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REVIEW

Intragastric balloons for obesity: critical review of device design, efficacy, tolerability, and unmet clinical needs

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ABSTRACT

Introduction: Sustaining a healthy weight is a challenge and obesity, with associated risk of co-morbidities, is a major public health concern. Bariatric surgery has shown a great promise for many where pharmacological and lifestyle interventions failed to work. However, challenges and limitations associated with bariatric surgery has pushed the demand for less invasive, reversible (anatomically) interventions, such as intragastric balloons (IGBs).

Areas covered: This review critically appraises IGBs used in the past, present, and those in clinical trials, discussing the device designs, limitations, placement and removal techniques, patient eligibility, efficacy, and safety issues.

Expert opinion: Several intragastric balloons were developed over the years that brought excitement to patients and healthcare professionals alike. Albeit good efficacy, there had been several safety issues reported with IGBs such as spontaneous deflation, intestinal occlusion, gut perforation, and mucosal ulcerations. This led to evolution of IGBs design; device material, filling mechanism, fluid type, inflation volume, and further innovations to ease ingestion and removal of device. There are some IGB devices under development aimed to swallow like a conventional pill and excrete naturally through defecation, however, how successful they will be in clinical practice in terms of their efficacy and tolerability remains to be seen in the future.

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Obesity; bariatric surgery; sustainable weight-loss; metabolic surgery; gastroretention; multidisciplinary team; bridge-to-surgery

1. Introduction

Obesity is an ongoing global epidemic, approximately 2.1 billion individuals are obese worldwide, which is 30% of the total population. According to the National Health Service (NHS) in England, hospital admissions due to obesity continued to rise by 15% i.e. 617 to 711 in 2017–18. The recent statistics showed that obesity has increased to 29% from 26% since 2016. Moreover, men aged between 45 and 74 and women aged between 65 and 74 tend to be more obese [1]. The economic impact of obesity is estimated around £27 billion to the society. It is estimated that the NHS cost associated with obesity and overweight patients across UK will increase to £9.7 billion by 2050 [2].

To date, various approaches have been used to treat obesity (Figure 1), despite lifestyle intervention remains the key strategy to manage obesity, other therapeutic interventions help to prevent the development of co-morbid conditions. The pharmacological treatment is used as an adjunct to diet and exercise, though new medications for the treatment of obesity have been introduced in the market they are subject to adverse effects including serious cardiovascular events and have shown limitation on long term maintenance of weight loss [4]. More recently, surgical interventions such as bariatric surgery has provided a sustained and effective treatment for obesity. However, it is only offered under NHS when BMI is ≥ 50 or ≥ 35 in individuals with comorbid conditions such as diabetes or hypertension. Regardless of its effectiveness, there are challenges in offering bariatric surgery to wider obese populations due to high costs, access limitations via national health services, patient's compliance, and due to being a non-reversible permanent change to the gut anatomy [5].

Over the years, scientists, bariatricians, and gastroenterologists have been actively looking for obesity treatments that are minimally invasive, effective, and are without complications. Intragastric balloons (IGBs) were one of the less invasive and reversible therapeutic option for obesity. They are inserted within the gastric chamber followed by filling up either with a fluid or air (gas), and thereby induces a sense of fullness, satiety, therefore reduces the urge to eat. IGBs are usually indicated to reduce weight in patients with BMI ≥ 35 who are at a risk of developing chronic conditions such as cardiovascular diseases and in particular those who do not respond to lifestyle intervention alone [6].

The balloon occupies most of the resident gastric volume, delays gastric emptying and induces satiety (the sense of fullness), thereby reducing the urge to eat. Consequently, it leads to significant reduction in food consumption [7]. Furthermore, it also induces the release of gastrointestinal hormones that

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Article highlights

- There are various approaches to treat obesity notably: lifestyle intervention, pharmacotherapy, and surgery.
- Intragastric balloons (IGBs) have been popular, and preferred over surgery because they are less invasive, and reversible (anatomically) than bariatric surgery.
- This article critically appraises various intragastric balloons devices, their design, mechanism, and administration/removal techniques, comparative efficacy, limitations, and safety concerns.
- A historical perspective of IGBs is also presented; from gastric bezoar to the first regulatory approved IGB and details of devices withdrawn from the market for various reasons (safety, efficacy, etc.)
- The use of IGBs as bridge to surgery in morbidly obese patients is also described, with an emphasis of the role of multidisciplinary team in weight loss interventions, and importance of bariatric training.
- The article concludes with current issues in using IGBs, devices under development, and future perspectives in improving IGBs efficacy, tolerability, and sustainability of the weight-loss.

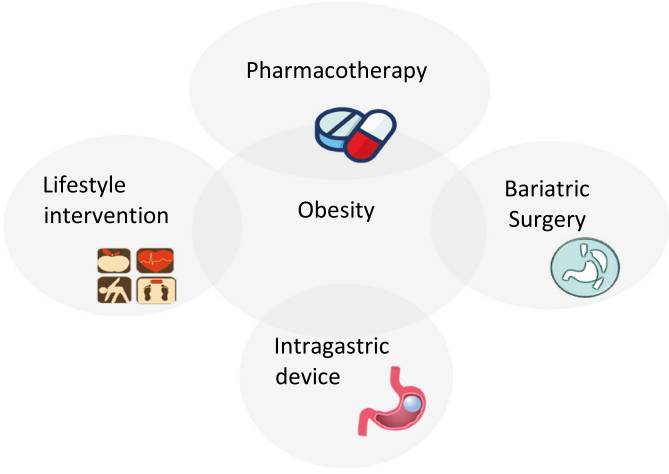

Figure 1. Obesity treatment approaches constructed using NICE obesity management pathway. The figure drawn using information from NICE clinical guideline CG189 [3].

contribute to the peripheral mediation of satiety including gut peptides such as ghrelin, leptin, cholecystokinin, peptide YY, pancreatic polypeptide and glucagon-like peptide-1 [5]. This review is focused on the IGBs used in the past, present, and the ones in clinical trials. It included a detail description of the device design, their limitations, placement and removal technique, patient eligibility criteria, efficacy (effect on weight reduction), and safety (adverse events).

2. Bezoar – the first intragastric balloon

The concept of the intragastric balloon evolved after evaluating the weight loss by Bezoar (formation of the mass of balls in the stomach causing a decrease in gastric emptying). This later led to the discovery of a free-floating balloon composed of 40% latex. It was administered as an intragastric pseudobezoar in obese patients for about 8 to 9 months, inflated with 450 cm^3 of atmospheric air. Although according to the preliminary study, the balloon was successful in diminishing appetite by increasing gastric load, a major limitation was inadequate strength of the balloon that increased the risk of adverse events associated with spontaneous deflation [8].

3. IGB devices pre-90s

In 1985, the Food and Drug Administration approved *Garren-Edwards Gastric Bubble* (GEGB, American-Edwards Laboratories, and Irvine, CA, U.S.A.), the first intragastric balloon marketed as an adjunct to diet, behavior, and exercise. The balloon comprised a polyurethane cylindrical device with a self-sealing valve, air filled 200-220 mL, that needed removing endoscopically with the help of a detachable catheter [9–13]. According to the studies conducted during 1987–89, and the weight loss achieved by GEGB was not significantly lower than the diet or behavior-modification. Moreover, several problems were reported including erosion, gastric ulcers, esophageal tear and intestinal obstruction [14,15]. Hence the GEGB was withdrawn in 1992 from the market. Following withdrawal of GEGB, there were several modifications proposed for the IGBs, but most did not survive the market due to clinical complications and limitations (Table 1).

Taylor balloon (1985, Mill Rose Technologies, Cleveland, Ohio) was a silicone, pear-shaped balloon, filled with 500-600 mL saline and intragastrically placed via endoscopy [18,19]. In a multi-center study Marshall et al [27] found that the gastric adverse events and the spontaneous deflations with Taylor balloon were comparatively better than the GEGB. However, the balloon failed to achieve an adequate weight loss for 4 months.

Likewise, the *Ballobes bubble* manufactured in 1988 (DOT Aps, Denmark), an oval air-filled, silicone balloon (500 cc), also inserted through endoscopy [20]. Ballobes bubble possesses major drawbacks similar to GEGB and the weight loss was not too dissimilar from controls experiencing diet restrictions [21].

Wilson-cook balloons (Wilson-Cook Medical, Winston Salem, NC, U.S.A.) were another IGB made using a polyurethane elastomer attached via catheter and inflated with 300 ml of air [16]. The balloon require also needed endoscopic insertion [17]. *Dow Corning* (Midland, Michigan) was another discontinued silicone based IGB inflated with a combination of 200 ml air and 200 ml saline [7].

4. IGB devices post-90s

4.1. Bioenterics

In 1987 Tarpon Springs workshop laid recommendations for an IGB such as durability of device material, low risk of gastric ulceration or obstruction, choice of filling mechanism (fluid or gas filled), using radiopaque markers to detect the device, and flexibility in adjusting the volume of the device to various sizes (personalization). This led to a novel saline filled IGB from *Bioenterics* (BIB) in 1991. The device was used for a short-term and radiopaque markers were used for deflation as it passes into the bowel [9]. Compared to its predecessors, the BIB had increased volumatic capacity, used resilient materials to prevent leakage and radiopaque marker enabled better monitoring [28]. The device was not very successful in the

Table 1. Discontinued intragastric devies.

IGB DEVICE	COMPANY NAME	LAUNCH YEAR	DEVICE	ELIGIBILITY CRITERIA BASED ON BMI	ADMINISTRATION/ REMOVAL	FLUID FILLINFG MECHANISM	COMPLICATIONS/REASONS OF DISCONTINUATION	REFERENCE
Garren edwards gastric bubble	American-Edwards Laboratories, and Irvine, CA, USA	1985	Polyurethane	30–50 kg/m^2	Endoscopic/ Endoscopic	Air filled	Erosion, gastric ulcer, esophageal tear and intestinal obstruction	[9,11–15]
Wilson-cook	Wilson-Cook Medical, Winston Salem, NC, USA	1985	Polyurethane elastomer	>35 Kg/m^2	Ingested/ Endoscopic	Air-filled	Oesophagitis Ulcer Balloon intolerance Premature balloon deflation	[16,17]
Dow corning	Midland, Michigan	1985	Silicon	>30 Kg/m^2	Endoscopic/ Endoscopic	Air/Saline filled	Balloon intolerance	[7]
Taylor balloon	Mill Rose Technologies, Cleveland, Ohio	1985	Silicone	>30 Kg/m^2	Endoscopic/ Endoscopic	Saline-filled	Spontaneous deflations	[18,19]
Ballobes bubble	DOT Aps, Rodovre Denmark	1988	Silicone	>30 Kg/m^2	Endoscopic/ Endoscopic	Air-filled	Gastric ulcer, erosion	[20,21]
Bioenterics	BioEnterics Corporation, Carpentry, Allergan Inc, Irvine CA, USA	1991	Silicone elastomer	≥27 kg/m^2	Endoscopic/ Endoscopic	Saline-filled	Gastric perforations, gastritis	[9,22]
Silimed	Slimed Rio de Janeiro – RJ-Brazil	2006	Silicone balloon	b/w 30–40 kg/ m^2	Endoscopic/ Endoscopic	Saline-filled	Epigastric pain Sudden deflation Balloon migration	[23–26]

United States and the Canada but had some success in Europe, Middle East, Asia and South America [9].

The BIB was made of silicone elastomer acid-resistant shell and a radiopaque self-sealing valve allowing positioning of BIB and volume adjustments up to 800 mL. The placement catheter was fixed by a metal guidewire connected to the valve to help balloon insertion into the stomach followed by inflation with 500 mL saline with methylene blue dye. The employment and deployment of the device was done either conscious or unconscious sedation using endoscopy. Additionally, the needle aspirator helped to deflate the balloon clasped by the snare or three-pronged grasper device [29].

Numerous studies were conducted to evaluate the safety of the BIB, the recent retrospective analysis included 1600 patients, comprising male (23%) and female (77%) with mean age 34.1 ± 10.354, mean body weight 112.45 ± 26.24, and mean body mass index (BMI) 40.32 ± 8.17. There were 109 patients with a BMI ranging from 25 to < 35 and 737 patients with a BMI ≥40 kg/m^2. 1567 patients who underwent weight consultation had MWL 17.35 ± 11.07 from Intragastric balloon implantation,33 patients from the total sample were not weighted after the removal of the balloon. % EWL was found and weight loss of more than 10% was considered significant. About 49.3% of patients showed significant weight loss > 10%, 24.7% of patients showed weight loss > 20%, while 26% of patients showed no significant weight loss < 10% p value 0.000* [30]. The weight loss at 3, 6 and 9 months in a comparative evaluation were 3 ± 2, 6 ± 1.5, and 11 ± 2 kg, respectively [31]. The Italian multi center cohort study assessed the safety and efficacy of BIB employing 611 patients, resulted in 44% weight loss at 6 months (p < 0.001) [32]. Safety and efficacy of BIB was evaluated in 6,406 subjects, where % EWL was 7.6% – 62.3%, with a rate of weight loss between 5.4 to 28.5 Kg over 6 months [33].

The effectiveness of the balloon was studied in 28 obese patients with BMI <32 kg/m^2 (n = 16) and ≥32 kg/m^2 (n = 12), on removal at 6 months and one-year follow-up after balloon removal. When the BIB was withdrawn, the BMI reduced from 32.4 to 28.5 kg/m^2 (p = 0.01). Except for the cholesterol level, all biochemical parameters improved considerably. The median %EWL of all patients upon BIB removal was 40.1, with 20 patients (71.4%) responded to the intervention. Compliance to dietician therapy was substantially higher in responders than in non-responders (85 vs. 25%, respectively; P0.01). At one year after BIB removal, the percentage of responders was substantially larger in patients with BMI < 32 (62.5 vs. 16.7%, respectively; P = 0.02) who maintained better weight loss at 1 year following removal. As per the safety profile, 9 patients (32.1%) had erosive esophagitis at the time of BIB removal whereas gastric ulcer with bleeding in a patient triggered early BIB removal. The BIB not only helped losing weight but also improved other co-morbidities. The adaptability was related to higher adherence with the dietician advice [34].

Prior studies regarding the safety and efficacy of the balloon showed no serious adverse events including gastritis, gastric perforation, or esophageal perforation. Although nausea and vomiting were the most common side effects. Despite a good safety and effectiveness of BIB in clinical trials, there were still reports of poor tolerance and spontaneous deflation leading to early endoscopic removals that prompted further developments and research in this area [22].

4.2. Heliosphere®

The heliosphere was a double-bag polymer balloon embedded in a silicon cover. It contained an insertion and extraction kit that also required endoscopic intervention under deep sedation. The safety loop allowed positioning and releasing of the balloon followed by inflation with 550 mL air. The weight of the fluid-filled balloons was attributed to nausea and vomiting causing tolerability issues, hence air-filled approach was aimed to improve tolerability. Heliosphere only weighted 30 g compared to 500–800 g of

a typical fluid – filled IGBs [35,36]. The device was deflated and removed after 6 months. The MWL and BMI reduction in 82 obese patients in a study after the removal of the balloon was 14.5 kg (SD 8.2) and 5.3 Kg/m^2 (SD,2.8)respectively (for difference $p < 0.001$) [37]. The BIB and Heliosphere showed similar weight reduction in comparative studies, numerous technical difficulties were nevertheless associated with air-filled balloon. For instance, spontaneous deflation, migration into small bowel and difficulties in passing it through cardia and the lower pharynx that prompted the need for further improvements [35,36].

4.3. Newtech 600 and 720

A newer generation of this IGB, Heliosphere Newtech® with a single layer balloon with a protective polymer coating to facilitate easy removal, has recently been introduced in the market. Implanted duration is 6 months, where Newtech 600 balloon is inflated with air to 600 cm^3. Newtech 720 is slightly larger than Newtech 600 and can be inflated to 720 cm^3. Newtech 600 or 720 is recommended as first-line treatment in a 6-month single balloon regimen. In a doble balloon regimen, the Newtech 600 is inserted as the first balloon and replaced by the Newtech 720 after six months; where the slight increase in volume of Newtech 720 is ought to boost weight loss [38]. The Newtech 600 is reported to produce a weight loss up to 24 kg [39,40].

4.4. Silimed

Originated from Brazil, the spherical silicone balloon is a similar to BIB in terms of its design and placement encased with a thin silicone sheath, placed in the proximal stomach by the help of attached snare using the tip of the endoscope. Both the placement and removal of SGB required sedation. The balloon is inflated with 650 mL saline, contrast medium and 10 mL of methylene blue under visual monitoring [23,24]. The SGB is extracted via polypectomy snare, which clasp and pull the tube attached with the entire IGB system after emptying by the needled catheter. Two clinical trials were conducted by Carvalho et al., first during 2006–7 [23] that included 52 patients, but only 14 patients were able to achieve a mean weight loss of 11.3 ± 6.2 Kg in a 6-month intervention (initial mean weight and BMI was 107.7 ± 25.1 kg and 35.7 ± 5.7 Kg/m^2 respectively, reduced to 89.4 kg, 31.8 ± 5.5 kg/m^2). The second trail in 2006–9 included 20 patients out of which 16 completed 5–6 months treatment. The initial mean weight and BMI of 74 kg and 27.5 kg/m^2 was reduced to 65.9 ± 9.4 kg and 24.5 ± 2.6 kg/m^2 respectively with the mean weight loss of 8.1 ± 4.7 Kg [41]. Whereas, 11 out of 51 patients (21%) suffered from epigastric pain that required early removal of the device. Moreover, spontaneous deflation and balloon migration to the intestine were also observed in two patients [23,24]. Nonetheless, the MHRA and EMA in 2015 suspended the CE mark for all the medical devices manufactured by Silimed including their gastric balloons due to the device surface being contaminated with particulates noticed during a regulatory inspection [25].

5. Second generation IGB devices

Over the years Intragastric balloons evolved in numerous ways that included an increased and adjustable volume capacity (up to 960 ml), shape and size (e.g. bi-lobed balloon), and also increased duration from 4–6 months to up to a year for some IGBs [42]. Despite the complexities of the previous balloons, numerous IGBs were described in literature and are used globally, they vary in their *in-vivo* placement procedure and design. These devises are summarized in Table 2.

5.1. Orbera®

Orbera®, approved by FDA in 2015 following acquisition of Inamed by Apollo Endosurgery, was a silicone elastomer similar to Bioenterics intragastric balloon (Figure 2) that was placed and removed endoscopically and inflated with saline to 400–700 mL marked with methylene blue. The device stays in the stomach for 6 months then removed endoscopically by puncturing through a grasper device. Orbera is indicated for obese patients who otherwise have a high-risk for bariatric surgery.

Several multicentre studies have shown remarkable weight loss achieved by Orbera. The systematic review and meta-analysis of 17 studies including 1683 patients treated with Orbera at 12 months lost 25.44% excessive weight loss 95% Confidence Interval CI, 21.47% – 29.41%. The pooled total body weight loss (TBWL) % at 3, 6 and 12 months were 12.3% (95% CI, 7.9%–16.73%), 13.16% (95% CI, 12.37%–13.95%), and 11.27% (95% CI, 8.17%–14.36%), respectively [63]. In a comparative study of fluid filled balloon versus gas-filled balloon, the % TBWL at 6 months for Orbera was 6.72% (95% CI, 5.55, 7.89) [64]. In another meta-analysis including 44 studies with 5,549 participants' taking Orbera, the %TBWL at 6 months was 13.2% (95% CI 12.3–14.0),$p = 0.268$. Interestingly, the prevalence of esophagitis was higher with less volume (9.4% with <600 ml compared to 2.4% in >600 mL) [65]. In a multi-center, randomized trial of IGB compared to lifestyle intervention, the weight loss at 6, 9 and 12 months for balloon plus lifestyle intervention was 10.2, 9.1, and 7.6% respectively, compared to 3.3, 3.4, and 3.1% for the lifestyle alone, respectively.

In terms of tolerability, it was noted that most of individuals who experienced abdominal pain and nausea ought to early device removal [66]. The meta-analysis showed that the incidence of nausea and vomiting was greater with Orbera as compared to Elipse, Obalon and ReShape [67], whereas the rate of balloon migration, gastric ulcers and gastroesophageal reflux disease (GERD) with Orbera were 1.4, 2 and 18.3%, respectively [68]. A major complication of gastric hemorrhage was also reported in one patient with Orbera. Gastritis was also noted in patients with Orbera during endoscopic evaluations [69]. Most studies confirm the safety and short-term effectiveness of Orbera, however, less serious complications also significantly affected patient's compliance.

In a recent retrospective study, the effect on weight loss attained by Orbera and endoscopic sleeve gastroplasty (ESG) was analyzed. The mean %TBWL by Orbera after 6 months in 124 patients was 15.2 and after 12 months in 61 patients was

Table 2. Intragastric balloon Available worldwide.

IGB DEVICE	COMPANY NAME	LAUNCH YEAR	DEVICE	ELIGIBILITY CRITERIA BASED ON BMI	ADMINISTRATION/REMOVAL	FLUID FILLING MECHANISM	COMPLICATIONS REPORTED	REGULATORY BODY	REFERENCE
Orbera®	Apollo Endo-surgery Inc.	2004	Silicone elastomer	≥30 and ≤40 kg/m^2	Endoscopic/Endoscopic	Saline filled	Balloon migration	FDA approved	[43]
Semistationary antral balloon	JP Industria Farmaceutica	2006	Silicone balloon	30 or more	Endoscopic/Endoscopic	Saline-filled	Spontaneous deflation	-	[44]
Atiip-endogast®	Districlass Médical - France	2007	Polyurethane Prosthesis	≥40 Kg/m^2	Endoscopic/Surgical	Air-filled	Mild abdominal cramps	-	[45]
Lexbal	Lexel Medical	2011	Polyurethane balloon	28 kg/m^2 or more	Endoscopic/Endoscopic	Saline-filled	Oesophageal candidiasis	CE marked	[46]
Spatz3	Spatz, Fort Lauderdale, FL, U.S.A.)	2012	Silicone	30–40 kg/m^2	Endoscopic/Endoscopic	Saline-filled	Balloon Intolerance	FDA Approved	[47,48]
Heliosphere	Helioscopie Medical Implants, Vienna,	2004	Polyurethane and silicone	30–40 or >35 kg/m^2	Endoscopic/Endoscopic	Air filled	Spontaneous deflation	Heliosphere Newtech 600, 720: CE marked [38–40]	[7,35,36]
Obalon®	Reshape Lifesciences Inc.	2012	Nylon and polyethylene	30–40 kg/m^2	Oral/Endoscopic	Nitrogen sulfur-hexafluoride mixture	Gastric superficial erosion lesions	FDA approved	[49–52]
Medsil™	Medispar	2013	Silicone	27–40 Kg/m^2	Endoscopic/Endoscopic	Saline filled	Gastric ulcer hemorrhage	ISO certified	[53,54]
Reshape duo	ReShape Medical, Inc., San Clemente, Calif	2015	Silicone	30–40 kg/m^2	Endoscopic/Endoscopic	Saline filled	Spontaneous deflations	FDA & CE approved	[55,56]
Allurion gastric balloon (ex-elipse balloon)	Allurion Technologies, Natick, MA USA	2015	Polyurethane balloon	≥27 kg/m^2	Oral/Naturally emptied/in rare cases endoscopic	Water-filled	Small bowel obstruction	CE marked	[57,58]
Corporea intragastric balloon	Medicone Cachoeirinha, RS, and Brazil.	2015	Silicone balloon	28 kg/m^2 or more	Endoscopic/Endoscopic	Saline-filled	Intolerance/ Spontaneous deflation	-	[59,60]
End-ball®	Endalis, Brignais, France	2015	Polyurethane	≥28 kg/m^{2}for super obese BMI >50 kg/m^2	Endoscopic/Endoscopic	Air and water	Esophagitis	CE marked	[61]

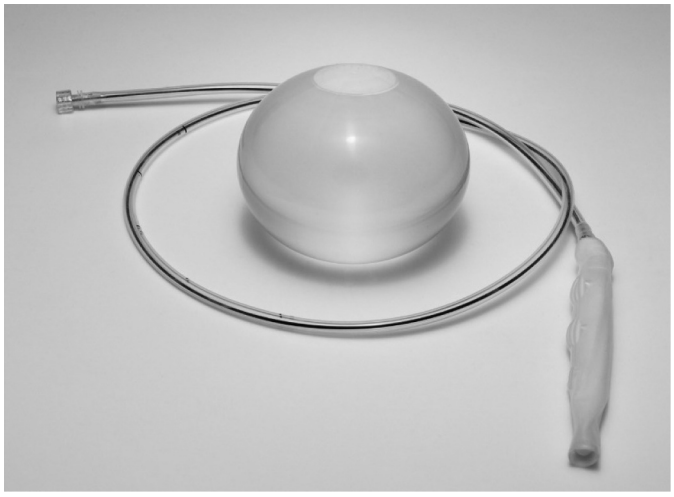

Figure 2. Orbera365™ IGB [62]. Figure provided by Apollo Endosurgery, reproduced with permission under license.

15.8 kg whereas with ESG at 6 and after 12 months in 42 and 34 patients was 26.5 and 28.7 kg, respectively. Additionally, no significant difference was reported in the mean %TBWL in patients undergoing Orbera placement for 6 or for 12 months (15.3% vs 14.7%, $P = 0.7$). Patients with ESG revealed notably higher %TBWL than IGB patients after 6 months (19.8% vs. 15.3% $P = 0.005$) and one year (22.5 vs. 14.7, $P < 0.001$), showing more efficacy with ESG than the IGB [70].

In a double-blinded RCT with 6-month Orbera IGB vs with sham endoscopy investigated outcomes including fasting glucose, lipid profile and physical measurements up to 2 years including a 10 year follow up. BMI of patients included was 27–35. The first RCT enrolled 99 individuals (50 IGB vs 49 sibutramine group). A 10-year review included 49 patients (26 IGB vs 23 control group) with a 51.6% follow-up rate. Total body weight loss favored the IGB group at 6 (9.75 vs 7.48 kg, $p = 0.03$), 12 (6.52 vs 4.42 kg, $p = 0.05$), 18 (5.42 vs 3.57, $p = 0.32$), and 24 months (4.07 vs 2.93 kg, $p = 0.56$) months. TWL at 10 years (0.03 vs 2.32 kg, $p = 0.05$) and % TWL (0.16 12.8% vs 2.84 5.6%, $p = 0.39$) were not substantially different between groups. The follow-up BMI (30.97 1.6 vs 30.38 1.8 kg/m2, $p = 1.00$) was also comparable. The incidence of new-onset diabetes mellitus, sleep apnea, metabolic syndrome, and arthralgia were not significant at 10 years ($p >$ 0.05). Twenty-three (81%) of the IGB group and 13 (56%) of the control group reported a preference for ongoing treatment (p 0.01). IGB was very effective for managing and promotes weight loss for two years. Yet, at 10 years, there were no appreciable differences in the development of new comorbidities. Those who underwent IGB therapy were afterward more receptive to additional bariatric metabolic management [71].

5.2. Orbera 365™

It is 700cc saline filled device, reporting a weight loss 3 times that of diet and exercise. Orbera 365 is a 12-month program aims to help reducing weight in adults with a BMI of 27–50 kg/m^2 who struggled to lose weight otherwise via weight-control program. Also, adults with BM >35 kg/m^2 with comorbidities prior to obesity or other surgery to lower the surgical risk. The complications were similar to those associated with other related procedures, for instance balloon induced partial or complete intestinal occlusion, insufficient or no weight loss, early balloon removal, gastric discomfort, obstruction of food entering the stomach, bacterial growth leading to infection due to the fluid filling the balloon, esophagitis or gastritis, and spontaneous deflation [62].

In a prospective study, 97 patients underwent Orbera 365 with mean baseline weight and BMI 93.8 ± 15.2 kg and 35.2 ± 4.4 kg/m^2, respectively, reduced to 80.6 ± 13.1 kg and 29.8 ± 4.0 kg/m^2 by 8.2 months and were 82.4 ± 16.1 (p value ≤ 0.001*) and 30.4 ± 4.6 (p value ≤ 0.001*) at the last day of follow-up after 12 months. The balloon intolerance was noted in 14 patients, 6 in the first week and 8 within the first 8 months of insertion. In addition, two patients had spontaneous balloon deflation (rupture), and further 3 patients had balloon removed due to the leakage at the time of insertion. Moreover, spontaneous balloon hyperinflation, pancreatitis, and balloon was vomited out by some patients. Total body weight loss (TBWL%) was 16.2 ± 10.1 p ≤ 0.05* and Excess weight loss %EWL was 54.6 ± 38.3. Orbera 365 was however found effective for weight loss but needed further studies to establish the safety of the balloon, in particular the rate of spontaneous deflation, device malfunction, tolerance and pancreatitis [72].

5.3. Semi-stationary antral balloon (SAB)

This pear-shaped silicone balloon was developed in Brazil that was conical at its distal end, unlike other IGBs, which was connected to a 30 cm long silicone duodenal stem with a 7 g metallic counterbalance on its tip. SAB induced satiety unique to its design, firstly by inducing intermittent occlusions to pyloric opening leading to delays in gastric emptying, secondly elongated duodenal stem initiated post prandial satiation by stimulating antral and duodenal receptors. The saline-filled balloon containing contrast and methylene blue occupies only 150-180 ml volume. The device is punctured and endoscopically removed after 6 months [44]. In a clinical trial 26 patients with the mean age 37.4 ± 1.7 years, median body weight was 93.0 Kg and the median BMI 34.3 Kg/m^2 were implanted with SAB. 22 patients successfully felt fuller with a 1250–15000 Kcal diet, 14 lost more than 6 kg body weight in comparison to 4 patients not experiencing increased satiety p = 0.03. The median weight recorded at the extraction was 87.3 Kg (median BMI 32.3 Kg/m^2). Moreover 9 out of 26 patients were able to tolerate the balloon for six months and achieved an average weight loss of 12 Kg. Like other IGBs, SAB was also subjected to spontaneous deflation (15%), and one case of bowel obstruction needing surgery was also reported [44].

5.4. Adjustable totally implantable intragastric prosthesis (ATIP) - endogast®

Endogast® employed a combined endoscopic-surgical technique known as ATIP. Endogast is an oval, polyurethane balloon

Figure 3. Adjustable totally implantable intragastric prosthesis (ATIP)-EndogAst® [45]. Credits Districlass Medical, figure reproduced with permission.

prosthesis (Figure 3) that is placed in the corpus-fundus region using endoscopic percutaneous gastrostomy [45]. The IGB is attached to a 15-cm polyurethane catheter extending over the gastric and abdominal wall connecting to a subcutaneous inflatable system. The balloon is inflated to a maximum of 300 mL air using a stainless steel chamber with a self-sealing silicone rubber membrane attached to the catheter [73]. The balloon interferes proximal gastric inhibitory reflex and the neuro-hormonal processes, thereby mediating satiety and induces weight loss [74–76]. The balloon's volume can be externally adjusted for prolonged period such as ≥12 months. The removal of ATIP- Endogast® is similar to the Silimed balloon.

Gaggiotti et al. [73] in a 1 year follow-up multicentre prospective clinical survey assessed 57 morbidly obese patients that received ATIP treatment. The reduction in BMI recorded after 3, 6 and 12 months were 7.4, 8.4, and 12.2 Kg/m^2 respectively. The mean % weight loss was 22.3, 28.7 and 39.2% at 3, 6, and 12 months, respectively. Interestingly, there was no weight loss observed in six patients that led to device removal before 12 months. In contrast, balloon was left longer than 12 months in five patients who achieved a significant weight loss and well tolerated the device. Whereas, two patients experienced a balloon-leak necessitating surgical and endoscopic intervention to remove the device. Mild abdominal cramps were reported by three patients (5.2%) during initial months of therapy, who developed pneumoperitoneum. Furthermore, the rate of subcutaneous infection at the incision site was 12.2% (7 patients) and one patient developed severe local infection required prosthesis removal and wound detersion. The skin erosion caused by the port was observed in 3 patients (5.2%) that followed its removal [73]. The device overall showed promising results but exhibited complications that needed technical improvements to improve its safety and efficacy.

5.5. Lexbal

Lexbal silicone rubber balloon (Figure 4) was approved in Europe in 2011 [46]. The balloon was similar to Orbera gastric balloon mostly in design and administration aspects (structural features, implantation, extraction technique etc.). Lexbal is enclosed in the sheath joined to the catheter ending with a Luer lock for an easy link to the filling system. Also, the catheter contained a guiding wire enabling the balloon implantation in the stomach under sedation. The balloon is filled with 500–800 mL of dye containing saline. A valve prevents the leak after catheter is detached following inflation. Similar to the SGB, LexBal is punctured and endoscopically removed by a needled steel guided wire.

LexBal was evaluated in a study comprising 63 morbidly obese patients with initial BMI 58.3 ± 10.5 Kg/m^2, reduced to 49.5 ± 8.7 Kg/m^2 with the mean BMI reduction of 7.1 kg/m^2 and an average weight loss of 25.2 ± 13.5 Kg at 6-months following the procedure. A substantial decrease in BMI value was observed after treating morbid obesity patients with Intragastric balloon implantation (p 0.001), both in the female (p 0.0001) and male groups (p 0.0001). No serious complications such as intestinal obstruction were reported in the study subjects, however, nausea (69.7%), vomiting (57.1%), upper abdominal pain (36.4%) was reported in subjects with BMI ≥50.0 kg/m^2. The subjects with BMI <50 kg/m^2 more complaint with heartburn and esophageal candidiasis [77].

5.6. Spatz adjustable balloon system

Spatz, an adjustable silicon balloon, saline-filled 400–700 mL (Figure 5), endoscopically implanted and was designed to be left in the stomach for 12 months. Spatz featured two loops of catheters to overcome the drawbacks encountered by other IGBS, one to help stabilize the device whereas the other to help with endoscopic removal and protection from balloon migrating into duodenum.

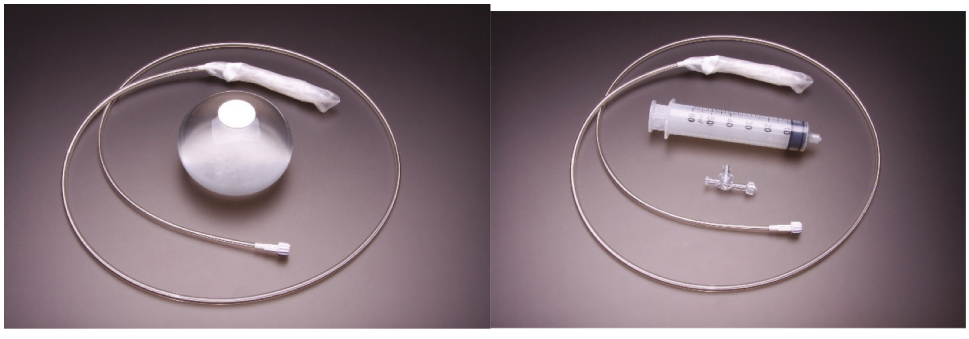

Figure 4. Lexbal IGB [46]. Figures provided by Lexel Medical, and reproduced with permission.

Figure 5. Spatz^3 adjustable balloon system [48]. Figure credits Spatz Medical, reproduced with permission.

Another unique feature with Spatz was a stretchable inflatable tube that can adjust the balloon volume following mealtime to help reducing weight. Several clinical trials studied the performance of the balloon. In a study, Spatz was implanted for 12 months in 18 patients with a mean BMI of 37.3 Kg/m^2. The mean weight loss was 15.6 Kg and 24.4 Kg at 6 and 12 months respectively, with the excess weight loss reduction of 26.4% and 48.8% at 6 and 12 months, respectively [78]. In another retrospective study, the device remained implanted for 10 ± 1.2 months in patients with initial BMI 40 ± 5 kg/m^2 reduced 31 ± 4 kg/m^2 with a mean weight loss of 25 ± 6 Kg. When comparing the readings before and after the gastric balloon, there is a statistically significant change (p: 0.001) [79]. In another study, 73 patients with a mean BMI 36.6 Kg/m^2 achieved a mean weight loss of 21.6 Kg loosing 45.7% excess weight in a year [80]. In a comparative study, Spatz was able achieve similar if not better weight losses as of BIB at 3, 6 and 9 months (4 ± 2, 6 ± 2, 10 kg respectively) there are no significant differences between the two procedures in terms of outcomes [31]. In a case-control study Spatz adjustable balloon was compared with a BIB for 12 months requiring 6 month for each balloon positioning. During this investigation, the Spatz balloon was modified with 200 cm^3 of saline inflation (total, 800 cm^3) in 9/40 (22.5%) patients who had not lost weight after the first 6-months of therapy. In the Spatz group, 7/40 problems were connected to the device, and the balloon was removed in 6/7 patients. The weight reduction metrics were similar between groups at the end of the study: BMI 31.0 11.8 (Spatz group) vs 31.3 12.3 (BIB group) (p = Ns) [81]. The unique anchoring feature of the Spatz was aimed to address the common challenges faced by other IGBs, such as spontaneous balloon deflation and migration into small intestine, gut perforations and bowel obstructions. However, spontaneous balloon deflation, esophageal laceration, late onset gastric perforation, intestinal occlusions, bowel migrations, asymptomatic ulcers and anchor system rupture was still observed in small number of patients. There were also tolerance issues in 11% of patients and tube related problems in 12% of patients [78,80,82–84], that required further technological developments to assure the long-term safety of the device.

The new generation Spatz^3® was authorized by the FDA in 2021, and has been used in 140,000 patients since [47]. The balloon has evolved to its modern form, that permitted increasing or decreasing IGB volume endoscopically to improve efficacy and tolerance to prolong treatment duration. Henceforth, proven to be effective in a prospective, multicentre, open-label, randomized clinical trial by Abu Dayyeh et.al. involving 288 patients in 2018. During the 32 weeks, the mean total bodyweight loss in the adjustable IGB group was 150% (95% CI 139–161) against 33% (20–46) in the control group ($p < 0.0001$). Clinical remission was reported in 171 (92%) of the IGB patients. 145 individuals (80%) had their aIGB adjusted resulting in weight reduction plateau or intolerance. This increase in volume allowed for an extra 52% total bodyweight reduction. Whereas the downward volume adjustment permitted 21 (75%) of the IGB patients to successfully finish the entire course of therapy. Despite, 31 (17%) patients had balloon intolerance leading to early balloon removal. The study concluded a significant weight loss that was maintained for 6 months follow up after IGB removal compared to lifestyle interventions. Individualised therapy was possible due to the balloon volume adjustability, which improved weight loss and tolerance [85]. Likewise, a longitudinal study conducted at a private endoscopic center in Mexico during 2019–2021 involving 27 female patients. At 12 months, a mean weight loss of 14.2 kg (14.6% of total body weight and 37.6% of excess weight reduced), demonstrating a substantial weight reduction [86].

5.7. MedSil

MedSil was another fluid-filled device inflated to 700 mL, was similar to BIB® and Orbera® devices in most of the aspects, however, MedSil device was lubricated on internal and external surfaces to improve patience compliance. The MedSil was indicated in obese patients with BMI 27 or more who were unable to reduce weight by diet and exercise.

In 22 obese patients, the initial mean BMI was reduced from 43.30 to 37.8 Kg/m^2 ($p < 0.001$) with mean body weight reduced from 128.5 to 110.1 Kg ($p < 0.001$) and 19.3% EWL. Besides, there were significant improvements in the glycated hemoglobin and glucose homeostasis and balloons were generally well tolerated [41]. Conversely, another study After IGB removal, 224 patients lost more than 10% of their body weight. Excess BMI reduction was considerably larger in participants who kept the IGB for more than 6 months, both after removal [43.44 ± 19.46 vs 55.60 ± 28.69) $P = 0.0001$] and at the end of 6 months' follow-up [46.57 ± 24.89 vs 63.52 ± 31.08 $P = 0.0001$). Some patients poorly tolerated the device necessitating early removal of the device. Two patients reported pancreatitis and one reported cardiac arrhythmia potentially unrelated to the balloon, whereas two patients experienced intestinal obstruction [87].

With most IGB devices, there have been risks associated with the device insertion and removal, most of which can be remedied easily, nevertheless, some complications can be potentially fatal. There was a case of gastric ulcer hemorrhage in a patient with IGB with concomitant Helicobacter pylori

infection taking aspirin. Therefore, it was recommended that more work was needed on patient education and communication, in particular those with an increased risk of surgery, gastric ulcers, and bleeding [53].

A short-term study comprising 86 morbidly obese individuals that had IGB implanted with a minimum of one-year of follow-up. The treatment was followed up after 6 months and a year for with post-procedure symptoms, risks, and the impact of the procedure on weight reduction as % excess weight loss and percentage excess BMI reduction. Initial BMI was 35.2–57.8 kg/m^2 with an average of 42.9 ± 4.8 kg/m^2. At 6 months BMI was reduced to 29.4–50.8 kg/m^2, with a mean of 37.14.2 kg/m^2, whilst at 12 months, it considerably increased to 29.8–51.6 kg/m^2, with a mean of 38.74.5 kg/m^2 in comparison to 6 months postoperatively. Even though MedSil IGB was found beneficial in reducing weight and alleviating associated comorbidities in the short term with manageable side effects, the weight gain was noticed over a 12 months period post IGB removal [88].

5.8. ReShape integrated dual balloon

The *ReShape* Integrated Dual Balloon was approved by the FDA in 2015 and contained a unique interconnected dual balloon system occupying 450 mL saline mixed with methylene-blue in each balloon. This balloon is endoscopically implanted in the stomach and left for up to 6 months before it is endoscopically removed. It was Duo's design that was aimed to induce more satiety than the single balloon system, and to prevent balloon migration as double balloon would provide a fail-safe approach to help balloon retention in the stomach even if one of the balloon was spontaneously ruptured [89].

A multicentre RCT reported that the %TBWL in 187 patients implanted with ReShape Duo was 4% at the end of 6 months [64]. In a retrospective study 202 subjects with mean age 47.8 ± 10.8 years; 83% female) with a baseline mean BMI of 36.8 + 8.4 kg/m^2 who had IGB implantation. BMI decreased significantly at 6 months from baseline (32.8 + 6.7 kg/m2 vs 36.8 + 8.4 kg/m2 respectively). ($P < 0.001$). The primary outcomes (%TBWL) at 1, 3, 6, 9, and 12 months were 4.8 ± 2.4%, 8.8 ± 4.3%, 11.4 ± 6.7%, ($P < 0.001$) 13.3 ± 7.8%, and 14.7 ± 11.8%, respectively. Most patients achieved greater than 10% TBWL at 6 months [90]. In the Spanish trial of the Duo, 60 patients demonstrated a total body weight loss of 16.6 ± 9.33 Kg following the treatment [91]. In a pivotal randomized trial of 326 patients, the treatment group received the Duo with lifestyle intervention compared to controls receiving a sham procedure with lifestyle intervention. The % EWL after six month for the group that received the Duo was higher than the control (25.1% vs, 11.3%) [55]. Moreover, the balloon also improved comorbidity biomarkers, such as systolic and diastolic blood pressure, and lipoproteins (high and low density).

Although the balloon exhibited promising weight loss in clinical trials, most patients did not tolerated the balloon well leading to early removal [91]. Despite the fail-safe double balloon design, the deflations rates were 6% and gastric ulcers and erosions were also reported [55]. Following acquisition of ReShape Medical in 2018 by Apollo (Apollo Endosurgery, Austin, TX, U.S.A.), Apollo decided to discontinue ReShape Duo but continued supplying their Orbera devices.

5.9. Corporea Intragastric Balloon

The saline-filled silicone balloon from Medicone was also placed and removed endoscopically, occupying 300–700 ml volume in the stomach [59,60]. The safety of the device was assessed in a trial involving 5,172 patients who received Corporea IGB, and observations were similar to other fluid-filled IGBs. The usual adverse event reported after placement was hyper-inflation leading to spontaneous deflation (1.5%) in some patients. Balloon migration to intestine was also noted in some patients that needed surgical removal. Moreover, gastric ulcer, bleeding and gut perforation were also experienced in some patients that needed early removal of the device [92].

In a retrospective study of 24 patients who received IGB with a mean weight of 97.09 ± 12 kg, reduced to a mean weight at 8–12 weeks of 89.39 ± 11.02 kg and 80 ± 11.01 kg at the time of removal. The weight held steady at 6-month follow-up (81.37 ± 11.04 kg). Mean BMI prior to IGB insertion was 35.58 ± 2.79 kg/m^2. There was also a statistically significant reduction in BMI at 6 and 12 months, 29.31 ± 2.83 kg/m^2 and 29.85 ± 2.84 kg/m^2 , respectively ($p < 0.001$). In multivariate analysis, an elevation in DeMeester score was significantly correlated with total body weight reduction ($p = 0.0125$) and change in GE ($p = 0.038$). The IGB caused a delay in gastric emptying of solids but not liquids. Adverse effects such as persistent abdominal pain, distension, intolerance and spontaneous hyperinflation were noted [93].

5.10. End-ball®

End-Ball® was an innovative, polyurethane IGB filled with both saline and air (300 ml each). In contrast to other similar devices, the End-Ball® did not have a pre-insertion kit. The balloon enclosed in the cap connected with the endoscope for a simultaneous insertion and inflation. Both placement and removal of the balloon required endoscopy, performed under deep sedation through direct visualization. Extraction of the balloon was very similar to Orbera. However, balloon rupturing for removal required more efforts due to the increased strength and firmness of the material used in the End-Ball, designed to prevent the spontaneous rupture of the balloon as reported previously with other devices.

The %EWL in 20 obese patients after six months was 38 ± 13% with a mean weight loss of 14 Kg [94]. In another retrospective analysis of 114 obese subjects, the MWL of 23.5 Kg, mean BMI drop of 6.4 Kg/m^2 and EWL of 39.2% was noted; the weight loss was sustained for 1 year after balloon removal. No serious adverse events were noted in clinical trials, however, esophagitis, early removals and balloon intolerance were still reported [95].

End-Ball IGB exhibited high effectiveness and safety in Korean obese patients. The retrospective cohort study included 80 patients that underwent End-Ball placement from 2013–2019 having initial BMI 34.48 ± 4.69 kg/m^2. At the time of removal, the reduction in BMI was 3.72 ± 2.63 kg/m^2 ($p < 0.001$). The %TBWL was 10.76% ± 6.76%, whereas %EBWL was 43.67%±27.59% ($p < 0.001$). Nausea, vomiting, or stomach discomfort, and other mild adverse events were reported by 71.4% of individuals [96].

In 74 obese women with BMI ≥25.0 kg/m^2 who received EndBall, the weight, fat mass, and waist-hip circumference ratio all decreased considerably following six months of IGB insertion. Women with morbid obesity (BMI 30 kg/m^2) reduced 33% of their extra weight; there was no notable loss of muscle mass or bone mineral density [97].

6. Third-generation IGB devices

Endoscopy assisted implantation and removal of the IGB devices had been a major limitation that needed specialist clinics and staff and associated costs and inconvenience. There was therefore a need for an ingestible balloon device that could be swallowed like an ordinary pill. This led to the invention of IGB balloon devices encapsulated in conventional capsules that could be swallowed by patients without needing endoscopic implantation, but most still needed endoscopy assisted removal after completion of residence period. Some devices were also designed to be self-degraded in the gastric environment (biodegradable) for natural excretion via gut and hence eliminating the need for specialist clinics for both implantation and removal of the IGBs.

6.1. Obalon®

The Obalon® was a swallowable, air-filled balloon approved by the FDA in 2016 [98] and was also available in NHS in United Kingdom. Unlike other IGBs, Obalon® was unique as it can be swallowed like a large pill and doesn't need endoscopic insertion, however, still required endoscopic removal under sedation. Fluoroscopy is used to locate the balloon in the stomach for removal. The balloon is enclosed in a gelatine capsule with a self-sealing valve attached to a thin catheter. After ingestion, the catheter tethered balloon reaches the stomach and inflated using nitrogen gas to 250 mL using an external canister. Following inflation, catheter detaches from the capsule and gelatine covering is dissolved in gastric fluids as usual leaving the balloon behind in the stomach for three to six months. Reshape Lifesciences has added Obalon to its portfolio of weight loss products and services [49]. In a study 87 patients ingested two balloons, one week apart, and reported 3 Kg/m^2 weight loss at the end of treatment. The adverse events reported included gastric superficial erosion lesions and spontaneous balloon deflation [50]. The weight loss offered by Obalon® was not too dissimilar to other IGB devices at the end of 6 months [64]. Another study in 17 obese patients who ingested up to 3 balloons, lost 2.2 Kg, 29.2 and 36.2 kg at the weight loss described after 4, 8 and 12 weeks, respectively [99]. There were less complications reported with the gas-filled devices compared to fluid filled devices, mostly attributed to their weight and buoyancy.

A retrospective cohort study compared the efficacy, tolerance and safety of Obalon® gas-filled and the Orbera fluid-filled IGB during 205–2020 that included 87 patients with BMI 35.5 ± 5 kg/m^2 and 38.8 ± 6 kg/m^2 for gas-filled and fluid-filled groups, respectively. There were no significant differences in % total body weight reduction among balloon systems at removal and 12 months follow ups ($p = 0.39$). Although both balloons demonstrated good safey, the gas-filled IGB had fewer side effects and was better tolerated than the fluid-filled IGB [100].

In another retrospective study consisting of 1343 patients with baseline BMI of 35.4 ± 5.4 kg/m^2, the weight loss for patients with BMI 30–40 kg/m^2 was 9.7 ± 6.1 kg, with a total body weight decrease of 10.0 ± 6.1%. (TBWL). The weight loss in other BMI categories was 8.2 ± 5.6 kg or 10.3 ± 7.0% total body weight loss (BMI 25 to 29.9 kg/m^2) and 11.6 ± 7.8 kg or percent total body weight loss 9.3 ± 6.0 (BMI >40 kg/m^2). Limitations observed were spontaneous deflation, however, none caused obstruction, the gas-filled intragastric balloon device was found generally safe and effective in inducing weight loss [101].

6.2. Allurion gastric balloon (previously elipse balloon)

It is also a swallowable fluid-filled polyurethane gastric balloon designed to self-empty and expelled out of the body naturally. The balloon is enclosed in a conventional capsule shell and attached to a thin catheter encompassing a self-sealing valve, inflated with 550 mL and designed to stay in the stomach for 4 months. The radiopaque markers inside the balloon help locating its position in the stomach through an abdominal X-ray. The balloon biodegrades in the gastric conditions with time allowing the release valve to expel the retained fluid, followed by its excretion naturally through the gut [102].

The efficacy of the balloon was determined in 42 obese patients who lost 12.9 Kg in 16 weeks with a mean BMI reduction of 4.5 Kg/m^2 ($p < 0.001$) and TBWL 11.6% [103]. In another study, 38 patients reported 12.7 Kg MWL, 26% EWL, and 4.2 Kg/m^2 mean BMI reduction ($p < 0.001$) [104]. A 12 month, prospective non-randomized safety study comprising 12 patients reported 14.6% and 5.9% TBWL at 4 and 12 months, respectively [105]. Albeit, the initial trials did not show any serious complications, however, small bowel obstruction due to balloon migration necessitating surgical removal was observed in some patients and called for further evidence on device safety [106].

Data collected from a multicentre study in which 1770 patients that received Elipse balloon were analyzed for weight reduction, metabolic parameters, ease of placement, device performance and complications. Initially patients mean weight was 94.6 ± 18.9 kg, and mean BMI 34.4 ± 5.3 kg/m^2. Four months following balloon insertion, overall mean weight loss (WL) was 13.5 ± 5.8 kg $p < 0.0001$, excess weight loss (EWL%) was 67.0 ± 64.1, $p < 0.0001$ mean BMI was 4.9 ± 2.0, $p < 0.0001$ and total body weight loss reported was 14.2 ± 5 (14.2%) $p < 0.0001$, along with the

improvement in the metabolic parameters, the triglycerides, cholesterol and HbA1c. The balloon was successfully swallowed by 99.9% of patients, with 35.9% needing stylet aid. 11 patients (0.6%) vomited empty balloon initially after residence but without causing any other adverse events, whereas The overall safety was reported remarkable, where 52 (2.9%) patients had balloon removed due to the intolerance. Another 11 (0.6%) patients reported spontaneous balloon deflation. However, in fewer case (0.02%) spontaneous hyperinflations was noted. Moreover, there was a case each for esophagitis, pancreatitis, gastric dilation, gastric outlet obstruction, delayed intestinal balloon transit and gastric perforation [107].

In another study involving 112 patients, the safety of Elipse intragastric balloon was studied with 85% patients being followed up for 1 year. The mean weight before the procedure was noted as 92.2 kg at 3 months 82.8 kg (p0.001) and BMI 34.3 kg/m^2 at 3 months 30.9 ($p < 0.000$). The total weight loss % was 10.7, 10.9, and 7.9% at 3, 6 and 12 months, respectively. Furthermore, 3 patients experienced early deflation, 6 had balloon intolerance and 1 encountered small bowel obstruction [108].

7. IGB devices under clinical trials

Despite IGBs being removable devices for weight loss compared to permanent modification of anatomy in a bariatric surgery, the safe implantation and removal of gastric balloons are the key for their success. The limitations associated with the currently in-use IGBs pushed the development of are novel and emerging technologies to overcome those challenges associated with balloon implantation, safe removal, balloon migration, gut perforation etc. As a result, several novel products are under development and are summarized in Table 3.

7.1. Ullorex®

Similar to Obalon, the orally ingestible intragastric balloon Ullorex® is enclosed in a large capsule, injected with citric acid and swallowed. The capsule does not require endoscopy for its placement or extraction. The self-inflatable polyurethane balloon contains a compressed pellet of sodium bicarbonate which upon interacting with citric acid produces carbon dioxide followed by the inflation of a balloon within 4 minutes up to 300 cm^3. The balloon is extracted naturally from the body following degradation of its biodegradable plug within 25–30 days subject to inter-subject differences in gastric physiology, which is then expelled naturally through the digestive tract.

The first safety and efficacy study established in 2007 in 12 individuals with a mean body weight of 146.7 ± 25.8 Kg, mean BMI 51 ± 3.5 Kg/m^2, observed a mean weight loss of 1.5 ± 1.7 Kg over ($p < 0.05$) 2 weeks [109]. The balloon successfully reduced the urge to eat in study subjects, but there were several issues reported including poor tolerance and premature deflation. The large size of the pill was another limitation causing swallowing difficulties, and a risk of esophageal inflation. Moreover, early erosion of the plug caused spontaneous

Table 3. Igbs under clinical trials.

IGB DEVICE	COMPANY NAME	DEVICE	ELIGIBILITY CRITERIA BASED ON BMI	ADMINISTRATION/ REMOVAL	FILLING MECHANISM	COMPLICATIONS	REGULATORY BODY	REFERENCE
Ullorex®	Phagia technologies, Inc	Polyurethane	30 or above	Oral/Natural excretion	CO_2 filled	Balloon deflation	Under preliminary studies	[109]
The Digestible Balloon	PlenSat, Inc	-	-	Oral/Naturally degraded	Self-inflated upon release of CO2	-	Not FDA approved	[110]
Magnetic Soft Endoscopic Capsule	NTU-NUS IGB	Polydimethylsiloxane	-	Oral/Naturally	CO_2 filled	-	Under clinical studies	[111]
Gelesis 100 & Gelesis 200	GELESIS	Hydrogel composed of citric acid and modified cellulose	25 to 40 kg/m2	Oral/Naturally excreted	Hydrogel occupies 1/4th of average stomach Volume	Diarrhoea, Abdominal discomfort	Plenity™ received FDA approval in 2019	[112–115]
IG Balloon ™	IG Balloon	Pliant foam layer	≥27 and ≤40 Kg/m2	Oral/Endoscopic	CO_2 filled	-	In final stages of development and Regulatory trials	[116]

NTU: Nanyang Technological University, NUS: National University of Singapore.

balloon deflation, and deflated balloons retained in the stomach longer than anticipated.

7.2. The digestible balloon

PlenSat designed a self-inflating, ingestible pill which upon contact with gastric acid at 37°C expands into the balloon by the release of carbon dioxide, branded as 'The Digestible Balloon.' The device was designed to stay in the stomach for 2 to 4 weeks until degraded by the stomach [110]. The visual elaboration of the prototype in humans seems unremarkable. The company expects the balloon to induce fullness similar to Bariatric balloons and Lap Band™. The balloon is pending pivotal safety and efficacy studies and yet to receive an FDA approval [110].

7.3. Magnetic soft endoscopic capsule (MSEC)

Do et al [117] presented a novel and noninvasive device called Magnetic Soft Endoscopic Capsule-Inflated intragastric balloon (Figure 6). A similar concept was already used previously in magnetically driven micro devices, capsules and drug-delivery devices and reported in the literature [118–121].

However, the MSEC was different to the prior inventions with regard to capsule material, its inflation and deflation mechanism and its biocompatibility. The encapsulated balloon after arriving in stomach would occupy 150–300 ml volume, comparatively much less than the other IGBs. The soft capsule shell was made using a scaffold-solvent method, whereas the outer spherical balloon is made of polydimethylsiloxane (PDMS) using 3D printing. The balloon is inflated externally using magnetic actuator activating the inflation valve to produce and release carbon dioxide following a chemical reaction in the chamber. The device deflation is time dependant that followed degradation of the biodegradable part in gastric fluids [111,117]. Secondly, modifications were proposed in deflation valve to avoid premature degradation [49]. MSEC has shown promising results in porcine stomach, however, its safety and efficacy in humans is yet to be established.

7.4. Gelesis

An innovative device from a biotech firm Gelesis comprised a superabsorbent hydrogel pill synthesized from modified cellulose cross-linked with citric acid to form a three-dimensional matrix when upon contact with gastric fluids [112]. Similar to conventional IGBs, Gelesis also works by occupying space in the stomach. Gelesis capsules encapsulating the hydrogel are ingested with water before meal, and on reaching stomach it expands into multiple small distinctive gel portions upon contact with gastric fluid that mixes with the food. The hydrogel occupies a quarter of the gastric volume by forming a three-dimensional gel network that does not biodegrade in stomach and is emptied into the small intestine.

These hydrogels are designed to degrade in large intestine by the action of microbial enzymes that deteriorates the three-dimensional network and water reabsorption, while the residual cellulose is available for microbial fermentation in colon and eliminated via defecation [113]. Gelesis 200 works by the same mechanism but its polymeric matrix had a higher

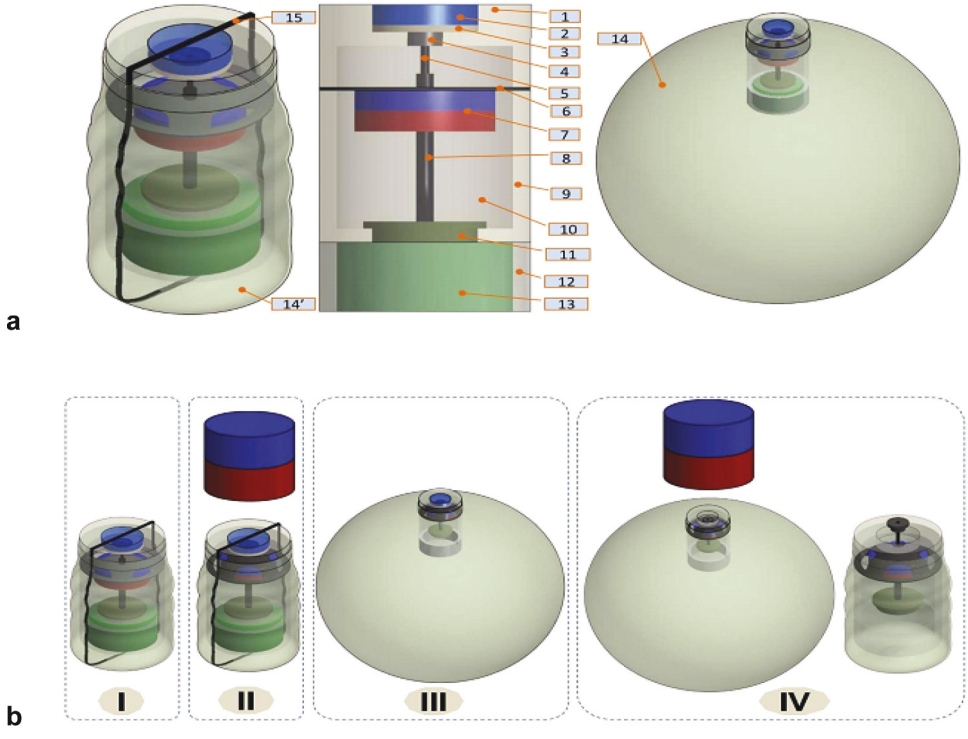

Figure 6. Magnetic soft endoscopic capsule [a]: magnetic capsule and structured balloon, (1) cover of inflation; (2) deflation valve nut; (3) layer of chitosan. (4) valve for deflation; (5) carbon rod fibre; (6) membrane; (7) internalised magnet; (8) large fibre-carbon rod; (9) acid containing chamber; (10) acid; (11) valve for inflation; (12) base containing chamber; (13) Base; (14) inflated balloon; (14′) deflated balloon; (15) flexible band. [b]: principle of inflation and deflation, (I) outer balloon and capsule; (II) inflation phase; (III) period of treatment; (IV) deflation phase. Figure credits Do et al. 2016 [117], reproduced under CC-BY 4.0 attribution.

hydration rate and elastic modulus than the Gelesis 100, further delaying its degradation in large intestine to help control glycemic index in high-risk obese patients [114].

FLOW (first loss of weight) and GLOW (Gelesis Loss of Weight) studies were aimed to evaluate the safety and efficacy of both hydrogels. In a recent randomized, double-blind, multicentre, and placebo-controlled trial [113], weight loss by Gelesis 100 was assessed following 24 weeks in patients with BMI ≥ 27 and ≤40 Kg/m^2 with fasting plasma glucose ≥ 90 and ≤145 mg/dL. Three capsules of Gelesis 100 or a placebo were administered with 500 mL of water 20–30 min before meals produced a 6.4% weight loss compared to 4.4% in placebo ($p = 0.0007$). Similarly, the Gelesis 200 also induced satiety in a single-center, double-blind crossover study in 24 overweight and obese individuals with BMI 27–35 Kg/m^2 with fasting plasma glucose between 90 and 126 mg/dL. The patients who ingested Gelesis 200 ten minutes prior to the meals reported feeling of fullness and consequent reduced food intake. Interestingly, this was not the case when Gelesis 200 was administered thirty minutes before meal [114].

The hydrogel pills are usually considered safe and effective; however, gastrointestinal infections, infestations and other adverse events were reported during trials. Common effects include diarrhea, abdominal discomfort, abdominal distension, sporadic bowel movements, abdominal pain and constipation [113,114]. While Gelesis 100 and 200 are still under FDA evaluation, Plenity™ have received FDA approval following successful pivotal trials on weight management in overweight and obese patients. It demonstrated a 10% average loss of body weight in 6 out of 10 patients [115].

7.5. IG balloon™

It is another swallowable gastric balloon, unique in its design it comprised an inactive, soft and pliant foam layer that limits its deflation in stomach. Moreover, an acid-resistant covering shields the inner material from acid damage and prolong the device resident time in stomach. The device is designed to address the problems of spontaneous deflation, a common limitation of gas and fluid-filled balloons. Additionally, the balloon is proposed to reside in the stomach for an infinite time unlike others that are designed to stay up to 12 months. Moreover, due to the bigger size of the balloon and its inability to pass through stomach, it was anticipated that in an event of spontaneous deflation, it can be endoscopically removed and may not need surgical intervention. The prototype still need to prove its safety and efficacy in clinic and yet to go through regulatory scrutiny to validate their ambitious claims [116].

8. Igbs as bridge to surgery in morbidly obese patients

Morbidly obese patients (BMI ˃60 kg/m^2) usually have a very high operative and postoperative risks that can be reduced by using a multidisciplinary approach. Intragastric balloons are efficient and have shown highest possible weight loss before surgery offering a non-operative (minimum invasive) approach. This helps to bridge interventions in morbidly obese patients who otherwise cannot undergoe bariatric or other surgeries safely [122,123].

In a case-summary of liver steatosis in a super morbid obese patient with a BMI 69.9 kg/m^2 who faced challenges undergoing sleeve gastrectomy in the first attempt, however, a gastric balloon was then placed endoscopically that acted as a bridge to laparoscopic sleeve gastrectomy. The results after 6 months showed 32% EWL (BMI 55 kg/m^2) in the patient. The patient underwent successful surgical attempt after 2-month post balloon removal. The weight loss reduced the fatty tissues that also reduced the liver size. Patient followed up with dietician and surgical unit 3 months' post-surgery and lost 14 kg. The patient lost lost 57 kg at 6 months (BMI 44.9 kg/m^2) [124].

In a retrospective, single-center study the effect of IGB on weight reduction post bariatric surgery, surgical and postoperative outcomes including complications was studied in 26 patients (BMI 69.26 ± 6.81) in comparison with 52 matched-pair controls. The weight loss was reported as 17.3 ± 14.1 kg, BMI 5.75 ± 4.66 kg/m^2 after 5 months. In comparison to the gastric balloon group, direct postoperative weight reduction was more significant in the control group (29.16 ± 7.53% vs 23.78 ± 9.89% after 1 year, $p < 0.05$ and 32.13 ± 10.5% vs 22.21 ± 10.9% after 2 years, $p < 0.05$) who have had a nadir (lowest BMI within 2 years postoperatively) and began to gain weight during follow-up. It was concluded that super-obese patients may benefit from a multistage treatment strategy using a gastric balloon prior to bariatric surgery to improve safety. Conversely, pre-treated participants with gastric balloon had a more moderate postoperative weight loss with an earlier nadir and an earlier body weight rebound, which should be taken into consideration in planning an intervention and managing patient expectations [125].

9. Multidisciplinary team in weight loss interventions

It has been recommended that all patients should undergo a comprehensive multidisciplinary assessment to ensure the patient understands the dietary changes and lifestyle commitment needed for a successful intervention. It is vital that the patient is motivated and willing to adhere to recommendations and follow-up requirements post-procedure. Multidisciplinary team (MDT) play a vital role in the treatment of obese patients and for preoperative patient evaluation; studies have demonstrated that weight-loss treatments work best when they are carried out as a part of a rigorous MDT [126]. The team comprises specialists treating obesity, with endocrinologist, psychologist (or psychiatrist if appropriate), bariatric surgeons, clinical nutritionists, and gastroenterologist/endoscopist playing key roles in the process [127]. Prior to any procedure are carried out, the patients are accessed by the MDT. The dietician (or a nutritionist) usually begins with a gradual modification of patient's gastronomic preferences and habits. The psychologist conducts an initial assessment of personality, anxiety evaluation, identification of eating disorders, and cognitive-behavioral support for the recommended changes in lifestyle. The patients are monitored throughout the duration of balloon placement, enabling to employ psychotherapy if needed. Relaxation techniques are also offered in case of anxiety. The physical trainer evaluates patient

respiratory limits. The surgeon and its team examines the metabolic syndrome and potential vitamin deficiencies in order to improve patient's overall health outcomes. A retrospective study of 159 patients treated with IGB evaluated the benefits of multidisciplinary team in management of obese patients with IGB placement. The study involved a multidisciplinary team consisting of two experienced psychologists trained in the care and consultation of bariatric patients, a dietician having vast experience of the procedures and the team of bariatric surgeons and their fellows. A dietary visit was done prior to the balloon placement following three additional visits throughout the procedure. The patients were also offered two psychological review before the procedure with additional three visits during the intervention. All visits were mandatory as part of the intervention. The endoscopist engaged with patients before balloon insertion. All patients attend bariatric surgery office at the beginning and were examined on a regular basis by the surgeons and their fellows, who coordinated bariatric care for the patients. The study concluded that psychological counseling and physical activity demonstrated better weight loss, whereas supervised diet did not had any direct correlation with improved weight loss [128].

10. Importance of bariatric training

With the increasing growth of bariatric endoscopy and bariatric surgery, the European Society of Gastrointestinal Endoscopy (ESGE) has advised that it is imperative to codify and improve training in bariatric endoscopy and endoscopic management of bariatric surgical adverse events. The Curriculum for bariatric endoscopy and endoscopic treatment of the complications of bariatric surgery from ESGE defines the criteria for the training, minimal number of procedures requried, stages of training, quality of training, and criteria for demonstrating proficiency prior to independent practise. This is to improve the patients outcomes in bariatric procedures and endoscopic treatment of bariatric adverse events based on clincial evidence.

The curriculum focuses on the need for standardisesd competency based training and intends to assist trainees in developing clincial competence and maintaining their abilities in bariatric endoscopy and the endoscopic management of bariatric surgery complications. The ESGE advises that all endoscopists must undertake upper gastrointestinal endoscopy training before commencing training in bariatric endoscopy and endoscopic therapy of bariatric surgical adverse events. Moreover, trainees must also have a profound understanding of the definition, classification, and social effect of obesity, as well as its pathophysiology and concomitant comorbidities commony found in these patients. ESGE made it essential that trainees must have compentencies for the identification and treatment of gastrointestinal disorders that are more common in obese people, as well as their participation in multidisciplinary teams to examine obese patients. The ESGE also proposes that expertise should be acquired via validated simulations, structured training courses, and subsequently hands-on training in tertiary referral hospitals. ESGE proposed that a minimum of 10 IGBs must be successfully implanted and retrieved by the trainee under supervision before independent practice [129].

11. Conclusion and future perspectives

Obesity is a global pandemic constituting a significant disease burden on health systems. The lack of efficacy, poor patients' compliance and cost-effectiveness of various pharmacological, lifestyle interventions, and invasive (surgical) options for treating obesity, has pushed the need for a noninvasive, safe and effective treatment option. The introduction of intragastric balloons (IGBs) to induce satiety back in 90s led to an excitement among patients and healthcare professionals but, surprisingly to many, brought significant challenges in practice. Several devices have been developed successfully since then employing diverse technological features but only a few received FDA approval and made their way to the clinic. Although IGBs have clinically demonstrated a significant weight loss, complications such as bowel obstruction, balloon migration, spontaneous deflation, mucosal ulceration and gut perforation have been reported posing challenges in clinical practice. The multidisciplinary team approach is vital in keeping patients motivated and committed for a successful intervention and maintaining the weight in long-term. The training and competencies of clinicians are also vital to enhance the safety of the procedure and efficient management of bariatric adverse events. Moreover, most devices currently available require endoscopy assisted insertion and removal in specialist clinical settings, hence pose other limitations such as cost, availability and compliance. There is, therefore, still a need for a device that required no external intervention for its insertion and removal, and that does not pose a risk of spontaneous deflation and intestinal occlusion. In this regard, a number of devices are under development that can be swallowed like a conventional pill and are anticipated to be biodegraded during their voyage through the gut to excrete out naturally through defecation, however, how successful they will be in clinical practice in terms of their efficacy and tolerability remains to be seen in the future.

12. Expert opinion

Intragastric balloons (IGBs) are currently approved medical devices for use to treat obesity, particularly in patients who otherwise would not respond to pharmacological and lifestyle interventions. IGBs have shown good clinical efficacy and resulted in substantial weight loss and therefore currently filling-in the therapeutic gap between pharmacotherapy and bariatric surgery. IGBs have also been successful as bridge to surgery in morbidly obese patients who otherwise cannot undergo surgery safety. They work by occupying gastric volume which reduces the urge to eat thereby inducing satiety. The approach is cost effective and anatomically reversible compared to the weight loss surgical interventions (e.g., bariatric surgery). Retaining weight loss over long term is, however, still a challenge, and it is vital that patient is willing to adhere to healthy lifestyle and committed to life-long dietary interventions, hence the crucial role of multidisciplinary team in preventing weight gain over the years. Often these factors are very difficult to evaluate in the device efficacy trials. Most devices available in the market does require endoscopic assisted administration and/

or removal under anesthesia. IGBs evolved significantly over the decades, emerging from the concept of gastric bezoar leading to the discovery of Garren Edward gastric bubble, the first FDA approved IGB marketed back in 1985. Despite several technological advancements over the decades, there are still challenges associated with currently used devices. Key adverse events include gastric ulceration, bleeding, spontaneous deflation, and the intestinal occlusion due to spontaneous balloon migration. It is, therefore, important to implement a universal standard in bariatric endoscopy and endoscopic management of bariatric surgical adverse events, for instance the standardized competency-based training recommended by the European Society of Gastrointestinal Endoscopy (ESGE). Since most IGBs require endoscopic assisted administration and/or removal, they can only be offered in specialist clinics that increases the cost of treatment. Moreover, the gastric balloons are mostly offered privately and a recurring course of three balloons in a typical regimen to achieve a meaningful weight loss in private settings can be very expensive. The next generation IGBs are aimed to address these issues. They are designed to be swallowed like an ordinary capsule and inflated automatically upon contact with gastric fluids. Some devices are designed using biodegradable materials so they could be broken down within the gut and excreted naturally through defecation. The concept and preliminary evidence is very promising, albeit further studies yet to determine their clinical efficacy and safety.

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Declaration of interests

H Merchant is the Head of Bioscience at University of East London, UK and also holds an adjunct Professorship at the Health Services Academy, Ministry of National Health Services Regulations & Coordination, Government of Pakistan. H Merchant has worked with pharmaceutical industry in their current and previous employments. Authors declare no direct relationship with device manufacturers mentioned in this manuscript and have received no funding or other reimbursements. Figures/images of some IGBs could not be included in the manuscript due to copyright restrictions. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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A peer reviewer on this manuscript has disclosed that they are a consultant for Allurion which produces the Allurion balloon. All other peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Authors contributions

S Ameen: Literature search and review, interpretation, drafting and editing the manuscript. H Merchant: Conceptualisation and design, funding (studentship) acquisition, project administration, drafting, reviewing, interpretation, and editing.

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