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Polycystic ovary syndrome and endometrial hyperplasia: an overview of the role of bariatric surgery in female fertility

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Abstract

One of the most effective methods to tackle obesity and its related comorbidities is bariatric surgery. Polycystic ovary syndrome (PCOS) and endometrial hyperplasia (EH), which are associated with increased risk of endometrial carcinoma, have been identified as potentially new indications for bariatric surgery.

PCOS is the most common endocrine disorder in women in the reproductive age and is associated with several components of the metabolic syndrome such as obesity, insulin resistance and hypertension. EH is a pre-cancerous condition which arises in the presence of chronic exposure to estrogen unopposed by progesterone such as both in PCOS and obesity.

The main bariatric procedures are Roux-en-Y gastric bypass, laparoscopic sleeve gastrectomy and laparoscopic adjustable gastric banding. These procedures are well established and when correctly selected and can safely achieve significant sustainable weight loss and remission of obesity-related co-morbidities when performed by experienced bariatric surgeons.

Studies have shown that bariatric surgery can play an important role in the management of patients with PCOS and improve fertility. Similarly, bariatric surgery has a positive effect on endometrial hyperplasia, making surgically induced weight loss a potentially attractive option for endometrial cancer prevention and treatment.

Obesity has an adverse impact on spontaneous pregnancy, assisted reproduction methods and feto-maternal outcomes. After bariatric surgery obese women with subfertility can achieve spontaneous pregnancy. However, while bariatric surgery reduces the risk of pre-eclampsia and

gestational diabetes, there is an increased risk of small for gestational age and possible increased risk of stillborn or neonatal death.

In this article we will review the evidence regarding the use of bariatric surgery as a treatment modality in patients with PCOS and EH. We also provide an overview of the common bariatric procedures.

Keywords: bariatric surgery, obesity, endometrial hyperplasia, polycystic ovary syndrome.

Introduction

Obesity is a global epidemic with over 2.1 billion people worldwide now regarded as overweight or obese [1], which is likely to increase despite various steps that have been taken to address this problem such as public education, instituting sugar tax schemes or reducing the calorific content in foods [2-4]. One of the more recent methods to treat obesity is bariatric surgery and current evidence support that it is an effective treatment that results in sustainable reductions in weight and in the risks associated with morbid obesity and the related co-morbidities [5]. In 2013 the registered bariatric procedures worldwide have reached a historic high number of 470,000 [6]. With improvement in all outcomes, the eligibility criteria for bariatric surgery continue to expand [7-9]. Moreover, new potential indications are emerging such as idiopathic intracranial hypertension, non-alcoholic fatty liver disease, chronic kidney disease, polycystic ovary syndrome (PCOS) and endometrial hyperplasia (EH) [10-12][13-14].

PCOS is the most common endocrinopathy of women of reproductive age that is associated with insulin resistance, hyperandrogenism, adverse cardiovascular risk factors and subferility. Identification and management of PCOS constitute a major burden for the healthcare system [15]. Endometrial hyperplasia is a relatively common condition that affects women of all age groups. It relates to excessive cellular proliferation leading to increased volume of the endometrial tissue [16]. EH is diagnosed three times more commonly than endometrial cancer, and can progress to cancer if left untreated. Without intervention, the risk of progression to carcinoma (EC) is less than 1% for women with simple hyperplasia, 3% for complex nonatypical hyperplasia, and up to 29% for women with atypical complex hyperplasia [17]. World Health Organisation guidelines in 2014 have re-classified EH by categorizing it as hyperplasia without atypia and hyperplasia with atypia [18].

A recent systematic review showed that the risk of EC was three times higher in women with PCOS compared to women without the disease. The risk is even higher, up to three folds in obese women, and obesity is a predominant feature in PCOS. Management strategies to reduce the risk of EC in women with PCOS are therefore vital [16].

Polycystic Ovary Syndrome

PCOS can affect up to 10% in women of reproductive age [19]. PCOS is a heterogeneous disorder in which the principal features are androgen excess (clinically or biochemically), ovulatory dysfunction, and polycystic ovaries [13,15].

The pathogenesis of PCOS remains uncertain and likely to be multifactorial including interactions between genetic and environmental factors such as fetal exposure to androgens,

obesity and sedentary lifestyle. These can lead to increased GnRH pulsatile secretion and hyperinsulinaemia/insulin resistance, both of which result in increased adrenal and ovarian androgen secretion. The overall effect is an increased level of free androgens (worsened by reducing SHBG) resulting in the clinical features of hirsutism, anovulation and infertility (by arresting follicular development) [15].

Anovulation results in subfertility and decreased progesterone release result in unopposed oestrogen effects causing breakthrough bleeds and increased risk of endometrial hyperplasia, which can progress to endometrial cancer (2.7-fold risk increase) [21].

PCOS in both lean and obese individuals is independently associated with impaired glucose tolerance, insulin resistance, metabolic syndrome, type 2 diabetes mellitus, hypertension, increased risk of cardiovascular disease, deranged lipid profile, sleep apnoea and obesity [7,13,20,22-23]. Obesity and PCOS additively contribute to the evolution of metabolic syndrome. The similarity in the background and mechanism has led to the opinion that PCOS constitutes a female type of metabolic syndrome (syndrome XX) [24]. Obesity is very common in PCOS with almost 60% of affected women being obese [25]. This obesity is predominantly central, contributing further to the establishment of metabolic syndrome even in very young individuals [22]. Hyperinsulinaemia plays a cardinal role in the pathophysiology of both PCOS and metabolic syndrome with hyperandrogenaemia. Both lean and obese women with PCOS have increased circulating insulin levels relative to those of serum glucose compared with healthy lean and obese women [26]. Such a finding strongly suggests a certain degree of hepatic insulin resistance irrespective of obesity. Of note is that lean PCOS females present only

hepatic insulin resistance while obese affected individuals present global insulin resistance [15]. Hence, there is a significant metabolic heterogeneity in women with PCOS strongly influenced by obesity. Forty percent of such women will develop diabetes by the age of 50. This is not always dependent on BMI. The development of diabetes is not only attributed to peripheral insulin resistance but also to insufficient β-cell response to meals [27].

The relationship between PCOS and obesity is multifactorial and bi-directional. PCOS can exacerbate obesity and obesity can exacerbate PCOS in a vicious cycle pattern [20]. Additionally, PCOS clearly negatively affects the main components of the metabolic syndrome which constitute the established indications for bariatric surgery (such as type 2 diabetes, hypertension or hyperlipidaemia) [13,15]. In this context, PCOS represents an indirect target of bariatric interventions.

The current treatment strategies for PCOS include mainly lifestyle modifications along with insulin sensitizers (predominantly metformin) and other symptomatic treatments (such as oral contraceptives and progestins, anti-androgens). As obesity plays an important role in the pathogenesis of PCOS, bariatric surgery is being increasingly utilized as a treatment strategy [15].

Endometrial hyperplasia

Endometrial hyperplasia (EH) is a pre-cancerous, non-physiological, non-invasive proliferation of the endometrium that results in increased volume of endometrial tissue with alterations of glandular architecture (shape and size) and endometrial gland to stroma ratio of greater than 1:1 [28]. The majority of cases of EH arise in the presence of chronic exposure to oestrogen

unopposed by progesterone such as in PCOS and obesity. EH is classified according to the WHO classification system (**Table 1**).

The main risk factor for endometrial hyperplasia is increased unopposed oestrogen levels. Consequently any related condition constitutes a risk factor.

Obesity and EH

Obesity leads to high oestrogen relative to progesterone levels by various mechanisms:

1. increased peripheral conversion of androstenedione to oestrone within adipose stores
2. decreased circulating sex hormone-binding globulins, and
3. increased rates of anovulation [29-30].

Women with a BMI≥40 kg/m^2 are at a 13-fold increased risk of EH with atypia and a 23-fold increased risk of EH without atypia, chronic anovulation and PCOS [30]. Furthermore, BMI ≥35 kg/m^2 is strongly associated with failure to regress and relapse of complex hyperplasia treated with levonorgestrel-releasing (progestogen) intrauterine system [17]. Interestingly PCOS associated abnormalities such as obesity, nulliparity, infertility and diabetes can all act as risk factors independently as well as in the context of the syndrome [29].

Oestrogen-only hormone therapy and selective oestrogen receptor modulators (tamoxifen but not raloxifen) are also strongly associated with EH [30-31]. Lynch syndrome (hereditary non-polyposis colorectal cancer, also related with other cancers including endometrial, ovarian, gastric, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin) have also been

indirectly related to endometrial hyperplasia due to relative findings from screening studies for endometrial cancer.

Current treatment strategies for EH

The risk reduction strategies include the addition of progestogens to post-menopausal oestrogen replacement regimes, the treatment of PCOS-related anovulation and the aggressive management of obesity, diabetes and metabolic syndrome [23]. The mainstay recommendation for the treatment of EH without atypia is with the levonorgestrel releasing intrauterine system (LNG-IUS) [32, 33, 17]. An RCOG guideline now provides a comprehensive management plan for women with EH and bariatric surgery is recommended for reducing the risk of EH without atypia (Evidence level 2-) [34].

Bariatric surgery, PCOS and EH

In patients with PCOS and/or EH, addressing obesity, when present, can have significant benefits to the patients metabolic health.

The most successful treatment that results in sustained long term weight loss is bariatric surgery as the benefits obtained from dietary and lifestyle interventions are usually not sustained over the long-term [40-41]. Bariatric surgery results in greater improvement in weight loss outcomes and obesity-related comorbidities when compared with nonsurgical interventions, regardless of the type of surgical procedure used [42-43]. The most well recognized obesity-related co-morbidities are: Type 2 diabetes mellitus (DM2), hypertension, sleep apnoea, dyslipidaemia, metabolic syndrome and osteoarthritis. More morbid conditions

are proven to be weight-related and consequently are added to the potential targets of bariatric surgery. Characteristic examples are PCOS and EH. Bariatric surgery also results in significant improvement on quality of life parameters [44].

Current bariatric procedures

Many different surgical options of a variety of magnitude are currently available. They can be broadly divided into restrictive and malabsorptive procedures. However with increasing evidence for the mechanism of action, these boundaries are getting increasingly blurred. Restrictive procedures work mainly by mechanically reducing portion sizes i.e., by creating gastric inlet restriction. Malabsorptive procedures induce their effect by reducing the amount of active bowel, by creating a by-passing effect. It is now felt that the mechanisms behind weight loss following surgery are multifactorial including changes in the gut hormones (increased GLP-1 and PYY and reduced ghrelin), changes to energy expenditure, reduction in food intake and changes in food choices favouring less calorie dense food, possibly due to changes in taste and food perception and changes to gut microbial and bile salts metabolism [40-43].

Roux-en-Y gastric bypass (GBP): GBP is considered nowadays to be the gold-standard and most commonly performed bariatric procedure worldwide [6]. It offers a sustainable excess weight loss (EWL) of 60-65% achieved in the first 18-24 months after the procedure.

GBP procedure can be divided in 2 steps (**Figure 1**):

- The creation of a small proximal gastric pouch (volume <50mls) with the use of surgical staplers excluding the distal stomach, duodenum and proximal jejunum from the passage of food
- The reconstruction of the continuity of the GI track with a Roux-en-Y loop consisting of 2 anastomoses (jejuno-jejunal and gastro-jejunal) and thus defining an alimentary limp (100-150cm from the gastro-jejunal to the jejuno-jejunal anastomosis), a biliopancreatic limp (50-100cm from the ligament of Treitz to the jejuno-jejunal anastomosis) and a common limp (the rest of the small bowel from the jejuno-jejunal anastomosis to the ileocaecal valve).

Sleeve Gastrectomy (SG): SG although more recently introduced, has gained significant attention and is becoming widely accepted as a single stage procedure [43]. It has become the most commonly performed bariatric procedure in Europe and the second popular worldwide, due to its technical simplicity and relatively low complication rate [6]. Excess weight loss is sustained to 60% even in the long term follow up (5 years) [45-46].

Sleeve gastrectomy is performed with the use of surgical staplers and by longitudinally transecting the stomach, sparing approximately 5cm of antrum and up to the Angle of His (to the left of the gastro-oesophageal junction), leaving a tubular gastric remnant of 100-150mls (**Figure 2**).

Adjustable gastric band (AGB): AGB has been a well-established method for many years mainly benefiting from a low peri-operative morbidity and mortality. It accounts for 10% of bariatric operations worldwide. Of note is that initial weight loss is slow and mainly depends on the aggressiveness of adjustments (centre-dependent), but generally is at the level of 45-50% of excess weight and has proven sustainable even 15 years after the procedure [36,47-48].

A silicon band is implanted around/just below the gastro-oesophageal junction and is connected to a subcutaneous port for access and adjustment of the chamber of the band thus adjustment of the inner diameter (**Figure 3**).

Mortality and morbidity following bariatric surgery

Bariatric surgery gained popularity as it was associated with favorable figures of peri-operative complications and mortality. A meta-analysis from Buchwald reported a 30-day mortality rate of 0.1% for combined AGB and gastroplasty and 0.5% for GBP, despite including open bariatric operations [36]. More recent data in the laparoscopic era report very low mortality figures ranging from 0.05, 0.11 and 0.14% for AGB, SG and GBP, respectively [49].

Immediate post-operative morbidity is also low and mainly reflects the risk of staple line and anastomotic leak after SG and GBP (approximately 1%) and bleeding (approximately 1%). Hospital stay is low and ranges usually from 0 (day-case gastric bands) to 2 days (stapled procedures).

Weight-loss outcomes after bariatric surgery

A meta-analysis for weight-loss was first published by Buchwald in 2004 and included 22,000 patients [36]. It confirmed an excess weight loss between 48 and 70% over 2 years for the 4 procedures analysed. Since then a large number of meta-analyses have been published with comparable or better outcomes. The most frequently index used to assess weight loss is percentage excess weight loss (%EWL) which is provided by the equation [50]:

%EWL = (preoperative weight – current weight)x100/(preoperative weight – ideal weight)

Co-morbidity resolution after bariatric surgery

Bariatric surgery has been shown to be superior to medical therapy in achieving glycaemic control targets and diabetes remission in patients with Type 2 diabetes. The remission rate of Type 2 diabetes varies between studies due to variation in the definition of remission, which is much stricter in recent studies, the diabetes duration, the beta cell reserve at the time of surgery and the follow up after surgery. Overall, remission rates decrease over longer follow up and with longer diabetes duration and mire advanced beta cell failure. In addition diabetes remission rates are different for the 3 main procedures and reveal the escalating complexity of their physiology. In general bariatric surgery is a fast and efficient treatment for diabetes. This was highlighted 20 years ago by Pories et al who reported diabetes and glucose tolerance impairment resolution rates of 83% and 99% respectively, with follow up of up to 14 years after GBP [51]. Buchwald's meta-analysis reported a remission rate that ranged from 48% for AGB, to 84% for GBP and to 98% for BPD [36]. This study did not include SG data. The above results have been confirmed by more recent studies that also included SG which offered a remission

rate of 66-71% [46,52]. The most recent meta-analysis reported remission rate after GBP to be 66% after applying stricter criteria and with a follow up 2-5years [53].

Similarly, bariatric surgery has significant impact on other obesity-related comorbidities. Hypertension remission rates are approximately 20-43, 40-70 and 45-68% for AGB, SG and GBP respectively. Sleep apnoea remission rates are 29-68, 57-87 and 66-80% and dyslipidaemia remission rates are 27-59, 40-62 and 63-97%, respectively [36,46,52].

Equally important is the positive effect of bariatric surgery on health related quality of life. An increasing number of studies indicate that quality of life, measured by both generic and obesity-specific instruments, markedly improves after a bariatric intervention, although it might not reach this of non-obese population [54].

Although the above comorbidities are almost consistently reported in every bariatric publication other significant obesity-related conditions, such as PCOS, EH and infertility, have attracted less attention.

The impact of bariatric surgery in patients with PCOS and/or EH

PCOS: Life style interventions remain the first-line treatment in women with PCOS, but bariatric surgery is increasingly recognized as a possible treatment for women with PCOS and was recently recommended by RCOG as a possible treatment option in women who fail to achieve significant weight loss with lifestyle interventions and a BMI above 40 kg/m^2 (or 35 kg/m^2 in the presence of other obesity comorbidities).

Meta-analysis of randomized and non-randomized trials and case-series found only 13 studies. The studies included 2130 female patients, with 10 out of 13 of the studies including <100 participants. The mean ages and BMI in the studies included in the meta-analysis ranged 16-44 years (weighted mean 30.8 years) and 44-52 kg/m^2 (weighted mean 46.3 kg/m^2) respectively, with a weighted mean of 14 months follow up duration. Overall bariatric surgery resulted in reductions in PCOS (OR 0.27, 95% CI 0.14-0.52; p<0.001), hirsutism (OR 0.12, 95% CI 0.04-0.36; p<0.001), menstrual irregularities (OR 0.07, 95% CI 0.03-0.21; p <0.001) and infertility (OR 0.35, 95%CI 0.19-0.65; p<0.001) [13]. While, the meta-analysis concluded that bariatric surgery effectively attenuated PCOS and its clinical symptomatology, including subfertility, in severely obese women the lack of RCTs and the heterogeneity of PCOS definitions amongst studies are major limitations. In another study of 20 women with obesity and PCOS who received GBP and were followed up for about 4 years, menstruation was corrected in 82%, and hirsutism resolved in 29% [55]. Of the 10 patients who did not conceive before surgery, 6 patients had become pregnant within 3 years of surgery [55].

The impact of bariatric surgery in women with PCOS seems to be mediated by improvements in insulin resistance and androgen levels after surgery [13]. However, improvements in menstrual cycling and hirsutism did not correlate with the weight loss after surgery, suggesting a role for weight-independent mechanisms in the impact of bariatric surgery in women with PCOS [56]. The changes in weight loss after GBP are similar in women with and without PCOS.

However, weight-loss via pharmacotherapy and/or life style intervention is also beneficial in women with PCOS. In a study of 59 obese adolescent females with PCOS aged 12–18 years, who

underwent 1 year of lifestyle intervention (nutrition education, exercise training, and behavioural therapy), in the 26 girls who lost weight (−3.9kg/m^2), testosterone concentrations decreased significantly by a mean of 0.3nmol/litre and SHBG concentrations increased significantly by a mean of +8ng/ml compared to the subjects with increasing weight. Furthermore, the prevalence of amenorrhea and oligoamenorrhea was reduced by 42% and 19%, respectively [57]. A recent meta-analysis suggested that orlistat-induced weight loss in overweight and obese women with PCOS can reduce testosterone, insulin resistance markers and improve lipid profile. But due to the small sample size the meta-analysis was inconclusive on whether orlistat is advantageous over the established second line treatment with metformin [58].

It is not possible to be certain whether bariatric surgery is superior to lifestyle interventions or weight loss pharmacotherapy in women with obesity and PCOS due to the lack of randomized controlled trials. However, bariatric surgery has been proven to be superior to other methods of weight loss in patients with BMI ≥35 kg/m^2 in regards to the durability of the surgical weight loss, the impact on cardiovascular disease factors, the impact on glucose metabolism and quality of life.

EH: EH can occur in 7-10% of patients with morbid obesity [30,59-62]. This represents a 23-fold increase of the risk of EH in morbidly obese females [28]. It has been shown that bariatric surgery has a positive effect on endometrial histological changes and can ameliorate the risk of endometrial pathology [30,59,62]. In a meta-analysis of 3 studies involving 890,110 participants, bariatric surgery lowered the risk of endometrial cancer compared with controls

(RR= 0.40, 95% CI 0.20 - 0.79) [63]. Surgically induced weight loss represents a potentially attractive option for EC prevention and treatments [61], but RCTs are needed. Unfortunately there are no well-designed studies to report the impact of medical weight management on EH and even more to compare surgical versus medical treatment. It has been suggested though that metformin can act as a preventive measure of progression of EH as it is a potent inhibitor of endometrial cell proliferation by reducing the metabolic syndrome and lowering insulin and testosterone levels in postmenopausal overweight women [64].

Infertility: Increased BMI is associated with hyperleptinaemia, insulin resistance and hyperandrogenism all of which contribute to chronic anovulation and subfertility [65]. Abnormal LH pulsatility might also lead to abnormal oocyte recruitment, poor oocyte quality and altered endometrial development which could affect the function of the corpus luteum [66]. In addition to its impact on ovulation, obesity affects endometrial development, uterine receptivity, implantation, and miscarriage [67]. Furthermore, obesity is associated with increased risk for the mother (miscarriage, gestational diabetes, hypertension, pre-eclampsia, dysfunctional labour and caesarean section) and for the neonate (congenital malformations, macrosomia, and admission to a neonatal care unit). The risk of stillbirth is also strongly related to maternal BMI.

According to a meta-analysis of 13 case-series including 2130 PCOS patients, bariatric surgery lowers the risk of infertility (OR 0.35, 95%CI 0.19-0.65; p<0.001) [13]. In a different a meta-analysis of 8 studies (589 women, age 31-45 years, baseline BMI 40.9-50 kg/m^2), the weighted mean incidence for successful pregnancy after bariatric intervention was 0.580 (95% CI 0.539-

0.621, $p < 0.001$) which is not very far for the expected incidence for the "healthy population", in which 1 in 4 couples is expected to be affected by infertility [66].

Obesity is associated with significant adverse outcomes to the mother and newborn. As a result the British Fertility Society policy and practice guidelines recommend deferring any treatment until a woman's BMI is <35 kg/m^2, and recommending that BMI <30 kg/m^2 is preferable [67].

For the neonate there is strong evidence that after surgically induced weight loss the risk for excessive fetal growth is reduced while prematurity and small-for-gestational-age infants is more frequently expected [65,68]. Interestingly a sub-group analysis showed no increased prematurity risk after gastric band suggesting a potential correlation of prematurity and micronutrients malabsorption following other bariatric interventions [68].

Assisted reproduction: Ovarian stimulation is less likely to be successful with clomifene in obese patients and higher doses of gonadotrophins were required [65]. Despite that more recent studies have shown that oocyte numbers retrieved and pregnancy rates were not worse in comparison to normal BMI counterparts [65]. Similarly in intrauterine insemination when medication dosages were adjusted to overcome the weight-effect, the success of the treatment cycle was comparable to that of normal-weight women [65]. On the other hand for IVF methods obese patients had a 65% lower odds of having a live birth (LB) following their first IVF cycle comparing to patients with a BMI<30kg/m^2 [69]. Data from the Society for Assisted Reproduction Technology (SART) show that the odds of failing to achieve live birth was 18-48% higher for overweight and obese women (depending on the BMI) and significantly increased

adjusted odds for fetal loss and stillbirth [70]. Thus, overweight and obese women undergoing ART appear to be disadvantaged with respect to the dosage and duration required for ovarian stimulation, embryo implantation, pregnancy and LB rates as well as in the frequency of miscarriage and recurrent early pregnancy loss. Specific data on IVF after bariatric surgery are limited and quite preliminary but it seems that the bariatric intervention reduces treatment costs without affecting oocyte or embryo quality [71].

Conclusion

Bariatric surgery results in significant and sustained weight loss and improvements in obesity-related comorbidities. Non-randomised studies suggest that bariatric surgery could play an important role in the management of patients with PCOS and/or endometrial hyperplasia but randomized controlled trials are needed.

Bariatric surgery is an expanding field that is offering sustainable results both for weight loss and remission of co-morbidities. As new indications for bariatric surgery emerge and more diseases are more closely linked to the epidemic of obesity, the wider acceptance of weight-loss surgery as an addition to the treatment options will assist the optimization of the multi-modality management of conditions such as PCOS and EH which affect a large number of young population of reproductive age.

Conflict of interest

All authors have no conflict of interest to declare

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Legends

Table 1: Endometrial Hyperplasia classification

Figure 1: Roux-en-Y gastric by-pass

Figure 2: Sleeve gastrectomy

Figure 3: Adjustable gastric band

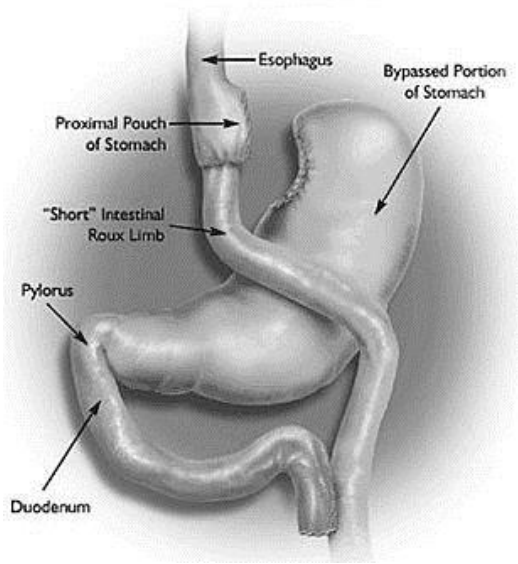

Figure 1: Roux-en-Y gastric by-pass

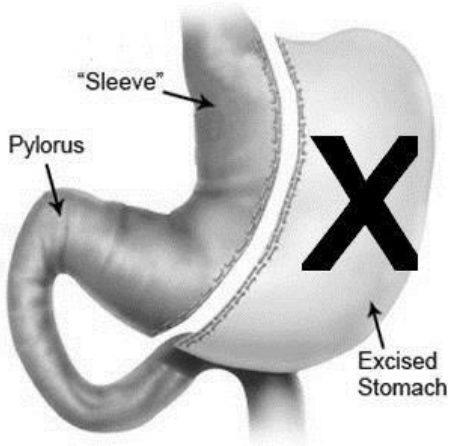

Figure 2: Sleeve gastrectomy

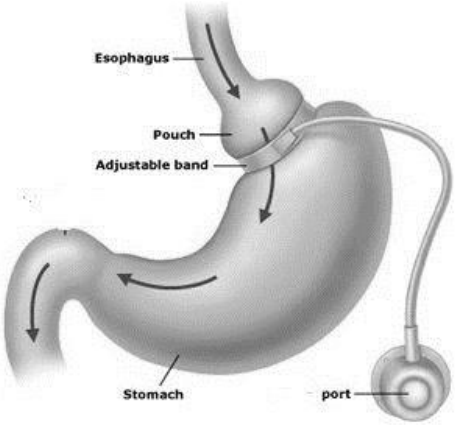

Figure 3: Adjustable gastric band

Table 1: Endometrial Hyperplasia classification

Classifying system	**Type**			
WHO (1994)	Simple hyperplasia	Complex hyperplasia	Simple hyperplasia with atypia	Complex atypical hyperplasia
Revised WHO (2003)	Proliferative endometrium	Simple hyperplasia	Complex hyperplasia	Complex atypical hyperplasia
WHO (2014)	Endometrial hyperplasia without atypia		Endometrial hyperplasia with atypia	