study was conducted to evaluate the effects of obesity on surgical outcomes of endometrial cancer. The results of this study will help gynaecologist to optimise patient's condition prior to surgery, thus reducing the intraoperative and perioperative morbidity.

2.0 LITERATURE REVIEW

2.1 Basic Epidemiology of Endometrial Cancer

2.1.1 Incidence

The worldwide incidence of endometrial cancer is increasing each year with an estimated 320,000 cases in 2012(Kiesel et al., 2020; Shaw et al., 2016). Endometrial cancer is the sixth most diagnosed cancer in women after breast, bowel, lung, cervical and ovarian malignancy. Global Cancer Statistic in 2020(GLOBOCAN) found that 417,000 new cases and 97,000 deaths were related to endometrial cancer. The incidence of endometrial cancer is more common in developed countries. The numbers are rising due to an increase in life expectancy, changes in lifestyle e.g., lack of physical activity and sedentary lifestyles as well as the increased rate of obesity. All these factors increased the risk of endometrial cancer. (Kean Ghee, n.d.; Kiesel et al., 2020; Onstad et al., 2016).

Endometrial cancer is a disease that occurs primarily in postmenopausal women. Data from SEER Programme, National Health Institute U.S(2010-2014) shows that the highest percentage of new cases of endometrial cancer were detected in women around and after menopausal age (16.7% for 45–54 years of age, 34.5% for 55–64 years, and 25.8% for 65–74 years). It is relatively uncommon in patients younger than 40 years. Another report by Wartko et al., found that the incidence of endometrial cancer was increase over time in women 50–74 years of age (annual percentage change 2004–2009: 2.8%; 2005–2009: 3.3%; and 2006–2009: 4.2%) after the introduction of the Women Health Initiative in 2002.

2.1.2 Mortality rates

It is estimated 42,000 women died from endometrial cancer every year. The overall 5 years survival rates are around 75-80% if presented at early disease. In the United States the 5-years survival rates is estimated to be 82% (Miller K et al.,2016; Siegel et al.,2018). The mortality rates are lower in developed countries compared to developing countries due to the presence of better screening and treatment programme.

In the general population of healthy women, disease specific mortality from endometrial cancer has been reported as 6.25-fold higher (95% confidence interval (CI) 3.75–10.42) in the comparison between obese versus non-obese women (Suidan et al.,2017).

In one of the populations – based study investigating the prognostic factors affecting the survival of younger women with uterine cancer, the overall 5-year disease –specific survival was 82% in women under 45 years, Pellerin et al (2005).

Gunderson et al concluded that obese women tend to have lower stage uterine cancer at presentation. The risk of recurrence and the disease specific mortality are similar to those normal weight patients. However, the mortality rates in obese women were related to all-cause mortality but not disease-specific mortality.

2.1.3 Types of endometrial cancer

Bokhman et al., in 1981 proposed the theory of two pathogenetic types of endometrial cancers. Type 1 is related to unopposed endogenous or exogenous oestrogen. This cancer is frequently associated with obesity, nulliparity, insulin resistance and hypoestrogenic state. It is also frequently arisen on the background of endometrial hyperplasia. Type 1 endometrial cancer are usually well differentiated and have better prognosis. Type II endometrial cancer occurs in older post-menopausal women who are thin and non-oestrogen dependent. It is less differentiated and has poor prognosis.

The characteristics of Type I and Type II are as shown in Table 2.1.

Table 2.1: Characteristics of Type 1 and Type 11 endometrial cancer

Characteristic	Type 1	Type II
Unopposed oestrogen	Present	Absent
Menopausal status	Pre and perimenopausal	Mostly postmenopausal
Obesity	Yes	No
Parity	Nulliparous or low parity	Multiparous
Grade	Low	High
Myometrial invasion	Minimal	Deep
Histology	Endometroid, adenoacanthoma	Papillary serous, clear cell
Behaviour	Less aggressive	Aggressive

2.1.4 Risk factors for endometrial cancer

The risk of endometrial cancer increases with age. The lifetime risk in a woman less than 75 years is 1-3%. Most cases are diagnosed at post-menopause and tend to be of higher grade and stage compared to younger women (Amant F et al., 2005). In the U.S., incidence rates are higher in African American compared to Caucasian, seven times higher compared to other ethnic groups, and mortality is significantly worse in black women compared to white women as the disease are usually associated with higher grade, poor histology types and late diagnosis (B. Long et al., 2013).

Other risk factors include unopposed oestrogens therapy, early menarche or late age of menopause, nulliparity, history of breast cancer and family history of endometrial cancer. Of all these factors, obesity is the most common cause of excessive endogenous production of oestrogens which predispose women to endometrial cancer. Co-existing medical illness such as diabetes mellitus, hypertension and heart disease are more commonly associated with endometrial cancer mortality (Fader A et al., 2009; Brinton L et al., 1992; Doccus L et al., 2010). Approximately 5% of endometrial cancer is associated with hereditary non-polyposis colon cancer syndrome (HNPCC) and lifetime risk is around 40-60% (Obermair et al., 2010). HNPCC is an autosomal dominant inheritance caused by germline mutation in DNA mismatch repair genes. These defect in MMR genes was found in 85% of HNPCC who had been diagnosed with endometrial cancer (Y. Hirai et al., 2008).

2.1.5 Standard management for endometrial cancer

Surgery for endometrial cancer is thorough exploratory laparotomy, peritoneal washing for cytology, extra fascial hysterectomy and bilateral salphingo-oophorectomy, together with or pelvic/ para-aortic lymphadenectomy. This is followed by adjuvant treatment in the form of radiotherapy and/or chemotherapy depending on the stage of the tumor and involvement of the lympho-vascular invasion. These surgical procedures can be carried out via three major approaches; laparotomy, laparoscopic or robotic assisted laparoscopy.

Bijen et al, conducted a randomised controlled trial on the outcomes from laparoscopic hysterectomy for early-stage endometrial cancer. The conversion rate from laparoscopic to laparotomy was similar between older women over 70years old and younger patients. However, they noted that there was a significant difference in conversion rate to laparotomy in obese women with a BMI $>35 \text{ kg/m}^2$ (32.3% vs 6.5%, OR: 1.17; 1.09–1.25). Increasing BMI also independently associated with occurrence of major complications (OR: 1.05 per increasing point BMI; 95% CI: 1.01–1.10). Thus, laparoscopic surgery for obese patients were not cost effective.

Panici PB et al evaluated the role of routine pelvic lymphadenectomy in stage 1 endometrial cancer in 524 patients from 31 centers for ten years durations. For stage 1 disease, no difference for relapse and death was noted regardless whether lymphadenectomy was performed or not.

In another large, controlled trial MRC ASTEC Trial (Efficacy of systematic pelvic lymphadenectomy) a total of 1400 women from 85 centers in 4 different countries with endometrial cancer suspected to be within endometrial cavity were recruited. There were two group i) control arm underwent standard surgery (hysterectomy, bilateral salphingo-oophorectomy, para-aortic lymph node palpation with suspicious node removal at surgeon's discretion, and ii) study arm above procedures plus iliac and obturator nodes dissection. The primary outcome was overall survival. This study echoed the findings reported by Panici et al where there was no benefit in the overall or recurrent free survival of pelvic lymphadenectomy in women with early endometrial cancer.

Both Panici and MRC ASTEC trial were not able to answer the question whether patient with intermediate/high risk required or benefited from pelvic lymphadenectomy. At present the accuracy of preoperative and intraoperative surgical staging, grade and tumor myometrial invasion is still inaccurate to decide whether patient required lymphadenectomy. Thus, complete surgery including pelvic lymphadenectomy is still being practice and become the gold standard for the treatment of endometrial cancer.

Pelvic and para-aortic lymph nodes metastasis is an important prognostic factor for staging in patient with endometrial cancer. FIGO staging for endometrial cancer 2009 has classified presence of metastasis to pelvic and para-aortic lymph nodes as stage IIIC1 and IIIC2 respectively.

New FIGO staging for endometrial cancer 2009 were shown in Table 2.2.

Table 2.2: International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging System for Endometrial Cancer

Stage 1	Tumour confined to the corpus uteri
1A	No or less than half myometrial invasion
1B	Invasion equal to or more than half of the myometrium
Stage 11	Tumour invades cervical stroma, but does not extend beyond the uterus
Stage 111	Local and/or local regional spread of the tumour
111A	Tumour invades the serosa of the corpus uteri and/or adnexa
111B	Vaginal and/or parametrial involvement
111C	Metastases to pelvic and/or para-aortic lymph nodes
111C1	Positive pelvic nodes
111C2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage 1V	Tumour invades bladder and/or bowel mucosa and/or distant metastases
1VA	Tumour invades bladder and/or bowel mucosa
1VB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

2.2 Obesity and endometrial cancer risk

Obesity had become one of the most challenging and alarming global health issues in this new millennium era. BMI is calculated as weight ($\text{kg}/[\text{height}(\text{m})]^2$) and categorized according to World Health Organization classifications. Obesity is defined when BMI $>30 \text{ kg/m}^2$ or higher while BMI between 25 kg/m^2 and 30 kg/m^2 were classified as overweight. The termed morbid obesity was used when the BMI is more than 40 kg/m^2 . Being overweight and obese is associated with increased risk of perioperative complications and higher morbidity and mortality. The rates and prevalence vary between countries and regions of the world. The rate of obesity is increasing especially in developed countries due to sedentary lifestyles and dietary habits. Among women, obesity is commonly associated with the development of endometrial cancer than any other cancer type (Ahmedkhanov et al,2001). Onstad et al stated that approximately 57% of endometrial cancers in the United States are related to being overweight or obese. This linear relationship has been well established and the incidence of endometrial cancer increases as BMI increases (Ward K et al,2013).

A meta-analysis of 26 studies by the American Institute for Cancer Research, found that for every increase of five units BMI, there was a 50% increment in the risk of developing endometrial cancer (Renehan A et al.,2008).

Comorbidities related to obesity such as diabetes mellitus, heart disease also contributes to the disease specific morbidity and mortality. Relative risk of disease specific mortality was up to 6.25 in obese women as compared with women with a normal BMI, the RR is 2.53(Calle E et al,2003).

2.3 Obesity and surgery

Obesity is associated with numerous disorders, such as diabetes, hypertension, and cardiovascular disease. Obese women also more commonly complicated with perioperative complications such as obstructive sleep apnoea, arrhythmias, acute cardiac events, and venous thrombotic events. Therefore, they would require more detailed and thorough preoperative assessment to reduce the morbidity and mortality.

Suidan et al in their study showed that women with a BMI ≥ 40 kg/m² had higher rates of wound infection, venous thromboembolism, and 30-day readmission to the hospital compared to other groups of patients. However, there was no difference in other complication types.

In another study involving 514 patient, 249 women had a BMI of < 30 kg/m², 195 had a BMI of 30–39.9 kg/m², and 70 women were morbidly obese (BMI ≥ 40 kg/m²). The total number of complications include wound complications, use of antibiotics and venous thromboembolism events were higher among obese vs non-obese group. However, obesity does not impact other outcomes including 30-day mortality (Bouwman F et al.,2015).

Akbayir et al., investigated the influence of BMI on surgical morbidity and outcome in three different group of patients (normal-weight, overweight, and obese patients). All the 370 women in the study underwent total abdominal hysterectomy, bilateral oophorectomy, and peritoneal cytology. There was no significant difference in duration of hospital stay, and estimated blood loss among the groups. However, those patients who are obese patients had significantly longer operation time.

Laparotomy performed for obese patients are usually more difficult due to technical aspects of the body habitus, limited exposure and poor visualization. It is also associated with anaesthetic complications such as higher ASA class, difficult intubation and ventilations (Mahdi et al., 2015). The American Association of Gynaecologic Laparoscopists stated that, within the past decade, minimally invasive surgeries have evolved and are often used to treat many gynaecologic cancers (Suidan et al., 2017; Uccella et al., 2016).

Pavelka et al in their study noted that intraoperative outcomes differed according to BMI. Patients with a BMI<40 had a longer mean operative time (205 min vs. 170 min, $P = 0.02$) and a significant amount of estimated blood loss (570 ml vs. 331 ml, $P = 0.002$). Despite that, rate of blood transfusion was similar. Intra-operative complications did not differ between strata of BMI. Postoperatively, there were remarkable differences between rates of wound infection (8.0% vs. 1.4%, $P<0.025$) and non-infectious wound breakdown (10.7% vs. 2.9%, $P<0.025$) for morbidly obese patients in comparison to normal weight patients. Other post operative morbidity such as ileus, venous thrombo-embolism, chest infection, lymphedema, nerve injury, and perioperative death were extremely rare and were not so much dissimilar between the group.

A gynaecologic oncology group, LAP2 ancillary data study, found that morbidly obese women tend to have lower stage, low risk disease upon diagnosis. Therefore, these group of women would benefit surgical staging by laparoscopic as they the risk of post operative were less as compare to laparotomy(Gunderson et al., 2014).

2.4 Biologic mechanisms on how obesity affects endometrial cancer risk

2.4.1 Endogenous Sex Steroid Hormones

Incidence of endometrial cancer is seen in women with high level of circulating oestrogen (Onstad et al.,2019; Akhmedkhanov et al.,2001). The “unopposed oestrogen” hypothesis explains that exposure of the endometrium to the circulating endogenous or exogenous oestrogen without progesterone opposition will cause endometrial proliferation and growth and increased risk of hyperplasia and malignancy (Figure 2.1). In obese women there is conversion of the fat adipocyte to androstenedione to estrone by aromatase (Moore K and Molly A. Brewer,2017). Generally, Type 1 endometrial cancer is attributed to the prolonged exposure to oestrogen either exogenous or endogenous in origin.

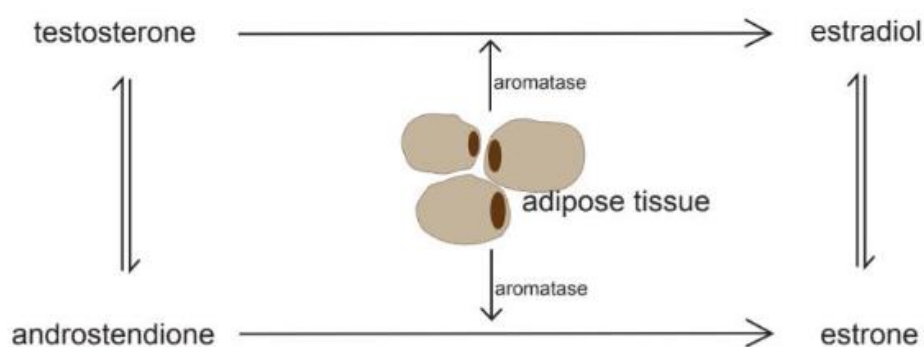


Figure 2.1: Steroid and endogenous hormone conversion

(Adapted from Kiesel et al.,2020)

Increase oestrogens level in plasma also cause increases IGF-1 receptor levels and reduces insulin growth factor binding protein (IGFBP), thus increasing the affinity of IGF-1 with its receptor within endometrial tissues (Potischman et al,1996) and causes proliferation of endometrium (Figure 2.2).

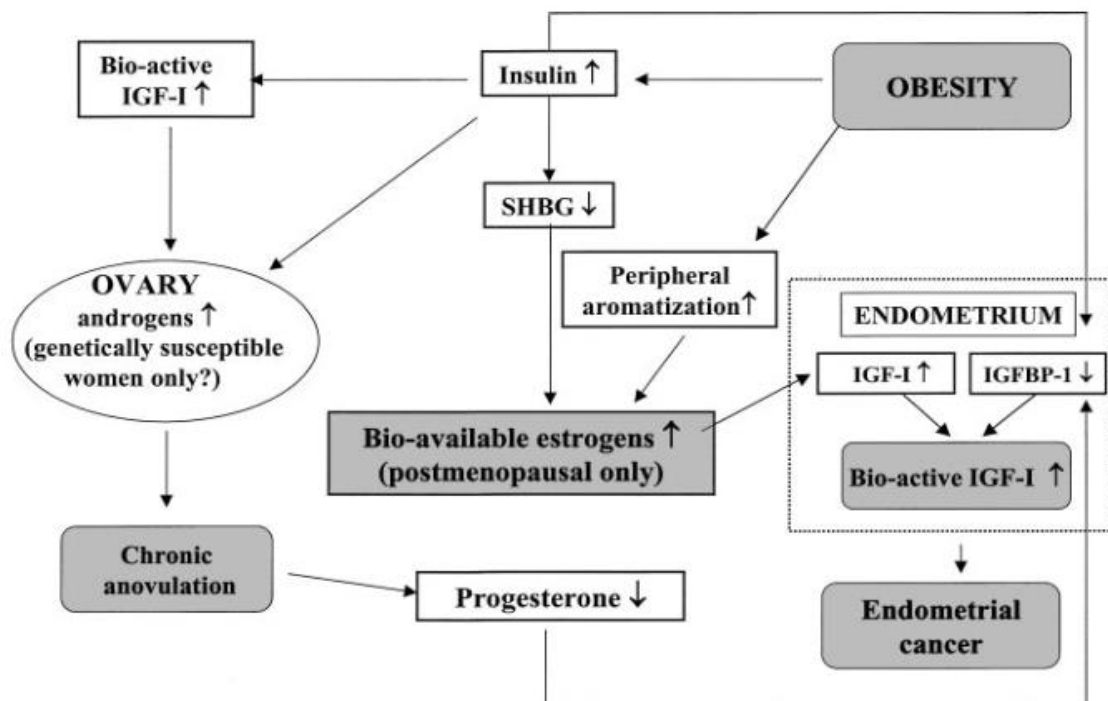


Figure 2.2: Relationship between endogenous hormones and endometrial cancer

(Adapted from Kaaks et al.,2002)

Similar to adipose tissue, hyperinsulinemia was also found to be associated with oestrogen dependent risk factor for endometrial cancer. Hyperinsulinemia increases the bioavailability of IGF-1 and directly promotes cell growth, inhibit cell death and stimulates cell proliferation and division in endometrial cancer cell lines (Nagle et al.,2012). High levels of IGF-1 and insulin then depress SHBG synthesis in the liver and induce steroidogenesis, increasing bioavailable oestrogen levels (Kaaks et al.,2002).

Several studies (Potischman et al.,1996, Nagle et al.,2012, Austin et al.,1991) have reported increased total oestrogen and bioavailable oestrogen levels (Pettersson et al.,1986) and decreased plasma SHBG levels (Potischman et al.,1996) in postmenopausal women with endometrial cancer compared to controls. Cauley et al demonstrated in postmenopausal women there is 40% increases in both circulating estrone and oestradiol in obese (BMI>30 kg/m²) versus normal BMI. Therefore, increased plasma levels of bioavailable oestrogen result from increased endogenous synthesis of oestrogen by adipose tissue combined with decreased SHBG production by the liver, increasing endometrial cancer risk in obese postmenopausal women.

Studies in women with polycystic ovarian syndrome (PCOS), a condition characterized by triad of chronic anovulation, insulin resistance and increased androgen levels, have shown some inter-relation between obesity, hyperandrogenism and endometrial cancer. Haoula et al stated that women diagnosed with PCOS had OR 2.89 (95% CI 1.52-5.48) of developing endometrial cancer as compared to general population. Prolonged anovulation in PCOS lead to exposure of endometrium with oestrogen without progesterone counter action which lead to development of endometrial hyperplasia/cancer.

Obesity also known to cause increase the release of pro-inflammatory markers, such as TNF- α and IL -6 while decreasing the release of anti-inflammatory markers. A variety of pro- (e.g., tumor necrosis factor (TNF)- α , leptin, interleukin (IL)-6, C-reactive protein (CRP) and anti- (e.g., adiponectin) inflammatory cytokines, known as adipokines, are secreted by adipose tissue and promoting a state of chronic low-grade inflammation (Kwon, H. and Pessin, J.E., 2013). Chronic, low-grade inflammation has been postulated to increase the risk of endometrial cancer by promoting cell proliferation and the production of free radicals that cause DNA damage. Defects in the DNA sequence will lead to genetic mutations and progression to endometrial hyperplasia and carcinoma.

3.0 RESEARCH OBJECTIVES

General: To evaluate the effects of obesity on the surgical outcomes in patients with endometrial cancer in Hospital Tengku Ampuan Rahimah.

Specific:

1.To compare the intra-operative complications (e.g.; blood loss, duration of operation, visceral organ injury) between obese and non-obese groups patient with endometrial cancer undergoing surgery.

2.To compare the post-operative complications (wound infections and venous thromboembolism) between the two studied group at 30 days post operation.

4.0 RESEARCH METHODOLOGY

4.1 Study design

This study was an observational retrospective study.

4.2 Study area

Data were collected from the Gynaecology ward, Department of Obstetrics and Gynaecology Hospital Tengku Ampuan Rahimah (HTAR).

4.3 Study duration

The study duration was for a period of 6 years (1st January 2014 till 31st December 2019).

4.4 Study population

The study involved all women who underwent surgical treatment for histologically-proven endometrial cancer at Hospital Tengku Ampuan Rahimah Klang in the time period January 2014 till December 2019.

4.5 Subject criteria

Inclusion criteria

All patients (obese and non- obese patients) who was diagnosed with endometrial carcinoma and underwent surgical intervention between study period 1st January 2014 until 31st December 2019. It also includes patients with other co-morbidities illness such as diabetes ,hypertension, heart disease and lung disease with or without medications.

Exclusion criteria

All patients who were diagnosed with endometrial carcinoma and underwent surgical intervention with unknown weight and height pre-operatively (unable to calculate BMI) and incomplete data.

4.6 Sample size estimation

Based on the prevalence of 5% endometrial cancer (Navaria I et al) the sample size was calculated by using single proportion formula.

Using single proportion formula

$$N = \frac{Z^2 P(1-P)}{C^2}$$

N= sample size

Z = statistic for a level of confidence

P = expected prevalence or proportion

C= precision

Value used in this study:

Z=1.96(confidence interval 95%), P= 5% (0.05), C=5 (0.05)

Thus, estimated sample size= 73 patients

Objective 1: Intraoperative complications

Using Raosoft sample size calculator, sample size is calculated for all the outcomes to be studied based on previous study by Gunderson et al (2014) and Mahdi et al(2015).

Outcomes/ Complications	Margin of error	Confidence level	Population size	Response distribution	Sample size
1. Mean blood loss	95	5	100	BMI <30kg/m ²	51
				BM1 30-39kg/m ²	54
				BMI >40kg/m ²	71
2.Need for blood transfusion	95	5	100	BMI <30 kg/m ²	60
				BM1 30-39 kg/m ²	66
				BMI >40 kg/m ²	68
3.Internal organ injury	95	5	100	BMI <30 kg/m ²	10
				BM1 30-39 kg/m ²	24
				BMI >40kg/m ²	14
4.Wound infections	95	5	100	BMI <30 kg/m ²	18
				BM1 30-39 kg/m ²	26
				BMI >40 kg/m ²	54
5.Venous thromboembolism	95	5	100	BMI <30 kg/m ²	26
				BM1 30-39 kg/m ²	14
				BMI >40 kg/m ²	29

Objective 2: 30-days post operative complication

Sample size calculation was done using the Raosoft calculator based on previous study by Suidan et al (2017)

Outcomes/ complications	Margin of error	Confidence level	Population size	Response distribution	Sample size
1.Wound infections	95	5	100	BMI <30 kg/m ²	32
				BM1 30-39 kg/m ²	32
				BMI >40 kg/m ²	51
2.Venous thromboembolism	95	5	100	BMI <30 kg/m ²	5
				BM1 30-39 kg/m ²	4
				BMI >40 kg/m ²	32

The biggest sample size was 71. Taking into consideration of 10% dropout, a minimum of 78 samples were required.

4.7 Methods of data collection

Sampling method/recruitment

Universal, non-probability sampling which include all the patients diagnosed with endometrial cancer between study period.

Data collection/recruitment

- 1.Consent from Director of Hospital Tengku Ampuan Rahimah to get access for the case notes obtained.
- 2.Cases of endometrial cancer who underwent surgery were collected from ward registration (cancer registry) notification and medical record notes.
- 3.The patient's data was collected and recorded on data sheet (proforma sheet).
- 4.The data was entered in the computer that is password protected.
- 5.On completion of study, data in the computer was copied to CDs and the data in the computer was erased. CDs and hardcopy were stored in locked office of the investigators and maintained for a minimum three years after completion of the study. The CDs and data will be destroyed after that period of storage.