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Introduction, aims and outline of this thesis

INTRODUCTION

Obesity

Obesity is worldwide a major health problem and has been labelled a pandemic, affecting both developed and developing countries[1]. According to the world health organization, more than 650 million people are obese[2]. Moreover, if the current trend continues, 58% of the world's population could be overweight or obese by 2030, with an estimated 1.12 billion obese individuals[3]. In Europe, the prevalence of obesity has even tripled since the 1980s. Overweight plus obesity are affecting about 50% of the European population[4-5].

Overweight and obesity are defined using body mass index (BMI) cut-off points. BMI, which was formerly known as the Quetelet index, is defined as a person's weight in kilograms divided by the square of the person's height in metres (BMI = kg/m^2). Normal weight is defined as a BMI of 18.5-24.9 kg/m^2. A BMI of 25.0-29.9 kg/m^2 is called pre-obesity or overweight. Obesity is defined as a BMI ≥30.0 kg/m^2, whereas a BMI ≥40.0 kg/m^2 is considered severe obesity[6].

Obesity is a chronic disease and is associated with several comorbidities, including type 2 diabetes (T2D), hypertension, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnoea, dyslipidaemia, cancer and cardio-vascular diseases[2]. As a result, obesity is associated with significant morbidity and mortality[2,7-8].

Obesity is caused by many different factors, including behavioural, environmental, genetic, and social factors[7,9]. The treatment of (severe) obesity is therefore challenging, even more because obesity affects all ages and socioeconomic groups.

Bariatric surgery

Bariatric surgery is increasingly used as treatment for severe obesity as it results in more successful and durable weight loss compared to lifestyle changes[10-13]. Another factor that explains the popularity of bariatric surgery is the efficacy regarding the improvement and even remission of obesity related comorbidities like T2D and cardiovascular diseases[11,14-16]. Next to this, bariatric surgery leads to a decrease of the disease related mortality[14,17].

Bariatric surgery has evolved enormously in the last five decades. Multiple innovative bariatric procedures have been developed, initially hypoabsorptive procedures and later restrictive and combined procedures, primarily performed by laparotomy. Several "old" bariatric procedures, like the horizontal and vertical banded gastroplasty and the

jejunoileal bypass are no longer performed due to severe complications[18-20]. In the last two decades, the sleeve gastrectomy (SG) (**Figure 1**) and the Roux-en-Y gastric bypass (RYGB) (**Figure 2**) have emerged as the dominant bariatric procedures, almost all performed laparoscopically[10]. The SG has become the most performed bariatric procedure in adults worldwide. However, there is a marked regional variation. In Western-Europe the RYGB is the most frequent performed bariatric procedure[10].

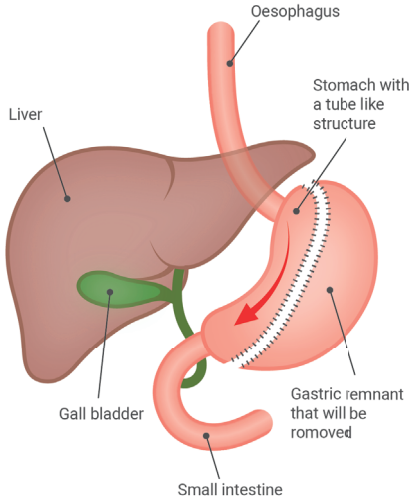

Figure 1 – Sleeve gastrectomy

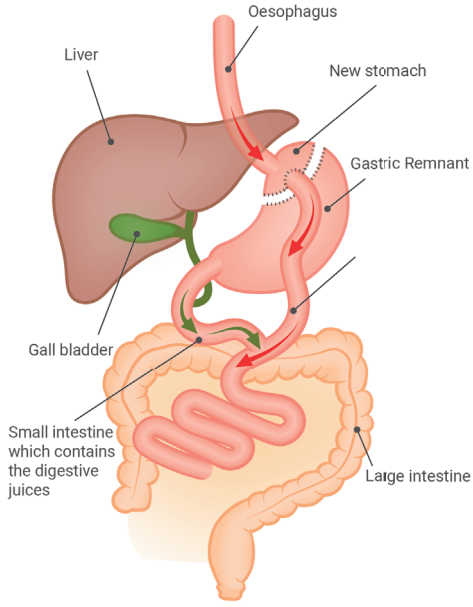

Figure 2 – Roux-en-Y gastric bypass

Proper treatment of severe obesity does not only require bariatric surgery. Perhaps even more essential is the treatment of underlying risk factors[7]. To be eligible for bariatric surgery, a patient has to meet several criteria. The international federation for the surgery of obesity and metabolic disorders (IFSO) has produced such criteria (**Table 1**)[21]. These criteria are widely used, also in the Netherlands[22].

Based on the IFSO-criteria, many bariatric centres in the Netherlands have an eligibility pathway, a screening process, for bariatric surgery. This screening is performed by a dedicated bariatric team including dieticians, psychologists, physical therapists, surgeons and bariatric nurses. The screening is thus not solely based on the assessment of the bariatric surgeon. During this screening process it is important for the dedicated bariatric team to identify the underlying risk factors causing severe obesity in the patient and addressing whether these risk factors first need treatment. In addition is it necessary

that the dedicated bariatric team as well as the patient balance out the benefits and downsides of the treatment. This all to make sure (for as much as possible) that patients really require bariatric surgery (as a last resort) and that they are motivated and able to make the required lifestyle changes and so make a success out of the treatment for their severe obesity.

Table 1 – Eligibility criteria for bariatric surgery (IFSO-guidelines)[21]

Major criteria
BMI > 40 by itself or >35 if there is an associated obesity illness, such as diabetes or sleep apnoea
Reasonable attempts at other weight loss techniques
Age 18-65
Minor criteria
No psychiatric or drug dependency problems
A capacity to understand the risks and commitment associated with the surgery
Pregnancy not anticipated in the first two years following surgery

Although bariatric surgery is known for its positive effects, patients can suffer from significant morbidity after bariatric surgery. Morbidity includes dumping syndrome, internal herniation (IH), gastric ulcer, gastro-oesophageal reflux disease, chronic abdominal pain, but also vitamin and mineral deficiencies and insufficient weight loss[23]. And although the risk is low, 0.1-0.4%, surgery can result in mortality[24].

Many studies have been performed regarding the positive as well as the negative effects of bariatric surgery. The majority of this research focused on the general eligible adult obese population. However, over the past decade, more studies have been performed regarding indications for bariatric surgery outside of the set IFSO-criteria and also regarding special risk groups. For example, studies regarding bariatric surgery in patients outside the set age criteria (<18 years and >65 years) and regarding patients with T2D but a BMI <35 kg/m^2. Studies in the last group show that it is safe and effective for the treatment of T2D[25-26]. Other special risk groups that received more attention are young adults and pregnant women after bariatric surgery.

Adolescents

In children and adolescents, the prevalence of overweight and obesity has increased by an alarming rate of almost 50% since 1980. In Western Europe, about 7% of the children <20 years have obesity, with a marked regional variation, ranging from 12.5% for boys in Malta to 4.1% in the Netherlands[1]. On top of this, the majority of children with obesity will remain obese into their adult life[27].

The impact of obesity in children and adolescents is extensive. Medical consequences include the alarming shift in the onset of obesity related comorbidities towards childhood including dyslipidaemia, hypertension, NAFLD and abnormal glucose tolerance[28-32]. T2D, primary known for its onset in elderly, is in particular more frequently seen in adolescents. Moreover, oral anti-diabetic treatments are failing earlier in patients with a youth onset of T2D, and they therefore require insulin therapy[33-35]. Next to this, obesity has also psychological consequences like poor self-esteem and depression[29-30]. All these factors contribute to a reduced life expectancy and quality of life in adolescents with (severe) obesity. Several studies indicate a reduction in life expectancy of almost 20 years[31,35-36].

The standard treatment for severe obesity in children and adolescents consists of multimodal lifestyle intervention programs focusing on eating patterns, physical exercise and behaviour. In the short-term, significant weight loss and improvement of cardiovascular risk factors have been reported[37-38]. However, it is mainly successful in children and less effective or in some cases not effective at all in adolescents with severe obesity[37,39].

Bariatric surgery in adolescents with severe obesity is an ethical issue and is not allowed in the Netherlands, unless it is performed in an approved clinical trial. Worldwide however, bariatric surgery has been performed in children and adolescents with severe obesity, especially in adolescents aged ≥16 years. Several studies have demonstrated that bariatric surgery in adolescents with severe obesity is safe and effective regarding weight loss and improvement of psychosocial impairment and quality of life[40-43]. Furthermore, the rates of remission of obesity related comorbidities are significant higher than those reported in adults, suggesting that adolescents may have a greater potential for reversal of the cardio-metabolic consequences of obesity[41,43]. Moreover, continuing with multimodal lifestyle intervention programs might lead to an increase in BMI with the possible consequence of worsening or a new onset of obesity related comorbidities[41]. Delay of surgical treatment until adulthood may result in development or worsening of obesity related comorbidities, weight gain and impaired quality of life. For this reason, in selected cases, bariatric surgery in adolescents with severe obesity should be an option.

However, also significant morbidity after bariatric surgery has been described in adolescents. Shoar et al. mentioned a reoperation rate of 9.6%, due to postoperative complications or inadequate weight loss[40]. Olbers et al. showed that as many as 25% of the adolescents required a surgical intervention for an abdominal complication after RYGB (although this was before they preventively closed the mesenteric defects at primary surgery). Furthermore, they showed that 66% developed ferritin/iron deficiency, 32% anaemia, 30% vitamin D deficiency and 22% vitamin B12 deficiency[41]. Inge et al. suggested that risks associated with the procedures, such as micronutrient deficiencies and

the need for additional abdominal surgical procedures, are more prevalent after RYGB compared to SG in adolescents[42].

Long-term data, with a follow-up more than five years, are scarce and no randomized controlled trials are yet performed to determine the long-term effects and to indicate which procedure, SG or RYGB, is most suitable for adolescents with severe obesity.

Elderly

When the IFSO-eligibility-criteria for bariatric surgery were first published in 1997[44], the worldwide life expectancy at birth was 66.8 years[45]. This life expectancy has increased to 72.4 years in 2017[45-46]. This has led to an increase of the population of people aged 65 years and older[47]. In the Netherlands, the life expectancy at birth has increased from 77.8 years in 1997 to 81.6 years in 2017[45].

The prevalence of severe obesity in the elderly, people aged 65 years and older, has increased worldwide[48]. This increased prevalence combined with a heightened life expectancy, leads to an increased request from the elderly for a surgical solution for their severe obesity. Nevertheless, bariatric surgery has been limited performed in the elderly. Reasons include the concern of higher complication and mortality rates[49-50] next to cost-effectiveness.

Over the past few years, several studies have examined the safety of bariatric surgery in elderly, showing controversial results. Some studies showed that the mortality rate and early complication rate are not increased in elderly compared to the general population that receive bariatric surgery[51-55]. However, other studies showed an increased rate of early complications[56-61]. In particular, the most recent systematic review published showed that bariatric surgery in the elderly is associated with an increased 30-day morbidity and mortality rate[57].

Bariatric surgery is cost-effective about 3.5 years after surgery in the general eligible population[62]. Looking at the quality-adjusted life-years (QALYs), less QALYs are gained by patients operated later in life. On the contrary, Hernandez et al. demonstrated that patients aged 55 years or older still gained 5.4 to 9.0 QALYs after RYGB compared to non-surgical controls[63].

In the Netherlands, the health insurances have tolerated that about 1% of the bariatric patients are allowed to receive bariatric surgery outside the set eligibility criteria. However, the question still remains whether bariatric surgery in the elderly is safe and effective.

Pregnancy

One of the specific risk groups about whom more scientific research is published are pregnant women after bariatric surgery.

During pregnancy, maternal physiological changes occur to accommodate the foetus and to prepare the mother for childbirth. These changes include an increased plasma volume, cardiac output and respiratory rate[64]. Pregnancy is a unique state of the maternal body, however it is not without risks. Common complications of a pregnancy, including bleeding, infection, pre-eclampsia, obstructed labour and ectopic pregnancy, result in maternal and foetal mortality each year[65].

Several aspects of the maternal health can increase the risk of a complicated pregnancy, for example maternal obesity. It increases the risk of gestational hypertension, pre-eclampsia, macrosomia and caesarean delivery[66]. Furthermore, women with obesity are more likely to suffer from infertility[67]. In the United States of America and Western Europe, pre-pregnancy overweight and obesity is present in 43% and 31% respectively[68].

Bariatric surgery has a positive effect on pregnancy related outcomes as it leads to an improved fertility[69-70] and a reduced risk of gestational diabetes[69-71], hypertensive disorders[70-72], caesarean delivery[72] and macrosomia[69-72]. These positive effects on pregnancy is another factor that contributes to the popularity of bariatric surgery.

However, negative pregnancy outcomes after bariatric surgery have also been described, including an increased risk of foetal growth restriction[69-70,73-74] and premature birth[69,74]. Furthermore, acute abdominal bariatric complications, such as small bowel obstruction, can also occur during pregnancy, especially after RYGB. Over the last few years, more case reports, case series and reviews of these case studies have been published, showing high risks for both mother and foetus[75-79]. Even maternal and foetal mortality have been reported[77,79]. However, these studies and case reports included small numbers of cases and the total number of studies is also small. With this, there is limited knowledge about and limited experiences with acute abdominal bariatric complications during pregnancy, especially within the obstetric care.

AIMS OF THIS THESIS

Based on the beneficial effects of bariatric surgery, the aim of this thesis was to explore whether bariatric surgery is also safe and effective in adolescents and elderly and thus whether it is acceptable to widen the age criteria for bariatric surgery on both sites of the age bar.

Furthermore, it aims to make bariatric surgeons and obstetricians aware of acute bariatric complications during pregnancy and to get more insight in the diagnostic and therapeutic plan to be able to improve maternal and foetal outcome.

OUTLINE OF THIS THESIS

This present thesis is divided into two parts which both consist of subgroups of patients who cover a small part (minority) of the bariatric surgical population.

Part I – Indications outside of the set eligibility criteria

In **Chapter 2**, a study protocol for an international, multicentre randomised controlled trial is presented, in which the RYGB and SG will be compared in selected adolescents with severe obesity. The aim of this study is to determine which of the two bariatric procedures is the most suitable for selected adolescents with severe obesity who do not benefit from formal lifestyle intervention. **Chapter 3** shows the perspective of paediatricians, parents of adolescents with severe obesity and adolescents with severe obesity regarding bariatric surgery in adolescents.

In **Chapter 4** it was investigated, with national data of the Netherlands, whether bariatric surgery is safe in the mid-term in elderly. **Chapter 5** provides an overview of the literature regarding the definitions for weight loss failure and weight regain. In addition, a more patient friendly terminology is suggested.

Part 2 – Long-term abdominal bariatric complications during pregnancy

The second part of the thesis focusses on acute abdominal bariatric complications during pregnancy. In **Chapter 6** the current practice and preferences of Dutch bariatric surgeons regarding fertile women undergoing bariatric surgery and pregnant women after bariatric surgery is studied. In **Chapter 7** more insight is given in the diagnostic accuracy of the magnetic resonance imaging (MRI) for the diagnosis of small bowel obstruction related to the bariatric surgery during pregnancy. **Chapter 8 and 9** describe different types of acute small bowel obstruction during pregnancy in patients with a history of bariatric surgery. In these chapters, clinical presentation, diagnostics with results, treatment with outcome, and the maternal and foetal outcomes are described.

This thesis will conclude with a general discussion including future perspectives in **Chapter 10**.

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PART I

Indications outside of the set age criteria

2

Laparoscopic Roux-en-Y Gastric Bypass Versus Sleeve Gastrectomy For Teenagers With Severe Obesity – TEEN-BEST: Study Protocol of a Multicentre Randomized Controlled Trial

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ABSTRACT

Background

Recent data support the use of bariatric surgery in adolescents with severe obesity following unsuccessful non-surgical treatments. Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) have demonstrated reasonably similar weight loss and reduction of obesity related comorbidities in randomized trials in adults. SG has internationally become the most commonly used procedure in adolescents, yet long-term outcome data are lacking. No randomized controlled trial comparing SG and RYGB has been performed in adolescents.

Objective

Determine whether SG is non-inferior to RYGB in terms of percentage total body weight loss (TBWL) in adolescents with severe obesity.

Methods

A multicentre randomized controlled non-inferiority trial. Two hundred sixty-four adolescents aged 13–17 (Tanner stage ≥IV) with severe obesity (corrected for age and sex) will be included. Adolescents agreeing to participate will be randomized to either RYGB or SG. The primary outcome is the proportion of participants achieving 20% TBWL loss at three years postoperatively. Secondary outcomes include (1) change in body weight, body mass index (BMI) and BMI standard deviation score, (2) incidence of adverse health events and need for additional surgical intervention, (3) resolution of obesity-related comorbidities, (4) prevalence of cardio metabolic risk factor measures, (5) bone health measures and incidence of bone fractures, (6) quality of life including psychosocial health, patient satisfaction and educational attainment and (7) body composition. Follow-up will extend into the long-term.

Results

Not applicable.

Discussion

This study will, to our knowledge, be the first randomized controlled trial comparing SG and RYGB in adolescents with severe obesity.

BACKGROUND

The prevalence of overweight and obesity in adults is still increasing worldwide. Parallel to this, the prevalence of overweight and obesity in children has increased by almost 50% between 1980 and 2013[1]. The majority of children with obesity will remain affected into their adult life[2], especially those with severe obesity post-pubertally[3].

Obesity is a chronic disease associated with several comorbidities including type 2 diabetes (T2D), cardiovascular disease (including hypertension and dyslipidaemia), musculoskeletal disorders and some cancers[4]. Correlated to the increase in prevalence of childhood obesity, an alarming shift in the onset of these obesity related comorbidities towards childhood has been noted, particularly for T2D[1,5-10]. The timeframe between the onset of T2D and the requirement of insulin therapy is shorter in adolescents than in adults, with medical treatments failing earlier[7,8]. Additionally, other comorbidities including metabolic disturbances also develop earlier in life[10]. All these factors contribute to a poor prognosis in adolescents with severe obesity, in whom studies have indicated a reduction in life expectancy of almost 20 years[5,11-12].

The standard treatment for obesity in children consists of multimodal lifestyle intervention programs, delivered by an expert multidisciplinary team focusing on eating patterns, exercise and behaviour. An updated Cochrane Review meta-analysed 37 studies, including a total of 27, 946 children, concluded that there is strong evidence for the beneficial effects of multimodal lifestyle intervention programs for childhood obesity. Results included a mean reduction of 0.15 kg per meter squared (kg/m^2) in body mass index (BMI). However, the reduction in the adolescent group (aged 13–18 years) was only 0.09 kg/m^2 [13]. A study from the Netherlands showed that a multimodal lifestyle intervention program resulted in significant weight loss and improvement of cardiovascular risk parameters in children with overweight, obesity and severe obesity, all to a similar degree. In children with severe obesity a decrease in BMI z-score of −0.23 ±0.32 (p=0.01) was observed after 2 years. Overall, 68% percent of the participants achieved a successful weight reduction, defined as 10% weight loss at 24 months follow-up[14]. However, despite these promising results, as much as one quarter do not experience weight reduction, which mainly applies to adolescents[14,15]. Lifestyle intervention is thus not a solution for a subgroup of adolescents with severe obesity, whereas comorbidity is high in this group, urging for other intervention possibilities. Bariatric surgery should be studied as an option.

A recent systematic review of medium- and long-term outcomes (minimum three-year follow-up) of bariatric surgery including 950 adolescents with severe obesity, aged twelve to nineteen years, showed an average decrease in BMI of 13.3 kg/m^2. Resolu-

tion of T2D/insulin resistance, hypertension and dyslipidaemia occurred in 69.95, 61.6% and 57.1% of patients respectively. The rate of reoperation was 9.6%, mostly because of postoperative complications and suboptimal weight loss[16]. Olbers et al. reported similar weight loss results over five years among adolescents and adults who received a Roux-en-Y gastric bypass (RYGB), with a mean BMI-reduction of 13.1 kg/m^2 in the adolescent intervention group. Notably, the control group of adolescents, who attended multimodal lifestyle intervention programs, experienced a mean increase in BMI of 3.3 kg/m^2 across the five-year study period. Regarding comorbidities among adolescents who received the RYGB, resolution of hypertension was seen in 100%, resolution of dyslipidaemia in 82.7% and complete resolution of T2D and disturbed glucose homeostasis in 100% (n=3) and 85.7%, respectively[17]. In recent years, Inge et al. have published three-year outcomes from the Teenage Longitudinal Assessment of Bariatric Surgery (Teen-LABS) prospective longitudinal study including adolescents undergoing sleeve gastrectomy (SG) and RYGB. This study showed a mean three-year BMI reduction of 15 kg/m^2 after RYGB and 13 kg/m^2 after SG. Furthermore, significant improvements were observed in weight related quality of life and cardio-metabolic health (95% remission of T2D, 86% remission of abnormal kidney function, 74% remission of elevated blood pressure, 76% remission of prediabetes and 66% remission of dyslipidaemia). This study suggested that risks associated with the procedures may be more prevalent after RYGB and included specific micronutrient deficiencies and the need for additional abdominal procedures[18]. The Teen-LABS group subsequently published 5-year outcomes after RYGB in comparison to adults in a similar study, LABS (Longitudinal Assessment of Bariatric Surgery). This confirmed similar weight loss outcomes between adolescents and adults, but a more favourable T2D and hypertension outcome in adolescents, supporting the case for early intervention[19].

The rates of remission of comorbidities after bariatric surgery observed in each of the previous mentioned studies were higher than those reported in adults, suggesting that adolescents may have a greater potential than adults for reversal of the cardio-metabolic consequences of obesity[17-19]. In addition, Panunzi et al. showed in the Swedish Obese Subjects study of adult patients that when T2D diagnosis was new (<1 year) bariatric surgery resulted in > 90% remission, whereas a diagnosis of T2D >4 years ago resulted in less than 40% remission[20]. Therefore, delay of surgical treatment until adulthood is negatively associated with the reduction of several comorbidities, cardiovascular risk profile and premature death.

In short, among adolescents with severe obesity who do not respond sufficiently to multimodal lifestyle interventions, bariatric surgery is a viable option. Although both SG and RYGB showed successful weight loss and reduction of obesity related comorbidities

in adolescents thus far, long-term outcome data of SG in adolescents has been limited and, to date, no randomized controlled trial (RCT) has been performed in adolescents directly comparing these two procedures. This clear knowledge gap hampers optimal procedure selection for adolescents and thus prevents evidence-based recommendation to eligible adolescents. Therefore, we propose an RCT comparing SG with RYGB in adolescents with severe obesity.

METHODS/DESIGN

Hypothesis

SG in combination with lifestyle intervention is non-inferior to RYGB in combination with lifestyle intervention in terms of proportion of participants achieving a total body weight loss (TBWL) of at least 20% at three years, with an equivalent or lower rate of complications.

Objective

The main objective of this trial is to obtain level one evidence regarding differences in clinical outcomes between RYGB and SG (both performed as add on to lifestyle intervention) in adolescents with severe obesity. By assessing efficacy and safety we aim to provide guidance regarding procedure choice based on reliable risk/benefit data overall as well as in subgroups.

Trial design

This trial is designed as a non-inferiority, parallel, international multicentre, randomized controlled trial, comparing two bariatric surgeries (RYGB and SG) in adolescents with morbid obesity. The TEEN-BEST flow-chart, including the participant timeline, is shown in **Figure 1**.

The trial consists of two phases. Phase 1 will be an internal pilot of twenty patients at each of the two initiating surgical sites (10 + 10 SG and 10 + 10 RYGB in total) to establish feasibility. The methods of recruitment and informed consent will be refined over this period. Phase 2 will be the full multicentre RCT. Patients will be recruited starting in May 2020 until May 2023. Follow-up within the RCT will be planned for a minimum of five years.

A matched group, identified from historical data in the multimodal lifestyle intervention program (COACH) of Maastricht University Medical Centre, will be used as a non-surgical comparator to the bariatric procedures.

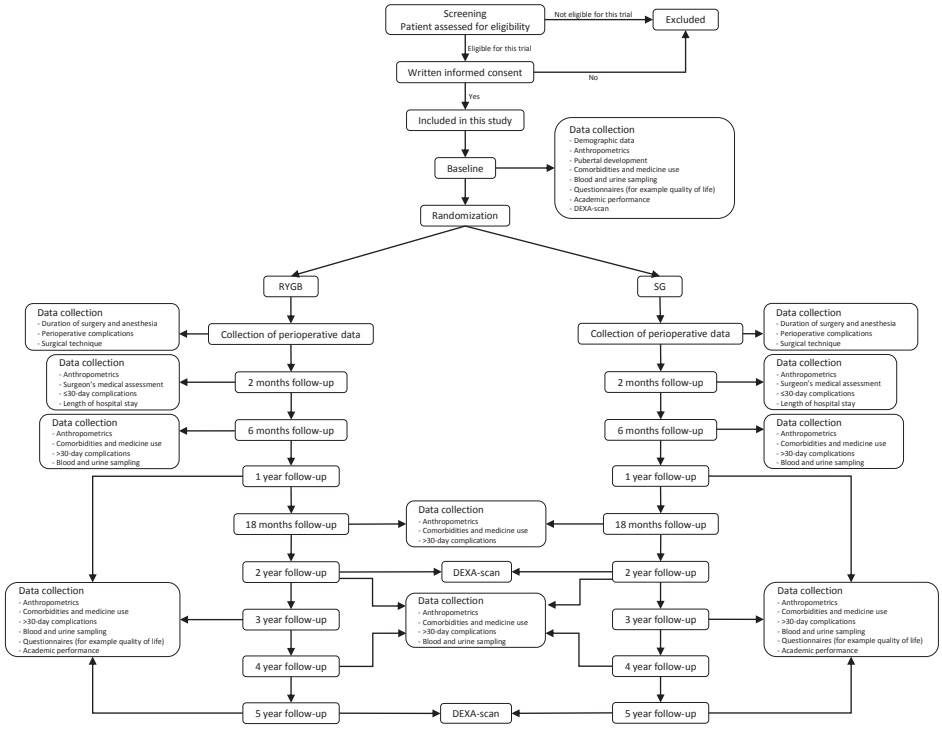

Figure 1 – TEEN-BEST flowchart and participant timeline
RYGB = Roux-en-Y gastric bypass, SG = sleeve gastrectomy, DEXA-scan = dual-energy x-ray absorptiometry scan

Study setting

This study will initially be conducted at two surgical sites (a non-academic Dutch centre and an academic Swedish centre), with the potential to recruit additional sites after successful initiation. All surgical centres will collaborate with a child obesity centre, which will initially be three sites (one academic and one non-academic Dutch centre and one academic Swedish centre). The list of study sites can be obtained from the corresponding author (bariatrics.resurge@mmc.nl).

Informed consent procedure

Participants will be identified by collaborators in the child obesity lifestyle programs at the participating child obesity centres or by paediatricians outside of these centres. Existing patients who have already participated for twelve months in a child obesity lifestyle program or prospective identification of new patients (minimum of twelve months in a lifestyle program) with the potential to meet eligibility will be screened for recruitment.

During a multidisciplinary meeting eligible patients will be identified. The multidisciplinary team will, as a minimum, consist of a paediatrician, a clinical psychologist, a

dietician and a bariatric surgeon. Patients identified as eligible for this study during the multidisciplinary meeting will be informed by their paediatrician about the trial. All patients will receive a written information leaflet and be required to provide written informed consent. When an adolescent is interested in participating in this trial, the paediatrician will ask the individual permission for the coordinating investigator to contact them providing more information about the trial and informed consent.

Informed consent will be obtained in the outpatient clinic prior to the participant undergoing any procedure that is specifically performed for the purposes of the trial at the participating site, including the collection of identifiable participant data. This informed consent conversation will be performed with the coordinating investigator. In adolescents, aged 13–14-15 years, we will additionally obtain informed consent from either both parents or caregivers.

Study population

All willing patients who meet age, Tanner stage and BMI criteria, and have participated for at least twelve months in a lifestyle intervention program, will be offered formal assessment for study inclusion. Patients who continue to meet eligibility criteria will be invited to be included in the trial.

Inclusion criteria

(1) Completed a minimum of twelve months in multidisciplinary lifestyle intervention and/or pharmacotherapy weight loss program;
(2) Consensus in the multidisciplinary child obesity team on the diagnosis of suboptimal outcome (defined as a TBWL of <10% after twelve months) following multidisciplinary lifestyle interventions;
(3) Age 13–17 years;
(4) Severe obesity meeting international federation for the surgery of obesity and metabolic disorders (IFSO) criteria for bariatric surgery: BMI ≥40 kg/m^2 with minor comorbidities, or BMI ≥35 kg/m^2 with at least one major comorbidity, corrected for age and sex according to the international obesity task force (IOTF) criteria.
(5) Tanner stage ≥IV;
(6) Consensus in the multidisciplinary child obesity team, during the multidisciplinary meeting, on a motivated participation during the lifestyle intervention program so far, likely to persist in the future. The participant must demonstrate commitment to a bariatric program in the knowledge that they will be expected to continue with this effort after the bariatric surgery;

Exclusion criteria

(1) Unable to consent as appropriate;
(2) Illiteracy (inability to read and understand questionnaires);
(3) Secondary obesity – obesity caused by a uncontrolled medical condition;
(4) Known syndrome or genetic disorder (such as Prader-Willi syndrome);
(5) Skeletal immaturity (Tanner stage ≤III) – premenarche – bone age less than fifteen years in boys;
(6) Ongoing addiction (alcohol, drugs, medication);
(7) Previous bariatric, gastro-oesophageal reflux or gastric surgery;
(8) Uncontrolled psychiatric disorder;
(9) Inflammatory bowel disease;
(10) Non-support of both parents / caregivers.

Eligibility criteria study centres and bariatric surgeons

Surgical sites are required to have (1) a bariatric team performing at least 300 adult bariatric procedures yearly, (2) an existing child obesity management program, or a close link with such a program in another institute and (3) an intensive care unit that treats adolescents, or access to such a facility nearby.

The bariatric surgeon(s) will be required to have a minimum experience of at least fifty of each bariatric procedure (SG and RYGB) in adults.

Intervention

Eligible participants will be randomized to receive either RYGB or SG (both in combination with lifestyle intervention). To assure high quality of both bariatric procedures surgical protocols have been written and will be monitored during the trial.

All patients included in the study will have a protein diet (Modifast or Weight care) 2 weeks prior the surgery, with a standard number of calories per day (approximately 600 Cal). This very low-calorie diet is given in order to decrease liver volume and increase laparoscopic workspace. It is proven that this very low-calorie diet reduces the postoperative complication rate in patients who underwent a laparoscopic RYGB[21].

Patients are required to take vitamins daily for the rest of their life (including extra Calcium+ Vitamin D, Vitamin B12 and Iron) according to local guidelines.

Laparoscopic RYGB

The surgical procedure has been described earlier by Dillemans et al. (circular anastomosis)[22] and by Lönroth et al. (linear anastomosis)[23]. In short, after induction of pneu-

moperitoneum and placement of five laparoscopic ports the majority of the stomach is disconnected from the normal digestive route using a linear stapler to leave a small (20–25 ml) gastric pouch in continuity with the oesophagus. The jejunum is transected approximately 100 cm from the ligament of Treitz and the distal end (Roux limb) is anastomosed to the gastric pouch, as a gastrojejunal anastomosis, using a 25 mm circular stapler or a 30–45mm linear stapler. Thereafter, the proximal end (the biliary limb) is attached approximately 50–150 cm distally along the jejunum, as a jejuno-jejunal anastomosis. Furthermore, the mesenteric defects beneath the jejunojejunostomy and at Petersen's space will be closed. Before closure of the skin incisions, the gastrojejunostomy is tested for leakage using methylene blue and an easy flow drain (optional) will be placed. After closure of the incisions bupivacaine will be injected subcutaneously.

Laparoscopic SG

The procedure was performed by Gagner[24]. SG involves the excision of the majority of the stomach on its greater curvature side, using a stapling device. In short, pneumoperitoneum is induced with the Verres needle and five laparoscopic ports are placed, as with the laparoscopic RYGB. The resection line begins from approximately five centimetres proximal to the pylorus, proceeding to the angle of His to result in a tube or sleeve-shaped remnant stomach of approximately 25% its original capacity. A calibration bougie, usually sized between 34 and 40 Fr, is used to standardize the sleeve size. Before closure, the stomach remnant will first be removed and the gastric tube will be tested for leakage with methylene blue. Furthermore, after closure of the incisions bupivacaine will be injected subcutaneously.

Placement of an easy flow drain is optional.

Outcomes

Primary outcome measure (non-inferiority)

The proportion of patients that achieve a TBWL of at least 20% at three years after surgery.

Secondary outcome measures

To compare outcomes between SG and RYGB. In addition, a historical cohort of adolescents who participated in a lifestyle intervention program only will be compared to both study arms on these secondary objectives (except for (2) and (7)).

(1) BMI, BMI standard deviation score and percentage TBWL [1, 3 and 5 years after the bariatric surgery]: weight loss is measured in kilogram and as percentage TBWL;

(2) Adverse health events [1, 3 and 5 years after the bariatric surgery]: including complications (within 30 days and beyond 30 days of bariatric procedure) and the

need for re-operation. Complications will be scored according to the Clavien-Dindo classification[25];

(3) Resolution of co-morbidities [1, 3 and 5 years after the bariatric surgery]: blood pressure (systolic and diastolic), lipid profile (HDL, LDL, TG), glucose control (HbA1c, fasting blood glucose level, fasting insulin, HOMA-IR), obstructive sleep apnoea (OSA) (Epworth sleepiness scale), kidney function (glomerular filtration rate, micro-albuminuria, creatinine), liver disease (i.e. non-alcoholic fatty liver disease) (alkaline phosphatase, gamma glutamyl transpeptidase, aspartate-aminotransferase, alanine aminotransferase, bilirubin, ultrasound (baseline, 3 and 5 years post-surgery) and decrease/change in medication for each of the co-morbidities;

(4) Resolution of OSA, T2D and pre-diabetes, hypertension, dyslipidaemia, deranged liver function [1, 3 and 5 years after the bariatric surgery];

(5) Prevalence of cardio-metabolic risk factor measures [1, 3 and 5 years after the bariatric surgery];

(6) Routine post-bariatric surgery nutritional blood tests at each assessment [1, 3 and 5 years after the bariatric surgery]: including full blood count, electrolytes, creatinine, fasting glucose, fasting insulin, HbA1c, liver parameters and function tests, iron, ferritin, vitamin B12, thiamine, folate/red cell folate, lipid profile, 25-hydroxyvitamin D, calcium and parathyroid hormone;

(7) Bone health measures and the incidence of bone fractures [baseline and at 2 and 5 years after the bariatric surgery]: bone mineral density (DEXA-scan), osteocalcin, PINP, CTX and bone-specific alkaline phosphatase;

(8) Generic and obesity-specific health-related quality of life [1, 3 and 5 years after the bariatric surgery]: IWQOL-Lite, RAND-36, Kidscreen-27;

(9) Psychosocial health measures and educational attainment [1, 3 and 5 years after the bariatric surgery]: education, depression (Beck Depression Inventory), anxiety (Beck Anxiety Inventory), self-esteem (Kidscreen-27, IWQOL-Lite), attention deficit hyperactivity disorder (AVL);

(10) Patient satisfaction [1, 3 and 5 years after the bariatric surgery]: single question scale 1–10 and net promotor score;

(11) Body composition [1, 3 and 5 years after the bariatric surgery]: DEXA-scan.

Sample size calculation

A clinical successful weight loss is defined as a TBWL of ≥20% for this study. We obtained unpublished summary statistics from the Teen-LABS study group, which were used to inform the power calculation. The proportion of participants losing at least 20% of their total body weight at three years in the Teen-LABS study was 63% after SG and 72% after RYGB. The power calculation requires the estimation of two parameters, i.e. the mean TBWL of participants at three years and the difference in mean percentage TBWL that

would be considered clinically important (the non-inferiority margin). The hypothesis is that 70% of the participants will achieve a TBWL of 20%. The non-inferiority margin was chosen on the basis of the opinions of the clinical applicants and was set at 20%. A group sample size of 132 patients/arm, allowing for a 15% dropout, is needed to achieve 90% power to detect non-inferiority using a one-sided Z-test (unpooled). The non-inferiority margin is – 0.20000. The true difference between the means is assumed to be 0. The significance level (alpha) of the test is 0.02500.

Randomization

Randomization will be performed by the coordinating investigator after trial eligibility and informed consent to participate in the trial have been confirmed. Randomization will be performed using a computerized randomization program (Research Manager), which will produce unchangeable computer-generated numbers. Randomization will be stratified according to centres in order to ensure balanced groups. Randomization will be on a 1:1 basis using block sizes of 6–8 participants.

Blinding

Patients and caregivers (but not the surgical team) will be blinded to which procedure was performed until the two-month follow-up visit, which gives unbiased data regarding the 30-day complications. Standardized management, appropriate to both SG and RYGB, will be conducted during the blinded period and dietary advice and supplementation appropriate to both procedures will be administered to all patients.

Within the first 2 months, the trial code will only be broken in exceptional circumstances when knowledge of the surgical technique is essential for the safety of the patient. If unblinding is required, a formal request for unblinding must be made. The principle investigator (PI) will enter Research Manager for unblinding and will contact the holder of the code break list as a back-up. The coordinating investigator will notify the Sponsor in writing as soon as possible following the code break including the reason(s) for the code break.

Data collection, data management and data analysis

After written informed consent is obtained, all patients will be assigned a study number. This moment is defined as baseline; the date when the participant is examined and found suitable to be randomized. Data will be pseudonymous inserted into a computerized database, Research Manager Software (certified by the 'Information Security Management System 27001'), by local investigators. All data will be handled confidentially, anonymously and in accordance with the international accepted Personal Data Protection Act. A subject identification list will be drafted. This list will be password

protected. The subject identification list and the password will be administered by the coordinating and principal investigator.

The follow-up of patients that withdrew from the study will continue according to the implemented standard care for adults who underwent bariatric surgery. This actually means that the follow-up just continues according to the follow-up schedule of the study, because the follow-up in the study is according to the standard care (including laboratory assays and quality of life assessment) for adults.

Primary analyses will be based on intention-to-treat and will include all randomized patients. In addition, a per-protocol analysis will be performed to explore the influence of protocol deviations and compare the results with the primary analysis. Furthermore, to explore the influence of contamination (switching between study arms) we will perform an as-treated analysis, the results of which will be compared with the results of the primary analysis.

The primary parameter, the proportion of patients achieving at least 20% TBWL at three years, will be compared using descriptive statistics and a logistic regression analysis.

Secondary parameters, including quality of life questionnaire scores and other continuous outcomes measured at multiple time points, will be compared using a mixed regression model with baseline and post-surgery measures modelled jointly. Changes in treatment effect with time will be assessed by adding a treatment by time interaction to the model and comparing models using a likelihood ratio test. Time to event outcomes will be compared using survival methods for interval censored data. Frequencies of adverse events will be described. Treatment differences will be reported with 95% confidence intervals (CIs). A detailed analysis plan will be prepared during the feasibility phase 1.

We will compare outcomes between groups at the end of phase 1. Other interim analyses will be decided in discussion with the data safety monitoring committee (DSMC).

In addition, one subgroup analysis is planned; outcomes will be described for male and female participants. Differences in treatment effect between the two subgroups will be tested by including interaction terms to the analysis model.

Missing data will be excluded and will not be imputed. To address possible bias of the missing values, the baseline characteristics of patients with and without missing values will be compared. We will do our utmost to collect outcome measures wherever possible to minimize the number of missing values. This means we will also accept patient

reported weight in case of missing weight data. In addition, we will try to retrieve the reason for the missing value, such as missing because of weight gain.

Monitoring

The DSMC will review the data periodically regarding the safety and efficacy of the trial procedures and advise the sponsor on the future management of the trial. They will review any unexpected adverse event and may ask to review outcomes or other data that may have an impact on the trial.

They will perform interim analyses, can decide to end the study prematurely and will send their advice to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMC, the sponsor will send the advice to the reviewing REC, including a note to substantiate why the advice of the DSMC (or part thereof) will not be followed.

Independence is a key characteristic of this committee, where the committee members are completely uninvolved in the running of the trial and the committee members cannot be unfairly influenced by people or institutions involved in the trial. The members of the DSMC will reflect the disciplines necessary to interpret the data from the trial; an epidemiologist/statistician, a surgeon, a paediatrician and a bariatric surgeon with experience in adolescents.

All adverse events (AE), related to the bariatric surgery, reported spontaneously by the subject or observed by the investigator or his staff and are unexpected, and serious adverse events (SAE) will be recorded and reported to the sponsor by the main coordinating investigator in accordance with the International Conference for Harmonization of Good Clinical Practice guidelines and the Sponsor's Research Related Adverse Event Reporting Policy. Abnormalities in blood- and urine samples will only be noted as an AE in case intervention is required. SAEs that are critical to the safety evaluation of the participant need to be reported directly (within 24 h) to the main coordinating investigator. The sponsor will report the AEs/SAEs to the Research Ethics Committee (REC) within seven days (death or life-threatening) or within fifteen days.

The Clinical Trial Centre Maastricht will perform the external monitoring audit of this study. The monitoring will be done in the first year and at the end of the study in all participating centres. In between, monitoring will be conducted using a risk-based approach that focuses on sites that have, for example, the highest enrolment rates, largest numbers of withdrawals, and/or the highest numbers of reported AEs or SAEs. Specific

attention will be payed to SAEs, informed consent, data monitoring and completeness of case record forms.

Ethics and dissemination

Research ethics approval

This study will be performed in accordance with the ethical standards of the institutional and/or national research committee (Medical Research Involving Human Subjects Act) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent will be obtained from all individual participants included in the study. The medical ethical reviewing committee Máxima Medical Centre approved the TEEN-BEST study protocol and all participating centres on June 5th, 2018 and approved TEENBEST study protocol version 5.0 on April 1th, 2020 (REC number W18.015).

Protocol amendments

The accredited REC will be informed of all substantial amendments. They will be responsible for approval of the amendment prior to implementation in the protocol. After approval, the protocol amendments will be communicated with the local investigators and the Netherlands Trial Register.

Confidentially

The participant will be assigned a study number after randomization and a subject identification list will be drafted. This list will be password protected and will be administered by the coordinating investigator and PI. All data will be handled confidentially, anonymously and in accordance with the internationally accepted Personal Data Protection Act. Data will be inserted into a computerized database, Research Manager Software, by local investigators. Registration will be monitored and is in line with Good Clinical Practice guidelines.

Archiving of the trial documentation will be authorized by the sponsor following submission of the end of trial report. Data and samples from this study will be stored for a period of fifteen years after completion of the trial. Destruction of essential documents will require authorization from the sponsor.

Access of data

Access to the data will be limited to the research team (local investigators, coordinating investigator and PI), Inspection for Healthcare/audits, monitors and auditors in line with participant consent.

Declaration of interests

The authors declare that they have no competing interests.

Ancillary and post-trial care

Both the sponsors/investigators have a liability insurance, which is in accordance with article 7 of the WMO. The sponsors also have insurance in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for harm to research subjects through injury or death caused by the study. The insurance applies to harm that becomes apparent during the study or within four years after the end of the study.

Dissemination policy

Research data can only be presented and/or published with agreement from the PI. The research data will be reported following the Consolidated Standards of Reporting Trials guidelines.

DISCUSSION

Recent data support the use of bariatric surgery in adolescents with severe obesity as an additional treatment to lifestyle intervention. Although both SG and RYGB have demonstrated successful weight loss and reduction of obesity related comorbidities thus far, long-term outcome data of SG in adolescents have been scarce. No RCT has been performed in adolescents directly comparing these two bariatric procedures. This knowledge gap hampers optimal procedure selection in adolescents and prevents evidence-based recommendation to eligible adolescents.

TEEN-BEST will be the first randomized controlled trial comparing SG and RYGB integrated in the stepped/matched care of adolescents with severe obesity, thus combining the benefits of both multimodal lifestyle intervention and surgical intervention, and will guide future adolescent bariatric practice.

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3

Bariatric Surgery in Youth: the Perspective of Dutch Paediatricians, Parents and Adolescents

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ABSTRACT

Background

Recent studies have indicated that bariatric surgery is effective for the treatment of youth with severe obesity. The attitudes of paediatricians, parents, and adolescents regarding this topic remain unclear. Therefore, the aim of this study was to assess the current thoughts and beliefs of Dutch paediatricians, parents, and adolescents regarding bariatric surgery in youth.

Methods

An online survey containing twenty questions on bariatric surgery in youth was distributed to paediatricians of the Dutch Society of Paediatrics. Parents and adolescents who participated in an interdisciplinary care program for overweight, obesity, and severe obesity filled out an online survey of twelve questions.

Results

One hundred and twenty-one paediatricians, 49 parents, and nineteen adolescents completed the surveys. Seventy-two paediatricians (59.5%) considered bariatric surgery to be an effective treatment for youth with severe obesity when conventional treatment fails, and intend to refer patients for bariatric surgery. The most frequently suggested conditions for bariatric surgery were a minimum age of sixteen years (n=59, 48.7%), a BMI threshold of 40 kg/m^2 (n=51, 42.2%), and a minimum Tanner stage of IV (n=59, 48.8%). Thirty parents (61.2%) and fourteen adolescents (73.7%) responded that bariatric surgery should become available for youth with severe obesity.

Conclusion

Dutch paediatricians, parents, and adolescents increasingly accept bariatric surgery as a treatment modality in youth with severe obesity who do not respond successfully to lifestyle intervention. Whether paediatricians will actually refer youth for bariatric surgery remains to be seen when this treatment option will be implemented in the Netherlands.

INTRODUCTION

The worldwide prevalence of overweight and obesity in youth has increased substantially in the last decades; in 2015 more than 100 million children and adolescents were obese[1-3]. Although the rising trends of overweight and obesity have plateaued, the rates of severe obesity are still growing with data from 2009 indicating that 0.6% of Dutch boys and 0.5% of Dutch girls were affected by severe obesity[4]. This upward trend is concerning when considering the substantial short- and long-term health risks related to severe obesity, such as type 2 diabetes (T2D), hypertension, fatty liver disease, and dyslipidaemia, even when compared to youth with obesity[5-9].

The standard treatment for youth with obesity in the Netherlands comprises of multimodal lifestyle intervention programs focusing on dietary behaviour, physical activity, and underlying individual and systemic factors, provided by a paediatric multidisciplinary team. These programs have shown to result in a significant decrease in body mass index (BMI) and improvement of cardio-metabolic risk parameters in youth with overweight, obesity, and severe obesity[10-13]. At the same time, a quarter of treated youth do not experience weight loss and adolescents with severe obesity have proven to be particularly difficult to treat[11-12].

As bariatric surgery is commonplace in the treatment of adult obesity, it can be considered in youth with severe obesity to achieve similar long-lasting weight loss and concurrent improvement of comorbidities when conventional treatment fails. A meta-analysis by Shoar et al. reported that bariatric surgery is safe and effective in the treatment of severe obesity in adolescents aged twelve to nineteen years old[14]. However, long-term follow-up is lacking[14-16]. A recently published guideline for the treatment of youth with overweight and obesity in the Netherlands advised reticence towards bariatric surgery, advocating its use in youth only in the context of scientific research. Furthermore, this guideline stated that referral should be considered by paediatricians of obesity expertise centres and after the unsuccessful completion of at least one year of multidisciplinary lifestyle intervention at named centres. A successful intervention is defined as weight loss of $\geq 10\%$[17]. In line with the cautious approach of this guideline, the opinions of professionals, parents, and adolescents worldwide on this subject are divided[18-23]. Studies among paediatricians from the USA dating from 2007 to 2009 reported that 47.0% and 88.5% of paediatricians would not refer patients for bariatric surgery[19-20]. Another qualitative report revealed that Dutch obesity specialists experience reluctance to refer youth for bariatric surgery as they endorse concerns that surgery might not treat the underlying psychological or behavioural problem. On the other hand, the obesity specialists, parents, and adolescents who felt that the ethology of obesity was predominantly

somatic were more in favour of bariatric surgery[21]. However, the current perspective of Dutch paediatricians, parents, and adolescents remains unclear.

With the goal of further investigating the efficacy and feasibility of bariatric surgery in youth, our aim was to explore the current attitudes of Dutch paediatricians towards these topics[24]. A secondary aim was to discover the thoughts and beliefs of Dutch parents and adolescents regarding bariatric surgery in youth.

METHODS

Study design

In January 2020, an online survey was distributed to all practicing members of the Dutch Society of Paediatrics in the Netherlands. To optimize response rates, a reminder was sent to the paediatric departments of all Dutch hospitals from September to November 2020.

Adolescents (13–18 years) who were treated for their overweight, obesity, or severe obesity in the outpatient, family-based, interdisciplinary care program of the obesity expertise Centre for Overweight Adolescent and Children's Healthcare (COACH) at the Maastricht University Medical Centre (MUMC+) were asked to fill out a survey during their follow-up visits from September to December 2020. Their parents, as well as parents to children under thirteen years of age who were treated for their overweight, obesity, or severe obesity in the COACH program, were asked to fill out a survey in the same period[11]. To optimize response rates, an email was sent to distribute the survey to the parents and adolescents.

The study protocol was submitted to our local Medical Ethical Research Committee, who deemed formal approval not necessary according to Dutch law (Medical Research Involving Human Subjects Act).

Survey

Anonymous surveys were designed using an online platform for questionnaires and surveys (Survey Monkey Inc., San Mateo, CA, USA) (**Appendix 1**). The surveys were self-administered and the study aim was explained before the start of all the surveys.

The survey for paediatricians consisted of 20 questions covering demographics, the current practice of youth with severe obesity including the results of this treatment, and the opinions of the respondents regarding bariatric surgery in youth. Youth was

defined as persons aged < 18 years old, and severe obesity defined as a BMI ≥ 40 kg/m^2 or a BMI ≥ 35 kg/m^2 with an obesity-related co-morbidity, both adjusted for gender and age according to the International Obesity Task Force cut-off points[25]. Regarding the questions on bariatric surgery in youth, the paediatricians had to assume that the youth followed a lifestyle intervention program for at least twelve months without successful weight loss, and that they had stable and supportive families.

The survey for parents and adolescents consisted of twelve questions covering their current treatment and their perspectives on bariatric surgery in youth. A short introduction was given to the parents and adolescents regarding bariatric surgery. Types of questions included dichotomous, multiple-choice, and Likert scale questions. In all surveys, some questions allowed textual remarks.

Statistical analysis

The sample size was based on the most important question; a dichotomous question regarding the willingness of paediatricians to refer for bariatric surgery. Accepting a maximal margin of error of 0.1 (precision) for proportions in our population of interest, we required a minimum sample size of 97 paediatricians to estimate proportions close to 0.5 with sufficient precision[26]. All completed surveys were used for analysis. Continuous data are presented as mean ±standard deviation (SD). Categorical data are presented as number (percentage). Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM, Armonk, NY, USA).

RESULTS

The results of the paediatricians, parents, and adolescents are presented separately.

Paediatricians

Of the 1461 paediatricians who are affiliated with the Dutch Society of Paediatrics, 176 (12.0%) filled in the questionnaire including 128 complete responses. After excluding the seven responses of paediatric residents, 121 responses were analysed. Most of the paediatricians were general paediatricians, working in a non-academic hospital and currently treating 1–5 children for severe obesity (**Table 1**).

Current Practice

One hundred and thirteen paediatricians (93.4%) reported that they always offered lifestyle advice to youth with severe obesity, and 84 paediatricians (69.4%) responded that they always referred to a dietician for dietary advice (**Figure 1**).

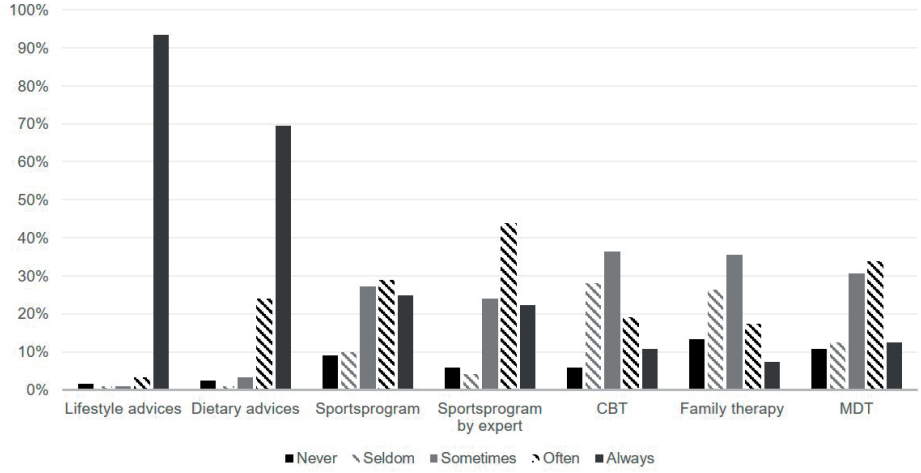
Table 1 – Baseline characteristics of respondents and their practice

	Paediatricians
Number of complete responses – No.	120
Years of working experience including residency – mean ±SD	18.8 ±8.2
Differentiation – No. (%)	
General paediatrician	95 (79.2)
Paediatric endocrinologist	2 (1.7)
Paediatric gastro-enterologist	5 (4.2)
Other	18 (15.0)
Hospital – No. (%)	
Centre of expertise for children with obesity	0 (8.3)
Non-teaching hospital	94 (78.3)
Teaching hospital	11 (9.2)
Other	5 (4.2)
Children currently on treatment for morbid obesity – No. (%)	
None	16 (13.3)
1-5 children	51 (42.5)
6-15 children	17 (14.2)
16-30 children	6 (5.0)
More than 30 children	16 (13.3)
Other	14 (11.7)

No. = number, SD = standard deviation

Different norms of treatment success were observed; 54 respondents (44.6%) considered stabilization of bodyweight after twelve months of intervention as successful and 33 (27.3%) considered improvement of obesity-related comorbidities as a successful treatment, independent of bodyweight change. Twenty-six (21.5%) and eight paediatricians (6.6%) reported that they considered a weight loss of respectively ≥ 5% or ≥ 10% after twelve months of intervention as successful. Ninety-three paediatricians (76.9%) estimated that ≤ 25% of the youth with severe obesity were treated successfully in their hospital. If their treatment was unsuccessful, referral to an obesity expertise centre could be the "add on" treatment according to 56 paediatricians (46.3%). Eighteen paediatricians (14.9%) reported that they would refer for inpatient treatment, and ten (8.3%) for bariatric surgery, assuming this would be an option. Seven out of the ten paediatricians who would refer for bariatric surgery were working at a paediatric obesity expertise centre.

Figure 1 – Reported frequency of providing different treatment modalities in children and adolescents with morbid obesity



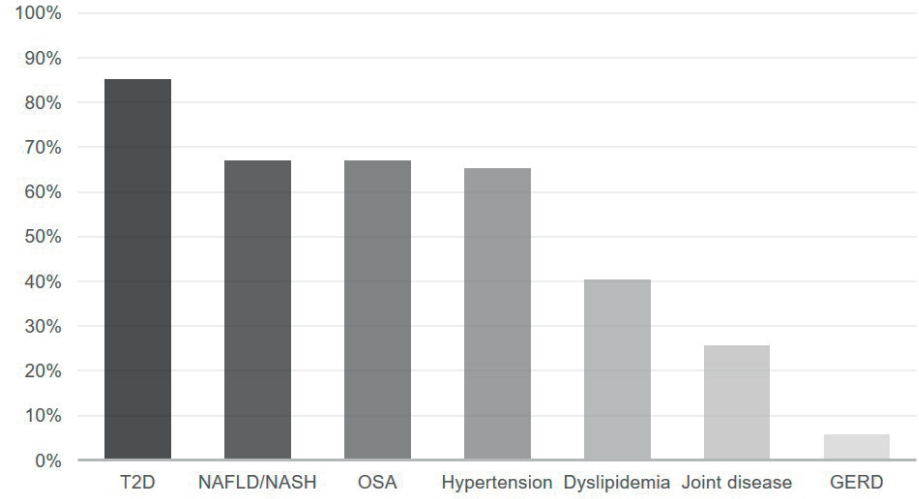
CBT = Cognitive behavioural therapy, MDT = Multidisciplinary treatment

Paediatricians' Perspective on Bariatric Surgery in Youth

Seventy-two paediatricians (59.5%) shared the opinion that bariatric surgery may be effective in treating youth with severe obesity that were unsuccessfully treated with lifestyle interventions. These paediatricians would also refer for bariatric surgery. Eleven paediatricians (9.1%) did not believe bariatric surgery could be an effective treatment and 38 (31.4%) were inconclusive. Forty-nine paediatricians (40.5%) responded that they would not refer for bariatric surgery, with the reasons varying from "lack of evidence and experience" to "referral via an obesity expertise centre."

The majority (n=113, 93.4%) of the respondents reported that there should be a minimum age for bariatric surgery in youth, with 59 paediatricians suggesting a minimum age of sixteen years (48.7%). Regarding a BMI threshold for surgery, 51 paediatricians (42.2%) suggested a lower limit of 40 kg/m^2 (sex and age adjusted) without comorbidities, whereas 38 respondents (31.4%) would prefer a BMI of 35 kg/m^2 without comorbidities. When comorbidities are present, the BMI threshold declined for 106 respondents (87.6%). Most often, T2D was chosen as an influential comorbidity, followed by non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH), obstructive sleep apnoea, and hypertension (**Figure 2**). Besides BMI and the presence of comorbidities, also physical development expressed by Tanner stage appeared to be of importance. According to 59 (48.8%) and 46 paediatricians (38.0%), a Tanner stage of IV or V respectively was the minimum for bariatric surgery in youth.

Figure 2 – Comorbidities associated with a lower limit of BMI for paediatric bariatric surgery



T2D = type 2 diabetes, NAFLD/NASH = non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, OSA = obstructive sleep apnoea, GERD = gastroesophageal reflux disease

The majority of the respondents (n=82, 67.7%) reported that bariatric surgery should become a common treatment modality for selected adolescents with severe obesity who do not benefit from lifestyle intervention. The most common reasons for reluctance were that "it should not become a common treatment modality, only a last resort treatment option" and "lack of evidence."

Parents of youth with overweight, obesity, or severe obesity

Of the 159 parents whose children were treated at COACH and were approached, 56 (35.2%) filled in the questionnaire including 49 complete responses. The children of the respondents were affected by overweight, obesity, or severe obesity for at least one year, the majority for 3–5 years (n=20, 40.8%) or 6–10 years (n=18, 36.7%). Thirty-three (67.3%) of their children were treated for their overweight, obesity, or severe obesity at the COACH program for at least one year.

Thirty parents (61.2%) reported that bariatric surgery should be available for youth with severe obesity if lifestyle intervention is not successful, and 22 (44.9%) would allow their child to be referred for bariatric surgery if the current treatment fails. Reasons for not allowing their child to be referred varied from "being too young" to "children are still growing." Twenty-six parents (53.1%) were in favour of a minimum age for bariatric surgery, with a minimum age of sixteen and eighteen years both answered most frequently (n=8, 16.3%).

Twenty-nine parents (59.2%) responded that their child could decide to undergo bariatric surgery without the approval of their parents, after reaching the age of sixteen or seventeen. Almost all respondents reported that bariatric surgery should be offered alongside a family-based program around the surgery (n=45, 91.8%). The most frequently reported main goal for surgery was weight loss according to the parents (n=20, 40.8%), followed by improvement of obesity-related comorbidities (n=10, 20.4%) and self-esteem (n=10, 20.4%).

Adolescents with overweight, obesity, or severe obesity

Of the 30 adolescents who were treated at COACH and were approached, 19 (63.3%) completed the questionnaire. The adolescents had a mean age of 15.5 ±1.6 years. All adolescents were affected by overweight, obesity, or severe obesity for at least one year, with a majority of twelve adolescents (63.2%) for 6 years or longer. Eleven (57.9%) of the adolescents were treated for their overweight, obesity, or severe obesity at the COACH program for at least one year.

Fourteen adolescents (73.7%) reported that bariatric surgery should be available, and 11 (61.1%) wanted to undergo bariatric surgery themselves if their current lifestyle intervention is not effective. Eight of the ten adolescents (80.0%) who were sixteen years or older responded that they could make the decision for bariatric surgery independently of their parents. There was no consensus on the program around bariatric surgery in youth; 31.6% of the adolescents would prefer an individual program (n=6), 36.8% a program with involvement of the parents (n=7), and 31.6% a program with involvement of parents, brothers, and sisters (n=6). The main goal of bariatric surgery reported by the adolescents was weight loss (n=12, 63.2%), followed by improvement of self-esteem (n=4, 21.0%) and improvement of obesity-related comorbidities (n=3, 15.8%).

DISCUSSION

To the best of our knowledge, this is the first study in the Netherlands to have surveyed the current attitudes of paediatricians, parents, and adolescents towards bariatric surgery in youth. Our findings demonstrate that the majority of responding paediatricians consider bariatric surgery as a potentially effective treatment for youth with severe obesity. An even larger proportion agreed that it should be a common treatment modality for selected adolescents with severe obesity who are not responding to lifestyle interventions. Besides insufficient response to lifestyle interventions, paediatricians proposed a lower limit of BMI ≥ 40 kg/m^2 (sex and age adjusted) without comorbidities, a minimum age of sixteen years old, and a minimum Tanner stage of IV as criteria for bar-

iatric surgery. This proposed minimum age criterion was comparable to the minimum age proposed by the parents.

Only a few studies have previously investigated the attitudes of paediatricians towards bariatric surgery in youth, revealing significant heterogeneity[19-21]. In 2009, an American report on paediatricians and family practitioners showed that 88.5% would be unlikely to, or would never refer a child for a bariatric procedure[19]. Conversely, another American study performed in 2007 with paediatricians reported that only 47.0% would decline referral for bariatric surgery[20]. In Europe, no studies have been conducted that have examined attitudes among paediatricians alone. However, a recent study among European paediatric surgeons has reported that 65.7% considered bariatric surgery to be a valuable contribution to obtain long-term weight loss in adolescents with severe obesity[27]. The findings in our study among paediatricians are most comparable to the European study among paediatric surgeons, revealing that 59.5% of the paediatricians would refer for bariatric surgery, and 67.7% supporting bariatric surgery as an acceptable treatment modality for a selected group of obese adolescents. We assume that that the accumulating evidence on safety and efficacy of bariatric surgery in youth explains why paediatricians are increasingly accepting this treatment modality[14-16].

Based on current American guidelines and Dutch guidelines, bariatric surgery in youth is accompanied by different selection criteria, including a lower limit of BMI[17,28]. No age limit has been set in these selection criteria. Although, in different explorative studies, professionals have indicated their preference for a minimum age for bariatric surgery, yet this has ranged from twelve to nineteen years old[18-20,29-30]. The proposed age of sixteen years for bariatric surgery in our study is in line with the preferred age reported by a survey among members of the British Obesity and Metabolic Surgery Society and general practitioners[30]. Currently there is no evidence on limiting access to bariatric surgery in youth based on age[28]. The preference of professionals for a minimum age for bariatric surgery in youth could be due to less knowledge about the procedures and their consequences. Education for paediatricians who treat youth with severe obesity would therefore be recommended. Education of the paediatricians might lead to less of a barrier in referring youth for bariatric surgery, and eventually lead to better treatment of youth with severe obesity[31].

Until now, the thoughts and beliefs of parents and adolescents regarding bariatric surgery in youth have not been studied extensively[21-23,32-33]. A recent study by Singh et al. reported that 84.6% of parents would consider bariatric surgery after counselling by paediatricians, compared with only 34.5% of the parents without counselling[22]. In our study, 61.2% of parents stated that bariatric surgery should be available for youth with

severe obesity, whereas only 44.9% of parents would allow their child to be referred for bariatric surgery if the current treatment was insufficiently effective. This discrepancy suggests that counselling by paediatricians could play a crucial role when discussing bariatric surgery in youth, which is supported by a qualitative study of parents and adolescents who underwent gastric banding[23].

Another important aspect of bariatric surgery in youth is family involvement, as concluded by Inge et al. in 2004, a motivated and supportive family is pivotal for successful bariatric surgery in youth[34]. This is in line with our findings that the majority of the parents and adolescents stated that bariatric surgery should only be offered with a perioperative family-based program.

A limitation of this study is the low response rate of the paediatricians. This might have led to selection bias in the results. To minimize this, the hospitals where the respondents worked at were compared with the hospitals where all the members of the Dutch Society of Paediatrics worked at, and the respondents more often worked at a non-academic hospital. Nevertheless, we still believe that this distribution of paediatricians across the Netherlands has provided an insight into their thoughts and beliefs regarding bariatric surgery in youth, as the paediatricians in non-academic hospitals are treating more youth with severe obesity compared to academic hospitals. Another potential limitation is that the parents and adolescents surveyed might not be a representative group, since they are being treated for their overweight, obesity, or severe obesity. Therefore, they may experience more positive attitudes regarding bariatric surgery in youth compared to the general population with overweight, obesity, or severe obesity. The third limitation is the small sample size and the limited response rate of the parents and adolescents. To minimize selection bias, the characteristics of the parents and adolescents were compared to the general COACH population, and they were comparable in terms of age and treatment duration.

CONCLUSION

Dutch paediatricians increasingly accept bariatric surgery as a treatment modality in youth with severe obesity who do not respond successfully to lifestyle intervention, as long as conditions such as a minimum BMI, age, and Tanner stage are met. Whether paediatricians will actually refer for bariatric surgery remains to be seen when this treatment option will be implemented in the Netherlands.

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APPENDIX 1

All surveys were administered in Dutch. Below is a translation of the questionnaires to English. This translation may lead to some nuanced differences.

Pediatricians – Treatment of children with severe obesity

Through this survey we want to assess the current treatment of children with severe obesity in the Netherlands and the opinion of Dutch pediatricians on bariatric surgery as 'add-on' treatment to the current lifestyle intervention programs for children and adolescents with severe obesity.

Demographic data

(1) What is your specialty?
   a. General pediatrician
   b. Pediatric endocrinologist
   c. Pediatric gastroenterologist
   d. Other, please provide further explanation _____

(2) What kind of hospital do you work in?
   a. Expertise center for the treatment of children and adolescents with severe obesity
   b. Non-teaching hospital
   c. Teaching hospital
   d. Other, please provide further explanation _____

(3) How many years have you worked as a pediatrician (*including pediatrician in training*)?
   _____ years

Current care and experience

The following questions are asked to gain insight into the current treatment of children and adolescents with severe obesity and the results of this treatment.

A child is defined as a person with an age < 18 years. Severe obesity is defined as a BMI ≥ 40 kg/m^2 or a BMI ≥ 35 kg/m^2 with an obesity related co-morbidity, adjusted for gender and age according to the IOTF cut-off points.

International IOTF Cut-off points:
Boys: http://s3-eu-west-1.amazonaws.com/wof-files/New_Cut_off_Points_Male_Children.pdf
Girls: http://s3-eu-west-1.amazonaws.com/wof-files/New_cut_off_points_female_children.pdf

(1) How many children with severe obesity do you currently treat in your hospital?
   a. None
   b. 1-5 children
   c. 6-15 children
   d. 16-30 children
   e. > 30 children
   f. Other, please provide further explanation _____

(2) Which forms of treatment do you use in your intervention program (never – seldom – sometimes – often – always)?
- □ Lifestyle advice
- □ Dietary advice provided by a dietician
- □ Sports program not provided by a physiotherapist
- □ Sports program provided by a physiotherapist
- □ Cognitive behavioral therapy provided by a psychologist/behavioral therapist
- □ Family therapy provided by a psychologist/pedagogue
- □ Multidisciplinary lifestyle intervention program
- □ Other, please provide further explanation _____

(3) When do you consider the provided treatment as successful?
- a. Weight stabilization after 12 months
- b. Weight loss ≥5% after 12 months
- c. Weight loss ≥10% after 12 months
- d. Improvement of obesity related comorbidities, independent of weight change

(4) According to the definition you gave in the previous question, in how many children with severe obesity is the provided treatment effective?
- a. ≤25%
- b. >25-≤50%
- c. >50-≤75%
- d. >75%

(5) What would be the best 'add on' treatment if the current treatment fails/is not effective (according to the definition you gave at question 6)?
- a. Continue current treatment
- b. Refer to primary care for lifestyle management
- c. Refer to inpatient treatment
- d. Refer to an expertise center
- e. Refer for bariatric surgery (assuming that this is an actual option)
- f. Other, please provide further explanation _____

(6) What percentage of the children with severe obesity without a successful treatment in your hospital will register for bariatric surgery in adulthood (18 years old)?
- a. ≤25%
- b. >25-≤50%
- c. >50-≤75%
- d. >75%
- e. I don't know

(7) What percentage of the children with severe obesity with a successful treatment in your hospital will register for bariatric surgery in adulthood (18 years old)?
- a. ≤25%
- b. >25-≤50%
- c. >50-≤75%

d. >75%
e. I don't know

(8) Is your treatment based on the policy described in the Section Guidelines: Obesity, guidelines for Pediatricians (2018)?
a. Yes
b. No
c. I don't know

Opinion bariatric surgery

The following questions concern your attitude towards bariatric surgery in youth. In all questions you can assume that children followed a lifestyle intervention program for a minimum of 12 months without success and that the child has a stable and supportive family.

(1) Do you believe that bariatric surgery can be an effective treatment for children with severe obesity who do not (sufficiently) respond to lifestyle intervention?
a. Yes
b. No
c. I don't know

(2) Would you refer a child with severe obesity who is not successful in the lifestyle intervention program for bariatric surgery?
a. Yes
b. No, explain why not: _____

(3) Do you think there should be a minimum age for bariatric surgery in youth?
a. Yes, specify the minimum age in years _____
b. No

(4) What would be the lower limit of BMI for bariatric surgery in youth (no comorbidities)?
a. 30 kg/m^2
b. 35 kg/m^2
c. 40 kg/m^2
d. Other, specify the lower limit_____

(5) Would the presence of a comorbidities influence the answer given at question 15?
a. Yes
b. No

(6) Which of the following comorbidities would change the lower limit of BMI for bariatric surgery in youth (multiple answers possible)?
□ Type 2 diabetes
□ Hypertension
□ Obstructive sleep apnoea
□ Dyslipidemia
□ Gastroesophageal reflux disease

- □ Joint problems
- □ Non-Alcoholic Fatty Liver Disease/ Non-Alcoholic Steatohepatitis
- □ Other (please provide further explanation) _____

(7) What would be the minimum Tanner stage for bariatric surgery in youth (no comorbidities)?
   a. Tanner stage I
   b. Tanner stage II
   c. Tanner stage III
   d. Tanner stage IV
   e. Tanner stage V

(8) Do you believe that bariatric surgery should become a conventional treatment for selected adolescents with severe obesity who do not benefit from lifestyle intervention?
   a. Yes
   b. No, explain why not _____

(9) If you have any comments or suggestions, please write them down below

Adolescents – Treatment of children with severe obesity

Severe obesity in adults is treated with modifications in lifestyle (lifestyle intervention). Examples of lifestyle intervention are adjustments in eating patterns and exercise.

In a selected group of adults, in which the lifestyle intervention is not successful, weight loss surgery is performed. The two most commonly performed operations in the Netherlands are gastric sleeve, an operation in which the stomach is shortened lengthwise, and the gastric bypass, in which the stomach is reduced and the small intestine is bypassed.

For several years now these operations have been performed in children with severe obesity who do not respond to lifestyle intervention. Children lose about 20 to 30% of their total weight after weight loss surgery and additional diseases such as type 2 diabetes, high blood pressure and sleep apnea can be cured. Next to this, the quality of life of these children improves.

However, surgery involves risks. Complications that can occur in the short-term are pneumonia, bleeding, wound infection and leakage of the bowels, and in the long-term gall stones, chronic abdominal pain and intestinal obstruction.

We want to investigate whether weight loss surgery is suitable for children, and therefore are curious about your opinion.

Current treatment

The following questions are asked to gain insight into your current treatment.

(1) How long have you been overweight?
   a. <1 year
   b. 1-2 years
   c. 3-5 years
   d. 6-10 years
   e. >10 years

(2) Which forms of treatment have you already had
(never – seldom – sometimes – often – always)?
- □ Lifestyle advice
- □ Dietary advice provided by a dietician
- □ Sports program not provided by a physiotherapist
- □ Sports program provided by a physiotherapist
- □ Cognitive behavioral therapy provided by a psychologist/behavioral therapist
- □ Family therapy provided by a psychologist/pedagogue
- □ Multidisciplinary lifestyle intervention program
- □ Other, please provide further explanation _____

(3) How long have you been at COACH?
- a. ≤6 months
- b. 6 months – ≤1 year
- c. 1 – ≤2 years
- d. 2 – ≤3 years
- e. 3 – ≤4 years
- f. 4 – ≤5 years
- g. > 5 years

Opinion on weight-loss-surgery in children

(1) Do you believe that weight loss surgery should be available for children with severe obesity, in which multimodal lifestyle intervention is not successful?
- a. Yes
- b. No, why not_____

(2) Do you think weight loss surgery in children with severe obesity should be an individual program for the child, or should the parents and possibly the brother(s) and/or sister(s) be involved?
- a. Individual program
- b. Program with parents
- c. Program with parents and brother(s)/sister(s)

(3) Which weight loss surgery would you prefer?
- a. An operation that is reversible
- b. An operation that is NOT reversible
- c. I don't know

(4) Which weight loss surgery would you prefer?
- a. Weight loss surgery with a lot of weight loss, but possibly more complications
- b. Weight loss surgery with slightly less weight loss, but less complications
- c. I don't know

(5) What would be your main goal in weight loss surgery?
- a. Weight loss

b. Improvement of concomitant diseases (for example type 2 diabetes, high blood pressure, sleep apnea)
c. Improving self-confidence/self-image
d. Better functioning at school/work
e. Other, please provide further explanation _____

(6) How old are you?
a. 13 years
b. 14 years
c. 15 years
d. 16 years
e. 17 years
f. 18 years

(7) Do you want to undergo weight loss surgery, if the current treatment has no effect, before you turn 18 years old?
a. Yes
b. No, why not_____

16-17 years old

Only complete the question if you are 16 or 17 years old.

(1) Do you think you can make the choice to undergo weight loss surgery completely independent of your parents?
a. Yes
b. No, why not _____

(2) If you have any comments or suggestions, please write them down below.

Parents - Treatment of children with severe obesity

Severe obesity in adults is treated with modifications in lifestyle (lifestyle intervention). Examples of lifestyle intervention are adjustments in eating patterns and exercise.

In a selected group of adults, in which the lifestyle intervention is not successful, weight loss surgery is performed. The two most performed operations in the Netherlands are gastric sleeve, an operation in which the stomach is shortened lengthwise, and the gastric bypass, in which the stomach is reduced and the small intestine is bypassed.

For several years now these operations are being performed in children with severe obesity who do not respond to lifestyle intervention. Children lose about 20 to 30% of their total weight after weight loss surgery and additional diseases such as type 2 diabetes, high blood pressure and sleep apnea can be cured. Next to this, the quality of life of these children improves.

However, a surgery involves risks. Complications that can occur in the short-term are pneumonia, bleeding, wound infection and leakage of the bowels, and in the long-term gall stones, chronic abdominal pain and intestinal obstruction.

We want to investigate whether weight loss surgery is suitable for children, and therefore are curious about your opinion.

Current treatment

The following questions are asked to gain insight into the current treatment your child receives.

(1) How long has your son/daughter been overweight?
   a. <1 year
   b. 1-2 years
   c. 3-5 years
   d. 6-10 years
   e. >10 years

(2) Which forms of treatment has your son/daughter already had
   (never – seldom – sometimes – often – always)?
   □ Lifestyle advice
   □ Dietary advice provided by a dietician
   □ Sports program not provided by a physiotherapist
   □ Sports program provided by a physiotherapist
   □ Cognitive behavioral therapy provided by a psychologist/behavioral therapist
   □ Family therapy provided by a psychologist/pedagogue
   □ Multidisciplinary lifestyle intervention program
   □ Other, please provide further explanation _____

(3) For how long have your son/daughter been treated at COACH?
   a. ≤ 6 months
   b. 6 months - ≤ 1 year
   c. 1 year - ≤ 2 year
   d. 2 year - ≤ 3 year
   e. 3 year - ≤ 4 year
   f. 4 year - ≤ 5 year
   g. ≥ 5 year

Opinions on weight loss surgery in children/adolescents

(1) Do you believe that weight loss surgery should be available for children with severe obesity, in which multimodal lifestyle intervention was not successful?
   a. Yes
   b. No, why not _____

(2) Would you allow your son/daughter to be referred for weight loss surgery, if the current treatment has no effect?
   a. Yes
   b. No, why not _____

(3) At what age would you let your son/daughter undergo weight loss surgery?
   a. <10
   b. 10 years
   c. 11 years
   d. 12 years

e. 13 years
f. 14 years
g. 15 years
h. 16 years
i. 17 years
j. ≥ 18 years
k. I would not let my son/daughter undergo weight loss surgery
l. Age is not an issue for me

(4) Do you think that your son/daughter, if he/she is 16-17 years old, can decide on whether he/she should undergo weight-loss-surgery (without your input and approval)?
   a. Yes
   b. No, why not _____

(5) Should weight loss surgery in children with severe obesity be an individual program or should the family be involved?
   a. Individual program
   b. Family program

(6) Which weight loss surgery would you prefer?
   a. An operation that is reversible
   b. An operation that is NOT reversible
   c. I don't know

(7) Which weight loss surgery would have your preference?
   a. Weight-loss-surgery with a lot of weight loss, but possibly more complications
   b. Weight loss surgery with slightly less weight loss, but also less complications
   c. I don't know

(8) What would be the main goal for you and your son/daughter in weight loss surgery?
   a. Weight loss
   b. Improvement of concomitant diseases (for example using less medication)
   c. Improving self-confidence/self-image
   d. Better functioning at school/work
   e. Other, please provide further explanation _____

(9) If you have any comments or suggestions, please write them down below

4

Safety of Bariatric Surgery in Elderly – Results from the Dutch National Registry

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ABSTRACT

Background

The increased human life expectancy and prevalence of obesity lead to more elderly with obesity. As the popularity of bariatric surgery continues to grow, more elderly apply for bariatric surgery. However, due to the potentially higher surgical risk in elderly, bariatric surgery has been performed in small numbers. Moreover, literature so far has shown controversial results.

Objective

To determine the safety of bariatric surgery in elderly regarding the 2-year morbidity and mortality.

Setting

Dutch nationwide mandatory registry for bariatric surgery.

Methods

A population-based retrospective cohort study. Elderly (people aged ≥65 years) who received primary bariatric surgery between January 2015 and January 2020 were compared to the general bariatric surgical population (people aged 18-65 years).

Results

Out of 49,553 patients, 838 (1.7%) elderly were included. An intraoperative complication was registered in 1.2% of the elderly and 1.1% of the non-elderly (p=0.814). A severe short-term complication (≤30 days) was registered in 38 (4.5%) elderly and 1,071 (2.2%) non-elderly (p<0.001). Short-term mortality rate was 0.2% and 0.1% respectively (p=0.173). Bleeding was the most reported short-term complication. Significantly more non-elderly had a follow-up visit; 560 (66.8%) elderly vs. 34,975 (71.8%) non-elderly (p=0.002). Severe mid-term complication rate (>30 days ≤2 years) was significantly higher in non-elderly (3.7% vs. 1.6%, p=0.008).

Conclusion

Bariatric surgery in elderly is safe regarding the perioperative outcome, mortality and mid-term complication rate. However, the elderly experienced twice as many severe short-term complications. Bariatric surgery in elderly should be recommended on a case-by-case basis.

INTRODUCTION

Bariatric surgery is the most effective long-term treatment for severe obesity[1]. Like adults with severe obesity, elderly (people aged ≥65 years) are seeking for a surgical solution of their obesity. However, bariatric surgery has been limited performed in elderly. Reasons for hesitancy include the concern of a higher morbidity and mortality rate and the cost-effectiveness. Several studies that have examined the safety of bariatric surgery in elderly showed controversial results[2-3].

The eligibility criteria for bariatric surgery (IFSO guidelines) were published in 1997, including people aged 18 to 65 years[4-5]. Based on the increase in human life expectancy since 1997[6-7], it is questionable whether this age-criteria is still valid. Moreover, in the Netherlands, mean retirement age was 60.7 years in 2002 and 65.6 years in 2020, with more than half of the people retiring aged ≥66 years[8]. Next to this, assessing patients based on their chronological age instead of their biological age is questionable.

Therefore, the aim of this study is to determine the safety of bariatric surgery in elderly with severe obesity in the Dutch population regarding the 2-year morbidity and mortality.

METHODS

Study design

A national population-based retrospective cohort study was conducted using pseudo-anonymized data from the Dutch nationwide mandatory registry for bariatric surgery, 'Dutch Audit for Treatment of Obesity' (DATO). Each Dutch bariatric clinic is obliged to register all bariatric patients in DATO.

Participants and setting

Inclusion criteria for performing bariatric surgery in the Netherlands between 2015 and 2020 were according to the IFSO guideline[4-5]. Patients, aged ≥18 years, who received a primary bariatric procedure between 1 January 2015 (start of the DATO registry[9-10]) and 31 December 2019 in the Netherlands were screened for inclusion. All patients who were registered in the DATO with a date of surgery, and a body mass index (BMI) ≥35.0 kg/m^2 prior to surgery were included. Exclusion criteria were revisional bariatric procedures, age <18 years, and BMI <35.0 kg/m^2 prior to surgery.

Elderly was defined as patients aged ≥65 years at time of surgery, whereas non-elderly was defined as patients aged 18 until 65 years old.

According to the Dutch law (Medical Research Involving Human Subjects Act), formal consent was not required for this study.

Outcomes

Primary outcome was morbidity (including intraoperative complications, overall and severe short-term and mid-term complications) and mortality up to 2 years after surgery. Secondary outcomes included length of hospital stay and readmission rate.

Elderly were compared to the general bariatric surgical population (people aged 18-65 years).

Variables

All variables were derived from the DATO and included basic demographic characteristics (age, sex, comorbidities, and BMI), type of bariatric procedure, length of hospital stay, and postoperative complications.

Complications

An intraoperative complication was defined as any significant deviation from the ideal intraoperative course occurring between skin incision and skin closure. A short-term complication was defined as a complication ≤30 days after the bariatric surgery (excluding intraoperative complications). A mid-term complication was defined as a complication >30 days up to 2 years after the bariatric surgery.

Both short- and mid-term complications were categorized according to the Clavien-Dindo Classification (CDC) of surgical complications (**Appendix 1**)[11]. A severe complication was defined as a complication categorized as CDC grade ≥III.

Bariatric procedures

The bariatric procedures were divided into three groups; 1. sleeve gastrectomy (SG), 2. gastric bypass (including Roux-en-Y gastric bypass (RYGB), one-anastomosis and banded bypass), and 3. other (including gastric band, biliopancreatic diversion and single anastomosis duodeno-ileostomy). A brief description of how the SG and RYGB are performed in the Netherlands is presented in **Appendix 2**.

Follow-up

In the Netherlands, patients have routine follow-up appointments at the outpatient clinic at 3 months, 6 months, 12 months, 18 months and then at two, three, four and five years after bariatric surgery. All periodic routine follow-up appointments must be reported at DATO. For this study, all patients with at least one registered follow-up visit,

at one – two – three - four or five years postoperatively, were included in the analysis for the mid-term complications.

Statistics

All analyses were performed on patient level; for every patient only one complication, the most severe one, was included (unless stated otherwise). Missing values were not replaced.

Descriptive statistics were used as appropriate. Differences in categorical baseline variables between elderly and non-elderly were compared using the chi-squared test or the Fisher's exact test for small numbers. Differences in continuous baseline variables were compared using the unpaired t-test unless stated otherwise.

Univariate and multivariate logistic regression analyses were performed to determine the effect of elderly on the risk of complications and mortality. Multivariate regression analysis was performed to correct for known confounders including pre-existing obesity related comorbidities, gender, and for potential other confounders, defined as variables associated with the outcome $p<0.1$ in univariate analysis.

The effect of age, as a continuous variable, on the primary outcome as well as on several secondary outcomes was analyzed using univariate and multivariate logistic analysis. In a secondary analysis age as an ordinal variable (10-year age categories) was included into the model.

Statistical analyses were performed using IBM SPSS statistic software, version 24.0, and $p<0.05$ was considered statistically significant.

RESULTS

Participants

A total of 50,694 unique patients were registered during the study period. After exclusion of patients with a BMI <35.0 kg/m^2 or missing BMI, 49,553 patients were included of which 838 (1.7%) were elderly (**Figure 1 – Flowchart of inclusion**). Of the elderly, 231 (27.6%) were 65 years, 288 (34.4%) were 66 years, 158 (18.9%) were 67 years, 92 (11.0%) were 68 years, 39 (4.7%) were 69 years, and 30 (3.6%) elderly were 70 years or older at the time of the bariatric surgery. The proportion of bariatric procedures in elderly has increased from 1.1% in 2015 to 2.4% in 2019.

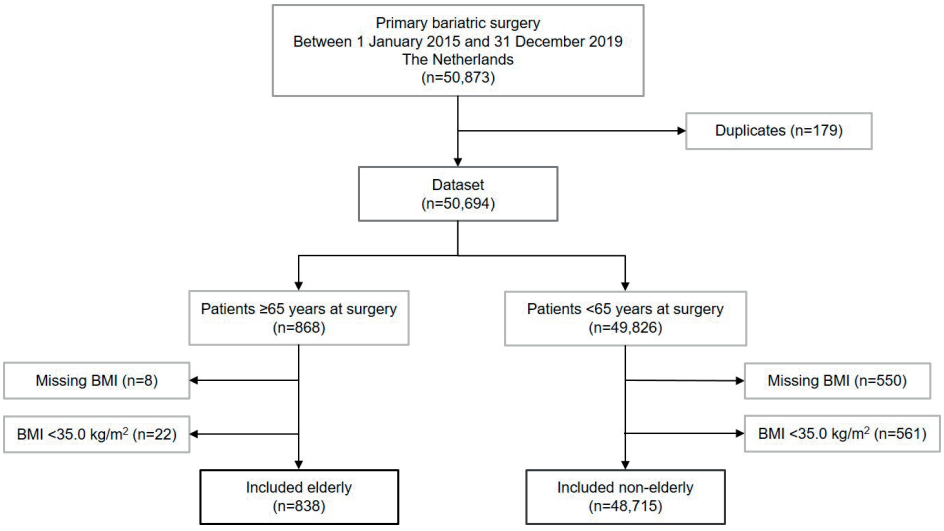

Figure 1 – Flow chart of inclusion

At baseline, the obesity related comorbidities (type 2 diabetes (T2D), hypertension, dyslipidemia, and obstructive sleep apnea (OSA)) were significantly more prevalent among elderly compared to non-elderly (**Table 1**).

Table 1 – Baseline characteristics

	Total	Non-elderly	Elderly	p-value
	n=49,553	n=48,715	n=838	
Age – years ± SD	44.2 ± 11.6	43.8 ± 11.3	66.5 ± 1.6	p<0.001
Female – No. (%)	39,007 (78.7)	38,454 (78.9)	553 (66.0)	p<0.001
Preoperative weight – kg ± SD	124.4 ± 19.9	124.4 ± 19.9	122.1 ± 19.7	p=0.001
Preoperative BMI – kg/m^2 ± SD	43.1 ± 5.3	43.1 ± 5.3	43.2 ± 5.6	p=0.892
Type 2 diabetes – No. (%)	9,868 (19.9)	9,422 (19.3)	446 (53.2)	p<0.001
Hypertension – No. (%)	17,245 (34.8)	16,612 (34.1)	633 (75.5)	p<0.001
Dyslipidemia – No. (%)	9,594 (19.4)	9,214 (18.9)	380 (45.3)	p<0.001
OSA – No. (%)	8,991 (18.1)	8,692 (17.8)	299 (35.7)	p<0.001

SD = standard deviation, No. = number, BMI = body mass index, OSA = obstructive sleep apnoea

Surgery

The majority of the bariatric procedures were performed laparoscopically (elderly 99.8% and non-elderly 99.9%). Gastric bypass was the most frequent performed bariatric procedure (elderly 76.6% and 76.8% in non-elderly), followed by the SG (elderly 22.7% and 22.8% in non-elderly).

Intraoperative complications

An intraoperative complication was registered in 547 (1.1%) patients, 10 (1.2%) in elderly and 537 (1.1%) in non-elderly (p=0.8 in both uncorrected as well as corrected analysis). In 28 patients (all non-elderly), >1 intraoperative complication was reported. In total 558 intraoperative complications were noted, of which perforation (n=188), bleeding (n=148), liver injury (n=75), and spleen injury (n=68) were the most frequent (similar between the two groups, all p>0.3). Intraoperative mortality was not reported. Six non-elderly were admitted to the ICU due to single-organ failure (n=4) or multi-organ failure (n=2). Median hospital stay was 1 (1, 2) day for both groups (p=0.976).

Short-term complications (≤30 days)

Including all CDC grades of short-term complications, 58 (6.9%) elderly experienced a complication compared to 2,468 (5.1%) non-elderly (p=0.015). However, this difference was not significant after correction for baseline differences (p=0.305, **Appendix 3 – Table 7**). **Table 2** shows the CDC grades of short-term complications. Bleeding was the most reported short-term complication (elderly 3.8% vs. non-elderly 1.5%, p<0.001), followed by anastomotic leakage (elderly 0.6% vs. non-elderly 0.5%, p=0.811) (**Table 3**).

Table 2 – Short-term complications

	Total	Non-elderly	Elderly	p-value
	n=49,553	n=48,715	n=838	
Complication within 30 days* – No. (%)	2,526 (5.1)	2,468 (5.1)	58 (6.9)	p=0.015
Severe complication within 30 days* - No. (%)	1,109 (2.3)	1,071 (2.2)	38 (4.5)	p<0.001
Clavien-Dindo classification* – No. (%)				
Grade 0 (No complication)	47,027 (94.9)	46,247 (94.9)	780 (93.1)	
Grade I	1,139 (2.3)	1,125 (2.3)	14 (1.7)	
Grade II	247 (0.5)	241 (0.5)	6 (0.7)	
Grade IIIa	169 (0.3)	163 (0.3)	6 (0.7)	
Grade IIIb	810 (1.6)	789 (1.6)	21 (2.5)	
Grade Iva	74 (0.1)	67 (0.1)	7 (0.8)	
Grade IVb	27 (0.1)	25 (0.1)	2 (0.2)	
Grade V	29 (0.1)	27 (0.1)	2 (0.2)	
Unknown	31 (0.1)	31 (0.1)	0 (0.0)	
Readmissions within 30 days* – No. (%)	1,160 (2.3)	1,140 (2.3)	20 (2.4)	p=0.930
Mortality within 30 days – No. (%)	29 (0.1)	27 (0.1)	2 (0.2)	P=0.086

* = Only the most severe complication has been registered for each patient, No. = number.

Table 3 – Types of short-term complications

	Total	Non-elderly	Elderly	p-value
	n=49,553	n=48,715	n=838	
Total number of complications* – No. (%)	2623 (5.3)	2560 (5.3)	63 (7.5)	p=0.003
Surgical complications* – No. (%)	1814 (3.7)	1761 (3.6)	53 (6.3)	p<0.001
Type of surgical complication				
Bleeding	753 (1.5)	721 (1.5)	32 (3.8)	p<0.001
Anastomotic leakage	273 (0.6)	268 (0.6)	5 (0.6)	p=0.811
Intestinal obstruction	100 (0.2)	100 (0.2)	0 (0.0)	
Vomiting	94 (0.2)	93 (0.2)	1 (0.1)	
Intra-abdominal abscesses	89 (0.2)	89 (0.2)	0 (0.0)	
Wound infection	72 (0.1)	70 (0.1)	2 (0.2)	
Bowel injury	40 (0.1)	40 (0.1)	0 (0.0)	
Anastomotic stricture	39 (0.1)	39 (0.1)	0 (0.0)	
Marginal ulcer	13 (0.0)	13 (0.0)	0 (0.0)	
Wound dehiscence	12 (0.0)	11 (0.0)	1 (0.1)	
Sepsis	8 (0.0)	5 (0.0)	3 (0.4)	
Bile leakage	2 (0.0)	2 (0.0)	0 (0.0)	
Liver failure	2 (0.0)	2 (0.0)	0 (0.0)	
Port infection	1 (0.0)	1 (0.0)	0 (0.0)	
Other	316 (0.6)	307 (0.6)	9 (1.1)	
General complications*,** – No. (%)	687 (1.4)	665 (1.4)	22 (2.6)	p=0.002
Type of general complication – No. (%)				
Pulmonary	164 (0.3)	159 (0.3)	5 (0.6)	
Cardiac	70 (0.1)	65 (0.1)	5 (0.6)	
Thrombotic	22 (0.0)	21 (0.0)	1 (0.1)	
Other	431 (0.9)	420 (0.9)	11 (1.3)	

* = Analyzed on complication level; so in case a patient experienced more than one complication, all complications are scored/included. No. = Number, ** = Pulmonary (e.g. infection, pleural effusion), cardiac (e.g. myocardial infarct, arrhythmia), thrombotic (e.g. deep vein thrombosis, pulmonary embolism).

A severe short-term complication (CDC grade ≥III) was registered in 38 (4.5%) elderly and 1,071 (2.2%) non-elderly (p<0.001). Also after correction of baseline variables, elderly was independently associated with an increased risk on severe short-term complications (OR 1.707 – CI 1.218, 2.392 – p=0.002). Nevertheless, short-term readmission and mortality rate were not statistically different (**Table 2**). Short-term mortality rate remained statistically not different after correction for baseline differences in multivariate analysis (p=0.173).

Multivariate analysis identified elderly (OR=1.707, p=0.002) as a risk factor for a severe short-term complication. Other risk factors were female gender, preoperative BMI,

hypertension, and OSA. Furthermore, SG was associated with more severe short-term complications compared to gastric bypass (**Appendix 3 – Table 8**).

In elderly, relatively more general complications were noted, 22 (2.6%) compared to 665 (1.4%) in non-elderly (p=0.003). However, after multivariate analysis only a trend toward significance was seen (OR=1.519, p=0.061, **Appendix 3 – Table 9**).

Mid-term complications (>30 days ≤2 years)

In 35,535 out of the 49,553 patients (71.7%) at least one follow-up moment was registered. Significantly more non-elderly had a follow-up; 34,975 (71.8%) non-elderly vs. 560 (66.8%) elderly (p=0.002). **Table 4b** presents the yearly follow-up numbers.

In contrast to short-term complications, overall mid-term complication rate as well as severe mid-term complication rate were significantly higher in non-elderly compared to elderly, also after correction of baseline characteristics in multivariate analysis (**Table 4a, Appendix 3 – Table 10 & 11**). Mortality rate was 0.1% for non-elderly and 0.4% for elderly (p=0.054), which remained not significantly different after correction for baseline variables (p=0.079). Mean number of days between surgery and mid-term complications was 321 days (±188 days).

Table 4a – Mid-term complications *(>30 days ≤2 years)*

	Total	Non-elderly	Elderly	p-value
	n=35,535	n=34,975	n=560	
Complication >30 days ≤2 years* – No. (%)	1,660 (4.7)	1,648 (4.7)	12 (2.1)	p=0.004
Severe complication >30 days ≤2 years* – No. (%)	1,318 (3.7)	1,309 (3.7)	9 (1.6)	p=0.008
Mortality >30 days ≤2 years* – No. (%)	24 (0.1)	22 (0.1)	2 (0.4)	p=0.054
Clavien-Dindo classification* – No. (%)				
Grade 0 (No complication)	33,875 (95.3)	33,327 (95.3)	548 (97.9)	
Grade I	259 (0.7)	257 (0.7)	2 (0.4)	
Grade II	75 (0.2)	74 (0.2)	1 (0.2)	
Grade IIIa	82 (0.2)	81 (0.2)	1 (0.2)	
Grade IIIb	1,203 (3.4)	1,198 (3.4)	5 (0.9)	
Grade IVa	7 (0.0)	6 (0.0)	1 (0.0)	
Grade IVb	2 (0.0)	2 (0.0)	0 (0.0)	
Grade V	24 (0.1)	22 (0.1)	2 (0.4)	
Unknown	8 (0.0)	8 (0.0)	0 (0.0)	
Readmissions >30 days ≤2 years* – No. (%)	964 (2.7)	957 (2.7)	7 (1.6)	p=0.032
Therapeutic intervention >30 days ≤2 years* – No. (%)	897 (2.5)	891 (2.5)	6 (1.1)	p=0.027

* = Only the most severe complication has been registered for each patient, No. = Number. Follow-up rates: 34,975 (71.8%) non-elderly vs. 560 (66.8%) elderly (p=0.002).

Table 4b – Follow-up numbers

	Total		Non-elderly		Elderly	
	n	No. (%)	n	No. (%)	n	No. (%)
Follow-up moment						
1 year	49553	33578 (67.8)	48715	33035 (67.8)	838	543 (64.8)
2 year	38848	18156 (46.7)	38262	17878 (46.7)	586	278 (47.4)
3 year	28950	9285 (32.1)	28557	9147 (32.0)	393	138 (35.1)
4 year	18516	3620 (19.6)	18287	3578 (19.6)	229	42 (18.3)
5 year	8593	387 (4.5)	8501	383 (4.5)	92	4 (4.3)

Table 5 – Types of mid-term complications reported

	Total	Non-elderly	Elderly
Hepatobiliary complication	543	543	0
Gallstones	528	528	0
Liver failure	2	2	0
Gastric complication	423	418	5
Motility disorder	152	149	3
Marginal ulcer	73	73	0
Gastric ulcer	71	70	1
Anastomotic stenosis	60	60	0
Delayed gastric emptying	5	5	0
Metabolic complications*	298	295	3
Esophageal complication	56	51	5
Esophageal motility disorder	11	10	1
Esophageal dilatation	5	5	0
Gastroesophageal reflux disease	0	0	0
Gastric band related complication	12	12	0
Motility disorder	0	0	0
Band erosion	3	3	0
Pouch dilatation/ band slippage	2	2	0
Port/band infection	1	1	0
Other complication	1,222	1,220	2
Internal herniation	692	692	0
Intestinal obstruction	60	59	1
Incisional hernia	55	55	0
Intolerance of bariatric procedure	46	46	0
No type of complication registered	192	192	0

Analyses are performed on complication level; so in case a patient experienced more than one complication, all complications are scored/included. The total number of complications in each subgroup may not be equal to the sum of the specific complications within the subgroup due to missings in reporting of the specific type of complication. * = Metabolic complication (e.g. dumping syndrome, vitamin deficiency, secondary hyperparathyroidism, peripheral neuropathy, electrolyte disorders).

The types of mid-term complications are presented in **Table 5**, with internal herniation being the most frequent reported complication.

Sensitivity analyses

Age, as a continuous factor, was identified as an independent risk factor for (severe) short- and mid-term complications (**Table 6**). However, elderly was not an independent risk factor for a short-term complication (including all CDC grades) (p=0.305). Looking at age as an ordinal variable (10-year age categories): with every 10 years increase in age, a higher odds ratio for severe-short term complications was noted (**Table 6**).

Table 6 – Sensitivity analyses

	Univariate		Multivariate	
	Odds ratio (CI)	p-value	Odds ratio (CI)	p-value
Short-term complication*				
Age (continuous)	1.015 (1.011, 1.018)	p<0.001	1.009 (1.005, 1.013)	p<0.001
Elderly vs. non-elderly	1.393 (1.064, 1.825)	p=0.016	1.154 (0.878, 1.517)	p=0.305
Severe short-term complication^				
Age (continuous)	1.025 (1.019, 1.031)	p<0.001	1.021 (1.015, 1.027)	p<0.001
Elderly vs. non-elderly	2.190 (1.591, 3.014)	p<0.001	1.707 (1.218, 2.392)	p=0.002
Age groups				
25-35 compared to <25	1.323 (0.923, 1.898)	p=0.128	1.349 (0.940, 1.936)	p=0.104
35-45 compared to <25	1.601 (1.133, 2.260)	p=0.008	1.614 (1.139, 2.286)	p=0.007
45-55 compared to <25	2.149 (1.538, 3.003)	p<0.001	2.032 (1.442, 2.863)	p<0.001
55-65 compared to <25	2.381 (1.687, 3.359)	p<0.001	2.119 (1.147, 3.037)	p<0.001
65-75 compared to <25	3.873 (2.454, 6.113)	p<0.001	3.300 (2.056, 5.298)	p<0.001
Mid-term complication*				
Age (continuous)	0.985 (0.981, 0.989)	p<0.001	0.981 (0.977, 0.985)	p<0.001
Elderly vs. non-elderly	0.356 (0.200, 0.631)	p<0.001	0.424 (0.253, 0.710)	p=0.001
Severe mid-term complication^				
Age (continuous)	0.984 (0.980, 0.988)	p<0.001	0.982 (0.977, 0.987)	p<0.001
Elderly vs. non-elderly	0.331 (0.157, 0.699)	p=0.004	0.388 (0.192, 0.782)	p=0.008

*= including all CDC grades, ^= including CDC ≥3. For all analyses, only the most severe complication has been registered for each patient. The independent variables included in each analysis are shown in the corresponding table in **Appendix 2**, in which 'elderly vs. non-elderly' was replaced by 'age (continuous)' or 'age group'.

DISCUSSION

This is the first Dutch nationwide study examining complication and mortality rate in elderly undergoing primary bariatric surgery. This study indicates that bariatric surgery in elderly tends to be safe in the short- and mid-term, as there was no perioperative mortality, severe short-term complications and mortality rates were low (4.5% and

0.2%), and mid-term complication rate was only 1.4% in elderly. Nonetheless, severe short-term complication rate was twice as high in elderly compared to non-elderly, even after correction for baseline variables (p=0.002). Perioperative safety outcome in elderly is comparable to non-elderly. In the general eligible population for bariatric surgery in North-West Europe, an intraoperative complication rate of 6.5% has been reported[12]. Giordano et al. showed a significant increase in intraoperative complication rate in elderly (patients aged ≥55 years) compared to patients aged <55 years, with rates of 14.4% and 5.3% respectively[13]. Furthermore, it has been reported that elderly are more likely to have a prolonged hospital stay, by one day on average, but a lower readmission rate compared to non-elderly[14-15]. The findings of the current study show an overall intra-operative complication rate of 1.1%, not significantly different between elderly and non-elderly (p=0.803). Furthermore, conversion to laparotomy was rarely performed in both groups, and no differences were found in hospital stay. Looking at perioperative outcome, bariatric surgery seems to be as safe in patients up to at least 70 years as in non-elderly.

Elderly who receive bariatric surgery do not have an increased mortality risk. Since laparoscopy has become the main surgical approach in bariatric surgery, the perioperative mortality is low, about 0.1%[12]. In elderly, mortality rates of 0.01%[13] and 0.4%[14] have been reported after bariatric surgery. In the current study, short-term mortality rate was 0.2% in elderly and 0.1% in non-elderly (p=0.086), a finding which is comparable to previous mentioned studies. So, also in elderly, short-term mortality rate is low and comparable to the general bariatric population.

With regard to severe short-term complications, elderly are at higher risk. A systematic review concerning older adults undergoing abdominal elective surgery showed that 24.7% of the elderly experienced a short-term complication[16]. Regarding bariatric surgery, several studies showed no difference in short-term complication rate between elderly and non-elderly[2,14,17]. However, one recently published review showed significantly more short-term complications in older patients, with an odds ratio of 1.88[3]. In the current study, severe short-term complications were significantly more prevalent in elderly compared to non-elderly (4.5% vs. 2.2% respectively, OR 1.707 (CI 1.218, 2.392)). This short-term complication rate of 4.5% in elderly is comparable to the complication rate (major adverse events) of 4.3% reported by Dorman et al., who showed no difference between elderly and non-elderly[14]. Moreover, overall short-term complication rate (6.9% in elderly) is lower than previous reported complication rates of 8.9%[17] and 14.7%[2]. An explanation might be a difference in type of study; national registry study vs. retrospective single center study vs. review. Another explanation might be the selection of relatively healthy elderly for elective bariatric surgery, while studies that focus on

acute abdominal surgery include all elderly. Bariatric surgery should be considered in elderly on an individual basis, in which the indication should be balanced against the risk of (severe) complications. Interesting aims for future research in elderly are long-term complications up to 5 years, efficacy, quality of life, and cost-effectiveness.

Pre-existing obesity related comorbidities and age are considered to negatively impact the short-term complication rate. Among others, age, comorbidities, frailty, ASA-score (American society of anesthesiologists score) and emergency surgery have been previously reported as risk factors[16,18-21]. Focusing on bariatric surgery, in a national sample of patients undergoing bariatric surgery in the USA, that age and male gender were independent risk factors for mortality after bariatric surgery[22]. The current study identified female gender (p=0.033), age (p<0.001), preoperative BMI (p=0.005), hypertension (p<0.001), and OSA (p=0.004) as independent risk factors associated with a severe short-term complication. Furthermore, the current study found that SG was associated with more severe short-term complications compared to gastric bypass (p<0.001), which is not complying with the existing literature[23-26]. In the SG group potentially more complex patients are included as the sleeve resection is an escape procedure when a gastric bypass is technically not possible. During the eligibility screening process of elderly for bariatric surgery, known risk factors should be taken into account and more research should be performed to determine the best suitable procedure in elderly.

General postoperative complications tend to occur more frequently in elderly. Khorgami et al. described 3.4% major adverse cardiovascular events in a retrospective cohort study including >100,000 adult patients after bariatric surgery[27]. A multicenter prospective database study regarding pulmonary complications after bariatric surgery showed a 30-day morbidity rate of 6.4%, with pneumonia and respiratory failure accounting for 18.7%[28]. In the current study, a general complication was scored in 22 (2.6%) elderly and 665 (1.4%) non-elderly (p=0.002). After correction for baseline variables, only a trend toward significance was seen (p=0.061). The pulmonary complication rate was 22.7% vs. 23.9% and the cardiac complication rate 22.7% vs. 9.8% in elderly vs non-elderly respectively. In case an elderly patient undergoes bariatric surgery, awareness and prevention (applying among others enhanced recovery after surgery) of general postoperative complications should be pursued. Prehabilitation, a process of improving the physical, nutritional, medical en mental conditions of a patient prior to a surgical procedure, has increasingly shown to be beneficial regarding reducing postoperative complications in various other types of surgery. It may also contribute to a reduction in postoperative complications in elderly undergoing bariatric surgery. However, more research is needed to support this hypothesis.

Bariatric surgery in elderly is safe regarding mid-term complications up to 2 years after the surgery. Literature so far has focused on efficacy in the mid/long-term, rather than safety[29-30]. The current study showed that overall mid-term complication rate as well as severe mid-term complication rate was higher in non-elderly compared to elderly (4.7% vs. 2.1% and 3.7% vs. 1.6% respectively). Of note, significant more non-elderly had a follow-up visit and the number of complications in elderly was low. This could have biased results and therefore results should be interpreted with caution.

The major strength of this study is the national, population-based design with an almost complete coverage of all patients who had bariatric surgery in the Netherlands between January 2015 and January 2020. However, this study has several limitations. DATO contains a large set of data points, but some outcomes are not registered and therefore missing, like operation time and cause of death. Furthermore, the administrative burden is extensive making errors more likely, but also leading to missing follow-up and complications, and thus selection bias. A third-party visits bariatric centers to validate data to correct for this possible bias, but not all errors are covered[9-10].

CONCLUSION

Bariatric surgery in elderly is safe regarding the perioperative outcome, short-term mortality and complications rate after 30 days up to two years. However, significantly more severe complications ≤30 days were noted for elderly. This data adds to the growing body of evidence that weight loss surgery is a possible option for elderly with severe obesity and that patients should not be solely denied surgery based on their chronological age. Bariatric surgery in elderly should be recommended on a case-by-case basis. Future studies with long-term follow-up should aim to determine long-term complication rate, efficacy and quality of life.

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APPENDIX 1

The Clavien-Dindo Classification of surgical complications[23]

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as anti-emetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anaesthesia
- IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	single organ dysfunction (including dialysis)
- IVb	Multi-organ dysfunction
Grade V	Death of a patient

APPENDIX 2

Laparoscopic Roux-en-Y Gastric bypass

After induction of pneumoperitoneum and placement of five laparoscopic ports the majority of the stomach is disconnected from the normal digestive route using a linear stapler to leave a small (20-25 ml) gastric pouch in continuity with the esophagus. The jejunum is transected approximately 130 centimeter (cm) from the ligament of Treitz and the distal end (Roux limb) is anastomosed to the gastric pouch, as a gastrojejunal anastomosis, using a 25 mm circular stapler or a 30 mm linear stapler. Thereafter, the proximal end (the biliary limb) is attached approximately 100 cm distally along the jejunum, as a jejuno-jejunal anastomosis. Furthermore, the mesenteric defects beneath the jejunojejunostomy and Petersen's space will be closed. Before closure of the skin incisions, the gastrojejunostomy is tested for leakage using methylene blue. After closure of the incisions bupivacaine will be injected subcutaneously.

Laparoscopic Sleeve Gastrectomy

The pneumoperitoneum is induced with the Veress needle and five laparoscopic ports are placed, as with the laparoscopic RYGB. The resection line begins from approximately five centimeters proximal to the pylorus, proceeding to the angle of His to result in a tube or sleeve-shaped remnant stomach of approximately 25% its original capacity. A calibration bougie, usually sized between 34 and 40 Fr, is used to standardize the sleeve size. Before closure, the stomach remnant will first be removed and the gastric tube will be tested for leakage. Furthermore, an easy flow drain will be placed and after closure of the incisions bupivacaine will be injected subcutaneously.

APPENDIX 3

Table 7 – Uni- and multivariate analysis of short-term complications*

Variable	Univariate		Multivariate	
	Odds ratio (CI)	p-value	Odds ratio (CI)	p-value
Elderly vs. non-elderly	1.393 (1.064, 1.825)	p=0.016	1.154 (0.878, 1.517)	p=0.305
Gender (male vs. female)	0.883 (0.803, 0.971)	p=0.010	1.002 (0.907, 1.107)	p=0.967
BMI	0.988 (0.980, 0.996)	p=0.002	0.989 (0.981, 0.997)	p=0.006
Diabetes Mellitus	1.329 (1.210, 1.459)	p<0.001	1.189 (1.072, 1.320)	p=0.001
Hypertension	1.347 (1.242, 1.462)	p<0.001	1.248 (1.142, 1.364)	p<0.001
Dyslipidemia	1.186 (1.077, 1.307)	P=0.001	0.980 (0.879, 1.092)	p=0.713
OSA	1.356 (1.232, 1.492)	p<0.001	1.268 (1.147, 1.402)	p<0.001
Type of bariatric procedure				
SG versus gastric bypass	1.081 (0.984, 1.187)	p=0.104	1.125 (1.023, 1.238)	p=0.015
Other versus gastric bypass	1.739 (1.023, 2.956)	p=0.041	1.688 (0.991, 2.874)	p=0.054

*=only the most severe complication is scored, CI = confidence interval, BMI = body mass index, OSA = obstructive sleep apnea

Table 8 – Uni- and multivariate analysis of **severe (CDC≥3)** short-term complications*

Variable	Univariate		Multivariate	
	Odds ratio (CI)	p-value	Odds ratio (CI)	p-value
Elderly vs. non-elderly	2.113 (1.518, 2.942)	p<0.001	1.707 (1.218, 2.392)	p=0.002
Gender (male vs. female)	0.737 (0.644, 0.843)	p<0.001	0.856 (0.742, 0.987)	p=0.033
Preoperative BMI	0.984 (0.972, 0.996)	p=0.009	0.983 (0.972, 0.995)	p=0.005
Diabetes Mellitus	1.329 (1,157, 1,526)	p<0.001	1.120 (0.960, 1.307)	p=0.151
Hypertension	1.453 (1.288, 1.638)	p<0.001	1.310 (1.148, 1.495)	p<0.001
Dyslipidemia	1.283 (1.115, 1.477)	p=0.001	1.025 (0.875, 1.200)	p=0.762
OSA	1.409 (1.224, 1.621)	p<0.001	1.242 (1.071, 1.439)	p=0.004
Type of bariatric procedure				
SG versus gastric bypass	1.399 (1,227, 1.596)	p<0.001	1.459 (1.276, 1.668)	p<0.001
Other versus gastric bypass	1.945 (0.910, 4,155)	p=0.086	1.838 (0.859, 3.936)	p=0.117

*=only the most severe complication is scored, CI = confidence interval, BMI = body mass index, OSA = obstructive sleep apnea

Table 9 – Uni- and multivariate analysis of general complications (short-term)*

Variable	Univariate		Multivariate	
	Odds ratio (CI)	p-value	Odds ratio (CI)	p-value
Elderly vs. non-elderly	1.955 (1.272, 3.007)	p=0.002	1.519 (0.980, 2.352)	p=0.061
Gender (male vs. female)	1.007 (0.838, 1.211)	p=0.939	-	
BMI	0.987 (0.972, 1.002)	p=0.084	0.990 (0.976, 1.005)	p=0.183
Diabetes Mellitus	1.570 (1.327, 1.858)	p<0.001	1.365 (1.132, 1.646)	p=0.001
Hypertension	1.464 (1.258, 1.705)	p<0.001	1.285 (1.088, 1.517)	p=0.003
Dyslipidemia	1.255 (1.050, 1.501)	p=0.013	0.954 (0.782, 1.165)	p=0.646
OSA	1.499 (1.259, 1.784)	p<0.001	1.356 (1.135, 1.621)	p=0.001
Type of bariatric procedure				
SG versus gastric bypass	0.473 (0.194, 1.156)	p=0.101	-	
Other versus gastric bypass	0.497 (0.201, 1.224)	p=0.128	-	

*=only the most severe complication is scored, CI = confidence interval, BMI = body mass index, OSA = obstructive sleep apnea

Table 10 – Uni- and multivariate analysis of mid-term complications*

Variable	Univariate		Multivariate	
	Odds ratio (CI)	p-value	Odds ratio (CI)	p-value
Elderly vs. non-elderly	0.443 (0.249, 0.786)	P=0.005	0.484 (0.272, 0.862)	p=0.014
Gender (male vs. female)	1.390 (1.215, 1.589)	p<0.001	1.360 (1.182, 1.565)	p<0.001
BMI	0.979 (0.970, 0.989)	p<0.001	0.985 (0.975, 0.995)	p=0.004
Diabetes Mellitus	0.856 (0.754, 0.972)	p=0.017	0.870 (0.759, 0.999)	p=0.048
Hypertension	0.912 (0.822, 1.013)	p=0.085	-	
Dyslipidemia	0.857 (0.753, 0.975)	p=0.019	0.880 (0.766, 1.011)	p=0.071
OSA	1.142 (1.010, 1.292)	p=0.034	-	
Type of bariatric procedure				
SG versus gastric bypass	0.444 (0.342, 0.515)	p<0.001	0.457 (0.393, 0.531)	p<0.001
Other versus gastric bypass	0.641 (0.262, 1.566)	P=0.329	0.687 (0.281, 1.682)	p=0.412

*=only the most severe complication is scored, CI = confidence interval, BMI = body mass index, OSA = obstructive sleep apnea

Table 11 – Uni- and multivariate analysis of severe (CDC≥3) mid-term complications*

Variable	Univariate		Multivariate	
	Odds ratio (CI)	p-value	Odds ratio (CI)	p-value
Elderly vs. non-elderly	0.420 (0.217, 0.814)	p=0.010	0.511 (0.263, 0.994)	p=0.048
Gender (male vs. female)	1.392 (1.198, 1.618)	p<0.001	1.239 (1.063, 1.444)	p=0.006
BMI	0.967 (0.956, 0.978)	p<0.001	0.970 (0.958, 0.982)	p<0.001
Diabetes Mellitus	0.719 (0.619, 0.836)	p<0.001	0.760 (0.646, 0.895)	p=0.001
Hypertension	0.860 (0.764, 0.967)	p=0.012	0.949 (0.837, 1.076)	p=0.414
Dyslipidemia	0.778 (0.671, 0.902)	p=0.001	0.840 (0.714, 0.988)	p=0.035
OSA	1.098 (0.956, 1.261)	p=0.187	-	
Type of bariatric procedure				
SG versus gastric bypass	0.416 (0.351, 0.494)	p<0.001	0.431 (0.362, 0.512)	p<0.001
Other versus gastric bypass	0.478 (0.152, 1.503)	p=0.207	0.513 (0.163, 1.613)	p=0.253

*=only the most severe complication is scored, CI = confidence interval, BMI = body mass index, OSA = obstructive sleep apnea

5

Lack of Standard Definitions of Primary and Secondary (Non)responders After Primary Gastric Bypass and Gastric Sleeve: a Systematic Review

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ABSTRACT

Lack of standard definitions of primary and secondary (non)responders after RYGB and SG makes it impossible to compare the literature. The aim was to analyse the different definitions used. MEDLINE® was searched for literature published between 01-07-2014 and 01-07-2017 concerning (1) patients who received a primary RYGB or SG and (2) the outcomes of primary and secondary (non)responders. One hundred twelve out of 650 papers were eligible. Forty out of 47 papers described a definition of weight loss success. Sixty-seven out of 112 papers mentioned weight loss failure of which 42 described a definition, in total 23 different definitions. Weight regain was mentioned in 77 papers; only 21 papers provided a definition. The recent literature regarding definitions of these outcomes is highly inconsistent. To compare the literature international consensus is required.

INTRODUCTION

A basic rule in science is to describe outcome parameters in the methods section of an article. Each parameter has to be defined to make it comparable to other studies. In 1960, the International System of Units (SI) standardized the metric system which is the most widely used system of measurement[1].

In bariatric surgery, several standardized outcomes have been published to provide consistency and to be able to compare the literature[2]. However, not all outcomes after bariatric surgery are standardized. With the increase of long-term follow-up data, more information has become available about the proportion of patients with inadequate weight loss and weight regain[3-7]. In the current literature, authors often use the terminology of weight loss "success", weight loss "failure", and weight "regain". Terminology that we question, as the use of "failure" may be tactfully incorrect for patients, but more important the result of a bariatric procedure is not a success but a response. Therefore, we propose the following terminology: primary responder ("success"), primary non-responder ("failure"), and secondary non-responder ("weight regain") (**Figure 1**). For these outcomes, no standardized definitions or systematic methods for reporting are published[8-10].

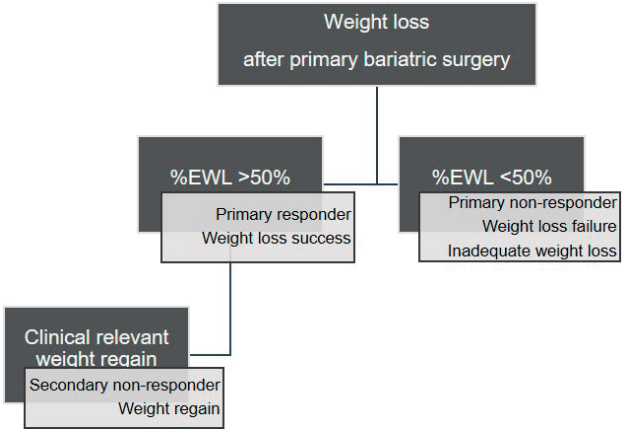

Figure 1 – Terminology weight loss outcomes
%EWL = Percentage excess weight loss.

Mann et al. showed back in 2015, in a systematic review of the literature, that the majority of the studies did not define "failure" of bariatric surgery and that percentage excess weight loss (%EWL) <50% at eighteen months was the most frequent definition identified for "failure"[9]. Nevertheless, several authors have reported criteria regarding primary responders and primary non-responders (**Table 1**)[11-14]. However, none of these criteria are widely used and the differences between these definitions are extensive. The lack of

uniform definitions may lead to alteration of results by adjusting the definition and thus creates bias. As an example, Diniz et al. reported that at five years postoperatively, the rates of success in their cohort, based on the Biron criteria and the modified Reinhold Criteria, were 50.0% and 74.0% respectively[15].

Table 1 – Criteria of "success" and "failure"[11-14]

	Reinhold[11]	Lechner and Elliot[12]	Christou et al.[14]	Biron et al.[13]	
				Superobese	Morbid Obese
Outcome measure	%excess weight	%EWL	BMI cut-off	BMI cut-off	BMI cut-off
Excellent	<25	≥80%	< 30 kg/m^2	-	-
Good	26 – 50	50% - 80%	30-35 kg/m^2	<40 kg/m^2	<35 kg/m^2
Fair	51 – 75	-	-	-	-
Poor	76 – 100	<50%	-	-	-
Failure	>100%	<25%	>35 kg/m^2	-	-

BMI = body mass index

The aim of this study was to analyse the currently used definitions of primary responders and primary and secondary non-responders after primary Roux-en-Y gastric bypass (RYGB) and primary sleeve gastrectomy (SG) in the recent literature, hereby determining if the situation Mann et al. described has improved. This in order to start an International System of bariatric outcomes to be able to compare future literature.

MATERIALS AND METHODS

This systematic review is performed according to the PRISMA guideline, where applicable.

Eligibility criteria

Studies that (1) included adult human patients who did receive either a primary RYGB or a primary SG procedure and (2) mentioned at least one of the three outcomes (weight loss success, weight loss failure and weight regain) were included. Synonyms used for the outcomes that were eligible for inclusion are the following:

- Weight loss success – adequate weight loss – sufficient weight loss – optimal weight loss
- Weight loss failure – inadequate weight loss – insufficient weight loss – suboptimal weight loss
- Weight regain – weight gain – weight recidivism

Studies including patients who received other bariatric procedures (e.g. gastric banding, vertical banded gastroplasty, biliopancreatic diversion, duodenal switch) were considered not eligible. Studies about patients who underwent a primary banded RYGB or banded SG were also excluded because of the relative new technique and the limited data available concerning the long-term results. Multiple articles from one research group were included. All papers had to be written in English. There were no exclusion criteria regarding type of article and no other patient exclusion criteria than mentioned above, because in this review we judge articles based on their methodology section instead of the results section.

Information sources and search

In October 2017, the electronic database MEDLINE® (PubMed®) was searched using the following combination of keywords with synonyms: gastric bypass, gastric sleeve, body weight, weight loss, fail*, *gain and success*. Only studies written in English concerning adult patients (19+ years) with a publication date between 01-07-2014 and 01-07-2017 were selected. This search was performed by two reviewers (DB and WL).

Study selection

All articles identified with our search strategy were first screened for duplicates. Two reviewers (DB and WL) assessed relevance by independently screening titles and abstracts. In case of a discrepancy, the reviewers discussed the paper together until consensus was achieved. The articles thought to be relevant were eventually assessed in full text for eligibility based on the above stated criteria (DB and WL).

Data collection process and data items

The following data was obtained from the included studies (DB and WL): year of publication, nationality, bariatric technique, outcomes (yes/no) and the definition(s) (if given). There was no assessment of bias in individual studies, as this was not relevant for the aim of the current study.

Summary measures and synthesis of results

All results are stated as absolute number or percentage. There is no comparative statistical analysis performed.

RESULTS

Study selection

The literature search identified 650 articles with limits applied. There were no duplicates. All 650 articles were screened on title and abstract for relevance. In total 171 studies were assessed in full text of which 112 articles were included (**Figure 2**).

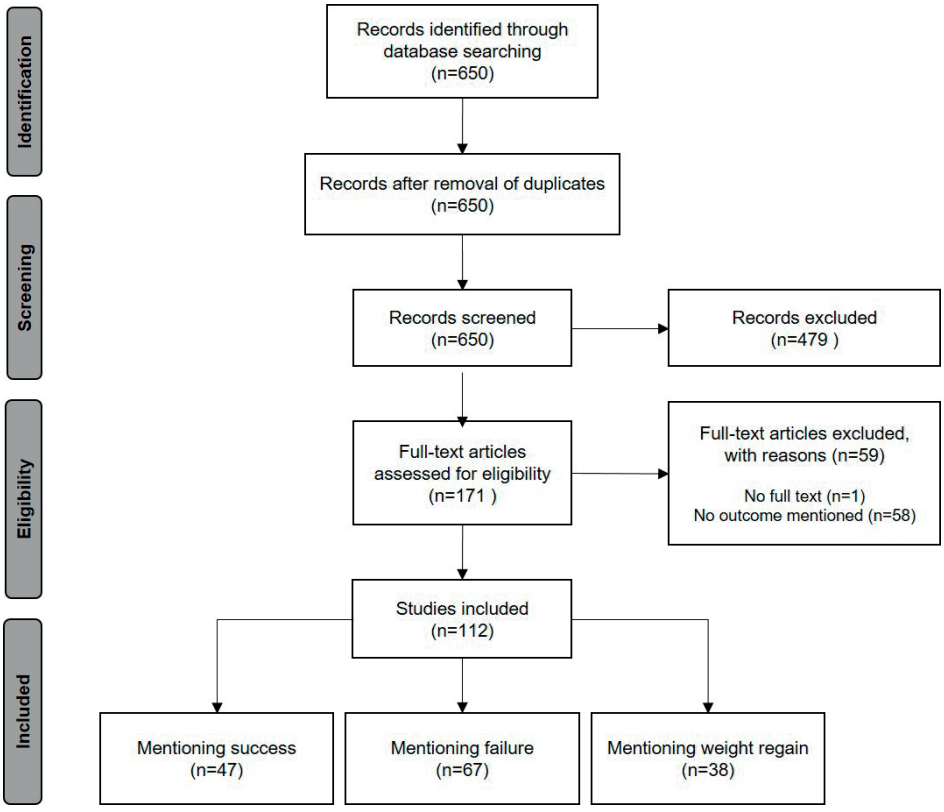

Figure 2 – Flowchart of the study selection according to PRISMA

Reporting of definitions

In the 112 articles selected, 191 outcome parameters were described. One hundred three out of 191 outcomes (54%) gave a definition and in one-third (64/191) no definition or description was given (**Figure 3**). In total thirteen different definitions of primary responders were described and 23 different definitions of primary non-responders were found (**Table 2**). Eighteen out of 77 papers used descriptive statistics to describe weight regain and only 21 authors gave a clear definition. The remaining studies (n=38) often mentioned "weight regain" as an indication for revisional bariatric surgery or as a con-

sequence of pouch dilatation after SG and did not mention a definition or descriptive statistics.

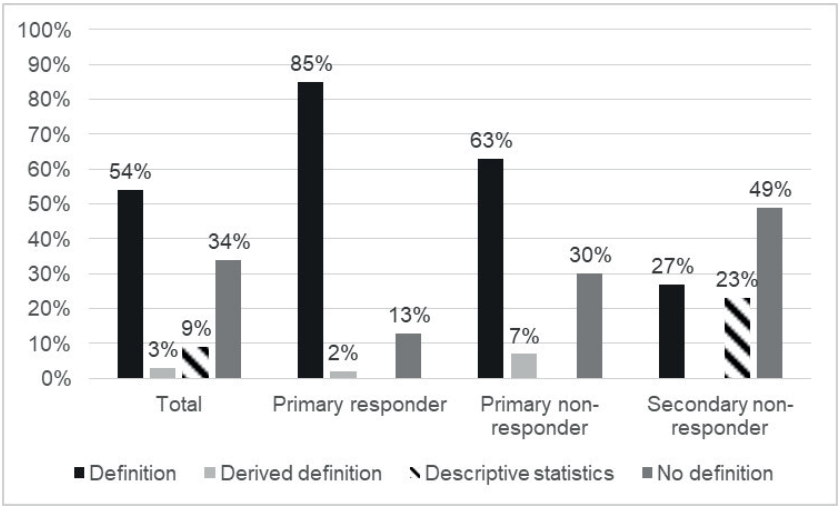

Figure 3 – Reporting of definitions

Content of the definitions

Primary responders were mainly defined using %EWL as outcome measure. %EWL was used in all but one of the definitions of primary responders and %EWL >50% as cut-off point was used in 9/13 definitions (n=33/38). Two definitions (n=3) included the remission of a comorbidity in the definition of success. No definition contained a patient-reported outcome measure (PROM).

Primary non-responders were mainly defined using %EWL as outcome measure (16/23). However, different outcome measures were used, including body mass index (BMI) cut-of points, excess BMI loss and total weight loss. Interestingly, primary non-responding was often combined with secondary non-responding as "failure" and used as an indication for revisional bariatric surgery (**Table 2**).

For secondary non-responders, many different weight loss outcome measures were used. Even within these outcome measures the cut-off points were far apart. For example, by the outcome measure maximum total weight loss, cut-off points 15%, 20% and 25% were used. The same applied for regain of a certain amount of kilograms and for the rebound in excess weight.

Table 2 – Definitions

A: Definitions of primary responder

Definition of primary responder	Frequency of use*
%EWL > 50%	XVI
%EWL > 50% one year after the surgery	IIII
%EWL > 50% two years after the surgery	III
%EWL > 50% during the whole follow-up after maximum weight loss	V
%EWL > 50% one year after the surgery to the end of the follow-up	I
%EWL > 50% at five years	I
%EWL > 60% one year after the surgery	I
%EWL > 60% and a BMI < 30 kg/m^2	I
%EBWL (excess body weight loss) ≥70% two years after the surgery	I
%EWL > 50% with resolution of co-morbid health condition	II
%EWL > 50% and good glycaemic control of T2D to HbA1c lower than 6%	I
%EBL (excess BMI loss) > 50%	I
Adequate %EWL at 3 years = mean – 1SD of the entire study's cohort	I

%EWL = percentage excess weight loss, %EBL = excess BMI loss, BMI = body mass index, T2D = diabetes type 2, *=Definitions repeatedly used by the same research group were just recorded once.

B: Definitions of primary non-responder

Definitions of primary non-responder	Frequency of use*
%EWL < 25%	IIII
%EWL < 25% at one year FU	I
%EWL < 30%	I
%EWL < 30% at the time of the last follow-up	I
%EWL < 50%	VII
%EWL < 50% one year after surgery	V
%EWL < 50% 18 months after the surgery	I
%EWL < 50% two years after the surgery	II
%EWL < 50% from 12 months FU to the end of FU	I
%EWL < 50% throughout FU	II
Excess body mass index loss (%EBMIL) < 25%	I
%EBMIL never exceeding 50%	I
<25% weight loss (equivalent to >50% EWL with BMI of 45-50)	I
No achievement of BMI < 35 kg/m^2 or after sufficient body weight reduction regained weight and exceeded BMI of 35 kg/m^2	I
%EWL <50% and BMI > 35 kg/m^2	II
%EWL < 50% without weight regain or when the IFSO criteria for bariatric surgery were still met	I

B: Definitions of primary non-responder (*continued*)

Definitions of primary non-responder	Frequency of use*
BMI > 40kg/m^2 - BMI> 35 kg/m^2 with co-morbidities or <50% EWL or significant weight regain associated with inability to maintain %EWL of 50% 24 months after RYGB.	I
<50%EWL or weight regain > 10kg body weight	I
%EWL < 50% at nadir weight and thereafter or %EWL ≥50% at nadir weight, but <50% at last FU visit (pronounced weight regain)	I
Patients weight was stable > 6 months with a %EWL < 50% or when a patient experienced weight regain	I
Significant weight regain	I
Excess weight loss < 50% at 2 years or weight gain > 15% from baseline	I
Unsatisfactory weight loss sustenance after the initial successful weight loss, with regain of >50% of the weight lost	I

%EWL = percentage excess weight loss, %EBMIL = excess BMI loss, BMI = body mass index, RYGB = Roux-en-Y gastric by-pass, FU = follow-up, *=Definitions repeatedly used by the same research group were just recorded ones.

C: Definitions of secondary non-responder

Definition of secondary non-responder	Frequency of use
Descriptive statistics (any weight regain)	XVIII
An increase in body weight of more than 5 kg	II
An increase in body weight of more than 10 kg from the nadir	II
An increase of at least 10% of the lowest postoperative weight	III
Any regain of lost weight from nadir weight	I
≥5% weight change between 1 and 2 years after surgery	I
Percentage excessive weight regain > 15%.	I
EWL regain >25% with respect to the minimal weight or when patient met the criteria for bariatric surgery again established by the IFSO	I
>25% rebound in EWL.	I
Any regain of lost weight after two years	I
Regained all their lost weight within 5% of baseline	I
>15% regain of maximum total weight loss	I
>20% regain of maximum total weight loss	I
>25% regain of maximum total weight loss	I
Any regained weight after achievement of %EWL > 50%	II
Any weight regain after successful loss (defined as achievement of body mass index ≤35kg/m^2)	I
Weight regain resulting in failure to maintain an %EWL ≥ 50% over time	I
Regained all their lost weight within 5% of baseline	I

EWL = percentage excess weight loss

Follow-up cut-off point in content of definition

Only in 8/13 definitions of primary responders a timeframe was set in which the weight loss needed to be achieved in order to being defined successful. For primary non-responders, eight definitions set a clear timeframe. The follow-up cut-off point was a marked dissimilar. The values one year, eighteen months, two years, three years, five years and during the whole follow-up were all used as cut-off points in the definitions.

Subgroups

There were no differences in definitions used for RYGB and SG. The same applied for the different nationalities. Within papers from the same research group, some papers reported a definition while others did not. Even more interestingly, sometimes different definitions were used by one and the same research group.

CONCLUSION

In the current study, a literature search regarding the definitions of primary and secondary (non)responders was performed and the recent literature is still comparing its own apples and oranges about these outcomes. Since the study of Mann et al. in 2015 this practice has not changed[9]. In one-third of the papers found in the current study, no clear definition was given. If present, the definitions differed between papers as we found thirteen, 23, and seventeen definitions for primary responders, primary non-responders, and secondary non-responders respectively. No standard follow-up cut-off point was found.

As long as there is no uniform definition, the literature regarding the outcomes is not comparable. Mann et al. showed that there was an inconsistency in reporting primary non-responders after primary bariatric procedure as 31 out of 51 papers did not gave a definition[9]. In addition, Lauti et al. showed that for secondary non-responders after SG in nine out of the 21 papers no definition was given[16]. In the current study, the percentage of articles that didn't give a definition of primary non-responders was lower, 30%. However, out of the 42 definitions given, there were 23 different definitions. Looking at secondary non-responders, the results are even worse: in halve of the articles no definition was given and in about a quarter only descriptive statistics were given. Twenty-one articles gave a definition of secondary non-responders, in total seventeen different definitions were found. To be able to compare the literature, all outcomes must be defined in the methods section of a paper and a uniform definition is required.

Moreover, due to the lack of a uniform definition, authors are able to manipulate their results by adjusting the definitions. Lauti et al. showed that, by applying six different

definitions of secondary non-responders in a cohort of 96 patients receiving a SG, the percentage of secondary non-responders ranged from 9% to 91%[17]. When applying the 21 definitions of secondary non-responders we found in the current study on a cohort, the range of secondary non-responders would possibly not be that much different from Lauti et al., as the extremes of the definitions are comparable. This shows that the results of studies using different definitions will differ greatly. A standardized definition is needed to minimise bias and to be able to compare results and thereby determine the proportion of primary and secondary non-responders.

Another notable finding is that several authors used primary and secondary non-responders combined as "failure", as if these outcomes are equal. AlSabah et al. showed that primary non-responders achieved better results after revisional bariatric surgery compared secondary non-responders[18]. On the contrary, Uittenbogaart et al. reported a difference in achievement of weight loss success between these two groups after secondary gastric banding, as secondary non-responders (n=15) were more likely to again reach %EWL > 50% and experienced significantly more weight loss compared to primary non-responders (n=25)[19]. In the current study, three definitions of secondary non-responders mentioned that first a %EWL of 50% must be achieved to be defined secondary non-responder In these three papers, primary non-responders was defined separately. Primary non-responders (weight loss failure) and secondary non-responders (weight regain) are two different outcomes and should therefore be both defined and reported separately.

For the current study, a limited search was used in which papers could have been missed that gave a definition of one of the three outcomes. Only papers regarding primary RYGB and primary SG were searched because these procedures cover almost 90% of all the bariatric procedures which makes it the most relevant "subgroup"[20-21]. Furthermore, only studies published the last three years were included. Even with this limited search, the current study shows the extreme diversity in the use of definitions and especially the lack of definitions in secondary non-responders.

Parallel to the differences in definitions, the outcome measures used are also diverse. To describe weight loss, some authors use %EWL while others use percentage total body weight loss (TBWL) or just change in BMI to describe weight loss. Outcome measures are not comparable with each other. Several authors have questioned the use of %EWL, as it is not suitable to compare groups in non-randomized studies. The range differs depending on the formula used, the ideal weight is hard to determine, and it is difficult to understand for patients[22-25]. In addition, several authors recommend the use of another outcome measure, such as percentage TBWL which is independent of the initial

BMI[23-24]. The majority of the definitions of (non)responders in the current study contain the outcome measure %EWL, but many different outcome measures were used (**Table 2**).

Bariatric surgery is performed to improve cardiovascular risk profile/metabolic syndrome, extend the life expectancy and improve quality of life (QoL). Striking is that 89.2% of the definitions did not include any of the previous mentioned factors and in the remaining 10.8% only remission of comorbidities was included. An interesting question is whether the cut-off point of the weight outcome measure in the definitions will change if there is remission of a weight related comorbidity or improvement of another outcome, or for secondary non-responders whether there is a re-emergence of a weight related comorbidity. DiGiorgi et al. reported that there is a relation between weight regain and the "re-emergence" of type 2 diabetes[26]. Results should not be about numbers but about the patients. Therefore, remissions of comorbidities, PROMs, and QoL should be taken into account when speaking about primary responders and primary and secondary non-responders (success, failure, and weight regain). However, for scientific purpose to compare the literature, uniform definitions of the outcomes purely based on a weight loss outcome measures should be defined.

The current study shows that definitions used in the recent literature regarding primary responders and primary and secondary non-responders are highly inconsistent. To be able to compare the literature standardized outcomes regarding these three outcomes should be formed and international consensus is required.

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PART II

Long-term abdominal bariatric complications during pregnancy

6

Pregnancy and Bariatric Surgery: Significant Variation in Bariatric Surgeons' Practices and Preferences – a National Survey

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ABSTRACT

Background

Bariatric complications may occur during pregnancy, potentially causing serious maternal and foetal problems. The aim of this study was to determine the current practice and preferences of bariatric surgeons regarding the pregnancy care of fertile women before and after bariatric surgery.

Methods

A 26-question anonymous online survey was designed and sent to all bariatric surgeons of the Dutch Society of Metabolic and Bariatric Surgery.

Results

At least one bariatric surgeon from each bariatric centre (n=18) completed the survey. In case of a future child wish sleeve gastrectomy became more popular than roux-en-y gastric bypass. All surgeons provided preoperative education regarding bariatric complications during pregnancy. Nine centres without neonatal intensive care, would not refer pregnant women with acute complications. Half of the centres had a standard operating procedure. 7/18 bariatric centres had seen at least one post-bariatric pregnant patient with severe maternal morbidity. One case of perinatal mortality was reported.

Conclusion

There is an inconsistent and often below guideline standard daily practice regarding pregnancy before and after bariatric surgery. There is limited experience with pregnant women with acute bariatric complications. Referral to tertiary centres is inadequate. Better information provision for both professionals and patients regarding possible complications is needed.

INTRODUCTION

Morbid obesity is known to negatively affect fertility, to increase the risk of complications during pregnancy and childbirth, and to enhance the chance of adverse perinatal outcomes[1-4]. Bariatric surgery is the most effective long-term treatment for morbid obesity[5]. It also results in improved pregnancy related outcomes[6-8], which contribute to the increase in bariatric procedures performed in fertile women.

However, bariatric surgery is also associated with various maternal and foetal risks. Over the last few years, more studies have become available regarding acute small bowel obstruction during pregnancy due to internal herniation or intussusception, especially after Roux-en-Y gastric bypass (RYGB)[9-14]. The diagnosis of these acute abdominal bariatric complications during pregnancy can be challenging because the clinical presentation might be similar to general pregnancy-related complaints and imaging techniques lack high sensitivity, specificity, or availability[13]. Furthermore, the incidence is low, whereas expertise is needed for adequate clinical decision-making[11-13].

Related to the increase in evidence of the pregnancy-related risks after bariatric surgery, various guideline articles with recommendations regarding the care of pregnant women after bariatric surgery have recently been published[15-16]. Recommendations are, among others, to postpone a pregnancy after bariatric surgery for 12-24 months so that maternal weight has been stabilized, to prescribe specific supplementation during the preconception and periconception period, and to avoid excessive gestational weight gain[9,15-16]. Recommendations regarding the diagnosis and treatment of acute abdominal bariatric complications are limited[15-16]. Moreover, it is unclear to what extent these guideline articles and recommendations are implemented in daily practice.

In 2018 and 2019, respectively 29.7% and 30.0% of the patients who underwent bariatric surgery in our clinic were women of childbearing age (18-40 years). As a tertiary referral centre, we have implemented various changes to improve the care for mother and child (**Appendix 1**).

The aim of this study was not only to get insight in the preoperative education regarding pregnancy-related outcomes of fertile women undergoing bariatric surgery but also in the current practice and preferences towards the care and referral of (non)pregnant women with a history of bariatric surgery and possible acute abdominal complications in the Dutch bariatric care.

MATERIAL AND METHODS

Study population

All bariatric surgeons of the Dutch Society of Metabolic and Bariatric Surgery were invited to participate in the survey. There are eighteen bariatric centres in the Netherlands with only one bariatric centre located in a facility with an obstetric high care (OHC) and a neonatal intensive care unit (NICU). There are no academic centres with a bariatric centre.

Survey

An anonymous survey was designed using an online platform for questionnaires and surveys (Survey Monkey Inc., San Mateo, CA, USA). The survey consisted of 26 questions regarding the care of pregnant women or women with an active child wish, just before or after bariatric surgery (**Appendix 2**). Seventeen questions addressed individual surgeon's practice and preferences, whereas nine questions were focused on visualizing current practice within the bariatric centre.

The 26 items consisted of ten dichotomous, two open, and fourteen multiple-choice questions. One open question required at least three answers; all other questions required only one. Some questions allowed textual remarks. In two questions conditional branching was used, creating a custom path for the respondents through the survey. The number of questions therefore varied between 25 and 26 questions.

The online survey was collected between April and June 2019. Reminders to participate in the survey were sent four and nine weeks after the initial invitation.

Analysis

All completed surveys were included and analysed. Questions that addressed individual surgeon's practice and preferences were analysed at surgeon level. Questions that addressed current practice within a bariatric centre were analysed at centre level, that is, one answer was included for each centre. For these latter analyses, discrepant answers by surgeons working at the same bariatric centre, were discarded. Categorical variables are presented as number only or as number (percentage). Continuous data are presented as mean (range: minimum-maximum). Descriptive statistics were calculated with IBM SPSS statistic software, version 24.0.

RESULTS

In total, 33 surveys were returned. Of these, six surveys were excluded as they were incomplete. From each bariatric centre, at least one survey was completed by a bariatric surgeon (**Figure 1**). A median of 4 (range: 2-6) bariatric surgeons were employed per centre and 15 (83%) centres had a bariatric surgeon 24/7 available on call. The following three paragraphs present analyses at surgeon level, whereas the last two paragraphs include analyses at centre level.

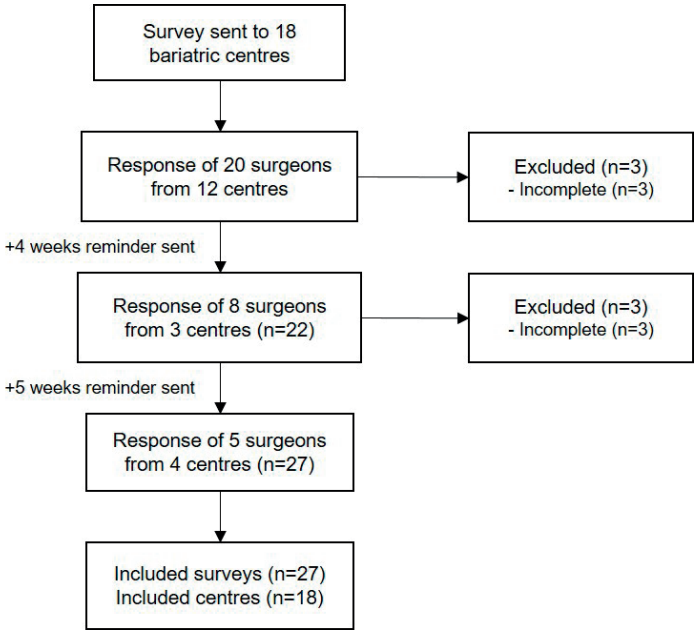

Figure 1 – Flowchart of study population selection

Advised type of bariatric procedure

The bariatric procedures that were advised by the respondents are presented in **Figure 2**. In fertile women (women <40 years), the majority of the surgeons gave no specific advice. Several surgeons, who did not give a specific advice, commented that they based their advice on several factors, including body mass index, comorbidities, and patients' preference. No surgeon advised a primary banded RYGB, a mini gastric bypass or a single anastomosis duodenal-ileal bypass with sleeve gastrectomy (SG).

In case of women with a specific future pregnancy wish, the SG became more popular compared to the RYGB, since six surgeons changed their initial advice to a SG. No surgeon changed his/her advice from SG to RYGB.

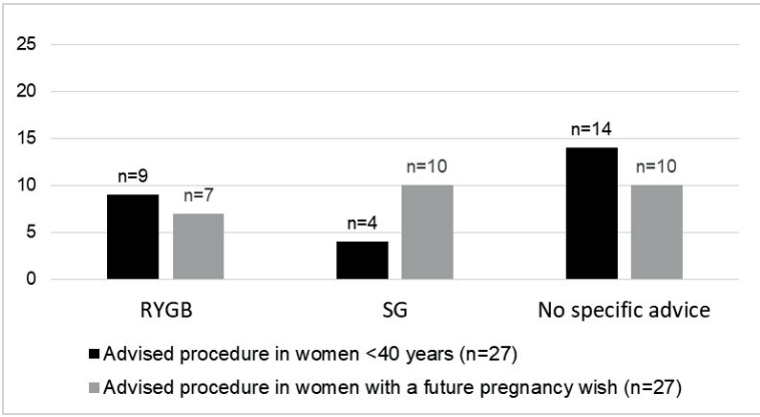

Figure 2 – Advised bariatric procedure for fertile women
RYGB = Roux-en-Y gastric bypass, SG = sleeve gastrectomy

Preoperative education

All surgeons provided preoperative education regarding possible bariatric complications related to mother and to unborn child in a future pregnancy after having BS. The recommended time to postpone a pregnancy after bariatric surgery was 12-18 months (n=17, 63.0%) or 18-24 months (n=10, 37.0%).

Pregnancy and postpartum counselling

The referral pattern for additional education, counselling, and monitoring of pregnant women or women with a future pregnancy wish after bariatric surgery is presented in **Figure 3**. In addition, fifteen respondents (55.6%) would invite pregnant patients for an additional consult at their outpatient clinic for information regarding the maternal and foetal risks related to their previous bariatric surgery. Weight gain during pregnancy was considered acceptable, but only within the normal limits of weight gain during a pregnancy (n=24, 88.9%). Breastfeeding was advised by a vast majority (n=25, 92.6%).

Diagnosing a pregnant patient with acute abdominal pain

If a pregnant woman presents with acute abdominal complaints after bariatric surgery, all respondents considered gastrointestinal related problems as a cause of the abdominal pain and 21 respondents (77.8%) also considered gynaecological-related problems. See **Figure 4** for the differential diagnoses. No respondent considered intussusception specifically as a differential diagnosis.

The first choice of imaging technique for a pregnant woman with acute abdominal pain was the abdominal ultrasound followed by the magnetic resonance imaging scan (n=21, 77.8%). One respondent preferred the computed tomography scan (CT-scan)

and another respondent would rather perform an abdominal ultrasound followed by a CT-scan.

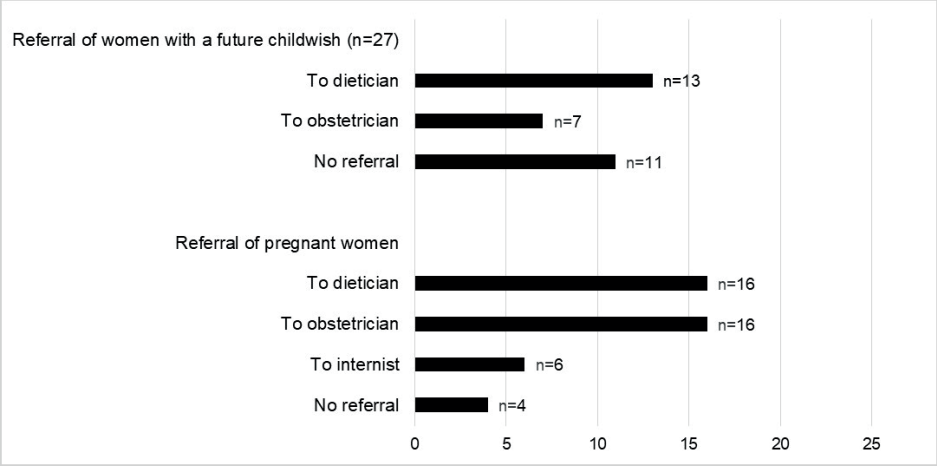

Figure 3 – Referral of women with a future child wish and pregnant women after bariatric surgery

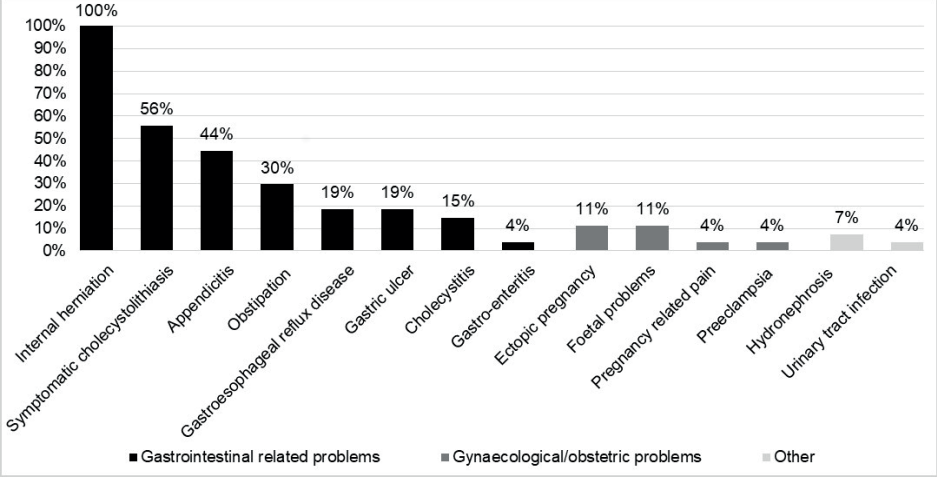

Figure 4 – Differential diagnoses in pregnant women with acute abdominal pain after bariatric surgery

Referral/treatment of a pregnant patient with acute abdominal pain

Ten bariatric centres would not refer pregnant women in case of acute abdominal pain. Of these centres, only one is a bariatric centre with an OHC and NICU. Furthermore, in one non-NICU bariatric centre, only patients with a gestational age (GA) below 24 weeks would be referred to a centre with an OHC and NICU (not necessarily a bariatric centre). The remaining seven bariatric centres would refer pregnant postbariatric women with

acute abdominal pain to a centre with an OHC, NICU and bariatric expertise. Of note, in one bariatric centre, different referral choices were noted between surgeons.

Nine of the eighteen bariatric centres had a surgical and/or gynaecological standard operating procedure (SOP), concerning the diagnosis and therapy of pregnant women who present with acute abdominal pain (two centres were excluded due to discrepant answers between the surgeons). The respondents of the seven centre that lack a SOP all indicated that they would prefer to have one.

Morbidity and mortality

Over the last five years, seven (38.9%) bariatric centres have seen at least one or more pregnant women, who previously had bariatric surgery and presented with acute abdominal pain, with severe morbidity. No case of maternal mortality was reported. Unfortunately, one case of perinatal death in the past five years was reported.

DISCUSSION

Current recommendations regarding the preconception care of women after bariatric surgery with a child wish are not adhered to. It is recommended to provide preconception care by a bariatric surgeon, dietician, and obstetrician. This is to monitor and prescribe micronutrient supplementation to prevent foetal complications, to inform and educate about possible complications of pregnancy following bariatric surgery, and to achieve adequate daily protein intake[17-20]. In this study, which focusses on bariatric surgical points of attention and not gynaecologic, eleven surgeons (40.7%) do not refer women with a future child wish to either an obstetrician or a dietician. More attention should be given to this specific preconception care, to prevent pregnancy-related complications.

Several recommendations regarding the care and education of *pregnant women* after bariatric surgery have been given. Ciangura et al. recommended that the antenatal care should be coordinated by an obstetrician and should include assessment of blood parameters at first presentation and after that once per trimester[15]. Furthermore, it was recommended to refer pregnant women to a dietician to ensure sufficient energy, micronutrient and protein intake[15,18]. Further weight loss during pregnancy should be avoided as well as excessive gestational weight gain[16-21]. Next to this, after labour, breastfeeding is advised with nutritional monitoring and supplementation[15-16,19-20]. In this study, only nine respondents (33.3%) refer pregnant women after bariatric surgery to both the obstetrician and dietician. Although many guidelines are available, there is a wide variation in the current practice and the guidelines are often not adhered to.

In order to achieve standardization, there is a need for better information provision for both professionals and patients.

There is no consensus regarding the type of bariatric procedure that should be performed in women with a child wish. RYGB is known for its long-term sustainable weight loss and reduced risks of obesity-related comorbidity[22-24]. However, it is also associated with many adverse pregnancy related outcomes[25-26]. SG is an alternative technique causing less perioperative and long-term complications as well as less adverse pregnancy related outcomes. However, long-term weight results appear inferior to RYGB and gastroesophageal reflux disease is a major problem[5,22,25-26]. The most performed technique in the Netherlands is the RYGB[27]. According to this survey, the RYGB is preferred over SG in fertile women. However, in case of a future child wish, the SG becomes more popular as primary advised procedure as several surgeons changed their advice from an RYGB or no specific advice to an SG. Ciangura et al. concluded that there is yet no evidence available to guide the choice of the most appropriate surgical procedure for fertile women[15]. Therefore, fertile patients should be educated preoperatively regarding the general but also the pregnancy related benefits and downsides (among others vitamin deficiencies and acute intestinal complications) of the different bariatric procedures. Only then they can make a well-informed decision, taking possible consequences for future pregnancy into account.

The incidence of acute abdominal bariatric complications with maternal or foetal morbidity and mortality is low, but can have disastrous consequences. Literature describes an incidence of internal herniation during pregnancy of as high as 10%, whereas the incidence of intussusception is lower[10,13]. In 7/18 of the Dutch bariatric centres maternal morbidity was seen. One case of perinatal death was reported. So, only a minority of the Dutch bariatric centres has experience with the severe consequences due to abdominal bariatric complications during pregnancy. Increasing the awareness and sharing the knowledge with surgeons and perinatologists regarding acute abdominal bariatric complications during pregnancy is of importance to provide the best care for these patients.

Referral of pregnant women for acute abdominal bariatric complications to a centre with a NICU is not standard of care. Nine bariatric centres, with no OHC and NICU, would not refer post-bariatric pregnant patients with acute bariatric complications to a NICU-centre. This means that some bariatric surgeons would perform surgery in pregnant patients with a gestational age below 32 weeks, although no specialized care for preterm neonates is available. The reluctance of referral might indicate that bariatric surgeons feel comfortable to take care of this specific group of patients. However,

literature has shown multiple cases of significant maternal and/or foetal morbidity and mortality, even when treated in a NICU-centre[10-11]. In addition, preterm born infants (<32 weeks gestation) born at a NICU-centre perform significantly better compared to infants born at a non-NICU-centre[28-29]. Based on these findings, we strongly recommend to refer pregnant patients, 24-32 weeks gestation, who possible require surgical intervention to a centre that has a NICU and an OHC to provide the best perinatal care. We also believe that this should be recommended by the official societies and in consensus statements. Especially in countries like the Netherlands, where the distance between the bariatric centre with a NICU/OHC and any other bariatric centre is (rather) small, exchange of patients is easy.

The main strength of this study is that it is a complete nationwide survey including all bariatric centres. A limitation is that not multiple bariatric surgeons of each bariatric centre were included. Furthermore, many discrepant answers were given between bariatric surgeons, even by those working within the same centre. Misinterpretation of a question due to unclear definition is possible but the discrepancies clearly show that there are different preferences and practices regarding the care of fertile women after BS. In addition, as is inherent in surveys, a response bias is present although limited due to the development of an anonymous survey.

CONCLUSION

This is the first study to investigate the current practice and preferences towards the care that is provided to women with an active child wish before and after bariatric surgery and to pregnant women after bariatric surgery. This study has shown that, despite the availability of international guidelines and consensus recommendations regarding the care for these women, there are many differences in the preferences and the current practise among bariatric centres and bariatric surgeons. These discordant practices are an indication for suboptimal care. A multidisciplinary international consensus statement for the treatment of this specific group of patients should be provided, to achieve better information provision for both professionals and patients and thereby provide the best possible care.

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APPENDIX 1

Pregnancy and bariatric surgery: current recommendations and practices in our clinic

Pre-operatively
Counselling and education regarding the general and pregnancy related benefits and downsides of the different bariatric procedures
Recommendation to avoid pregnancy for twelve months after surgery[A1]
Referral to dietician for adequately monitoring of micronutrient and adequate daily protein intake[A2-5]
Antenatal care
Referral to dietician to ensure sufficient energy, micronutrient and protein intake[A3,A6]
Additional multivitamin supplementation (among others; calcium/vitamin D3 500mg(400IE)/day and folic acid 400ug/day) according to Uittenbogaart et al.[A7]
Evaluation and check-ups by an obstetrician during the entire pregnancy
Laboratory assessment at first presentation and thereafter once per trimester[A2xA4-A6,A8]
Additional ultrasound third trimester[A6]
Recommendation to avoid additional weight loss and excessive weight gain[A2,A8]
Referral to facility with neonatal care in case of suspicion of acute bariatric abdominal complication between 24-32 weeks of gestation
Vaginal delivery is encouraged[A3]
After childbirth
Lactation is encouraged[A2,A6]
Follow-up with dietician for nutritional supplementation monitoring[A4-A6,A8]

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APPENDIX 2

Survey Bariatric surgery and pregnancy

Demographics

(1) In which clinic/hospital are you employed?

- □ Almere Flevoziekenhuis
- □ Amsterdam Obesitas Centrum
- □ Arnhem Vitalys Kliniek tegen overgewicht
- □ Bergen op Zoom Bariatrisch Centrum Zuid West
- □ Beverwijk Nederlandse Obesitas Kliniek
- □ Den Haag Nederlandse Obesitas Kliniek West
- □ Dordrecht Albert Schweitzer Ziekenhuis
- □ Eindhoven Catharina Obesitascentrum
- □ Heerlen Nederlandse Obesitas Kliniek Zuid
- □ Hengelo ZGT Obesitascenrum
- □ Hoofddorp Spaarne Gasthuis
- □ Leeuwarden Centrum Obesitas Noord Nederland
- □ Nieuwegein Nederlandse Obesitas Kliniek
- □ Rotterdam Obesitas Centrum Franciscus Gasthuis & Vlietland
- □ Terneuzen Bariatrisch Centrum Zorgsaam
- □ Tilburg Obesitas Centrum Midden Brabant
- □ Veldhoven Obesitas Centrum Máxima

(2) What is your current working position/job title?

- □ Surgical resident
- □ PhD-student
- □ Surgeon
- □ Physician assistant/nurse practitioner
- □ Other, namely….

(3) How many bariatric surgeons are currently employed in your clinic/hospital? (Permanent employees include bariatric surgeons and fellows working bariatric shifts)

- □ 2
- □ 3
- □ 4
- □ 5
- □ 6
- □ 7
- □ 8
- □ 9
- □ 10

(4) Are the bariatric surgical consultants in your clinic/hospital 24/7 available on call?
- □ Yes
- □ No
- □ I don't know

(5) Does your clinic/hospital have an obstetric high care (OHC)?
- □ Yes
- □ No
- □ I don't know

(6) Does your clinic/hospital have a neonatal intensive care unit (NICU)?
- □ Yes
- □ No
- □ I don't know

Preconception

(1) Is preoperative counselling provided concerning the potential bariatric complications in a future pregnancy?
- □ Yes
- □ No

(2) What type of bariatric surgery do you generally advise in women who are <40 years old?
- □ Sleeve gastrectomy
- □ Gastric bypass
- □ No specific advice, comment….
- □ Other, namely….

(3) Does the advice change if the patient has a future pregnancy wish?
- □ Yes, to a sleeve gastrectomy
- □ Yes, to a gastric bypass
- □ No change
- □ No specific advice, comment …
- □ Other, namely….

(4) Do you standardly refer patients after bariatric surgery who have a future child wish to a gynaecological gynaecologist?
- □ Yes
- □ No

(5) Do you standardly refer patients after bariatric surgery with a child wish to a dietitian?
- □ Yes
- □ No

(6) How long after bariatric surgery would you recommend a patient to wait with a pregnancy?
- □ The patient does not need to wait
- □ <1 year
- □ 1 - 1.5 years
- □ 1.5 – 2 years
- □ > 2.5 years

Pregnancy

The following questions concern the following scenario, where a pregnant woman is seen after having undergone bariatric surgery.

(1) If a pregnant patient presents in your bariatric clinic/hospital, does she receive an extra check-up at the bariatric surgery department to provide counselling on maternal and foetal risks?
- □ Yes
- □ No
- □ Other, namely….

(2) Do you normally refer a pregnant patient to a gynaecological?
- □ Yes
- □ No

(3) Do you normally refer a pregnant patient to an internal medicine specialist?
- □ Yes
- □ No

(4) Do you normally refer a pregnant patient to a dietician?
- □ Yes
- □ No

(5) What is your advice on body weight for a pregnant patient during her pregnancy?
- □ No advice is given
- □ Maintain the same weight
- □ Weight gain is acceptable, but only within the normal limits of weight gain during a pregnancy
- □ Weight gain is no problem

(6) Does your clinic/hospital have a protocol for the diagnosis and therapy of a pregnant patient who presents with acute abdominal pain?
- □ Yes, the surgery department has a protocol
- □ Yes, the gynaecology department has a protocol
- □ Yes, both the surgery and the gynaecology department have a protocol
- □ No, but there is need for one
- □ No, and there is no need for one

(7) If a pregnant patient presents with acute abdominal pain, which diagnoses would be in the top of the list of your differential diagnosis?
(Give at least 3 answers)
- □ Diagnosis 1…….
- □ Diagnosis 2……..
- □ Diagnosis 3…….
- □ Diagnosis 4…….
- □ Diagnosis 5 …….

(8) When do you refer a pregnant patient with acute abdominal complaints to another clinic/hospital?
- □ When the gestational age is <24 weeks
- □ When the gestational age is <32 weeks
- □ When the gestational age is <37 weeks
- □ I refer everyone, regardless of the gestational age
- □ I do not refer these patients

(9) To what kind of centre do you refer these patients to?
- □ To a bigger bariatric centre
- □ To a centre with OHC and NICU
- □ To a centre with OHC and NICU and what has bariatric expertise
- □ Other, namely….

(10) If a pregnant patient presents with acute abdominal complaints, what would be your first choice of imaging techniques?
- □ An abdominal ultrasound only
- □ An abdominal ultrasound followed by CT-scan
- □ An abdominal ultrasound followed by CT-scan and MRI-scan
- □ An abdominal ultrasound followed by MRI-scan
- □ A CT-scan only
- □ CT-scan followed by abdominal ultrasound
- □ MRI-scan only
- □ Other, namely….

Morbidity and mortality

The following questions concern the following scenario, where a pregnant woman is seen after having undergone bariatric surgery.

(1) Has a pregnant patient with severe maternal morbidity presented itself with acute abdominal complaints at least once in the past five years in your bariatric centre? For example, presentation with an ischemic small bowel that needed resection?
- □ Yes
- □ No

(2) Has maternal mortality occurred in a pregnant patient with acute abdominal complaints as consequence of a bariatric complication in the last 5 years in your bariatric centre (at least once)?

- □ Yes
- □ No

(3) Has foetal mortality occurred in a pregnant patient with acute abdominal complaints as consequence of a bariatric complication in the last 5 years in your bariatric centre (at least once)?

- □ Yes
- □ No

Postpartum

(1) What is your advice on breastfeeding to post-bariatric patients?

- □ Breastfeeding is preferred
- □ Preferably no breastfeeding
- □ Breastfeeding is strongly discouraged

(2) Does you clinic/hospital provide standard post-partum counselling at the bariatric surgery department?

- □ I don't know
- □ No, only regular follow-up
- □ Yes, what subjects are discussed

7

Pregnant Women after Bariatric Surgery: Diagnostic Accuracy of Magnetic Resonance Imaging for Small Bowel Obstruction

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ABSTRACT

Background

Small bowel obstruction (SBO) is a late complication of Roux-en-Y gastric bypass (RYGB). In non-pregnant patients computed tomography (CT) is the first choice of imaging. During pregnancy, magnetic resonance imaging (MRI) is preferred to limit exposure to ionizing radiation. However, literature regarding the diagnostic accuracy of MRI for SBO is scarce.

Objective

To describe the diagnostic accuracy of MRI for SBO during pregnancy.

Methods

Pregnant women with a RYGB suspected for SBO who presented at our centre between September 2015 and April 2020, received an MRI-scan (index) and underwent surgery (reference) were included. Original reports were retrospectively evaluated. Available MRI-scans were structurally reinterpreted by two experienced radiologists. Statistical analysis included sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Cohen's kappa.

Results

Twenty-seven original MRI reports were included. Twenty-four (88.9%) MRIs were of good quality. Sensitivity was 66.7% (confidence interval (CI) 0.43-0.85), specificity 66.7% (CI 0.13-0.98), PPV 93.3% (CI 0.66-0.99) and NPV 22.2% (CI 0.04-0.60). MRI was unable to detect SBO in 1 out of 3 patients. Presence of swirl-sign, SBO-sign or clustered-loop-sign increases the likelihood of SBO. The interobserver agreement was overall wide, with the highest score for swirl-sign (κ0.762).

Discussion

MRI is a safe and feasible alternative for CT. The value is doubtful as diagnostic accuracy shows wide ranges with considerable variability in the interobserver agreement. We would cautiously advise to perform MRI in case of a mild clinical presentation, but in case of a severe clinic the diagnostic laparoscopy should remain the gold standard.

INTRODUCTION

Advantages of the Roux-en-Y gastric bypass (RYGB) are extensively described[1-3]. However, RYGB is also associated with several short- and long-term complications[1,4]. Small bowel obstruction (SBO), due to internal herniation (IH) or intussusception, is a well-known long-term complication. It can lead to intestinal ischemia, perforation and sepsis[5-6]. SBO also occur in pregnant women after RYGB[7-10].

The standard imaging technique to diagnose IH is computed tomography (CT)[6,11]. The sensitivity of CT for detecting IH has a wide range, varying from 28.6% to 83.3%[11-16]. The same applies for the specificity, ranging from 29.0% to 90.0%[13-16]. Positive predictive value (PPV) varies from 65.5% to 66.6% and negative predictive value (NPV) from 64.3% to 71.4%[13-14]. Several articles have described the diagnostic accuracy of specific signs for IH[12,17]. More recently, the diagnostic accuracy of a combination of these specific IH-signs was examined, enhancing the sensitivity and specificity[18]. However, diagnostic laparoscopy remains the gold standard for detecting IH[13].

In pregnant women, magnetic resonance imaging (MRI) might be a good alternative for CT as it has no biologic risks, no exposure to ionizing radiation, for the developing foetus and it provides more detailed information about soft tissues[19-23]. However, MRI has some disadvantages, like long imaging times and more expensive nature. Only one study has been published regarding the diagnostic accuracy of MRI for IH in pregnant women after bariatric surgery, in which fifteen patients were included. According to this study, MRI has a comparable specificity to CT and a lower but approaching sensitivity. They concluded that MRI might be a reasonable and safe alternative to CT in diagnosing IH during pregnancy[24].

Aim of this study is to describe the diagnostic accuracy of MRI for the diagnosis of SBO in pregnant women after RYGB.

METHODS

Study design

This retrospective study was reported according to the standards for reporting diagnostic accuracy studies (STARD), where applicable. This study consists of 2 parts. Part 1 of this study determined the feasibility and diagnostic accuracy of MRI for SBO based on the original radiology reports. In part 2, the MRI-scans were systematically reinterpreted to determine whether this improved the diagnostic accuracy.

Participants

Pregnant women with a history of a (banded) RYGB, who presented at our centre (tertiary centre for acute abdominal bariatric complications during pregnancy) with acute abdominal pain suspected for SBO between September 2015 and April 2020 were screened for inclusion. All patients who received an MRI-scan (at our centre or the referral centre) and underwent surgery were included. In case the MRI-images could not be obtained from the referral centre, patients were only included in part 1.

Test methods

Index test

The index test for this study is the MRI. The MRI-scans at our centre were all performed with a clinical 1.5-T MRI Philips Achieva dStream (Philips Medical Systems, Best, Netherlands). An integrated posterior phased-array coil combined with anterior coil, 32 channels, was used for each patient. The gradient strength was maximal 33 mT/m. The specific absorption rate (SAR) was limited to a maximum of 2W/kg. In all cases, after a three-plane localizer image was obtained, coronal, sagittal and transversal breath-hold T2-weighted sequences (without fat saturation) and coronal and transversal respiratory triggered T2-weighted sequences (with fat saturation) were performed. Diffusion-weighted images were also performed (b-factor 0-400-800 s/mm2). Oral contrast and gadolinium was not administered. The MRI-scans performed at the referral centres were performed with local strategies.

Assessment of original reports

All MRI-scans have been assessed by the radiologist on-call of the centre where the MRI was performed, as part of standard care. The report that was produced by this assessment is included as the original report.

Reassessment of the MRI-scan

Two abdominal radiologists (HB & AL) experienced (respectively seven and 25 years) and specialized in bariatric and abdominal radiology independently reinterpreted the MRI-scans. All scans were presented randomly and anonymized to the radiologists in our PACS (picture archiving and communication system). The radiologists did not have access to the original report and clinical information (symptoms, operative findings, diagnosis). Furthermore, no review of previous imaging tests was allowed. However, they were allowed to see the information included in the original request.

All MRI-scans were systematically evaluated for the presence of specific IH-signs, previously described in studies evaluating diagnoses of IH with CT. These IH-signs were specifically validated for the radiologic diagnosis of IH. The presence of an established IH-sign was scored as 1. Suspicion of IH-sign or 2. No suspicion of IH-sign.

The radiologists were also asked to provide their overall (subjective) conclusion of the diagnosis of SBO. Radiologic overall conclusion was rated as 1. Suspicion of SBO or 2. No suspicion of SBO. If the radiologic conclusion was scored as 1, the radiologist was asked to define the specific subtype of SBO (see below).

Reference standard

The reference standard was the surgical exploration. The surgeons were not blinded for the results of the MRI-scan as this was a retrospective study. The definition of SBO diagnosis was; the presence of a bowel obstruction related to the previous (banded) RYGB at the time of the surgical exploration. The subtypes of SBO were defined as follows;

(1) Intussusception: presence of a small bowel intussusception.
(2) Internal herniation: presence of a herniated bowel through a mesenteric defect.
    - In case no IH was present, but the mesenteric defect(s) was (were) wide open and was (were) closed during surgery and postoperatively the symptoms diminished, patients were also scored as IH.
(3) Gastric band obstruction: presence of a herniated small bowel through the silicone ring.
(4) SBO due to adhesions: a small bowel 'trapped' in adhesions with obstruction of the small bowel.

Additional data collection

The following data was retrospectively collected from the patient electronic files: maternal age – gestational age (GA) at presentation at our centre – year and type of RYGB – timeframe between RYGB and onset of symptoms (years) – type of surgical intervention (laparoscopy / laparotomy) – surgical diagnosis.

Analysis

Continuous variables are presented as mean ±standard deviation (SD) or as median with interquartile range (Q1, Q3) if the normality assumption is not met. Categorical variables are stated as number (percentage). The statistical analyses were performed with IBM SPSS Statistics version 24 for Windows. A p-value < 0.05 was considered to be significant.

Estimating measures of diagnostic accuracy

The diagnostic accuracy was expressed in terms of sensitivity, specificity, PPV, NPV and diagnostic odds ratio (DOR). The precision was expressed by using a 95% confidence interval (CI). The interobserver agreement was calculated with the Cohen's kappa statistic and interpreted according to Landis and Koch[25].

Additional analysis

The decision-tree models, as described by Dilauro et al., exist of a combination of different IH-signs for the determination of the diagnostic accuracy. Model 1 (swirl-sign and SBO-sign) and 2 (superior mesenteric vein (SMV) beaking and SBO-sign) were used[18].

Furthermore, evaluation of various combinations of IH-signs was performed. A combination was valued suspicious if at least one IH-sign was present. The combination of IH-signs evaluated was based on the IH-signs with the highest sensitivity found in part 2 (systematic reinterpretation of the MRI-scans).

RESULTS

Sixty-four pregnant women with a history of a RYGB, who presented with acute abdominal pain suspected for SBO at our centre between September 2015 and April 2020, were identified. Thirty-two (50.0%) women received an MRI-scan. Twenty-six (40.6%) also underwent surgery and were included. One patient was included twice. This woman had two MRI-scans and two surgeries during her pregnancy for two different episodes of abdominal pain. Therefore, the total number of included cases is 27 (**Figure 1**). The baseline and clinical characteristics are presented in **Table 1**.

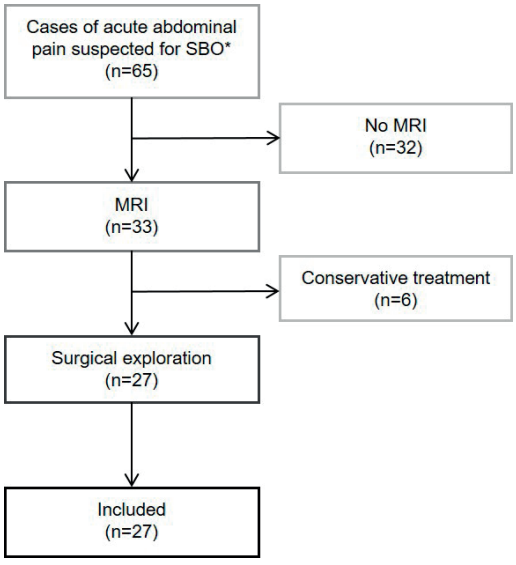


Figure 1 – Flow diagram of cases inclusion
MRI = magnetic resonance imaging, SBO = small bowel obstruction, * Cases of acute abdominal pain suspected for SBO related to the previous bariatric surgery presenting at our centre between September 2015 and April 2020.

Table 1 – Baseline and clinical characteristics

Included cases – No.	27
Maternal age – Years – Mean ±SD	31 ±4
GA at presentation* – Weeks^{+days} – Median (Q1, Q3)	29^{+4} (26^{+6}, 30^{+6})
Trimester of pregnancy at presentation* – No. (%)	
First trimester	1 (4)
Second trimester	6 (22)
Third trimester	20 (74)
Singleton pregnancy / Twin pregnancy – No. (%)	
Singleton pregnancy	25 (93)
Twin pregnancy	2 (7)
Type of bariatric procedure – No. (%)	
Primary RYGB (antecolic)	22 (81)
Primary banded RYGB (antecolic)	1 (4)
Revisional RYGB after gastric banding (antecolic)	4 (15)
Timeframe RYGB and onset symptoms – Years – Mean ±SD	4 ±2, range; 10 months – 8 years

No. = number, SD = standard deviation, GA = gestational age, Q1 = first quartile – equal to the 25th percentile of the data, Q3 = third quartile – equal to the 75th percentile of the data, * = presentation at our centre, RYGB = Roux-en-Y gastric bypass.

Part 1

Twenty-four MRI-scans (88.9%) were of good quality. Fourteen out of fifteen women suspected of SBO on MRI-scan indeed had SBO. Two women with an intussusception were actually suspected for IH. Nine MRI-scans were not suspected for SBO. However, seven women actually did have SBO during surgical intervention (**Figure 2**).

In three patients, the quality of the MRI-scan was degraded due to movement and breathing motions artefacts as result of the abdominal pain (n=2) and claustrophobia despite sedation (n=1). One MRI-scan was still reported as highly suspected for SBO. All three patients had SBO.

Based on the original reports, with exclusion of the three MRI-scans of impaired quality, a sensitivity of 66.7% (CI 0.43-0.85) and a specificity of 66.7% (CI 0.13-0.98) of MRI for the diagnosis of SBO can be calculated. In addition, PPV was 93.3% (CI 0.66-0.99) and NPV was 22.2% (CI 0.04-0.60).

Part 2

Five MRI-scans could not be obtained from the referral centres. Two MRI-scans were of impaired quality and were excluded. Therefore, the total number of MRI-scans included in part 2 is twenty.

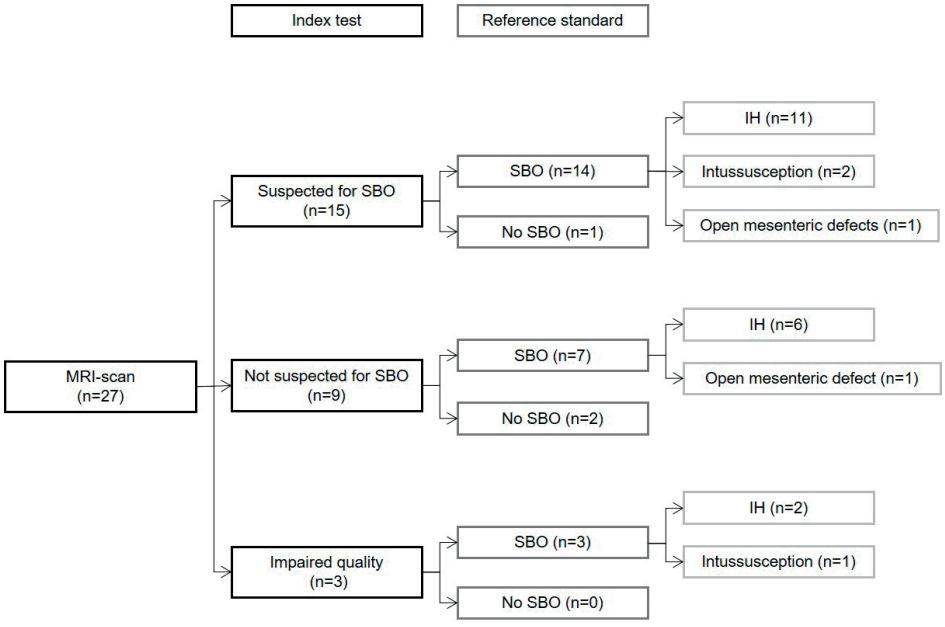


Figure 2 – Original reports of MRI with reference standard
MRI = magnetic resonance imaging, SBO = small bowel obstruction, IH = internal herniation

Eighteen women had SBO. The sensitivity, specificity, PPV, NPV, DORs, and the interobserver agreement of the individual characteristic IH-signs as well as the overall conclusion of each radiologist are presented in **Table 2**.

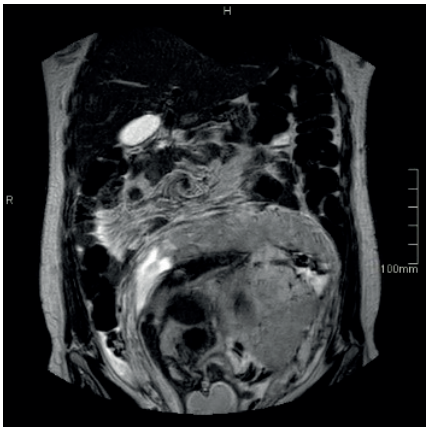
Looking at the overall conclusion, for observer 1 and 2 a sensitivity of 55.6% (CI 0.31-0.78) and 55.6% (CI 0.31-0.78) is seen and a PPV of 90.9% (CI 0.58-1.00) and 100.0% (CI 0.66-1.00) respectively. Interobserver agreement was 0.700 (good agreement). Regarding the individual IH-signs, sensitivity is low, ranging from 0.0% (CI 0.00-0.22) for criss-cross-sign to 50.0% (CI 0.28-0.73) for SBO-sign. **Figure 3** shows images of four of the IH-signs. Specificity and PPV are overall high, although the CIs show wide ranges (**Appendix 1**). The highest interobserver agreement for the individual IH-signs was seen for the swirl-sign with a kappa of 0.762 (good agreement).

Looking at the presence of at least one of the following three IH-signs, SBO-sign / swirl-sign / clustered-loop-sign, observer 1 noted a sensitivity of 83.3% (CI 0.58-0.96), specificity of 50.0% (CI 0.03-0.97), PPV of 93.8% (CI 0.68-1.00) and NPV of 25.0% (CI 0.13-0.78). Observer 2 noted a sensitivity of 61.1% (CI 0.36-0.82), specificity of 50.0% (CI 0.03-0.97), PPV of 91.7% (CI 0.60-1.00) and NPV of 12.5% (CI 0.07-0.53).

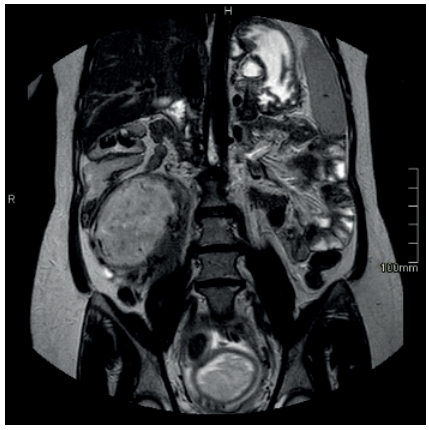
Table 2 – Statistics of individual MRI-signs

Sign	Sensitivity (percentage)		Specificity (percentage)		PPV		NPV		Diagnostic odds ratio		Interobserver agreement (κ)
	Observer 1	Observer 2	Observer 1	Observer 2	Observer 1	Observer 2	Observer 1	Observer 2	Observer 1	Observer 2	
Overall conclusion	10/18 (56%)	10/18 (56%)	1/2 (50%)	2/2 (100%)	10/11 (91%)	10/10 (100%)	1/9 (11%)	2/10 (20%)	1.25	-	0.700
Small bowel obstruction sign	5/18 (28%)	9/18 (50%)	1/2 (50%)	2/2 (100%)	5/6 (83%)	9/9 (100%)	1/14 (7%)	2/11 (18%)	0.38	-	0.479
Swirl-sign	6/18 (33%)	6/18 (33%)	2/2 (100%)	2/2 (100%)	6/6 (100%)	6/6 (100%)	2/14 (14%)	2/14 (14%)	-	-	0.762
Clustered loops sign	6/18 (33%)	5/18 (28%)	0/2 (0%)	1/2 (50%)	6/8 (75%)	5/6 (83%)	0/12 (0%)	1/14 (7%)	-	0.38	0.135
SMV beaking (strangulation)	1/18 (6%)	5/18 (28%)	2/2 (100%)	2/2 (100%)	1/1 (100%)	5/5 (100%)	2/19 (11%)	2/15 (13%)	-	-	0.273
Ascites	1/18 (6%)	4/18 (22%)	2/2 (100%)	2/2 (100%)	1/1 (100%)	4/4 (100%)	2/19 (11%)	2/16 (13%)	-	-	0.348
Hurricane eye sign	2/18 (11%)	4/18 (22%)	2/2 (100%)	2/2 (100%)	2/2 (100%)	4/4 (100%)	2/18 (11%)	2/16 (13%)	-	-	-0.154
Dilated remnant stomach / biliopancreatic limb	1/18 (6%)	3/18 (17%)	2/2 (100%)	2/2 (100%)	1/1 (100%)	3/3 (100%)	2/19 (11%)	2/17 (12%)	-	-	0.459
Engorged lymph nodes	2/18 (11%)	2/18 (11%)	2/2 (100%)	2/2 (100%)	2/2 (100%)	2/2 (100%)	2/18 (11%)	2/18 (11%)	-	-	0.444
Mushroom sign	2/18 (11%)	2/18 (11%)	2/2 (100%)	2/2 (100%)	2/2 (100%)	2/2 (100%)	2/18 (11%)	2/18 (11%)	-	-	-0.111
Small bowel behind SMA sign	0/18 (0%)	2/18 (11%)	2/2 (100%)	2/2 (100%)	0/0 (-)	2/2 (100%)	2/20 (10%)	2/18 (11%)	-	-	0.000
Criss-cross	0/18 (0%)	1/18 (6%)	2/2 (100%)	1/2 (50%)	0/0 (-)	1/2 (50%)	2/20 (10%)	1/18 (6%)	-	0.06	0.000
Model 1 (Swirl-sign + SBO-sign)	2/18 (11%)	4/18 (22%)	2/2 (100%)	2/2 (100%)	2/2 (100%)	4/4 (100%)	2/18 (11%)	2/16 (13%)	-	-	
Model 2 (SMV beaking + SBO-sign)	0/18 (0%)	3/18 (17%)	2/2 (100%)	2/2 (100%)	0/0 (-)	3/3 (100%)	2/20 (10%)	2/17 (12%)	-	-	

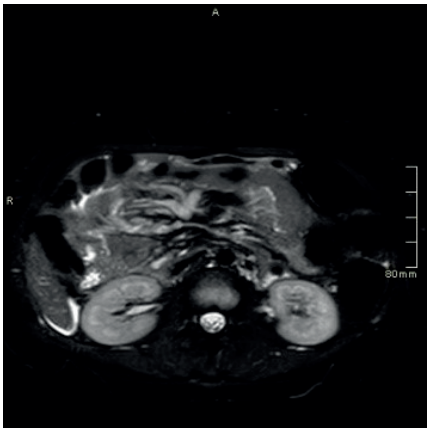
PPV = positive predictive value, NPV = negative predictive value, κ = Kappa, SMV = superior mesenteric vein, SMA = superior mesenteric artery, SBO = small bowel obstruction. Confidence intervals of all results are mentioned in Appendix 1.



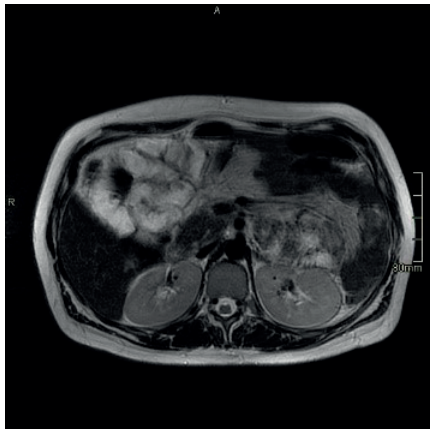
A = Swirl sign



B = Dilated gastric remnant



C = Engorged lymph nodes



D = Clustered loop sign

Figure 3 – MRI images of four IH-signs

Adverse events

No adverse events by performing the index test did occur. Regarding the reference standard, one patient was admitted to the intensive care due to a pneumonia and intra-abdominal abscesses, preterm contractions started in two patients postoperatively (successfully treated with tocolytics) and two patients developed a superficial wound infection.

DISCUSSION

This retrospective study investigated the diagnostic accuracy and clinical value of MRI for SBO in pregnant women with a history of a RYGB and whether systematic reassessment improves diagnostic accuracy. Diagnosis of SBO with MRI shows an overall acceptable diagnostic accuracy however with a considerable interobserver variability and therefore a restrictive use of MRI in this settings seems warranted. Systematic assessment of MRI with focus on swirl-sign, SBO-sign and clustered-loop-sign, is advised, as presence of one of these IH-signs increases the likelihood of presence of SBO.

MRI is increasingly used as diagnostic instrument for the diagnosis of SBO in pregnant women. Several studies concluded that MRI is a good imaging technique for various abdominal and pelvic disease processes in pregnant and non-pregnant patients with acute abdominal pain[19-23]. One study, regarding the diagnostic accuracy of MRI for detecting IH during pregnancy, concluded that MRI might be a reasonable and safe alternative to CT[24]. In the current study, 50.0% of the women suspected for SBO underwent an MRI-scan. Reasons for not performing MRI were among others a mild clinical presentation with improvement of symptoms with conservative treatment, immediate transport to the surgical theatre due to high clinical suspicion and presentation at night with no lab technician directly available for MRI. Of the MRI-scans performed, 24 (88.9%) were of good quality. No adverse events of the index test were observed. Therefore, MRI is a safe and feasible alternative for CT in pregnant women in an acute setting.

The diagnostic accuracy of MRI for detecting SBO during pregnancy after RYGB is not well studied. Only one study has been published regarding this subject which reported that MRI has a comparable specificity (86-100%) to CT and a lower sensitivity (75-88%)[24]. The current study shows lower numbers with a sensitivity and specificity of 66.7% and a NPV of only 22.2%. PPV was 93.3%. Fifteen out of 27 (55.6%) MRI-scans were performed at our tertiairy referral centre and assessed by our radiologists, who may be more experienced in assessing these MRI-scans. But despite this possible learning curve, the diagnostic accuracy is evident lower than previously described. So, MRI may be less reliable than previously stated.

Systematic assessment of the MRI-scans might improve the diagnostics accuracy. The systematic approach of the IH-signs used for the diagnosis of IH in CT could also be valuable for MRI[24]. Surprisingly, the current study shows even lower numbers regarding the diagnostic value after systematic re-assessment. These lower numbers might be due to the lower number of included MRI-scans in part 2 compared to part 1. Another factor that might have played a role is that the radiologists were not allowed access to the original report, clinical information and previous imaging tests. Looking at the individual

IH-signs and the combination models, overall high specificity and PPV is seen. However, the CIs are extremely wide (**Appendix 1**). A prospective research with larger numbers of MRI-scans is required to determine whether the diagnostic accuracy of the MRI can be comparable to the CT. For now, diagnostic laparoscopy remains the gold standard.

The combination of clinical parameters with MRI should lead to a risk-model for the treatment of acute abdominal pain in pregnant women after bariatric surgery. Literature has not provided any risk model, but it is expressed by many that the diagnosis of this acute abdominal pain is very difficult as symptoms are often similar to general pregnancy symptoms[26-28]. In addition, the diagnostic value of MRI for SBO during pregnancy is not well known. Based on our data, in a moderate-to-high risk group, no conclusion can be made regarding a diagnosis-treatment model as MRI was not combined with the clinical suspicion. Therefore, research that combines MRI with clinical parameters should be performed, ideally in a prospective design, so that a treatment algorithm for these difficult to diagnose patients can be achieved.

It is not known whether it is acceptable and safe to perform diagnostic imaging and thus delay surgery. Vennevel et al. reported that surgery should be performed <48 hours to prevent serious harm to mother and child[29]. In a previously published study of our centre, we demonstrated that this timeframe is not evident and that in individual cases delaying surgery might be the preferred option[9]. In the current study, only one case of maternal morbidity was seen and no mortality. However, MRI could not detect SBO in almost 1 out of 3 (29.2%) patients. Moreover, due to the high variety in the interobserver agreement, results are dependent on the assessor. Based on the data from the current study, a strong advice cannot be provided when to perform MRI, but in case of a mild clinical presentation it seems safe to perform diagnostic imaging. **Figure 4** shows the clinical-diagnostic-treatment plan that is currently used in our centre.

The first limitation of this study is the small sample size. The total number and also the number of patients who did not have SBO are too small to demonstrate a significant difference in diagnostic accuracy between systematic re-evaluation and the original reports and they lead to wide CIs. Furthermore, selection bias is present as only half of the patients received MRI and because of the exclusion of the women who were treated conservatively. This leads to a cohort in which the incidence of SBO is much higher than in the normal population. On top of this, the retrospective nature of the study without a control or comparison group is a risk for selection and information bias.

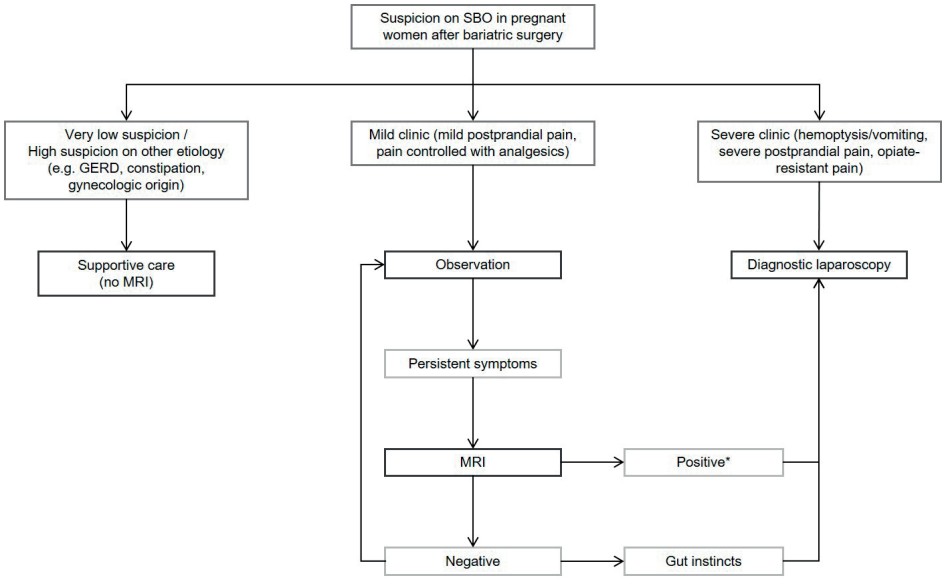


Figure 4 – Flow chart of clinic-diagnostics-treatment plan
SBO = small bowel obstruction, GERD = gastroesophageal reflux disease, MRI = magnetic resonance imaging, *MRI is scored positive if the overall conclusion of the radiologist is suspected for SBO or if at least one of the following IH-signs is present: swirl-sign, SBO-sign and cluster loop sign.

CONCLUSION

MRI is a safe and feasible alternative for CT for the diagnosis of SBO during pregnancy after bariatric surgery. However, the diagnostic accuracy is only 'acceptable' and the interobserver variability relatively high. Moreover, MRI is unable to detect SBO in almost 1 out of 3 (29.2%) patients. Therefore, we would cautiously advise to not perform an MRI-scan in pregnant women with a high clinical suspicion on SBO or hemodynamically unstable pregnant women, as the diagnostic laparoscopy remains the gold standard. In women who are hemodynamically stable with a mild to moderate clinical suspicion we would advise to perform an MRI-scan, because with a positive MRI-scan the chance on SBO is high (high PPV). Furthermore, we would advise to assess the MRI-scan systematically on the presence of especially swirl-sign, SBO-sign and clustered-loop-sign, as presence of one of these IH-signs adds to the suspicion of SBO. Additional prospective research, ideally with a combination of MRI and clinical parameters to develop a diagnostic-therapeutic algorithm, should be performed to improve the diagnostic-therapeutic plan and therewith reduce unnecessary maternal and foetal risks.

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APPENDIX 1

Table 3 – Statistics of individual MRI-signs with confidence intervals

Sign	Sensitivity (percentage)		Specificity (percentage)		PPV		NPV		Diagnostic odds ratio		Interobserver agreement (κ)
	Observer 1	Observer 2	Observer 1	Observer 2	Observer 1	Observer 2	Observer 1	Observer 2	Observer 1	Observer 2	
Overall conclusion	10/18 (56%) (CI 0.31-0.78)	10/18 (56%) (CI 0.31-0.78)	1/2 (50%) (CI 0.03-0.97)	2/2 (100%) (CI 0.20-1.00)	10/11 (91%) (CI 0.58-1.00)	10/10 (100%) (CI 0.66-1.00)	1/9 (11%) (CI 0.05-0.49)	2/10 (20%) (CI 0.04-0.56)	1.25	-	0.700
Small bowel obstruction sign	5/18 (28%) (CI 0.11-0.55)	9/18 (50%) (CI 0.28-0.73)	1/2 (50%) (CI 0.03-0.97)	2/2 (100%) (CI 0.20-1.00)	5/6 (83%) (CI 0.36-0.99)	9/9 (100%) (CI 0.63-1.00)	1/14 (7%) (CI 0.07-0.36)	2/11 (18%) (CI 0.03-0.52)	0.38	-	0.479
Swirl-sign	6/18 (33%) (CI 0.14-0.59)	6/18 (33%) (CI 0.14-0.59)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	6/6 (100%) (CI 0.52-1.00)	6/6 (100%) (CI 0.52-1.00)	2/14 (14%) (CI 0.03-0.44)	2/14 (14%) (CI 0.03-0.44)	-	-	0.762
Clustered loops sign	6/18 (33%) (CI 0.14-0.59)	5/18 (28%) (CI 0.11-0.55)	0/2 (0%) (CI 0.00-0.80)	1/2 (50%) (CI 0.03-0.97)	6/8 (75%) (CI 0.36-0.96)	5/6 (83%) (CI 0.36-0.99)	0/12 (0%) (CI 0.00-0.30)	1/14 (7%) (CI 0.07-0.36)	-	0.38	0.135
SMV beaking (strangulation)	1/18 (6%) (CI 0.00-0.29)	5/18 (28%) (CI 0.11-0.54)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	1/1 (100%) (CI 0.05-1.00)	5/5 (100%) (CI 0.46-1.00)	2/19 (11%) (CI 0.02-0.35)	12/15 (13%) (CI 0.02-0.42)	-	-	0.273
Ascites	1/18 (6%) (CI 0.00-0.29)	4/18 (22%) (CI 0.07-0.48)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	1/1 (100%) (CI 0.05-1.00)	4/4 (100%) (CI 0.40-1.00)	2/19 (11%) (CI 0.02-0.35)	2/16 (13%) (CI 0.02-0.40)	-	-	0.348
Hurricane eye sign	2/18 (11%) (CI 0.02-0.36)	4/18 (22%) (CI 0.07-0.48)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	4/4 (100%) (CI 0.40-1.00)	2/18 (11%) (CI 0.02-0.36)	2/16 (13%) (CI 0.02-0.40)	-	-	-0.154
Dilated remnant stomach / biliopancreatic limb	1/18 (6%) (CI 0.00-0.29)	3/18 (17%) (CI 0.04-0.42)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	1/1 (100%) (CI 0.05-1.00)	3/3 (100%) (CI 0.31-1.00)	2/18 (11%) (CI 0.02-0.35)	2/17 (12%) (CI 0.02-0.38)	-	-	0.459
Engorged lymph nodes	2/18 (11%) (CI 0.02-0.36)	2/18 (11%) (CI 0.02-0.36)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	2/18 (11%) (CI 0.02-0.36)	2/18 (11%) (CI 0.02-0.36)	-	-	0.444
Mushroom sign	2/18 (11%) (CI 0.02-0.36)	2/18 (11%) (CI 0.02-0.36)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	2/18 (11%) (CI 0.02-0.36)	2/18 (11%) (CI 0.02-0.36)	-	-	-0.111
Small bowel behind SMA sign	0/18 (0%) (CI 0.00-0.22)	2/18 (11%) (CI 0.02-0.36)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	0/0 (-)	2/2 (100%) (CI 0.20-1.00)	2/20 (10%) (CI 0.02-0.33)	2/18 (11%) (CI 0.02-0.36)	-	-	0.000

Table 3 – Statistics of individual MRI-signs with confidence intervals (*continued*)

Sign	Sensitivity (percentage)		Specificity (percentage)		PPV		NPV		Diagnostic odds ratio		Interobserver agreement (κ)
	Observer 1	Observer 2	Observer 1	Observer 2	Observer 1	Observer 2	Observer 1	Observer 2	Observer 1	Observer 2	
Criss-cross	0/18 (0%) (CI 0.00-0.22)	1/18 (6%) (CI 0.00-0.29)	2/2 (100%) (CI 0.20-1.00)	1/2 (50%) (CI 0.03-0.97)	0/0 (-)	1/2 (50%) (CI 0.03-0.97)	2/20 (10%) (CI 0.02-0.33)	1/18 (6%) (CI 0.00-0.29)	-	0.06	0.000
Model 1 (Swirl-sign + SBO)	2/18 (11%) (CI 0.02-0.36)	4/18 (22%) (CI 0.07-0.48)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	4/4 (100%) (CI 0.40-1.00)	12/18 (11%) (CI 0.02-0.36)	2/16 (13%) (CI 0.02-0.40)	-	-	
Model 2 (SMV beaking + SBO)	0/18 (0%) (CI 0.00-0.22)	3/18 (17%) (CI 0.04-0.42)	2/2 (100%) (CI 0.20-1.00)	2/2 (100%) (CI 0.20-1.00)	0/0 (-)	3/3 (100%) (CI 0.31-1.00)	2/20 (10%) (CI 0.02-0.33)	2/17 (12%) (CI 0.02-0.38)	-	-	

PPV = positive predictive value, NPV = negative predictive value, κ = Kappa, SMV = superior mesenteric vein, SMA = superior mesenteric artery, SBO = small bowel obstruction.

8

The Acute Abdomen in Pregnant Women After Roux-en-Y Gastric Bypass: Encouraging Results from a National Referral Centre

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ABSTRACT

Background

Pregnant women with a history of bariatric surgery may develop acute abdominal pain related to this surgery, especially after Roux-en-Y gastric bypass. Studies showed alarming results regarding maternal and foetal morbidity and mortality. The aim of this study was to analyse these outcomes for pregnant women and their offspring.

Methods

Single-centre retrospective cohort study in a tertiary referral centre for bariatric complications during pregnancy. Pregnant women with a history of bariatric surgery referred between September 2015 and November 2019 with acute abdominal pain suspected for a bariatric complication were included. Data were retrospectively collected from the patient files, and a questionnaire was sent regarding the postoperative course and childbirth.

Results

Fifty women were included. At presentation, mean maternal age was 31 ±4 years, and median gestational age was 28^{+4} (25^{+4}, 30^{+5}) weeks. Thirteen women were treated conservatively. Thirty-seven women underwent surgery for, among others, internal herniation (n=26) and intussusception (n=6). Six women required small bowel resection. Two women underwent an emergency caesarean section shortly after the surgery due to foetal distress. Eight women delivered preterm of whom five infants required respiratory support. There was one intrauterine foetal death. Surgery >48 h after the onset of the symptoms was not associated with an increase in small bowel resections or preterm birth.

Conclusion

Acute abdominal pain in pregnant women may be related to a bariatric complication. Further awareness of bariatric complications within the obstetric care and transferal to specialized care to prevent diagnostic delay may improve maternal and neonatal outcome.

INTRODUCTION

As bariatric surgery is the most effective treatment for morbid obesity in the short and long-term, an increasing number of women of childbearing age receive BS[1-2]. A side effect of this trend is the growing number of pregnant women with a history of BS.

The positive effects for pregnancy outcomes after bariatric surgery are well described, including improved fertility[3-4] and reduced risk of gestational diabetes[3-9], hypertensive disorders[4-6], caesarean delivery[6] and macrosomia[3-9]. However, several negative effects on pregnancy outcomes after bariatric surgery have been described[3-6,10-11]. There is an increased risk of foetal growth restriction[3-4,8-9] and premature birth[3,9]. Pregnancy after bariatric surgery should therefore be considered a high-risk pregnancy.

Abdominal pain after bariatric surgery is a common problem, which results in 30% of the patients consulting an emergency department within the first years after BS[12-13]. The spectrum of diagnoses ranges from biliary colic, gastric ulcer disease to small bowel obstruction (SBO)[12]. Internal herniation (IH) and intussusception can lead to acute SBO which is sometimes accompanied by strangulation of the small bowel and may require surgical intervention[14-15].

Abdominal bariatric complications can appear during pregnancy and can cause serious maternal and foetal problems[16-23]. A Danish register-based cohort study of women who gave birth after Roux-en-Y gastric bypass (RYGB) reported that 9/286 (3.1%) women underwent a surgical procedure during pregnancy that was possibly related to the RYGB. One woman died from complete bowel necrosis[17]. Furthermore, Vannevel et al. showed two maternal (3.8%) and three perinatal (5.8%) deaths in a review of 52 cases of IH requiring surgical intervention during pregnancy. All deaths occurred in patients who had surgery more than 48 h after the onset of symptoms[18]. Because of these serious complications, a recent published consensus recommendation stated that pregnant women after bariatric surgery who present with acute abdominal pain should be assumed to have SBO due to IH until proven otherwise[24]. In addition, several authors reported that pregnant women with abdominal complaints after bariatric surgery should be urgently assessed by a surgeon with bariatric expertise and treated by multidisciplinary teams with experience and expertise in the management of bariatric complications during pregnancy[5,19,25].

The Netherlands (eighteen million inhabitants, approximately 170.000 births a year) has approximately 90 hospitals. Only one hospital has a combination of bariatric surgery with tertiary pregnancy care (obstetrical high care and neonatal intensive care (level III neonatal intensive care unit (NICU)). The multidisciplinary team in our hospital consists of bariatric surgeons, obstetricians (perinatologists) and neonatologists (BON) and has a nationwide referral function.

The aim of this study was to analyse the maternal and foetal outcome and the diagnostic and treatment trajectory in pregnant women with a (possible) abdominal bariatric complication referred to a tertiary care centre.

METHODS

Study design and population

A single-centre retrospective cohort study of a tertiary referral centre for bariatric, obstetric and neonatal care. Pregnant women, with a history of BS, admitted between September 2015 and November 2019 with acute abdominal pain suspected for a bariatric complication were included.

Approval of the medical ethical committee was requested, but no further review was necessary as this study included retrospective observational data.

Data collection

Data regarding the abdominal symptoms (e.g. onset – timeframe bariatric surgery and symptoms – presentation), maternal characteristics (e.g. type bariatric surgery – gestational age (GA) – body mass index (BMI)), laboratory and imaging findings, surgery (e.g. intervention – diagnosis – complications), childbirth (e.g. GA – mode of delivery) and maternal and neonatal outcome were retrospectively collected from the electronic patient files.

In addition, all women were contacted to fill out a questionnaire regarding the postoperative course and childbirth (**Appendix 1**).

Neonatal morbidity was defined as prematurity (GA <37 weeks). Short-term neonatal comorbidity was defined as the occurrence of wet lung or respiratory distress syndrome (RDS). Severe long-term neonatal comorbidity included intraventricular haemorrhage, periventricular leukomalacia, necrotizing enterocolitis (NEC), sepsis, bronchopulmonary dysplasia and retinopathy. Perinatal asphyxia was defined as pH umbilical cord <7.00 and 5-minute Apgar score <7.

Statistics

Continuous variables are presented as mean ±standard deviation (SD) or as median (Q1, Q3) if the normality assumption was not met. Categorical variables are stated as number (percentage). Differences in categorical variables were compared using Fisher's exact test with IBM SPSS statistic software, version 24.0. $P<0.05$ was considered statistically significant.

RESULTS

We identified fifty pregnant women of whom 38 (76.0%) were referred to our centre after being hospitalized elsewhere. An increase in pregnant women was seen during the study period, ranging from one woman in 2015 to nineteen in 2019. The baseline characteristics are presented in **Table 1**.

Table 1 – Baseline characteristics

Year of visit – Number (%) – (n=50)	
2015	1 (2)
2016	6 (12)
2017	6 (12)
2018	18 (36)
2019	19 (38)
Maternal age – Years – Mean (±SD) – (n=50)	31 (±4)
Pre-pregnancy BMI – kg/m^2 – Median (Q1, Q3) – (n=46)	27.1 (24.5, 29.0)
BMI at presentation* – kg/m^2 – Median (Q1, Q3) – (n=45)	29.1 (27.2, 31.1)
GA at presentation* – $Weeks^{+days}$ – Median (Q1, Q3) – (n=50)	28^{+4} (25^{+4}, 30^{+5})
Trimester of pregnancy at presentation* – Number (%) – (n=50)	
First trimester	1 (2)
Second trimester	16 (32)
Third trimester	33 (66)
Parity – Number (%) – (n=50)	
Nulliparous	16 (32)
Multiparous	34 (68)
Singleton pregnancy / Twin pregnancy – Number (%) – (n=50)	
Singleton pregnancy	48 (96)
Twin pregnancy	2 (4)
Type of bariatric procedure – Number (%) – (n=50)	
Primary RYGB	45 (90)
Primary banded RYGB	1 (2)
Revisional RYGB after gastric banding	4 (8)
Timeframe (banded) RYGB and onset symptoms – Years – Mean (±SD) – (n=50)	3.5 (±1.9), range: 5 months – 8 years

SD = standard deviation, Q1 = first quartile – equal to the 25th percentile of the data, Q3 = third quartile – equal to the 75th percentile of the data, BMI = body mass index, GA = gestational age, RYGB = Roux-en-Y gastric bypass, * = Presentation at our centre.

Presentation

All pregnant women presented with abdominal pain. Nausea was reported by 34 (68.0%) women of whom 23 (46.0%) also reported vomiting. Increase of the abdominal pain after intake was noted in 22 (44.0%) women. The median time between the onset of symptoms and admission to our centre was 1 (0, 4) day (range: 0–35 days). The timeframe between the bariatric surgery and the onset of symptoms was 3.5 ±1.9 years (range: 5 months–8 years). The woman who had symptoms five months after her bariatric surgery was already five weeks pregnant (unaware) at the time of the BS.

Diagnostics

Laboratory analysis was performed in 45 women (90.0%). The relevant abnormalities are shown in **Table 2**. Two women had as incidental finding a cystitis.

Gastroscopy (n=1), abdominal radiography (n=4), abdominal ultrasound (n=19), abdominal computed tomography scan (CT-scan) (n=2) and abdominal magnetic resonance imaging scan (MRI-scan) (n=24) were used as diagnostics (**Table 3**). Ten women with a suspected IH on the MRI-scan had an IH during surgery, and the suspected intussusception was an intussusception.

Table 2 – Abnormalities in the laboratory analysis

Anaemia – haemoglobin count <6.5 mmol/L	n=11
Leucocytosis – leucocytes count >12 x 10^9/L)	n=13
Elevated CRP – CRP >30 mg/L	n=2
Elevated lactate – Venous – Lactate >2.2 mmol/L	n=1
Low potassium – potassium < 3.5 mmol/L	n=5
Partial haemolytic liver enzymes	n=1

CRP = C - reactive protein

Conservative treatment

Thirteen women (26.0%) were treated conservatively. Four women had a clinical presentation of IH, but symptoms were mild and the oral intake could be normalised during hospitalisation. Diagnoses in the other nine women were gastroenteritis (n=2) and abdominal pain of unknown aetiology (n=7).

One woman was readmitted after discharge with abdominal pain of unknown aetiology, and treated conservatively.

Table 3 – Diagnostic interventions with outcome

Gastroscopy – Number (%) – (n=1)	
Finding possible related to abdominal pain	0 (0)
No findings possible related to abdominal pain	1 (100)
Ultrasound – Number (%) – (n=19)	
Finding possible related to abdominal pain	2 (11)
Intussusception/close loop obstruction (n=1)	
Internal herniation (n=1)	
No findings possible related to abdominal pain	17 (89)
CT-scan – Number (%) – (n=2)	
Finding possible related to abdominal pain	1 (50%)
Internal herniation (n=1)	
No findings possible related to abdominal pain	1 (50%)
MRI-scan – Number (%) – (n=24)	
Finding possible related to abdominal pain	14 (58)
Internal herniation (n=13)	
Intussusception (n=1)	
No findings possible related to abdominal pain	10 (42)

CT-scan = computed tomography scan, MRI-scan = Magnetic Resonance Imaging scan

Surgical treatment

Thirty-seven women (74.0%) underwent surgery (**Figure 1**). Median GA at surgery was 28^{+6} (26^{+5}, 30^{+5}) weeks (range: 12^{+3}–35^{+0} weeks). Glucocorticoids for foetal maturation were administered to all women before surgery, except one, due to a GA of 12^{+3} weeks.

Thirty-six women were treated by bariatric surgeons, and one woman was treated by an obstetrician. The women treated by the obstetrician received an acute caesarean section (C-section) due to suspicion of IH (MRI-scan) in combination with a GA of 34^{+6} weeks. Preoperatively, the cardiotocography (CTG) showed no abnormalities. Perioperative, no inspection of the RYGB was performed as this was difficult due to the large uterus. Postpartum, the woman did not experience abdominal pain, nor signs of SBO were present and she was treated conservatively.

Median operative time (by bariatric surgeons) was 52 (42, 82) minutes (range: 29–261 minutes). Twenty-seven women were treated laparoscopically, and nine women required conversion to laparotomy (**Figure 1**). In women without an active IH but open mesenteric defects (n=3), closure of the defect(s) was performed and their complaints diminished postoperatively. In six women (23.1%) with an IH, the mesenteric defects were closed before.

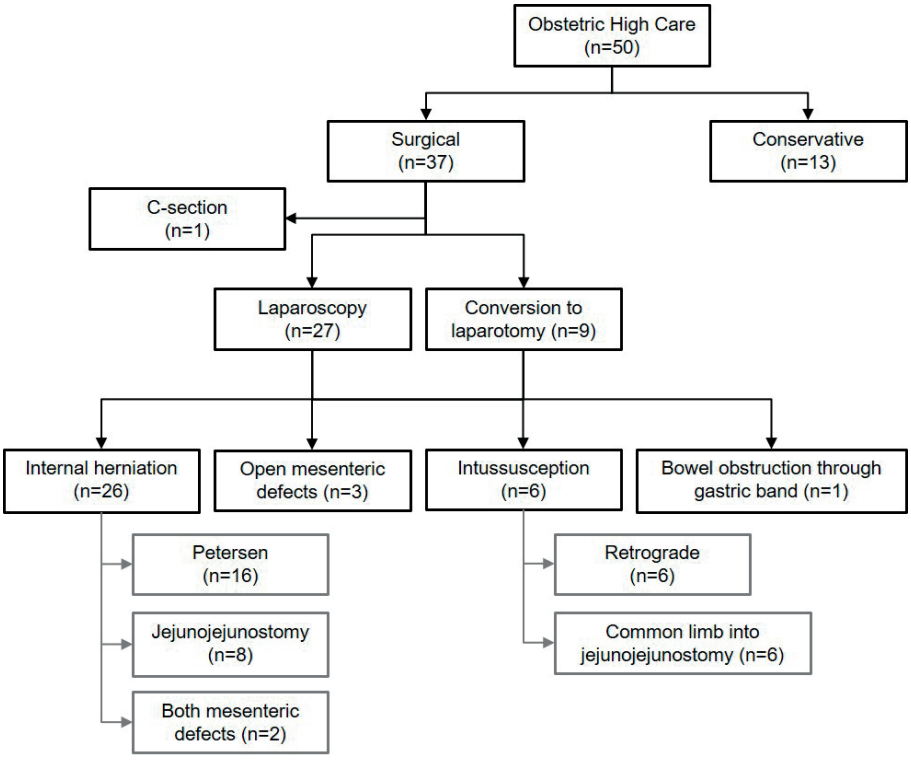

Figure 1 – Flow chart treatment and diagnosis

Regarding the intussusceptions, one was reduced manually and in five women resection was performed with revision of the jejuno-jejunal anastomosis. Six women (16.7%) required small bowel resection due to critical ischemia, five women with an intussusception and one woman with an IH. The GA of these women ranged from 25^{+6} to 32^{+0} weeks and all were treated by laparotomy.

Time between admission to our centre and surgery (n=37)

Twenty-one women (56.8%) underwent surgery <24 h of admission to our centre and one woman (2.7%) <48 h. Fifteen women were operated >48 h after admission. In eleven women (29.7%), the surgery was intentionally delayed to enable completion of the glucocorticoids (48 h) for foetal maturation. Delay of surgery for more than one week was decided in four women (10.8%). The GA of these women at admission was between 23^{+5} and 24^{+4} weeks. They were bridged to a GA >25 weeks (n=1) and >26 weeks (n=3) to avoid the risk of extremely premature birth at the border of neonatal treatment (in the Netherlands, preterm infants receive treatment from 24 weeks onwards). One woman received total parental feeding and three women nasogastric tube feeding. In all four women, the abdominal pain was absent during the bridging period.

Postoperative course during hospital stay (n=37)

Median hospital stay was 3 (2, 5) days (excluding the bridged women). Three women were admitted to the intensive care unit (ICU) postoperatively. One woman was suspected of an aspiration pneumonia, for which she received antibiotics. The second woman had a small bowel resection of >1m due to critical ischemia caused by an IH. An emergency C-section was performed in the same surgical session due to foetal distress at a GA of 30^{+5} weeks. She was scheduled to restore continuity of the small bowel, without complications. The third woman was admitted to the ICU after open correction of an intussusception, as her course was complicated by a pneumonia and small intra-abdominal abscesses for which she received antibiotics. An emergency C-section due to foetal distress was performed several hours after the surgery at 32^{+1} weeks' gestation.

Preterm contractions started in three women postoperatively. The CTG showed foetal decelerations in one woman. All were administered tocolytics to suppress premature contractions, with success.

Postoperative course after discharge (n=37)

Nine women (24.3%) were readmitted after discharge. Four women were readmitted due to abdominal pain diagnosed as constipation (n=1) and abdominal pain of unknown aetiology (n=3), treated conservatively. One woman was readmitted due to dehydration. The woman with the small intra-abdominal abscesses was readmitted with persistent abdominal pain, for which the antibiotics were restarted. One woman developed an acute appendicitis, treated surgically by 33-week gestation (elsewhere), and one woman experienced biliary colic treated with a laparoscopic cholecystectomy several weeks after childbirth. Finally, one woman (IH at 24^{+4} weeks) was readmitted twice, due to the suspicion of a recurrent IH. During the first readmission, GA of 27^{+0} weeks, laparoscopy was performed showing indeed an IH at Petersen's space, despite previous closure. During the second readmission, GA of 30^{+4} weeks, laparoscopy was performed, without abnormalities.

Pregnancy, maternal and foetal outcome

Data regarding maternal and perinatal outcome are available for 45 women (**Table 4**). Three women delivered during the hospital admission after surgical intervention (8.1%), all preterm and iatrogenic. In two of these women an emergency C-section due to foetal condition was performed within several hours of the surgery.

Data regarding the outcomes of the premature infants are presented in **Table 5**. Nine infants were born alive premature, of whom four were admitted to the NICU. Three infants were born below 32-week gestation and developed RDS. One infant was born at 32^{+1}

Table 4 – Pregnancy and neonatal outcome

GA at childbirth – Weeks^{+days} – Median (Q1, Q3) – (n=45)	39^{+0} (37^{+5}, 40^{+0})
Timing of childbirth – Number (%) – (n=45)	
Preterm	8 (18)
Full-term	37 (82)
Timeframe onset symptoms and childbirth – Weeks^{+days} – Median (Q1, Q3)) – (n=45)	$10+^{2}$ (8^{+1}, 13^{+0})
Timing of childbirth after surgical intervention (n=37) – Number (%) – (n=37)	
Preterm	7 (19)
Full-term	26 (70)
Not available	4 (11)
Timeframe surgery (n=37) and childbirth – Weeks^{+days} – Median (Q1, Q3) – (n=31)	9^{+4} (8^{+1}, 12^{+4}) (range: 0 days – 27^{+5} weeks)
Mode of childbirth – Number (%) – (n=45)	
Vaginal – Spontaneous*	33 (73)
C-section – Elective	7 (16)
C-section – Emergency	5 (11)
Maternal mortality – Number (%) – (n=50)	0 (0)
Birthweight – Grams – Median (Q1, Q3) – (n=46)	3066 (2429, 3315) (range: 1100 – 4085 grams)
Admission to NICU – Number (%) – (n=47)	4 (8.5)
Foetal/neonatal mortality – Number (%) – (n=47)	1 (2)

GA = gestational age, Q1 = first quartile – equal to the 25th percentile of the data, Q3 = third quartile – equal to the 75th percentile of the data, SD = standard deviation, C-section – caesarean section, NICU = neonatal intensive care unit, *= one woman delivered her first child vaginal spontaneously and her second child was born by breech extraction.

weeks and required endotracheal intubation and ventilation and surfactant for RDS. All infants survived. One of the infants developed NEC, which was treated conservatively. None of the infants experienced perinatal asphyxia.

One intra-uterine foetal death occurred at 35^{+1} weeks' gestation, seventeen weeks after conservative treatment. No cause was found for the foetal death.

Adverse outcomes in relation to timing of the treatment

Surgery >48 h after admission (<48h=4/22 (18.2%) versus >48h=3/15 (20.0%), p=1.000) and surgery >48 h after onset of the symptoms (<48h=2/15 (13.3%) versus >48h=5/22 (22.7%), p=0.677) were not associated with an increase in preterm birth. All women who required small bowel resection were treated <48 h after admission and after onset of the symptoms. Of the women who experienced serious complications, all were treated more than 48 h after admission, except for the woman with the acute appendicitis.

Table 5 – Neonatal morbidity

Case	Singleton or twin	GA at surgery (weeks^{+days})	GA at birth (weeks^{+days})	Mode of childbirth	Time surgery – childbirth (days)	NICU	Antenatal glucocorticoids	Short-term comorbidity	Severe long-term comorbidity	Birth weight (gram (percentile))	Apgar scores*	pH umbilical cord
Surgical treatment												
1	Twin	25^{+0}	28^{+5}	Vaginal	26	+	19 days before birth	CPAP for RDS	-	1100 (p16)	4/7/9	7.32 (BE -8)
2	Twin	25^{+0}	28^{+5}	Vaginal	26	+	19 days before birth	CPAP for RDS	NEC	1170 (p30)	6/9/10	7.28 (BE -8)
3	Singleton	30^{+5}	30^{+5}	C-section	0	+	<24 hours before birth	Endotracheal intubations and ventilation for RDS	-	1630 (p50)	1/4/4	7.19 (BE -7)
4	Singleton	32^{+0}	32^{+1}	C-section	1	+	<24 hours before birth	Endotracheal intubations and ventilation for RDS	-	2180 (p90-95)	1/5/8	7.07 (BE -12)
5	Singleton	25^{+6}	34^{+0}	Vaginal	57	-		-	-	2500 (NA)	NA	NA
6	Twin	25^{+5}	34^{+5}	Vaginal	63	-	48 hours before birth	-	-	1730 (NA)	NA	NA
7	Twin	25^{+5}	34^{+5}	Vaginal	63	-	48 hours before birth	-	-	2270 (NA)	NA	NA
8	Singleton	35^{0}	35^{+0}	C-section	0	-	<24 hours before birth	-	-	2790 (p50-p90)	9/9/9	7.28 (BE-7)
9	Singleton	24^{+4}	35^{+2}	C-section (elective)	75	-	<24 hours before birth	Short duration CPAP for wet lung	-	2294 (NA)	NA	NA
Conservative treatment												
1	Singleton	- **	35^{+4}	Vaginal	-**	-	-	-	-	2770 (NA)	-	-

GA = gestational age, NICU = neonatal intensive care unit, *0/5/10 minutes, C-section = caesarean section, BE = Base Excess, CPAP = Continuous Positive Airway Pressure, NEC = Necrotizing Enterocolitis, NA = Not Available, **Treated conservatively

DISCUSSION

Pregnancy following bariatric surgery is a high-risk pregnancy with possible consequences for the mother and (unborn) child. Maternal and perinatal mortality due to bariatric complications requiring surgical intervention during pregnancy has been reported[17-20,23]. Furthermore, Vannevel et al. reported that 17.3% of the women required bowel resection and that 44.2% delivered during hospital admission after surgery[18]. Petersen et al. reported that 26.7% of the women delivered preterm after diagnostic laparoscopy or laparotomy[22]. In our study, of the 37 women who were treated surgically, six (16.2%) required small bowel resection, three (8.1%) delivered during the admission at our hospital and seven (18.9%) delivered preterm. Neonatal morbidity was seen in ten infants (21.3%). One infant had a severe neonatal complication. No maternal or perinatal mortality was seen after surgery. We had one case of intrauterine foetal death of unknown cause, seventeen weeks after conservative treatment. The treatment of pregnant women suspected of an abdominal bariatric complication in a tertiary care referral centre results in improved maternal and foetal outcome. These women should be treated in a NICU-centre as five infants required respiratory support, of whom two infants were even born after 32-week gestation (**Table 5**). In addition, several studies concluded that premature infants (<32 weeks of GA) born at a NICU-centre have better prognosis compared to infants not born at a NICU-centre[26-27].

IH is the most frequently described acute bariatric complication during pregnancy. Several authors have stated the theory that pregnant women have an increased risk of IH due to small bowel displacement by the growing uterus, especially in the third trimester[18,21]. In this study, the majority was seen at the end of the second/beginning of the third trimester. Moreover, next to IH also intussusception (n=6) and SBO through the gastric band (n=1) were seen. So, abdominal bariatric complications occur mostly at the transition of the second to the third trimester of pregnancy and besides IH, intussusception and also gastric band related problems should be considered.

Diagnosis of abdominal bariatric complications during pregnancy is difficult. Many symptoms of SBO are often also encountered during pregnancy and physical and radiologic examinations are unreliable due to displacement of the small bowel[20,28-29]. The clinical presentation in this study was often comparable to general pregnancy symptoms and the diagnostic value of MRI is not clear[22]. There is a need for additional research to improve the diagnostic process of acute abdominal pain in pregnant women after BS.

Surgical intervention within a 48h cut-off point is not always necessary. Vannevel et al. concluded that surgical treatment should proceed as soon as possible to prevent adverse maternal and foetal outcome, as surgery >48 h after the onset of symptoms was

associated with worse outcomes[18]. In our study, this cut-off point was not related to an increase in small bowel resections or preterm birth. In four patients, the surgical intervention was delayed to reduce foetal risk due to an extremely premature GA. Three of them gave birth at term without maternal or neonatal complications. The fourth woman (twin pregnancy), delivered spontaneously preterm at 28^{+5} weeks, almost four weeks after the surgical intervention. Timing of surgical intervention should be individualised keeping both maternal and foetal risk in mind.

A limitation of this study is the retrospective approach and therefore the risk of selection and information bias. Another limitation associated with this approach is the missing data, especially regarding pregnancy outcome, which is largely due to the loss-to-follow-up after the transfer of patients back to the referring centre.

This single-centre cohort study regarding abdominal pain possibly related to a bariatric complication in pregnant women after bariatric surgery shows encouraging results from a national BON-referral centre. Pregnancy following BS, especially after RYGB, should be considered a high-risk pregnancy. Further awareness of bariatric complications within the obstetric care to prevent delay in diagnosis and transferal to specialized care is advised to improve maternal and neonatal outcome.

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APPENDIX 1

QUESTIONNAIRE: Bariatric complication during pregnancy

(1) What was your pre-pregnancy weight?

(2) How long (hours) did the acute abdominal pain exist before you were admitted to the emergency department of Maxima Medical Centre?

(3) What was you gestational age when you were admitted to the emergency department of Maxima Medical Centre?

(4) Could you tell us, as precise as possible, how your abdominal pain started, where the pain was located and if there was anything that could reduce or worsen the pain?

(5) Was the pain absent after you were discharged from the hospital? Yes / No* (*strike out whichever option does not apply to you). In case No applies to you, could you describe the pain?

(6) Did any problems occur during the pregnancy or the childbirth after discharge from the hospital?

(7) What was you gestational age when you delivered your child?

(8) What was the type of your childbirth? Vaginal delivery / Caesarean delivery * (*strike out whichever option does not apply to you).

In case of a vaginal delivery à continue to question 9 and skip question 12 and 13.

In case of a Caesarean delivery à continue to question 12

(9) Was your childbirth induced? Yes / No* (*strike out whichever option does not apply to you). In case yes applies to you, what was the reason for the induction?

(10) What was the position of your baby? Head / Breech* (*strike out whichever option does not apply to you).

(11) How was the delivery? Without assistance / Forceps / Vacuum* (*strike out whichever option does not apply to you).

(12) Which type of C-section applies? Elective C-section / Emergency C-section (*strike out whichever option does not apply to you). What was the reason for the C-section?

(13) Did any complications occur during childbirth? Yes / No* (*strike out whichever option does not apply to you). In case of yes, which complication(s) and how was this treated?

(14) Did there occur any complications regarding the health of your child(ren) in the first couple of days after the childbirth? Yes / No* (*strike out whichever option does not apply to you). In case of yes, which complication(s) and how was this treated?

(15) What was the length of your baby at childbirth?

(16) What was the body weight of your baby at childbirth?

In case you gave birth to a twin à

(17) What was the length of your second baby at childbirth?

(18) What was the body weight of your second baby at childbirth?

9

Small Bowel Intussusception in Pregnant Women with a History of a Roux-en-Y Gastric Bypass: a Case Series and a Systematic Review of the Literature

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ABSTRACT

Intussusception of the small intestine has been described in pregnant women with a history of a laparoscopic Roux-en-Y gastric bypass. This study provides a systematic review on the characteristics of intussusception in this population. MEDLINE, Embase, Cochrane Library, and our own hospital's electronics health records were searched for eligible studies/cases. Fifteen papers were eligible, containing seventeen cases. Our hospital search included 6 cases. Seventeen of 23 intussusceptions were retrograde and were mostly (18/23) located at the jejunojejunostomy. Six patients were treated successfully with manual reduction only and seventeen patients required surgical resection. Fifteen (65%) patients had an ischemic segment. Six (26%) patients delivered during the same hospital admission. One foetal death (1 of twins) was reported. Awareness of this rare but serious complication by obstetricians and bariatric surgeons is necessary to limit maternal and foetal complications.

INTRODUCTION

Bariatric surgery is being performed more frequently over the past few years, with its positive effects extensively described as well as the related complications in the short and long-term[1-5]. The Roux-en-Y gastric bypass (RYGB) is currently one of the most commonly performed bariatric procedure to treat morbid obesity[6]. A long-term abdominal complication of the RYGB is intestinal obstruction, with an incidence up to 5.2%[6-7]. The most frequently described cause of intestinal obstruction after RYGB is internal herniation (IH)[7-9]. One other cause of intestinal obstruction that has been described is intussusception[9-10].

Intussusception of the small intestine is a pathologic condition in which a part of the small intestine telescopes within the lumen of an adjacent part of the small intestine[11]. It is a quite rare complication after RYGB surgery, with a lifetime incidence of 0.1% to 0.2%[10]. However, it is believed the true incidence is higher and will further increase in the following years, because of an increasing number of patients with a history of a RYGB and an increased awareness[10,12]. Intussusception of the small intestine can lead to serious complications, such as bowel obstruction, intestinal ischemia, and necrosis[9-10].

In adults, intussusception is mostly associated with a pathologic area in the small intestine, the so-called "lead point." By normal peristalsis this "lead point" is pulled forward into another segment of the intestine, causing an antegrade intussusception[11]. The pathogenesis of intussusception in patients with a history of RYGB is under debate. Several authors suggest that dysmotility of the small intestine, because of the development of ectopic pacemakers, plays an important role in creating some sort of lead point that predisposes to intussusception[9-10,12].

With the increasing absolute number of RYGB procedures performed in women of reproductive age, the number of pregnant women with a history of a RYGB rises accordingly[6,13]. Intestinal obstruction, as a complication of the RYGB, can also occur during pregnancy[14-16]. A review regarding 52 cases of IH during pregnancy in women with a history of a laparoscopic RYGB showed striking results regarding maternal and foetal mortality, 3.8% and 5.8%, respectively. In addition, 17% required bowel resection and almost half of the women gave birth during the hospital admission[14]. Recently, several cases of intussusception during pregnancy after laparoscopic RYGB were seen at our clinic, all requiring surgical intervention.

The aim of this study was to provide an overview of the clinical presentation, the diagnostics, the type and location, the treatment, and the maternal and perinatal outcomes of intussusception in pregnant women with a history of a laparoscopic RYGB. The study

is based on a case series treated at our tertiary-care teaching hospital extended with a systematic review of the literature. With this overview, we aim to make obstetricians and bariatric surgeons aware of the characteristics of intussusception, after RYGB, during pregnancy.

METHODS

This systematic review was reported according to the preferred reporting items for systematic reviews and meta-analysis guidelines, where applicable. Approval of the local research ethical committee was requested, but the research ethical committee deemed approval not necessary as this review included only retrospective data.

Protocol and registration

The protocol is registered at PROSPERO – International prospective register of systematic reviews – ID 123528.

Eligibility criteria

Studies about (1) pregnant patient(s) with a history of a laparoscopic RYGB and (2) pregnancy(ies) complicated by intussusception were eligible. No limits on language, publication date, sample size, and study type were used. Congress abstracts and studies that were not available in full text were also included in order to include the largest possible number of cases.

Information sources and search strategy

The database of our hospital, a tertiary-care referral centre for abdominal complications during pregnancy after bariatric surgery (bariatric expertise as well as an obstetric high care unit and a neonatal intensive care unit), was searched from January 2014 to August 2019 for cases presenting with an intussusception during pregnancy after a laparoscopic RYGB. Electronic searches of the MEDLINE® (PubMed®), Embase, and Cochrane databases were performed in July 2019. The search strategies consisted of a combination of index terms and free text words related to pregnancy, RYGB, intestinal obstruction, and intussusception. The last search was performed on July 31, 2019. The search performed in MEDLINE is presented in **Appendix 1**.

In addition, the reference lists of the included studies were scanned for additional relevant publications (citation tracking) by one author (D.B.).

Study selection

After removal of duplicates, the titles and abstracts of the remaining studies were independently evaluated for relevance by 2 authors (D.B., F.D.). Studies judged as relevant were assessed in full text for eligibility (D.B., F.D.). In case full text could not be obtained eligibility was assessed only based on the abstract. If there was a disagreement between the 2 authors, a third author (W.L.) made the decision.

Data collection

A piloted database was used for the data collection, which was drafted by 2 authors (D.B., F.D.). Data from the included studies were extracted by one author (D.B.). To limit the amount of missing data, we contacted the original authors by email. One reminder was sent in case no response was received. Patient data from cases identified with our hospital search were retrospectively extracted from the electronic patient files by one reviewer (D.B.).

Data items

The following data was collected: author and publication characteristics; maternal characteristics; pregnancy characteristics; clinical presentation and physical examination; diagnostics with results test with outcome; (surgical) treatment; intussusception characteristics; and maternal and perinatal outcome. See Prospero ID 123528 for the extended data items.

Risk of bias

Risk of bias, both within and across studies, was not assessed, because most studies were case reports.

Data analysis

Only descriptive statistics were used. Medians with interquartile ranges (Q1, Q3) and percentages were calculated for selected variables. The statistical analyses were performed with IBM SPSS Statistics (IBM Corp, Armonk, NY, USA) version 24 for Windows.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent statement

For the systematic review, formal consent was not required. Informed consent was obtained from the patients identified with our hospital search.

RESULTS

A total of 71 unique studies were identified, of which fifteen were included in this systematic review (**Figure 1**). One study was a retrospective cohort study regarding digestive surgical complications, not only intussusception, in pregnant women with a history of obesity surgery. The other included studies were all case reports or congress abstracts, of which 2 studies also provided a revision of the existing literature in addition to their case report. In total, the literature search provided seventeen individual cases (**Table 1**).

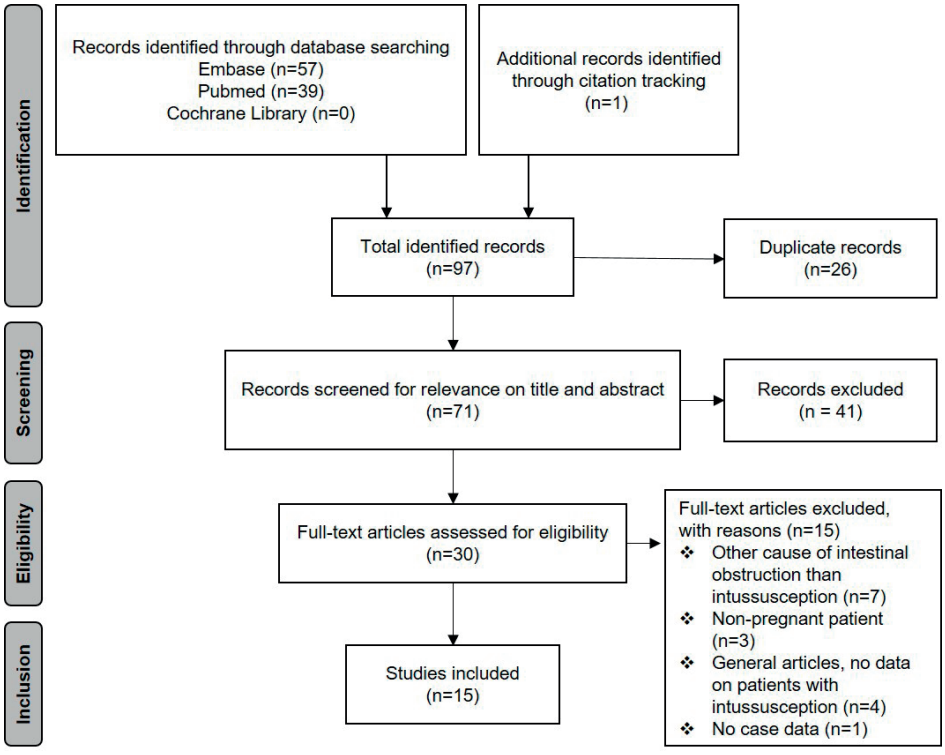

Figure 1 – Flowchart of the study selection

Next to this, the search of our hospital's electronic health records identified 6 cases. Five patients were treated in 2018 and one in 2019. Short case reports of these patients are provided in **Appendix 2**. Overall, 23 unique patients were included (**Table 2**).

Table 1 – Study characteristics

First author [reference]	Publication year	Country	Type study	Cases (n=)*	Cases literature (n=)**
Wax JR [17]	2007	United States of America	Case report	1	-
Tohamy AE [18]	2008	United States of America	Case report	1	-
Cabrera A [19]	2011	Spain	Congress abstract	1	-
Tuyeras G [20]	2012	France	Case report	1	-
Beffa L [21]	2014	United States of America	Congress abstract	1	-
Bokslag A [22]	2014	Netherlands	Case report	2	-
Chevrot A [23]	2015	France	Retrospective cohort study	2	-
Mortelmans D [24]	2016	Belgium	Case report	1	-
Boccalatte LA [15]	2017	Argentina	Case report, revision literature	1	6
Arapis K [25]	2017	France	Case report, revision literature	1	5
Gray S [26]	2018	United States of America	Case report	1	-
Le Tinier B [27]	2018	Switzerland	Congress abstract	1	-
Khan K [28]	2018	United States of America	Case report	1	-
Moliere S [29]	2018	France	Case report	1	-
Bhadra R [30]	2018	United States of America	Case report	1	-

* Cases regarding intussusception

** Cases described from the existing literature in addition to their own case description regarding intussusception

Clinical presentation

The clinical presentation was characterized by acute abdominal pain in all 23 patients. Three patients (13%) experienced intermittent abdominal pain and in one patient (4%) the abdominal pain worsened after oral intake. The abdominal pain was located in the epigastrium and periumbilical region (n=6), epigastric region (n=3), left hypochondriac region (n=2), upper abdomen region (n=2), and periumbilical region (n=1). In nine patients, no specific region of the pain was described. The abdominal pain was associated with nausea and vomiting in 20 (87%) and 16 (70%) patients, respectively. In two patients, the vomiting was described as bilious and in five patients as hematemesis. Twenty patients visited the hospital within a day from the onset of the pain. The remaining three patients were admitted to the hospital within two to seven days from the onset of the abdominal pain.

Physical examination

Physical examination showed abnormal vital signs in three patients, two with a heart rate of >100 beats/min and one with a blood pressure of 170/100 mm Hg. In ten patients, evident tenderness of the abdomen was noted and in two patients minimal peritoneal signs were found.

Table 2 – Characteristics of included patients n=23

Maternal age – Years – Median (Q1, Q3) – (n=21)	32 (28, 35)
Gestational age – Weeks^{+days} – Median (Q1, Q3) – (n=22)	27^{+1} (20^{+0}, 32^{+2})
Trimester of pregnancy at occurrence intussusception – No.(%) – (n=23)	
First trimester	4 (17)
Second trimester	7 (31)
Third trimester	12 (52)
Multiparous / Nulliparous – No. (%) – (n=15)	
Nulliparous	3 (20)
Multiparous	12 (80)
Singleton pregnancy / Twin pregnancy – No. (%) – (n=23)	
Singleton pregnancy	22 (96)
Twin pregnancy	1 (4)
Timeframe laparoscopic RYGB and onset of symptoms – Years – Median (Q1, Q3) – (n=21)	4 (2.5, 6)

Q1 = first quartile – equal to the 25th percentile of the data, Q3 = third quartile – equal to the 75th percentile of the data, No. = number, RYGB = Roux-en-Y gastric bypass

Laboratory and radiologic examination

Laboratory assays (of at least C-reactive protein, leukocytes, and lactate) were performed in fourteen patients, of which three patients had normal results. Nine patients had a leucocytosis (defined as a leukocytes count >12 $\times 10^9$/L). In four patients, the leucocytosis was accompanied by an elevated C-reactive protein (defined as C-reactive protein >30 mg/L) and in one patient with an elevated lactate (defined as a lactate >2.4 mmol/L analysed in an arterial blood gas). In two patients the urine was examined, one showing a urinary tract infection and one was normal. As shown in **Table 3**, the abdominal magnetic resonance imaging (MRI) scan and abdominal computed tomography (CT) scan diagnosed the intussusception in 86% and 100%, respectively.

Treatment

Of 23 included patients, 22 underwent surgery within 24 hours of admission to the hospital. At least seventeen intussusceptions were retrograde and one was antegrade (**Figure 2**). The intussusception was located at the jejunojejunostomy in eighteen patients (**Table 4**). In ten cases it was stated that the small intestine was distended proximal to the intussusception. Ischemia/necrosis of the small intestine was noted (or highly suspected) in fifteen patients, of whom one patient also showed a perforation. In one other patient there was ischemic perforation and necrosis of the proximal fundus of the gastric remnant, which was partially resected. All patients with ischemia of the small intestine were treated with surgical resection. Two patients, without ischemia, were also treated with surgical resection due to an irreducible intussusception.

Table 3 – Diagnostic tests

Imaging technique	n=	Normal	Intussusception	Other diagnosis	Description other diagnosis
Abdominal ultrasound	12	7*,**	2	3	I - Dilatation of small intestine I - Lobulated solid mass of the small intestine I - Evident sign of internal herniation
Abdominal MRI-scan	7	-	6	1	I - Signs of necrosis of the small intestine, possible due to an Internal Herniation
Abdominal CT-scan	5	-	5	-	-
Abdominal radiography	2	1*	-	1	I - Signs of an ileus and a kidney stone in the left kidney
Endoscopy	2	1	Not applicable	1	I – Stenosis at the gastrojejunostomy which was discarded.

n = number, * = Normal, except for intra-uterine pregnancy, ** = in five cases, the abdominal ultrasound was only performed for the foetal condition, CT = computed tomography, MRI = magnetic resonance imaging

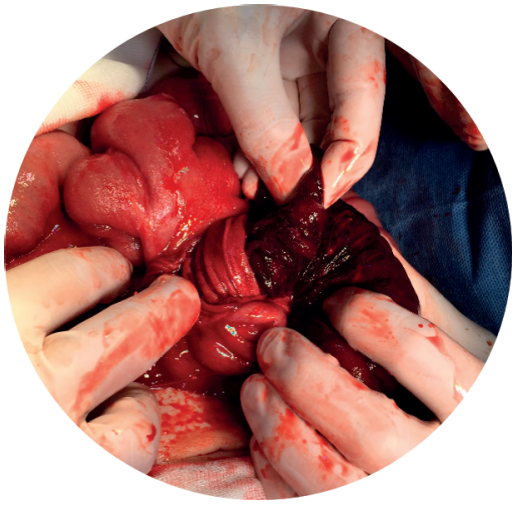

Figure 2 – Retrograde intussusception of the common limb into the jejunojejunostomy

Postoperative period

In ten patients, a complicated course after the surgical intervention for the intussusception was noted (**Table 5**). Two patients required surgical intervention; one with a superinfected intraperitoneal hematoma and one with an IH with faecal peritonitis after manual reduction of the intussusception. There was no maternal mortality.

Data regarding childbirth and perinatal outcome were available for fourteen patients (**Table 6**). Six patients gave birth during the hospital admission for the intussusception. One patient give birth during the hospital admission for the IH with faecal peritonitis.

Table 4 – Results

First author [reference]	Gestational age (weeks^{+days})	Time since RYGB (months)	Clinical Presentation	Diagnosis	Type of surgery	Type intussusception	Location intussusception	Treatment
Wax JR [17]	21^{+0}	12	Intermittent sharp non radiating upper abdominal pain, exacerbated by meals, V+N-	Surgery	Laparoscopy	Retrograde	Common limb into jejunojejunostomy	Manual Reduction
Tohamy AE [18]	33^{+0}	48	Abdominal pain and bilious vomiting	CT-scan	Laparoscopy	Retrograde	NR	Manual Reduction
Cabrera A [19]	35^{+0}	NR	Acute abdominal pain in the left hypochondriac region with repeated vomiting	Surgery	Laparotomy	NR	Jejunojejunostomy	Surgical resection
Tuyeras G [20]	17^{+0}	48	Acute epigastric pain, V+N+	Surgery	Conversion to laparotomy	Retrograde	Common limb into jejunojejunostomy	Manual reduction and surgical resection
Beffa L [21]	28^{+0}	84	Acute abdominal pain and hematemesis	CT-scan	Laparoscopy	Retrograde	NR	Manual reduction and surgical resection
Bokslag A [22]	34^{+3}	17	Abdominal pain worsened after defecation, V+N-	Surgery	Laparotomy	Retrograde	Jejunojejunostomy	Surgical resection
Bokslag A [22]	24^{+1}	108	Abdominal pain, V+N-	MRI-scan	Conversion to laparotomy	Retrograde	Common channel into jejunojejunostomy	Surgical resection
Chevrot A [23]	31^{+0}	60	NR	Surgery	Laparotomy	NR	Common limb into Jejunojejunostomy	Manual Reduction
Chevrot A [23]	17^{+0}	36	Epigastric pain, V+N+	Surgery	Conversion to laparotomy	NR	Ileo-ileal	Surgical resection
Mortelmans D [24]	33^{+5}	NR	Acute abdominal pain with coffee-ground vomiting	Ultrasound	Laparotomy	Retrograde	Common limb into jejunojejunostomy	Manual Reduction
Boccalatte LA [15]	30^{+6}	48	Intermittent abdominal pain with bile stained vomiting	CT-scan	Conversion to laparotomy	Retrograde	10 cm from the foot of the Roux-en-Y	Surgical resection

Table 4 – Results (*continued*)

First author [reference]	Gestational age (weeks^{+days})	Time since RYGB (months)	Clinical Presentation	Diagnosis	Type of surgery	Type intussusception	Location intussusception	Treatment
Arapis K [25]	25^{+0}	24	Persistent abdominal pain, V+N+	CT-scan	Laparotomy	Retrograde	Common limb into jejunojejunostomy and Roux limb	Surgical resection
Gray S [26]	6^{+0}	NR	Sudden onset of epigastric and periumbilical pain, V+N+	MRI-scan	Conversion to laparotomy	Retrograde	Jejunojejunostomy	Surgical resection
Le Tinier B [27]	37^{+0}	108	Upper abdominal pain	CT-scan	NR	Antegrade	Biliary limb into jejunojejunostomy	Surgical resection
Khan K [28]	6^{+0}	24	Sudden onset of epigastric and periumbilical pain, V+N+	MRI-scan	Conversion to laparotomy	Retrograde	Common limb into jejunojejunostomy	Surgical resection
Moliere S [29]	27^{+0}	48	Abdominal pain, V+N+	MRI-scan	Laparotomy	NR	Jejuno-jejunal	Manual Reduction
Bhadra R [30]	NR	108	Tearing abdominal pain epigastric and periumbilical , V+N+	MRI-scan	Laparotomy	NR	Jejunojejunostomy	Surgical resection
Case series								
1	30^{+3}	48	Acute intermittent abdominal epigastric pain with radiation to the back, V-N-	Surgery	Conversion to laparotomy	Retrograde	Common limb into jejunojejunostomy	Surgical resection
2	26^{+6}	36	Acute abdominal pain periumbilical, V+N-	Surgery	Conversion to laparotomy	Retrograde	Common limb into jejunojejunostomy	Surgical resection
3	25^{+6}	12	Acute abdominal pain epigastric and periumbilical , V+N+	Ultrasound	Conversion to laparotomy	Retrograde	Jejunojejunostomy	Surgical resection
4	12^{+0}	84	Acute abdominal pain epigastric and periumbilical radiating to the back, V+N+	Surgery	Conversion to laparotomy	Retrograde	Common limb into jejunojejunostomy	Manual Reduction

Table 4 – Results (*continued*)

First author [reference]	Gestational age (weeks^{+days})	Time since RYGB (months)	Clinical Presentation	Diagnosis	Type of surgery	Type intussusception	Location intussusception	Treatment
5	27^{+1}	60	Acute abdominal pain left hypochondriac region, V+N+	Surgery	Conversion to laparotomy	Retrograde	Common limb into jejunojejunostomy and biliary limb	Surgical resection
6	32^{+1}	60	Acute abdominal pain in the epigastric region, N+,V-	MRI-scan	Conversion to laparotomy	Retrograde	Jejunojejunostomy	Surgical resection

RYGB = Roux-en-Y gastric bypass, NR = Not Reported, N = Nausea, V = Vomiting, CT-scan = computed tomography scan, MRI-scan = Magnetic resonance imaging scan

Table 5 – Maternal outcome

First author [reference]	Complication	Treatment	Readmission for complication
Cabrera A [19]	Clinical deterioration based on a superinfected intraperitoneal hematoma	Surgical	No
Bokslag A [22]	Superficial wound infection	Antibiotics	No
Bokslag A [22]	I - Wound infection I – Pneumonia	I - Conservative I - Antibiotics	No
Chevrot [23]	Internal herniation of common limb through mesenteric defect at jejunojejunostomy with faecal peritonitis	Surgical	Yes
Mortelmans D [24]	Wound infection	Antibiotics	No
Case series			
1	Wound infection	Flushing of the wound	No
2	I - Wound infection I - Vitamin Deficiencies	I - Conservative I - Supplements	No
4	Abdominal pain	Laxatives	Yes
5	I - Wound infection I - Biliary colic pain	I - Conservative I - Buscopan	No
6	I – Reactive thrombocytosis I – Pneumonia I – Intra-abdominal fluid collections (no abscesses)	I – Conservative I – Antibiotics I – Expectative + antibiotics	No

Six neonates were admitted to the neonatal intensive care unit of whom one died (one of twins) due to complications after laparotomy for necrotizing enterocolitis (**Table 6**).

DISCUSSION

Intussusception is a rare complication after RYGB surgery that can also occur during pregnancy. Intussusception is described in up to 7% of the cases of small bowel obstruction after RYGB in non-pregnant patients[10]. The incidence of intussusception after RYGB during pregnancy is not well known. From 2007 until now, as far as we know, only seventeen cases regarding intussusception during pregnancy in patients with a laparoscopic RYGB have been described in the literature and only one case of intussusception during pregnancy in a patient with an open RYGB[15,17-31]. However, in our tertiary-care referral centre, we have already observed six cases of intussusception in pregnant women after laparoscopic RYGB in the last two years. In addition, two more cases described in the literature were also Dutch. Based on a total of eight Dutch cases, it can be hypothesized the actual incidence is higher than the incidence that is expected based on the previous literature.

Table 6 – Childbirth and neonatal outcome

First author [reference]	Timing childbirth	Additional information	Foetal condition	Modus birth	Single/ twin pregnancy	Preterm Full-term	GA at childbirth	NICU +/-	Foetal complications
Tohamy AE [18]	Normal course	-	-	Vaginal	Single	Full-term	38^{+0}	-	-
Cabrera A [19]	Simultaneously with surgery	-	-	Emergency C-section	Single	Preterm	35^{+0}	-	-
Beffa L [21]	Not specified	-	-	C-section	Single	Preterm	NR/UN	-	-
Bokslag A [22]	Simultaneously with surgery	-	Foetal distress	Emergency C-section	Single	Preterm	34^{+3}	+	Continuous airway pressure à directly to low-flow nasal cannula. Antibiotics. No signs of hypoxic ischemic encephalopathy. Good recovery.
Bokslag A [22]	7 days after surgery	Preterm contractions - fully dilated	-	Vaginal	Twin	Preterm	25^{+1}	+	Baby died ten days after birth due to complications of laparotomy for necrotizing enterocolitis.
		Preterm contractions - fully dilated	-	NR/UN	Single	Preterm	25^{+1}	+	Infant respiratory distress syndrome grade 3-4 and sepsis with E. coli. Discharged after 11 weeks, good condition.
Chevrot A [23]	13 days after surgery	-	Abnormal CTG: decelerations	Emergency C-section	Single	Preterm	32^{+6}	+	-
Chevrot A [23]	Normal course	-	-	Vaginal	Single	Full-term	39^{+0}	-	-
Mortelmans D [24]	7 hours after surgery	2 hours after surgery premature contractions à tocolysis	Abnormal CTG (7 hours after surgery)	Emergency C-section	Single	Preterm	33^{+5}	+	-

Table 6 – Childbirth and neonatal outcome (*continued*)

First author [reference]	Timing childbirth	Additional information	Foetal condition	Modus birth	Single/ twin pregnancy	Preterm Full-term	GA at childbirth	NICU +/-	Foetal complications
Arapis K [25]	Normal course	-	-	C-Section	Single	Full-term	NR/UN	-	-
Le Tinier B [27]	Hours before surgery	Abdominal pain - uterine contraction - pre-eclampsia - acute pancreatitis	Good foetal vitality and heart rate	Vaginal (induced)	Single	Full-term	37^{+0}	-	-
Cases own hospital									
1	Normal course	-	-	Vaginal	Single	Full-term	39^{+5}	-	-
2	Normal course	-	-	Vaginal	Single	Full-term	40^{+0}	-	-
3	Normal course	Preterm contractions postoperatively with suboptimal CTG à tocolytics	-	C-section (elective)	Single	Full-term	38^{+4}	-	-
4	Normal course	-	-	Vaginal	Single	Full-term	40^{+1}	-	-
5	Normal course	Preterm contractions postoperatively with suboptimal CTG à tocolytics	-	Vaginal	Single	Full-term	39^{+6}	-	-
6	Several hours after surgery	-	Foetal distress	Emergency C-section	Single	Preterm	32^{+0}	+	Endotracheal intubation and ventilation for RDS

NR/UN = Not Reported/Unknown, C-section = caesarean section, GA = gestational age, NICU = neonatal intensive care unit

Although the incidence of intussusception during pregnancy after RYGB may be limited, it is a severe complication that often requires immediate surgical intervention. When the small intestine folds into an adjacent part of the small intestine, the mesentery is also drawn into the small intestine leading to oedema with compression of the intramural vessels and an impaired perfusion of the intestinal wall. As a consequence, ischemia can occur, which ultimately can lead to necrosis, perforation, and peritonitis[32]. Daellenbach et al., who published a review regarding intussusception in 63 non-pregnant patients with a laparoscopic RYGB, described seven patients with an ischemic segment of the jejunum, including one with a perforation[9]. All 23 patients described in our study required surgical intervention, of which the majority required immediate intervention (within 24 hr). In addition, at least fifteen patients (65%) had an ischemic segment. Furthermore, six patients (26%) delivered during the same hospital admission for the intussusception and unfortunately one neonatal death was reported. For this reason, timely diagnosis and treatment is necessary as intussusception can have serious maternal and neonatal consequences.

Intussusception after RYGB differs in characteristics from intussusception in the general population. Intussusception in adults without a history of bariatric surgery has no clear sex predominance, the mean age is approximately 50 years and the intussusception is typically antegrade[12,33-35]. On the contrary, Simper et al. reported, in a single-centre cohort study, 23 cases of only retrograde intussusception in patients with a history of bariatric surgery, all in females with a mean age of 32 years (range: 20–50)[10]. Daellenbach et al. published data of 62 female cases and only one male case[9]. The median age of the women in this review was 32 years. Intussusception in adults with a history of an RYGB is mostly seen in females and occurs at a younger age compared with adults without a history of a RYGB.

The aetiology of intussusception after RYGB is not clear and might differ from the general population. In the general population, the aetiology is based on the lead point with an antegrade intussusception, proximal to distal direction. The most accepted theory for the development of retrograde intussusception after RYGB surgery is that of motility disturbances of the small intestine, because of the development of ectopic pacemakers that play a crucial role in creating an unstable zone with reverse peristalsis[9,10]. Whether pregnancy in itself increases the risk of intussusception is not clear. At least two cases are described of spontaneous intussusception in pregnant women without a history of bariatric surgery[36-37]. Covali et al. speculated the advanced pregnancy (29 weeks) may have provoked the intussusception, by pushing upward the mobile small intestine, which is associated with intense physical effort that stresses the abdominal wall muscles[37]. This

might indeed have played a role, although this mechanism is less likely in the patient described by Achour et al. who was just 9-weeks pregnant[36].

The nonspecific and variable clinical symptoms in combination with a wide range in the diagnostic accuracy of radiologic imaging (ultrasound, CT, MRI) makes the preoperative diagnosis of intussusception challenging. Most symptoms of intussusception are non-specific symptoms that are often experienced during pregnancy[12,35,38]. Abdominal CT is considered the most sensitive imaging technique for the diagnosis of intussusception in non-pregnant patients with a diagnostic accuracy ranging from 58% to 100%[33,39-40]. However, diagnosis of intussusception preoperatively has a reported rate of 40% to 50%[12,41-42]. In this review, the clinical presentation was not contributing to the diagnosis and only in twelve cases (52%) the intussusception was diagnosed preoperatively, which is comparable to the literature. The diagnostic accuracy for intussusception in pregnant patients in this review was 100% for the CT and 86% for the MRI (**Table 3**). Although the CT is probably the most sensitive technique to detect intussusception, the MRI would be the preferred imaging technique during pregnancy to limit the amount of exposure of the foetus to ionizing radiation.

Both manual reduction and surgical resection seem sufficient treatment options for intussusception during pregnancy. In children, a 1% recurrence risk of intussusception has been described after manual reduction, compared with a virtually non-existent recurrence risk after surgical resection[32,39]. However, Daellenbach et al. recommended resection of the affected segment for intussusception after RYGB surgery, as resection resulted in less recurrences[9]. Looking at our results, six patients were treated successfully with manual reduction. One patient was treated with manual reduction but eventually required surgical resection of the small intestine due to ischemia. No recurrence of the intussusception was reported. However, it is of note that surgical repair of intussusception is associated with a high rate of wound infection; 6 (26%) of the total 23 cases described in this review developed a wound infection and 3 (50%) of 6 cases at our centre. Although, the evidence in the current literature to support surgical resection instead of manual reduction is limited, based on our experience we would advise to perform, at the slightest doubt of non-recoverable ischemia, surgical resection.

As most evidence is derived from case reports, instead of prospective cohort studies or clinical trials, a publication bias might have led to overestimation of the severity of this problem in previous literature. The cases identified with our hospital search showed more full-term childbirths, less perinatal complications, and less frequent admission to the neonatal intensive care unit compared with the literature. Other limitations of this review are the small number of cases that prevents us from providing well-founded ad-

vises and the incomplete information obtained from the studies and from our hospital database, even though the patients and authors were contacted for additional information.

CONCLUSION

Intussusception is a rare complication of RYGB surgery that can also occur during pregnancy, in all trimesters. An MRI, the preferred imaging technique during pregnancy to limit the foetal exposure to ionizing radiation, should be performed to establish the diagnosis preoperatively. The intussusception is mostly retrograde and located at the jejunojejunostomy. Being a severe complication leading to maternal morbidity and neonatal morbidity and mortality, timely diagnosis and intervention with surgical resection if non-recoverable ischemia or necrosis is encountered is warranted. Therefore, awareness of this complication by obstetricians and bariatric surgeons is of importance.

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APPENDIX 1

The following search was performed in MEDLINE® (PubMed®): ("Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR pregnan*[tiab] OR gravidit*[tiab] OR gestation*[tiab]) AND ("Anastomosis, Roux-en-Y"[Mesh] OR "Gastric Bypass"[Mesh] OR roux-en-y[tiab] OR roux en y[tiab] OR RYGB[tiab] OR LRYGB[tiab] OR gastric bypass*[tiab] OR gastroileal bypass*[tiab] OR gastrojejunostom*[tiab]) AND ("Intestinal Obstruction"[Mesh] OR intestinal obstruction*[tiab] OR intussusception*[tiab] OR intususception*[tiab] OR intestinal invagination*[tiab]). No limits were applied. A similar search strategy was used for the search in Embase and Cochrane Library.

APPENDIX 2

Case reports of the patients identified with the search of our hospital's electronic health records.

Case 1

A 33-year old female, 30^{+3} weeks pregnant (G4P1), with a history of a laparoscopic Roux-en-y Gastric Bypass (four years ago), was referred from another bariatric centre in the Netherlands with the clinical suspicion of internal herniation. She presented at our emergency department with intermittent acute epigastric pain, existing since the early evening, Nausea-, Vomiting-. On physical examination impaired peristalsis, epigastric pain and minimal peritoneal signs were found. She was admitted to the obstetric high care and was given corticosteroids for the foetal lung maturation. A MRI-scan could not be performed as the patient could not lay still due to the severe abdominal pain. An emergency diagnostic laparoscopy was performed. A retrograde intussusception of the common limb into the jejunojejunostomy with an ischemic segment of the small intestine was seen. Laparoscopy was converted to a median laparotomy, because reduction of the intussusception was not possible. Surgical resection with resection of about 70cm of the small intestine and revision of the jejunojejunostomy was performed. Postoperatively, preterm contractions started which was successfully treated with tocolysis, with a good foetal condition. She unfortunately developed a wound infection, which was treated with flushing of the wound. After eleven days she was discharged in good condition.

Case 2

A 26^{+6} weeks pregnant patient (G2P1), 25 years old, presented at our emergency department after being referred from another bariatric centre with the suspicion of internal herniation. She had a history of a laparoscopic Roux-en-Y Gastric Bypass, three years ago. A continuous abdominal pain periumbilical with an acute onset was the main complaint, accompanied with nausea. Physical examination showed pain in the left upper abdomen and the midline, with some peritoneal signs. Laboratory assays showed a low haemoglobin and a leucocytosis. A diagnostic laparoscopy was performed which showed a retrograde intussusception of the common limb into the jejunojejunostomy. After conversion to a median laparotomy, the intussusception was resected and a revision of the jejunojejunostomy was performed. Postoperatively, the patient recovered well, with a good foetal condition. Laboratory assays had revealed a deficiency of iron calcium and vitamin B12, for which she started on supplements. After discharged, she developed a wound infection which was treated with flushing of the wound.

Case 3

A 30-year old, 25^{+6} weeks pregnant woman (G5P1A3) with a previous laparoscopic RYGB (one year ago) presented with sudden onset of epigastric and periumbilical pain concomitant with nausea and vomiting. Blood analysis showed elevated infection parameters and normal urine and liver function. Abdominal ultrasound showed a thickening of the intestinal wall with a closed loop obstruction suspected of an intussusception. An emergency diagnostic laparoscopy was performed and a distended small intestinal loop was seen at the site of the jejunojejunostomy. Due to insufficient visualization caused by the enlarged uterus conversion to a median laparotomy was performed. Intussusception of the common limb into the jejunojejunostomy with a necrotizing small intestine was identified. The decision was made to perform a resection and revision of the jejunojejunostomy. Postoperatively the patient recovered well and was discharged in good clinical condition.

Case 4

A 32-year old, twelve weeks pregnant women (G4P2A1) was admitted to our emergency department with acute periumbilical and epigastric pain radiating to the back with nausea and vomiting. She had undergone a laparoscopic RYGB seven years earlier. Blood analysis showed no abnormalities. Abdominal ultrasound revealed an intussusception. A laparoscopy was performed shortly after diagnosis and intussusception of the common limb in the jejunojejunostomy was confirmed. Manual reduction of the intussusception was unsuccessful and therefore conversion to a median laparotomy was performed, after which manual reduction was accomplished. Postoperatively a significant decrease in haemoglobin concentration was noted. Ultrasound examination excluded intra-abdominal blood loss and it was attributed to iron deficiency anaemia. After iron injections the haemoglobin level increased and the patient left the hospital in good condition. During the pregnancy and also after childbirth so far, no recurrence of the intussusception has occurred.

Case 5

This patient had a laparoscopic RYGB five years earlier and was referred with acute severe pain in the left hypochondriac region along with nausea and vomiting. She was 31 years old and 27^{+1} weeks pregnant (G2P1A0). Infection parameters were slightly elevated and the MRI-scan showed a distended small intestine. The patient was scheduled for an emergency diagnostic laparoscopy which showed a retrograde intussusception located at the jejunojejunostomy with necrosis. Laparoscopic intervention was converted to a median laparotomy, after which a necrotic intestine was removed and the jejunojejunostomy was revised. Postoperatively the condition of the foetus deteriorated briefly but stabilized after tocolysis. Patient recovery was complicated by colic pains in the left

flank, with no signs of kidney stones on the X-ray, treated with Buscopan. Two days later she developed a wound infection, which was treated with flushing. Eleven days after the surgical intervention, the patient was discharged with a good clinical condition.

Case 6

The patient presented with intermittent abdominal pain located at the epigastric region for about a week, which became constant since the night. The abdominal pain is accompanied by nausea without vomiting. At presentation, it was five years after the RYGB and the patient was 32^{+1} weeks pregnant of her second child (G2P1). She was admitted to the obstetric high care and a MRI-scan was performed, which showed an intussusception of the small intestine with obstruction. The patient was admitted to the surgical theatre. Laparoscopy was converted to a median laparotomy in which a retrograde intussusception was seen at the jejunojejunostomy with an ischemic part of the small intestine. Resection of the ischemic part and revision of the jejunojejunostomy were performed. Postoperatively, the CTG showed signs of foetal distress. A C-section was performed after which the neonate was transferred to the NICU and the patient to the ICU. Both recovered well.

10

General discussion & future perspectives

GENERAL DISCUSSION

Part 1 Indications outside of the set age criteria

In 1997, several eligibility criteria were developed for bariatric surgery (IFSO-guidelines)[1-2]. In the meantime, bariatric surgery has evolved substantially, from open hypoabsorptive procedures to laparoscopic restrictive or combined procedures[3-4], and the number of bariatric procedures as well as the human life-expectancy has increased significantly[5-6]. The eligibility criteria are therefore somewhat outdated and might require modifications. Part 1 of this thesis aimed to investigate whether the age limits for bariatric surgery should be adjusted.

Although bariatric surgery in adolescents (<18 years) with severe obesity was already performed in the early 1970s[7], it was only in the past decennium that two major prospective studies were published. These studies both support bariatric surgery in adolescents as a safe and effective treatment in addition to lifestyle intervention[8-9]. However, very little research has been conducted comparing the two most commonly performed bariatric surgical procedures, the Roux-en-Y gastric bypass (RYGB) and the sleeve gastrectomy (SG). This knowledge gap hampers optimal procedure selection and prevents evidence-based recommendation to eligible adolescents. To address this paucity of knowledge, the TEEN-BESTrial, a multicentre, international, randomized controlled trial comparing RYGB with SG in adolescents (aged 13-17 years) with severe obesity was developed (**Chapter 2**).

However, bariatric surgery in adolescents is a controversial subject and should be performed cautiously. One of the pioneers of bariatric surgery in adolescents, Professor T. Inge, stated the following; "institutions providing bariatric care to youth should only provide these services if care can be offered utilizing multidisciplinary teams dedicated to paediatric patients and if processes are in place to ensure safety and excellent delivery of clinical care"[10]. The study presented in **Chapter 2** is in line with this statement, because it is a collaboration of surgeons and paediatricians, the screening process for eligibility will be performed by an independent (no study personnel included) dedicated multidisciplinary bariatric team, and the bariatric surgery will be integrated in the stepped/matched care of adolescents with severe obesity (combining the benefits of both lifestyle intervention and surgery).

Nonetheless, the adolescents and their parents need to fully support the bariatric surgery with the required lifestyle changes and the accompanying follow-up trajectory, while the paediatricians should inform and refer adolescents about/to bariatric surgery. Therefore, the attitude regarding bariatric surgery in adolescents was explored among

Dutch paediatricians, adolescents with severe obesity and their parents by using an anonymous survey (**Chapter 3**). In 2010, a study among American paediatricians and family physicians showed that 48% would never refer an adolescent with obesity for bariatric surgery[11]. A Dutch study among family physicians reported in 2019 even more reluctance for referral (58.7%)[12]. The study described in **Chapter 3** shows that bariatric surgery in adolescents is increasingly accepted as potential effective treatment option by Dutch paediatricians, whereas 59.5% would refer adolescents for bariatric surgery, and 67.7% support bariatric surgery as an acceptable treatment modality. These findings are in line with a recent study among European paediatric surgeons, reporting that 65.7% considered bariatric surgery in adolescents to be a valuable option to obtain long-term weight loss[13]. The difference with the other two studies may be related to the accumulating evidence on safety and efficacy of bariatric surgery in adolescents and possibly due to the difference in type of physician; paediatricians and paediatric surgeons versus family practitioners.

Regarding the parents of adolescents with severe obesity, only 44.9% would allow their child to be referred for bariatric surgery (**Chapter 3**), a finding comparable to the results found in a qualitative study regarding adolescents who underwent gastric banding[14]. Besides, the majority of the parents (61.2%) and adolescents (73.7%) stated that bariatric surgery should only be offered within a family-based program, which corresponds to another quote by Professor T. Inge: "a motivated and supportive family is pivotal for successful bariatric surgery in youth"[15]. Yet, it remains to be determined which bariatric procedure is most effective and whether bariatric surgery in adolescents is safe and effective in the long-term.

Further exploring the age limits, in **Chapter 4** a national population-based retrospective cohort study is described in which the safety of bariatric surgery in elderly patients (defined as patients aged ≥65 years) was determined. Pseudo-anonymized data from the Dutch nationwide mandatory registry for bariatric surgery, were used.

Perioperative outcome in elderly was comparable to non-elderly, with an overall intra-operative complication rate of 1.1%. This percentage is lower compared to a study regarding bariatric surgery in North-West Europe, who showed an intra-operative complication rate of 6.5%[16]. Like perioperative outcome, short-term mortality was also low, 0.2% for elderly, and not significantly different from non-elderly. However, with regard to severe short-term complications, elderly are at higher risk compared to non-elderly (4.5% vs. 2.2% respectively, odds ratio 1.707). Interestingly, next to elderly, SG was also associated with more severe short-term complications compared to gastric bypass (odds ratio 1.459). The severe short-term complication rate of 4.5% is just not that dif-

ferent from the 4.3% reported by Dorman et al., who showed no difference between elderly and non-elderly[17]. Furthermore, overall short-term complication rate (6.9% in elderly) was not significantly different between elderly and non-elderly, and also lower compared to existing literature which reported complication rates of 8.9%[18] and 14.7%[19]. Interestingly, in the mid-term, significantly more complications were reported in non-elderly (5.9% vs. 2.3% in elderly). Of note, follow-up rate in elderly was much lower and the total number of complications was low, which could both have biased results.

In conclusion, bariatric surgery is an option for elderly with severe obesity, although the benefits and risks should be outweighed on a case-by-case basis.

Focus in **Chapter 5**, a systematic review of the literature, was the importance to use uniform definitions for treatment outcomes after bariatric surgery to be able to compare the literature. First a more patient friendly terminology was suggested; primary responder ("success"), primary non-responder ("failure") and secondary non-responder ("weight regain"). Second, results showed that two-third of the articles provided a definition, but many different definitions for the same treatment outcome were found. Lauti et al. showed in an illustrative way the impact of using different definitions. By applying six different definitions, the percentage of secondary non-responders ranged from 9.0% to 91.0%[20]. Van Rooijen et al. mentioned in a comparable matter, that the incidence of colorectal anastomotic leakage ranged from 1.5% to 23.0% in the literature[21]. Despite the fact that the inconsistency in reporting definitions in bariatric surgery has been previously reported[20,22], practise has not changed. It is obvious that these results indicate that it is possible for authors to 'manipulate' their results and that comparison of treatment outcome between articles is therefore impossible.

Chapter 2 and **4** both described study populations based on age, in which we defined adolescents as patients aged 13-17 years and elderly as patients aged ≥65 years. However, in comparable studies, adolescents were defined as patients up to 20 years of age[9,23-24], and elderly as patients aged ≥60 years[25]. Although **Chapter 5** focuses on treatment outcomes instead of population, one can imagine that results will also be significantly different when using different age groups for the same study population.

In conclusion, it is of utmost importance that study populations and treatment outcomes are defined in the methods section of an article to minimize bias. Standardized populations and outcomes, ideally with international consensus, are required to prevent manipulation of results and to be able to compare the literature.

Part 2 – Long-term abdominal bariatric complications during pregnancy

The majority of patients experience a positive outcome regarding weight loss and even remission of obesity related comorbidities after bariatric surgery[26]. However, some patients develop complications. These complications can present either in the short-term, like a leaking anastomosis and bleeding, or in the long-term, like gastro-oesophageal reflux disease, unexplained abdominal pain, and small bowel obstruction[16,27]. As mentioned in the introduction, small bowel obstruction can also occur during pregnancy, possibly requiring immediate surgical intervention, with high maternal and foetal risks. The second part of the thesis focused on small bowel obstruction during pregnancy in patients with a medical history of a RYGB. Maternal and perinatal outcomes were addressed as well as several pitfalls that possibly result in a delay in diagnosis and/or worse outcome.

The first pitfall is the unfamiliarity and lack of experience under bariatric surgeons (and probably also perinatologists), which is potentially leading to a doctors' delay. This pitfall was studied by using an online survey which was distributed among Dutch bariatric surgeons (**Chapter 6**). Only 38.9% of de bariatric surgeons had seen a case of severe maternal morbidity due to RYGB-related small bowel obstruction during pregnancy and only one perinatal death was reported. Literature regarding this subject is also scarce, primarily existing of case reports and case series. Although, it can be hypothesized that the actual incidence is higher than is expected based on the literature, because a substantial amount of the published cases are Dutch or Belgian. We believe that greater awareness among bariatric surgeons (and obstetricians) is of essence and will probably improve the timely diagnosis and treatment, and therewith reduce adverse maternal and perinatal outcomes.

The second pitfall is patients' delay and poor antenatal care. Several international consensus and guideline recommendations advice antenatal care by an obstetrician and dietician, to monitor micronutrient status and to inform and educate about RYGB-associated complications[28-30]. The current practice and preferences of Dutch bariatric surgeons towards this antenatal care provided to pregnant women after bariatric surgery was also studied (**Chapter 6**). Only 33.3% of the bariatric surgeons refer pregnant women to both the obstetrician and dietician. Furthermore, merely half of the Dutch bariatric surgeons invite pregnant patients for an additional consult at their outpatient clinic for (repeat) education regarding RYGB-related risks during pregnancy. However, small bowel obstruction may not manifest until years after the bariatric surgery and thus years after the preoperative education. Patients forget several aspects about the preoperative education, especially the negative aspects, which can contribute to a patients' delay[31]. Current guideline recommendations regarding antenatal care are not followed

and there is much variety in the preferences and practises. These discordant practices are an indication for suboptimal care. Multidisciplinary consensus statements might improve this care and every pregnant woman after bariatric surgery should be educated about the alarm symptoms of abdominal bariatric complications during pregnancy.

Treatment of pregnant women with RYGB-related small bowel obstruction in a centre with a neonatal intensive care unit (NICU) is the third pitfall, and is also studied in **Chapter 6**. In this study, at least one complete response from each Dutch bariatric centre was obtained. It showed that referral of pregnant women to a centre with a NICU is not standard care in the Netherlands, since 52.9% of the bariatric centres without a NICU, would never refer these patients. This means also no referral of pregnant patients below a gestational age of 32 weeks and thus not having specialized care for preterm neonates available. The reluctance of referral might indicate that bariatric surgeons feel comfortable to treat these patients and consider the chance of inducing labour to be negligible. However, multiple cases of significant perinatal morbidity and mortality have been reported, even when treated in a NICU-centre[32-35]. Moreover, preterm born infants (<32 weeks gestation) born at a NICU-centre perform significantly better compared to infants born at a non-NICU-centre[36-37]. Based on these findings, we recommend to refer women, between 24-32 weeks gestation, who require surgical intervention to a centre that has a NICU.

In addition to referral to a specialized hospital with a NICU and bariatric expertise, it is also important to optimize the diagnostic process. In **Chapter 7** a retrospective cohort study is described, which assessed the diagnostic accuracy of magnetic resonance imaging (MRI) for RYGB-related small bowel obstruction during pregnancy. Furthermore, the study gave insight in the fourth pitfall; delayed or missed diagnosis by medical imaging. Results showed an acceptable sensitivity and specificity of the MRI (both 66.7%), with a high positive predictive value (93.3%). Furthermore, structural assessment focussing on a combination of specific internal herniation signs (swirl-sign, small-bowel-obstruction-sign, and clustered-loop-sign) was advised, as presence of one of these signs increases the likelihood of small bowel obstruction. However, in **Chapter 7** it is also reported that MRI will not detect small bowel obstruction in almost 1 out of 3 patients. Delay by MRI or missed diagnosis does not seem to worsen maternal or perinatal outcome, as no perinatal morbidity and mortality was seen and only one case of maternal morbidity was reported. Nonetheless, the diagnostic accuracy found is worse compared to a study by Krishna et al. who reported a specificity of 86-100% and sensitivity of 74-88%[38]. Of note, both studies have a small sample size and no comparison with clinical presentation/ suspicion was made. There is a need for additional research to improve the diagnostic process of acute abdominal pain in pregnant women after bariatric surgery and we

would only recommend to perform medical imaging if the diagnosis of small bowel obstruction is uncertain due to the high change of missed diagnosis.

A single-centre retrospective cohort study regarding maternal and foetal outcome in pregnant patients with acute abdominal pain suspected for small bowel obstruction is presented in **Chapter 8**. Seventy-four percent required surgical intervention, and 16.2% required small bowel resection. Diagnoses during surgery were internal herniation (72.2%), intussusception (16.7%), open mesenteric defects (8.3%), and bowel obstruction through the silicone ring from a banded bypass (2.8%). No maternal or perinatal mortality was seen in the surgical group. However, 8.1% delivered during the hospital admission, 18.9% delivered preterm, and 8.5% of the neonates required admission to the NICU. The results are promising compared to a large review regarding this subject, which reported that 17.3% required bowel resection, 44.2% delivered during hospital admission, and maternal and perinatal mortality rate was 3.8% and 5.8% respectively[33]. Furthermore, Petersen et al. reported in a cohort study that 26.7% of the women with a history of RYGB delivered preterm after surgical intervention for a suspected abdominal bariatric complication[32].

Another focus of the study outlined in **Chapter 8** was the clinical presentation of RYGB-associated small bowel obstruction during pregnancy. The study showed that the clinical presentation is non-specific, which is the fifth pitfall. Main symptoms found were abdominal pain (different regions), nausea, and vomiting. The occurrence of pain in different abdominal regions can be explained by the growing uterus, which compresses the underlying viscera, but also leads to displacement of the viscera from their normal position. This also masks peritoneal signs[39-41]. These non-specific symptoms are also often encountered during pregnancy, and can be mistaken for common benign pregnancy related complaints[42-43]. Furthermore, these symptoms are also present in other diseases like appendicitis, gastro-enteritis, and acute severe pregnancy related problems such as placental abruption, and uterine torsion[44-45]. Of the same note, laboratory parameters are non-specific as well. For example, leucocytosis, often a physiological finding during pregnancy, is also present in several other abdominal diseases[40]. The non-specific clinical presentation is in line with the existing literature regarding this subject, and also with the known difficulties of the management of abdominal pain during pregnancy[33-34,40]. Multidisciplinary consultation seems warranted in these patients with a difficult to diagnose pathology.

The next pitfall (the sixth), studied in **Chapter 8**, is the timing of the surgical intervention. As mentioned in the previous paragraphs, patients' delay, doctors' delay, and delay by medical imaging are causes for delay of the surgical intervention. Unlike the study

published by Vannevel et al.[33] the results in **Chapter 8** showed that surgery >48 hours after onset of symptoms did not result in an increase in small bowel resections or preterm birth (p=0.677). Besides, in four cases, surgical intervention was on purpose delayed to reduce foetal risk due to an extremely premature gestational age. Three of them gave birth full-term without maternal or perinatal complications. The fourth woman (twin pregnancy), delivered spontaneously preterm at 28^{+5} weeks, about four weeks after the surgery. Timing of surgical intervention should be individualised keeping both maternal and foetal risk in mind.

A rare presentation of small bowel obstruction in pregnant women after bariatric surgery is intussusception. In **Chapter 9**, a systematic review regarding cases of intussusception during pregnancy in women with a history of a RYGB, published between January 2007 and August 2013, is described. This systematic review included only seventeen cases and was completed with six cases of a Dutch tertiary centre. All patients required surgical intervention, 73.9% required small bowel resection, and 26.1% gave birth during hospital admission. The intussusception was mostly retrograde and located at the jejunojejunostomy. Furthermore, six (33.3%) neonates required admission to the NICU and one neonate died. These results are comparable to two main studies about this subject[35,46], but worse compared to chapter 8, in which mostly patients with an internal herniation were included. This might indicate that intussusception is a more critical diagnosis than internal herniation. Overall, pregnancy following bariatric surgery is associated with the risk of acute small bowel obstruction with risks for both mother and (unborn) child.

FUTURE PERSPECTIVES

Bariatric surgery is rarely performed in adolescents and elderly. However for both groups it is a feasible treatment for their severe obesity. It will therefore be more frequently performed and/or implemented as standard care in both adolescents and elderly, although this must be under strong eligibility criteria.

Regarding adolescents, it has yet to be determined which bariatric procedure is most effective and whether bariatric surgery in adolescents is safe and effective in the long-term. Future studies should expand the follow-up, because a follow-up of ≥20 years is necessary to really determine the safety and efficacy. Furthermore, education and counselling of paediatricians, parents and adolescents might play a crucial role when discussing bariatric surgery in adolescents. It is evident that some of the controversy is concerning safety and efficacy[47-48], but also several ethical aspects have been mentioned, such as informed consent, personal autonomy and non-maleficence[47,49]. Therefore, it is

interesting and also important to gain a better understanding in the reasons for the reluctance to perform bariatric surgery in adolescents.

Focussing on elderly, it is interesting to explore if the following finding can be confirmed; sleeve gastrectomy is associated with increased severe short-term complications compared to gastric bypass in elderly. Another interesting future aim can be the development of a risk-model for complications, including factors like hypertension, obstructive sleep apnoea, female gender, and preoperative body mass index. These factors were all associated with increased severe short-term complications in our study (Chapter 4). Eventually, the indication for the surgery in elderly could better be balanced against the risk of complications with the help of a risk-model. Furthermore, future research should focus on long-term complicate rate, efficacy and quality of life. At last, prevention of complications should be a focus of interest in elderly. Prehabilitation has increasingly been proven to be beneficial in reducing postoperative complications, primarily in oncologic surgery. It would be interesting to see whether this can also be beneficial in patients undergoing bariatric surgery, for the general population but also specifically in elderly.

Part 2 of this thesis focused on small bowel obstruction during pregnancy after bariatric surgery. This is a rare complication of which knowledge and literature so far has been scarce. National registries for this specific group, and collaboration between several nations can increase knowledge of the severity of the problem, and can provide more inside in the best diagnostic approach and therapeutic plan. Multidisciplinary consensus statements (including among others bariatric surgeons, obstetricians, midwifes, and general practitioners), nationally and internationally, should be developed to optimize the antenatal and perinatal care, but also increase knowledge among doctors and possibly patients.

CONCLUSION

The prevalence of severe obesity is increasing worldwide and affecting all age groups. Bariatric surgery is the most durable treatment for severe obesity regarding weight loss and obesity related comorbidities and should therefore be available, under strong eligibility criteria, for all age groups. Patients should be assessed based on their biological age instead of chronological age. Regarding adolescents, literature has shown that bariatric surgery is safe and effective, but the best type of bariatric procedure for adolescents has to be determined. Focussing on elderly, the results in this thesis show that bariatric surgery is an acceptable option for elderly, with a comparable perioperative complication rate and 30-day mortality rate to non-elderly. However, 30-day complication rate was

twice as high. Therefore, bariatric surgery in elderly should be recommended on a case-by-case basis, in which the indication should be balanced against the risk of developing postoperative complications.

Despite the benefits, bariatric surgery also has some downsides, mainly the complications. Especially in pregnant patients, small bowel obstruction may lead to high risks for mother and (unborn) child. Therefore, awareness of this complication during pregnancy among doctors and patients, adequate antenatal care, multidisciplinary consultation and timely referral to tertiary centres with a NICU and bariatric expertise is advised to improve maternal and foetal outcome.

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11

Impact paragraph

IMPACT PARAGRAPH

A reflection of the scientific and social impact of the results of the research described in this thesis is described in this 'impact paragraph'.

(1) (Research) What is the main objective of the research described in the thesis and what are the most important results and conclusions?

Main objectives

Based on the known beneficial effects of bariatric surgery, the aim of part I of this thesis was to explore whether bariatric surgery is also safe and effective in adolescents and elderly and thus whether it is acceptable to widen the age criteria for bariatric surgery on both sites of the age bar.

The second part of this thesis aimed to make bariatric surgeons and obstetricians aware of small bowel obstruction related to the bariatric surgery during pregnancy and to get more insight in the diagnostic and therapeutic plan in order to improve maternal and foetal outcome.

Most important results and conclusions

As provided in the conclusion of the general discussion (Chapter 10) of this thesis; "The prevalence of severe obesity is increasing worldwide and affecting all age groups. Bariatric surgery is the most durable treatment for severe obesity regarding weight loss and obesity related comorbidities and should therefore be available, under strong eligibility criteria, for all age groups. Patients should be assessed based on their biological age instead of chronological age. Regarding adolescents, literature has shown that bariatric surgery is safe and effective, but the best type of bariatric procedure for adolescents has to be determined. Focussing on elderly, the results in this thesis show that bariatric surgery is an acceptable option for elderly, with a comparable perioperative complication rate and 30-day mortality rate to non-elderly. However, 30-day complication rate was twice as high. Therefore, bariatric surgery in elderly should be recommended on a case-by-case basis, in which the indication should be balanced against the risk of developing postoperative complications.

Despite the benefits, bariatric surgery also has some downsides, mainly the complications. Especially in pregnant patients, small bowel obstruction may lead to high risks for mother and (unborn) child. Therefore, awareness of this complication during pregnancy among doctors and patients, adequate antenatal care, multidisciplinary consultation and timely referral to tertiary centres with a NICU and bariatric expertise is advised to improve maternal and foetal outcome."

(2) (Relevance) What is the (potential) contribution of the results from this research to science, and, if applicable, to social sectors and social challenges?

Over many years, treating obesity and overweight is a main social challenge worldwide. This thesis provides evidence that for several populations outside of the set criteria, bariatric surgery is also a treatment option, which might help with the challenge of reducing the number of patients with severe obesity. With respect to this, the current thesis;

- Provides confirmation and education to the social sector that bariatric surgery is safe and effective to perform in selected adolescents and elderly with severe obesity.
- Lays the foundation for possible future implementation of bariatric surgery in adolescents as standard care (not only performing bariatric surgery in adolescents in the context of a scientific trial).
- Adds to the growing evidence that bariatric surgery in elderly in the Netherlands is safe in selected cases. For this reason, besides from other existing evidence that it is safe and effective in elderly, it should be implemented and standard care in the Netherlands.

Furthermore, the several studies in this thesis provide education to midwifes, obstetricians and bariatric surgeons, in order to make everyone aware of the risks and symptoms of small bowel obstruction during pregnancy after RYGB, so that timely diagnosis and treatment can be established.

Finally, providing definitions of the population and treatment outcomes is of utmost importance for science in general. Whatever the subject of the research is, defining study populations and treatment outcomes in the methods section of an article minimizes bias and enables comparison within literature. Standardized populations and outcomes, ideally with international consensus, would provide a solution.

(3) (Target group) To whom are the research results interesting and/or relevant? And why?

Part I of this thesis is relevant to adolescents and their parents and to elderly with obesity, as education about the treatment option of bariatric surgery for their obesity is of importance. Furthermore, for the same reasons, general practitioners as well as paediatricians should be made aware of this possible treatment option, as they are the physicians who are the first to be able to discuss this treatment option with elderly and adolescents respectively. Consequently, bariatric surgeons/centres will possibly see an increase in applications of these two groups. They also might have to adjust their preop-

erative screening process. Finally, the results regarding elderly can also be of relevance for the insurance companies. As bariatric surgery has been known as a cost-effective procedure, in elderly this can be an extra argument for insurance companies to allow bariatric surgery in selected patients.

Part II of this thesis is relevant for fertile women undergoing bariatric surgery or with a history of bariatric surgery. They should be made aware of the risk on small bowel obstruction during pregnancy, so that they can react fast and prevent delay from their side. Furthermore, midwifes and obstetricians as well as bariatric surgeons also need to be made aware of this complication to prevent doctor's delay.

(4) (Activity) In what way can these target groups be involved in and informed about the research results, so that the knowledge gained can be used in the future?

First of all, the main results of most of the chapters described in this thesis have been presented at national and international congresses. Second, this thesis will be distributed among all bariatric surgeons who are member of the DSMBS. Third, Chapter 8 has been translated to Dutch and is published in the Dutch magazine for Obstetrics and Gynaecology, which is distributed among all members of the Dutch Society of Obstetrics and Gynaecology. At last, our research team has provided their collaboration in several national guidelines, among others the new guideline for bariatric surgery in which we contributed to the part regarding adolescents. Next to this, we also collaborated in a 'factsheet' of the Dutch society for midwifes regarding pregnancy after bariatric surgery.

12

Samenvatting (Dutch summary)

SAMENVATTING

Deel 1 – Indicaties buiten de geldende leeftijdscriteria

In 1997 werden verschillende criteria opgesteld, ook wel indicaties, waaraan een patiënt moet voldoen om in aanmerking te komen voor bariatrische chirurgie (IFSO-richtlijnen). Sinds 1997 heeft de bariatrische chirurgie zich doorontwikkeld, waarbij open technieken plaats hebben gemaakt voor laparoscopische technieken en het aantal uitgevoerde bariatrische operaties per jaar sterk is toegenomen.

Daarnaast is de levensverwachting van zowel mannen als vrouwen aanzienlijk toegenomen. De indicaties die zijn opgesteld in 1997 zijn daarom verouderd en moeten mogelijk worden aangepast aan de huidige situatie. Deel 1 van dit proefschrift had als doel om te onderzoeken of de leeftijdscriteria voor bariatrische chirurgie kunnen worden aangepast.

Hoewel bariatrische chirurgie bij adolescenten (<18 jaar) met obesitas al in de jaren '70 werd uitgevoerd, werden pas in het afgelopen decennium twee grote prospectieve studies gepubliceerd. Deze studies concludeerden dat bariatrische chirurgie bij adolescenten een veilige en effectieve behandeling is als aanvulling op leefstijlinterventie. De twee meest uitgevoerde bariatrische chirurgische procedures, Roux-en-Y gastric bypass (RYGB) en gastric sleeve (SG), zijn echter beperkt met elkaar vergeleken. Dit kennishiaat belemmert een optimale procedure selectie voor adolescenten.

Dit hiaat is precies waar de TEEN-BESTrial een antwoord op wil gaan geven. De TEEN-BESTrial is een internationale, gerandomiseerde multicenter studie, waarin de RYGB wordt vergeleken met de SG bij adolescenten (leeftijd van dertien t/m zeventien jaar) met obesitas (**Hoofdstuk 2**). De studie is een samenwerking tussen bariatrisch chirurgen en kinderartsen. Het screeningsproces voor inclusie wordt uitgevoerd door een onafhankelijk multidisciplinair team en wordt gecombineerd met leefstijlinterventie.

Desalniettemin dienen de adolescenten en hun ouders achter de bariatrische chirurgie inclusief het natraject te staan, terwijl de kinderartsen adolescenten en hun ouders dienen te informeren en door te verwijzen. Daarom is de mening ten aanzien van bariatrische chirurgie bij adolescenten onderzocht door middel van een anonieme enquête onder Nederlandse kinderartsen, adolescenten met ernstig overgewicht en hun ouders (**Hoofdstuk 3**). De studie laat zien dat bariatrische chirurgie bij adolescenten in toenemende mate wordt geaccepteerd als mogelijk effectieve behandeloptie door Nederlandse kinderartsen. Bijna drie op de vijf kinderartsen zou een adolescent doorverwijzen. Wat betreft de ouders van adolescenten met ernstig overgewicht, zou slechts

44,9% toestaan dat hun kind wordt verwezen voor bariatrische chirurgie. Bovendien gaf de meerderheid van de ouders (61,2%) en adolescenten (73,7%) aan dat bariatrische chirurgie alleen moet worden aangeboden in de vorm van familiegerichte zorg.

In **Hoofdstuk 4** wordt een studie beschreven die het doel had om te onderzoeken wat de veiligheid van bariatrische chirurgie bij ouderen (≥65 jaar) is. Het betreft een retrospectieve cohortstudie waarbij gebruik is gemaakt van een nationale database. Deze database bevat pseudo-anonieme gegevens voortkomend uit de verplichte registratie voor bariatrische chirurgie in Nederland (DATO). Resultaten lieten zien dat er perioperatief bij 1,2% van de ouderen complicaties zijn geregistreerd versus 1,1% bij niet-ouderen (p=0.733). Een ernstige complicatie ≤30 dagen van de bariatrische chirurgie werd gemeld bij 4,5% van de ouderen en 2,2% van de niet-ouderen (p<0.001). Daarentegen was het percentage heropnames als ook het sterftecijfer binnen 30 dagen na de operatie niet significant verschillend. De complicaties na 30 dagen tot twee jaar na de operatie waren zelfs meer prevalent onder niet-ouderen (5,9% versus 2,3%, p<0.001). Bariatrische chirurgie bij ouderen met obesitas is een veilige optie, al dient wel per patiënt beoordeeld te worden of de verwachte voordelen opwegen tegen de mogelijke complicaties.

De focus in **Hoofdstuk 5**, een systematische review van de literatuur, lag op het gebruik van uniforme definities om resultaten van behandelingen in de literatuur te kunnen vergelijken. In dit artikel hebben we een patiëntvriendelijkere terminologie voorgesteld voor enkele uitkomstmaten na bariatrische chirurgie: primaire responder (“succes”), primaire non-responder (“falen”) en secundaire non-responder (“weight regain”). Voor deze uitkomstmaten werd in een derde deel van de artikelen geen duidelijke definitie gegeven. In de overige artikelen werden wel definities gegeven, maar bleken deze flink van elkaar te verschillen; er werden thirteen, 23 en seventeen verschillende definities gevonden voor respectievelijk primaire responder, primaire non-responder en secundaire non-responder. Door het gebruik van verschillende definities voor uitkomstmaten, maar ook voor bijvoorbeeld onderzoekspopulaties, is het mogelijk voor het auteurs om de resultaten te ‘manipuleren’ en dat maakt vergelijking tussen artikelen onmogelijk. Gestandaardiseerde populaties en uitkomsten, idealiter met internationale consensus, zijn nodig om deze ‘manipulatie’ van resultaten te voorkomen en om literatuur te kunnen vergelijken.

Deel 2 - Abdominale bariatrische complicaties tijdens de zwangerschap

De meerderheid van de patiënten ervaart een positief resultaat na bariatrische chirurgie t.a.v. gewichtsverlies en genezing van comorbiditeiten, zoals hypertensie en type II diabetes. Sommige patiënten ontwikkelen echter complicaties. Deze complicaties kunnen

zich op korte termijn voordoen, zoals een nabloeding of naadlekkage, of op de lange termijn, zoals zuurbranden, onverklaarbare buikpijn en obstructie van de dunne darm[1]. Een obstructie van de dunne darm kan ook optreden tijdens de zwangerschap, waarbij een operatie soms direct geïndiceerd is. Een operatie gaat echter gepaard met risico's voor zowel moeder als ongeboren kind.

Het tweede deel van dit proefschrift richt zich op het optreden van een obstructie van de dunne darm tijdens de zwangerschap bij vrouwen met in de voorgeschiedenis een RYGB. Er wordt gekeken naar de maternale en perinatale uitkomsten. Daarnaast worden ook zes mogelijke valkuilen besproken, waarbij er ruimte is voor verbetering van de huidige zorg.

De eerste valkuil is de onbekendheid en het gebrek aan ervaring onder bariatrische chirurgen, wat kan leiden tot 'doctors' delay'. In **Hoofdstuk 6** is deze valkuil onderzocht met behulp van een online enquête die is verspreid onder Nederlandse bariatrische chirurgen. Slechts 38,9% van de bariatrische chirurgen had een casus gezien met ernstige complicaties bij moeder en/of foetus/neonaat. Er was één kliniek die een casus vermeldde met perinatale sterfte.

De tweede valkuil is 'patients' delay' en slechte prenatale zorg. De huidige praktijk en voorkeuren van Nederlandse bariatrische chirurgen ten aanzien van de prenatale zorg voor zwangere vrouwen na bariatrische chirurgie zijn ook bestudeerd in **Hoofdstuk 6** middels een online enquête. Slechts 33,3% van de bariatrische chirurgen verwijst zwangere vrouwen door naar zowel de verloskundige als de diëtist. Verder roept maar de helft van de bariatrisch chirurgen een zwangere patiënt op voor een aanvullend consult op hun polikliniek voor (herhaalde) voorlichting over RYGB-gerelateerde risico's tijdens de zwangerschap. Elke zwangere vrouw zou na bariatrische chirurgie moeten worden voorgelicht over de alarmsymptomen van mogelijke abdominale bariatrische complicaties tijdens de zwangerschap. Multidisciplinaire richtlijnen kunnen de zorg verbeteren.

De derde valkuil is de behandeling van zwangere vrouwen met RYGB-gerelateerde obstructie van de dunne darm in een ziekenhuis zonder een neonatale intensive care unit (NICU). Dit wordt bestudeerd in **Hoofdstuk 6**. Van elk bariatrisch centrum werd ten minste één volledige respons verkregen. Uit de enquête bleek dat verwijzing van zwangere vrouwen naar een centrum met een NICU in Nederland geen standaardzorg is, aangezien 52,9% van de bariatrische centra zonder NICU deze patiënten nooit zou doorverwijzen. Dit betekent ook dat er geen verwijzing van zwangere patiënten onder een zwangerschapsduur van 32 weken is en er dus geen gespecialiseerde zorg voor premature neonaten aanwezig is. Wij raden aan om vrouwen die een bariatrisch chirur-

gische ingreep nodig hebben tussen 24 en 32 weken zwangerschap, door te verwijzen naar een centrum met een NICU.

Naast doorverwijzing naar een gespecialiseerd ziekenhuis met een NICU en bariatrische expertise, is het ook zaak om de diagnostiek zo veel mogelijk te optimaliserne. **Hoofdstuk 7** beschrijft een retrospectieve, single-center cohortstudie, waarin de diagnostische nauwkeurigheid van de MRI-scan voor RYGB-gerelateerde obstructie van de dunne darm tijdens de zwangerschap werd beoordeeld. Verder gaf het onderzoek inzicht in de vierde valkuil: vertraagde of gemiste diagnose door medische beeldvorming. De resultaten lieten een acceptabele sensitiviteit en specificiteit van de MRI zien (beide 66,7%), met een hoge positief voorspellende waarde (93,3%). Verder werd een structurele beoordeling geadviseerd, gericht op een combinatie van specifieke tekens ('swirl-sign', 'small-bowel-obstruction-sign' en 'clustered-loop-sign'), aangezien de aanwezigheid van één van deze tekens de kans op aanwezigheid van een obstructie van de dunne darm vergroot. In **Hoofdstuk 7** wordt echter ook vermeld dat de MRI bij bijna één op de drie patiënten geen obstructie van de dunne darm zal detecteren (gemiste diagnose). Vertraging door de MRI of gemiste diagnose lijkt de maternale of perinatale uitkomst niet te verslechteren, aangezien er slechts één geval van maternale morbiditeit werd gemeld. We raden een MRI alleen aan als de klinische verdenking op een obstructie van de dunne darm laag is. Bij een hoge klinische verdenking blijft diagnostische laparoscopie de gouden standaard.

Hoofdstuk 8 presenteert een single-center, retrospectieve cohortstudie, gericht op de maternale en foetale uitkomsten bij zwangere patiënten met acute buikpijn die verdacht worden van een obstructie van de dunne darm. Van de vrouwen werd 74,0% geopereerd, waarbij in 16,2% resectie van een stuk dunne darm noodzakelijk was. Diagnoses waren onder andere inwendige herniatie (72,2%), open mesenteriale defecten (8,3%) en invaginatie (16,7%). Er werd geen maternale of perinatale mortaliteit gezien in de chirurgische groep. Echter, 8,1% van de vrouwen beviel tijdens de ziekenhuisopname, 18,9% van de vrouwen beviel prematuur en 8,5% van de pasgeborenen moest worden opgenomen op de NICU.

Een ander doel van de studie beschreven in **Hoofdstuk 8** was het in kaart brengen van de klinische presentatie. De studie toonde aan dat de klinische presentatie niet-specifiek is: de vijfde valkuil. De belangrijkste symptomen die werden gevonden waren buikpijn (in verschillende regio's), misselijkheid en braken. Deze symptomen zijn vaak onschuldig tijdens de zwangerschap, maar kunnen ook wijzen op ersntige aandoeningen, zoals appendicitis, gastro-enteritis en loslating van de placenta. Multidisciplinair overleg lijkt gerechtvaardigd bij deze patiënten.

De laatste (zesde) valkuil, bestudeerd in **Hoofdstuk 8**, is de timing van de chirurgische ingreep. De resultaten laten zien dat chirurgie >48 uur na het begin van de symptomen niet resulteerde in een toename van resecties van de dunne darm of vroeggeboorte. Bovendien werd de operatie bij vier patiënten met een zeer vroege zwangerschapsduur (amenorroeduur tussen 23^{+5} en 24^{+4} weken) bewust uitgesteld om het foetale risico te verminderen. Drie van hen zijn à terme bevallen zonder complicaties. De vierde vrouw (tweelingzwangerschap) beviel spontaan preterme bij 28^{+5} weken, ongeveer vier weken na de operatie.

Een zeldzame presentatie van dunne darm obstructie tijdens zwangerschap na bariatische chirurgie is invaginatie. In **Hoofdstuk 9** wordt een systematische review beschreven over casussen van zwangere patiënten na bariatrie met een invaginatie. Alle casussen gepubliceerd tussen januari 2007 en augustus 2013 werden geïncludeerd. Daarnaast werden zes casussen van een Nederlands tertiair centrum toegevoegd. De studie liet zien dat alle patiënten moesten worden geopereerd. Bij 73,9% van de vrouwen was resectie van een stuk dunne darm noodzakelijk en 26,1% van de vrouwen beviel tijdens ziekenhuisopname. De invaginatie was meestal retrograad en gelokaliseerd bij de jejunojejunostomie. Verder moesten zes pasgeborenen (33,3%) worden opgenomen op de NICU en werd er één perinatale sterfte gerapporteerd. Zwangerschap na bariatrische chirurgie is geassocieerd met het risco op een dunne darm obstructie gerelateerd aan de eerdere bariatrische ingreep, met mogelijke risico's voor zowel moeder als (ongeboren) kind.

CONCLUSIE

De prevalentie van ernstige obesitas neemt wereldwijd toe, in alle leeftijdsgroepen. Bariatrische chirurgie is de meest succesvolle behandeling voor ernstige obesitas op de lange termijn ten aanzien van gewichtsverlies en remissie van comorbiditeiten. Daarom zou bariatrische chirurgie voor alle leeftijdsgroepen beschikbaar moeten zijn. Patiënten moeten worden beoordeeld op basis van hun biologische leeftijd in plaats van chronologische leeftijd. Met betrekking tot adolescenten heeft onderzoek aangetoond dat bariatrische chirurgie veilig en effectief is, maar welke procedure het meest geschikt is moet nog verder worden onderzocht. Ten aanzien van ouderen heeft dit proefschrift laten zien dat bariatrische chirurgie een acceptabele optie is, waarbij de perioperatieve complicaties en 30-dagen mortaliteit vergelijkbaar zijn met de algemene bariatrische populatie. Echter, de ernstige complicaties binnen 30 dagen waren twee keer zo hoog bij ouderen (4,4% versus 2,2%). Daarom moet op individuele basis bekeken worden of bariatrische chirurgie is geïndiceerd, waarbij de indicatie moet worden afgewogen tegen de risico's.

Een bekende complicatie na RYGB is obstructie van de dunne darm. Dit kan ook voorkomen tijdens een zwangerschap en geeft risico's voor zowel moeder als foetus. Het advies is om artsen en patiënten bewust te maken van deze complicatie tijdens de zwangerschap, om patiënten adequate prenatale zorg te geven en om multidisciplinair overleg met (indien nodig) tijdige verwijzing naar tertiaire centra met een NICU te bewerkstelligen om de maternale en perinatale uitkomsten te optimaliseren.

Dankwoord (acknowlegdments)
List of publications
Curriculum Vitae

DANKWOORD

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CURRICULUM VITAE

Daniëlle Susan Bonouvrie was born on the 7th of February 1992 in Arnhem, the Netherlands. She grew up with two sisters and one brother in Huissen. She graduated from high school in 2010 at the Olympus College in Arnhem. Afterwards, she studied Medicine at the Radboud University of Nijmegen. In the first year of her studies she moved to Nijmegen.

Her passion for surgery was aroused during her regular surgical internship at Rijnstate Hospital, after which she decided to apply for the 'dedicated transition year surgery'. She was accepted and performed here clinical internships during this year also at Rijnstate Hospital. For her scientific internship, she went to Perth, Australia, were she was supervised by surgeon Harsha Chandraratna, who has a private clinic for bariatric surgery.

After receiving her doctor's degree in March 2017, she started working for three years as a PhD student at Máxima Medical Centre, Veldhoven, focusing on bariatric surgery, a specialization she was already familiar with. She was supervised by Professor Jan Willem Greve, Dr. Francois van Dielen, and Dr. Wouter Leclercq.

Since 2020 she has been working as a medical doctor (ANIOS), first at the surgical department of Hospitalgroup Twente. She currently works at the surgical department of hospital Gelderse Vallei. Daniëlle lives with her husband Matt and daughter Linde in Doorwerth.