Female fertility and bariatric surgery - Getting past the wall?

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- Getting past the wall?

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DOCTORAL DISSERTATION

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The overarching aim of this thesis was to investigate patients' expectations and the effects of bariatric surgery on female fertility in terms of changes in body image, sexuality, sex hormones and IVF results, along with exploring patients' experiences of surgery.

In the qualitative study I, 12 women were interviewed and answered HADS and FSFI questionnaires before and after bariatric surgery. In the prospective cohort study II, anthropometric and questionnaire data were analysed together with hormones in 48 women operated with bariatric surgery and followed for one year. Study III consists of a national population-based register-study where live-birth rate in first IVF cycle, and birth outcomes were compared between women previously operated with bariatric surgery and controls matched on post-surgery BMI, age, and parity.

We found that young women seeking bariatric surgery seem to have high expectations on future childbearing, considering the operation as a mean to achieve normality including improved fertility. Hormonal imbalances were corrected after surgery, with a lowered free androgen index, but we also found decreased AMH levels below the expected normal age-related decline. Psychological and sexual quality of life outcomes were improved, related to improved body image and self-esteem. There was no difference in live-birth rate after IVF for women with previous bariatric surgery compared to non-operated control women matched for a BMI corresponding to post-surgery BMI, but the mean birth weight of the infants was lower in the bariatric surgery group.

Improved psychological and sexual quality-of-life outcomes as well as correction of hormonal imbalances could contribute to increased fertility after bariatric surgery and are in line with the high expectations on future childbearing. When needing IVF, there was no negative effect of bariatric surgery on the live birth rate.

Key words: Obesity, Female fertility, bariatric surgery, anti-Müllerian hormone, Sexual function, Assisted reproductive technology

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"I'm sure that my problems to get pregnant are related to my weight. But let me tell you, I've already tried EVERYTHING. Can't you just refer me for bariatric surgery?"

(Female Patient)

Table of Contents

Thesis at a glance

STUDY	PAPER	AIM	RESULTS & CONCLUSIONS
I	I: To Get Back on Track: A Qualitative Study on Childless Women's Expectations on Future Fertility Before Undergoing Bariatric Surgery.	To explore the motives behind young women's wishes to go through a major surgical procedure, and their expectations on future fertility.	The master theme "To get back on track" was identified along with three subthemes, "A better me", "A fertile me" and "A pregnant me". The participants were hoping that weight-loss would make them feel more content with themselves, break isolation and make it easier to find a partner. The participants considered fertility to improve after bariatric surgery, mainly based on stories from other patients of bariatric surgery. Having a child was expressed to be of great importance to them. The operation was regarded a means to achieving normality including improved fertility.
II	II: Impact of diet and bariatric surgery on anti-Müllerian hor-mone levels.	To evaluate changes in serum levels of AMH and sex hormones following weight loss first achieved by very low-calorie diet (VLCD) and then the more pronounced weight-loss after bariatric surgery.	The Free Androgen Index was significantly lower after twelve months, compared to BL (0.012 vs 0.035, p<0.0005).Median AMH levels were 30.0 pmol/L at BL and rose significantly after VLCD (median: 35.0 pmol/L; p=0.014). Median AMH at six and twelve months postoperatively were significantly lower (19.5 pmol/L and 18.0 pmol/L, respectively; p=0.001). Hormonal imbalances are corrected after bariatric surgery, however, AMH levels decreased below the expected normal age-related decline.
I	III: A New Beginning: Young Women's Experiences and Sexual Function 18 Months After Bariatric Surgery.	To explore how women perceive the effects of bariatric surgery on quality of life, focusing on sexual health and fertility.	"A new beginning" was identified as the master theme, with three underlying subthemes: "Being worthy of love", "Exploring sexuality" and "Considering parenthood". The participants described a transformation into being more comfortable with themselves that affected all areas of life, including sexual life. These findings were supported by lower scores for depression, 6.5 vs 2, and improved total FSFI scores, median 23.3 preoperatively and 29.1 postoperatively, p = 0.012. Improved quality-of-life, psychological well-being and sexuality seem related to improved body image and self-esteem.
III	IV: Outcomes of in vitro fertilitzation after bariatric surgery: A national register-based case-control study.	To investigate if outcomes of IVF differ between women with a history of bariatric surgery compared with non-operated control women matched for a BMI corresponding to post-surgery BMI.	There was no significant difference in cumulative live-birth rate between the BS group and the matched controls (29.4% compared to 33.1%), even though the number of retrieved oocytes (7.6 vs 9.0, p = 0.005), and frozen embryos (1.0 vs 1.5, p = 0.032) were significantly fewer in the BS group. The birth weight was significantly lower in the children born to mothers with previous BS, mean (SD) 3190 (690) g vs 3478 (729) g, p = 0.037. There was no negative effect of bariatric surgery on IVF outcomes.

List of papers

This thesis is based on the following papers, which have been reprinted with permission from the publishers. Throughout the thesis, the four studies are referred to with Roman numerals.

I. Nilsson-Condori E, Jarvholm S, Thurin-Kjellberg A, Sidlovskaja I, Hedenbro JL, Friberg B. To Get Back on Track: A Qualitative Study on Childless Women's Expectations on Future Fertility Before Undergoing Bariatric Surgery. Clin Med Insights Reprod Health 2019;13:1-7.

II. Nilsson-Condori E, Hedenbro JL, Thurin-Kjellberg A, Giwercman A, Friberg B. Impact of diet and bariatric surgery on anti-Mullerian hormone levels. Human reproduction, 2018;33(4):690-93.

III. Nilsson-Condori E, Jarvholm S, Thurin-Kjellberg A, Hedenbro JL, Friberg B. A New Beginning: Young Women's Experiences and Sexual Function 18 Months After Bariatric Surgery. Sex Med, 2020;8(4):730-739.

IV. Nilsson-Condori E, Mattsson K, Thurin-Kjellberg A, Hedenbro JL, Giwercman A, Friberg B. Outcomes of in vitro fertilitzation after bariatric surgery: A national register-based case-control study. *Manuscript*

Abstract

Obesity is an increasing global epidemic with serious comorbidities leading to a shorter life expectancy. In women, obesity also causes problems related to the ability to conceive, to miscarriage and pregnancy complications. Bariatric surgery is the most effective treatment for obesity, but there is yet no consensus regarding recommending obese infertile women to undergo bariatric surgery due to lacking studies.

The overarching aim of this thesis was to investigate patients' expectations and the effects of bariatric surgery on female fertility in terms of changes in body image, sexuality, sex hormones and IVF results, along with exploring patients' experiences of surgery.

In the qualitative study I, 12 women were interviewed and answered HADS and FSFI questionnaires before and after bariatric surgery. In the prospective cohort study II, anthropometric and questionnaire data were analysed together with hormones in 48 women operated with bariatric surgery and followed for one year. Study III consists of a national population-based register-study where live-birth rate in first IVF cycle, and birth outcomes were compared between women previously operated with bariatric surgery and controls matched on post-surgery BMI, age, and parity.

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Improved psychological and sexual quality-of-life outcomes as well as correction of hormonal imbalances could contribute to increased fertility after bariatric surgery and are in line with the high expectations on future childbearing. When needing IVF, there was no negative effect of bariatric surgery on the live birth rate.

Sammanfattning på svenska

Fetma, definierat som BMI 30 kg/m^2 eller högre, är ett ökande hälsoproblem med risk för allvarlig sjuklighet och därmed förkortad livslängd. I Europa har mer än 20% av befolkningen fetma. En vanlig konsekvens av fetma hos kvinnor, är nedsatt fertilitet. Graviditetsfrekvensen är lägre hos kvinnor med fetma, och fetma är kopplat till en fördubblad tid för att uppnå graviditet jämfört med normalviktiga kvinnor hos par som försöker uppnå graviditet på egen hand. Viktnedgång utan kirurgisk behandling ger förbättrad möjlighet att uppnå graviditet.

På grund av fetmans negativa effekt på fertiliteten, framförallt i form av graviditetskomplikationer, finns idag BMI-gränser för behandling av infertilitet med IVF, som i Sverige varierar mellan 30 och 35. De kvinnor som har högre BMI än så, hänvisas till viktnedgång med hjälp av livsstilsförändringar innan de kan bli aktuella för behandling. Allt fler patienter med fetma genomgår idag överviktskirurgi, för att minska i vikt. För att bli aktuell för operation krävs dock BMI över 40 alternativt BMI över 35 och annan samsjuklighet såsom t.ex. diabetes.

Av de opererade patienterna är ca 75% kvinnor, varav 50% i fertil ålder. Graviditet efter överviktskirurgi anses som en riskgraviditet p.g.a. en ökad risk för en kortare graviditetslängd och att barnen föds små för tiden, även om vissa andra risker minskar. Vad gäller betydelsen av överviktskirurgi för att uppnå graviditet finns det ännu ej konsensus. De studier som finns, tyder på att viktminskningen efter operation bidrar till normaliserade nivåer av könshormoner, regelbundnare menstruationer och förbättring av polycystiskt ovariesyndrom (PCOS). Därför diskuteras det internationellt om huruvida PCOS, och även infertilitet skulle kunna betraktas som samsjuklighet och därmed vara en indikation för överviktskirurgi om BMI är över 35.

Avhandlingens syfte var att undersöka effekten av överviktskirurgi på kvinnans fertilitet genom att studera påverkan på kroppsbild, sexualitet och könshormoner inklusive markören för äggstocksreserven AMH, som är kopplad till utfallet vid IVF. Vi ville även undersöka operationens påverkan på IVF-resultat, tillsammans med kvinnors specifika förväntningar på, och erfarenheter av, operationen.

I den första studien, publikation I och III, djupintervjuades tolv kvinnor före och efter överviktskirurgi om sina förväntningar, skäl till att opereras, och erfarenheter rörande kvinnohälsa efteråt. De fyllde också i enkäter som mäter depression, ångest och sexuell funktion. I den andra studien mättes hormonnivåer inklusive AMH på 48 kvinnor före operation, och vid tre tillfällen fram till ett år efter operation. Kvinnorna fyllde även i en enkät rörande kvinnohälsa. I den tredje studien använde vi data från tre svenska kvalitetsregister för att undersöka hur IVF-resultaten ser ut efter överviktskirurgi. Resultaten för opererade kvinnor jämfördes med jämgamla kvinnor, som också hade fött barn/eller inte, och som hade samma vikt som de opererade kvinnorna hade efter sin operation.

Resultaten av våra studier har visat att unga kvinnor som ännu inte har fött barn har höga förväntningar på livet efter operationen, och att den även ska leda till ökade chanser för barnafödande. Även om fertilitet inte är huvudanledningen till att opereras, så är det en starkt bidragande orsak till att välja operation.

Efter operationen beskrev kvinnorna ett förbättrat allmänt mående, bättre självförtroende och kroppsbild, som de ansåg bidrog till ett förbättrat sexliv. Detta kunde även utläsas av enkätsvaren. Det manliga könshormonet testosteron sjönk efter operationen, vilket är positivt för kvinnor med PCOS. Vi fann dock även lägre AMH-värden efter operation, vilket tyder på att man riskerar att övervärdera överviktiga kvinnors äggstocksreserv. Ett lägre AMH är negativt vid IVF, och när vi jämförde IVF-resultaten såg vi också att de opererade kvinnorna fick ut färre ägg, och färre embryon - men resultaten avseende antal födda barn var trots detta likvärdiga, kanske för att andra mekanismer kompenserar. Barnen till de opererade kvinnorna hade dock en betydligt lägre födelsevikt.

Sammantaget visar avhandlingen att efter överviktskirurgi förbättras allmänt mående, hormonnivåer och sexliv, vilket kan bidra till en förbättrad fertilitet. De kvinnor som behöver hjälp med IVF efter operationen kan förvänta sig likartade resultat som för icke-opererade kvinnor med samma BMI, dock med en lägre födelsevikt för barnen.

Abbreviations

AGB	Adjustable Gastric Banding
AgRP	Agouti-Related Peptide
AMH	Anti-Müllerian Hormone
ART	Assisted Reproductive Technologies
BMI	Body Mass Index
BPD	Biliopancreatic Diversion
CCK	Cholecystokinin
CI	Confidence Interval
CLBR	Cumulative Live Birth Rate
CPR	Clinical Pregnancy Rate
FAI	Free Androgen Index
FSFI	Female Sexual Function Index
FSH	Follicle Stimulating Hormone
GDM	Gestational Diabetes Mellitus
GH	Growth Hormone
GLP-1	Glucagon-like peptide 1
GnRH	Gonadotropin Releasing Hormone
HADS	Hospital Anxiety and Depression Scale
hCG	Human Chorionic Gonadotropin
HRQL	Health-related quality of life
ICSI	Intracytoplasmic Sperm Injection
IL-6	Interleukin 6
IVF	In *vitro* fertilization
LBR	Live Birth Rate
LGA	Large for Gestational Age
LH	Luteinizing Hormone
MBR	Medical Birth Register
α-MSH	α-melanocyte-stimulating hormone
NPY	Neuropeptide Y
OP-9	Obesity Problems scale
OR	Odds Ratio
PCOS	Polycystic Ovary Syndrome
POMC	Proopiomelanocortin
PTB	Preterm birth
PYY3-36	Peptide YY
Q-IVF	National Quality Register for Assisted Reproduction
QoL	Quality of Life
RYGB	Roux-en-Y-Gastric Bypass
SF-36	Short Form 36
SG	Sleeve Gastrectomy
SGA	Small for Gestational Age
SHBG	Sex Hormone-Binding Globulin
SOReg	Scandinavian Obesity Surgery Registry
SRHR 2017	Sexual and Reproductive Health and Rights 2017
T2DM	Type-2 Diabetes Mellitus
TNF-α	Tumour Necrosis Factor alfa
VLCD	Very Low-Calorie Diet

Preface

While doing my specialist training in Obstetrics and Gynaecology at the regional hospital of Kristianstad, I got interested in the field of reproductive medicine. Meeting couples facing problems with infertility, I recognised that many of them were obese. This was troublesome in two ways. First, obesity itself could be a probable cause of the infertility, and secondly, because of that and obstetric risks related to obesity, there is a BMI limit for access to fertility treatments. Knowing how difficult it is to lose weight, you might imagine that it is not very positively received advice to recommend life-style changes and weight loss. Obesity is classified by WHO as a disease, but in the eyes of the patient the individual is still held responsible for their situation because of the BMI limits – a wall between them and the desired children – as there is no offer of other treatments than the ones most had already tried and failed. I got many questions about bariatric surgery, but at that time, there was not much research on how bariatric surgery affects female fertility and the results of assisted reproduction. Hence, I decided this to be my subject.

This thesis was carried out within the Reproductive Medicine Group, Lund University, the Department of Obstetrics and Gynaecology, the Regional Hospital of Kristianstad and the Centre for Reproductive Medicine, Skåne University Hospital. An interdisciplinary and national collaboration was developed while designing the studies to be included in the PhD project, including bariatric surgery expertise from Aleris Obesity, the department of Surgery, psychology expertise and colleagues from the Reproductive Medicine unit at the Sahlgrenska University Hospital, together with epidemiological expertise from Division of Occupational and Environmental Medicine, Lund University. The design of the study protocols was performed jointly, as were the applications to the Regional Ethical Review board. I planned and performed the data collections, including co-ordinating blood samples and questionnaires. I also co-ordinated and performed interviews and obtained register data. In collaboration with my supervisors and co-authors, I performed the data analyses and wrote the four papers included in this thesis.

Introduction

Obesity is an increasing global epidemic with comorbidities such as high blood pressure, cardiovascular disease and diabetes that are common causes of death, thus leading to a shorter life expectancy. In women, obesity causes problems related to the ability to conceive, miscarriage and pregnancy complications.

Bariatric surgery is the most effective treatment for obesity, indicated in patients with a BMI > 40, or in patients with comorbidities and a BMI > 35. There is yet no consensus regarding recommending obese infertile women to undergo bariatric surgery. But could infertility be regarded a comorbidity, and does bariatric surgery improve fertility?

Obesity

Body mass index (BMI) is a measure for indicating nutritional status in adults. It is defined as a person's weight in kilograms divided by the square of the person's height in metres (kg/m^2).[1] Obesity, the accumulation of excess fat-mass, is defined as a BMI over 30 kg/m^2; the range 25–30 kg/m^2 is defined as overweight. See Table 1 for definitions.

Table 1.
BMI classes

BMI	CATEGORY
<18.5	Underweight
18.5–24.9	Normal Weight
25–29.9	Overweight (Preobesity)
30–34.9	Obesity Class I
35–39.9	Obesity Class II
≥40	Obesity Class III (Morbid obesity)

Prevalence

The prevalence of obesity has nearly tripled worldwide since 1975 and is now considered a global health epidemic. In the world, in 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese.[1] In Sweden, statistics from 2018, showed a prevalence of overweight or obesity among persons aged 16-84 years of 51%, of those 16% were obese.[2]

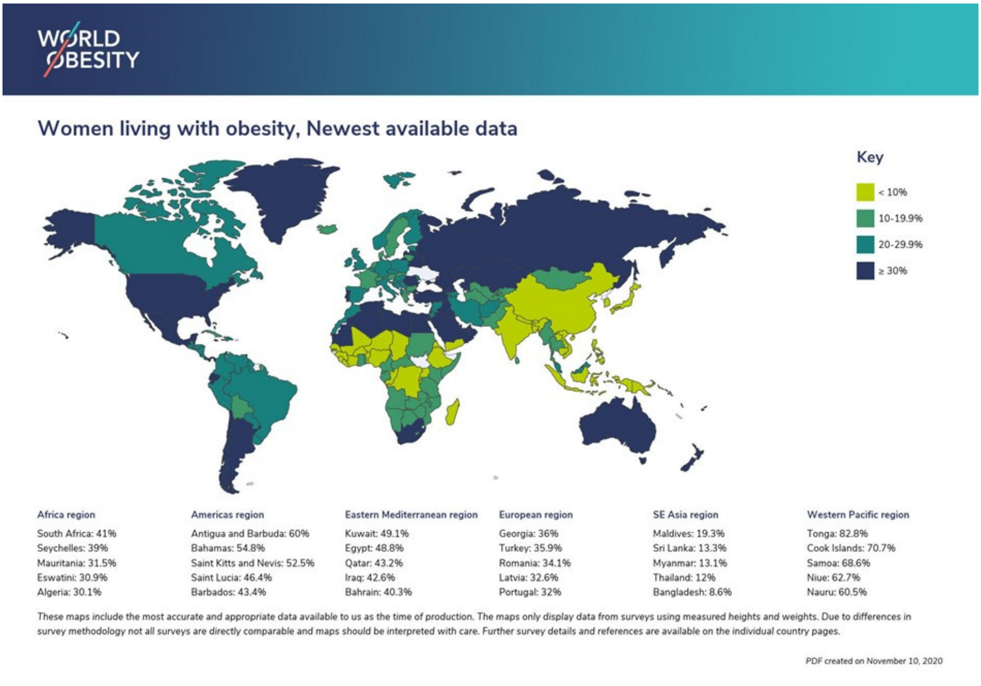

Figure 1. Women living with obesity, Newest available data.
Source: World Obesity Federation. Presentation map available as a PDF from https://data.worldobesity.org/maps/

Aetiology

Still, many people believe that obesity is a matter of individual responsibility and mainly an issue in affluent countries. That is not true - obesity is not a choice.[3] Most of the world's population live in places where overweight and obesity kill more people than underweight.[4 5] Obviously, obesity is caused by an imbalance of energy consumption, i.e. eating more calories than the energy expenditure, which is basic metabolism and physical activity.[6] Side effects of certain medicines, including some corticosteroids, medications for epilepsy and diabetes, some mood stabilisers and antipsychotics can sometimes also contribute to weight gain.

Obesogenic behaviours in an obesogenic environment

Urbanisation and sedentary work due to industrialisation, paired with the easy access of food aided by globalisation, has led to reduced energy expenditure, and increased caloric intake. These societal changes are now termed the 'obesogenic' environment.[7] On the other hand, exposure to obesogenic environments will not always result in obesity in the individual. Instead, the propensity to obesity is determined by biological factors such as age, sex, in utero factors, microbiome, epigenetics, and genes.[3] Predominantly there is a susceptibility to obesity by genetic traits that many of us carry, as discussed already in the 1940's.[8] Twin and family studies have convincingly demonstrated that 40–75% of body mass index (BMI) variation is attributed to genetic factors.[9 10] Monogenic disorders of obesity, where Prader-Willi and Bardet-Biedl are among the most recognized, are very rare and co-occur with clinical features such as intellectual disability, dysmorphic features or organ-specific abnormalities.[11] It has also been shown that there is a genetic continuum between monogenic and polygenic forms of obesity, that points out the role of genes involved in the central regulation of food intake and genetic predisposition to obesity.[12]

Hormonal Regulation of Metabolism

Adiponectin is an insulin-sensitivity regulator secreted by white adipose tissue. Levels of adiponectin are lower in patients with obesity, because of decreased hepatic expression of adiponectin receptors. Low levels are associated with insulin-resistance. Weight loss, on the other hand, increases adiponectin levels.[13] Cholecystokinin (CCK) is secreted from the duodenum in response to food, and functions to decrease food intake, and delay gastric emptying.[14] Leptin (from Greek *leptos = thin*), a long-term mediator of satiety, is mainly secreted from adipocytes and correlates to the amount of energy stores. Leptin levels are elevated in obese people, but treatment with leptin has failed hence suggesting a state of leptin resistance.[13]

Table 2.
The key hormonal regulators.

HUNGER	SATIETY
GHRELIN	Adiponectin
	CCK
	Leptin
	PYY3-36
	GLP-1

Peptide YY 3-36 (PYY3-36), secreted from the small bowel, delays gastric emptying, reduces food intake, and induces satiety.[14] Glucagon-like peptide-1 (GLP-1) is co-secreted with PYY3-36, and induces satiety by delaying gastric emptying and suppressing appetite centrally. GLP-1 also promotes insulin secretion and can increase glucose sensitivity.[14] Ghrelin, secreted from gastric and duodenal enteroendocrine cells, is the only hunger-stimulating hormone. Ghrelin receptors are found in the appetite control centre in the arcuate nucleus of the hypothalamus. During fasting, ghrelin is increased, which contributes to the difficulty of hypocaloric dieting for weight loss.

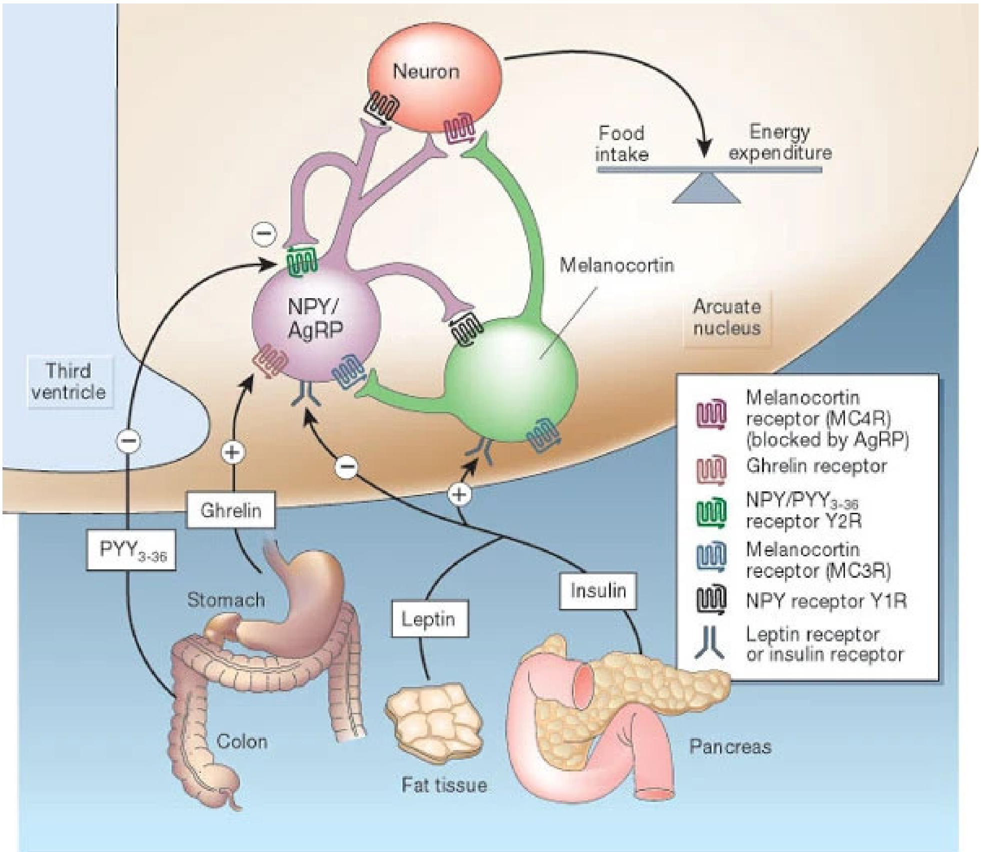

Figure 2. Hormonal regulation of food intake and energy expenditure

The target neurons in the arcuate nucleus produce different neurotransmitters, such as neuropeptide Y (NPY) and agouti-related peptide (AgRP). These are activated when the body lacks energy, thus stimulated by Ghrelin. In the opposite situation, in cases of high energy levels, the neurons are instead inhibited by leptin. Proopiomelanocortin (POMC) neurons are activated by increasing glucose levels, and release α-melanocyte-stimulating hormone (α-MSH) that activates the melanocortin receptor 4 (MC4R) and subsequently acts as a stop signal for feeding behaviour. However, there are negative feedback signals by NPY/AgRP on the POMC system. These cause a bias towards a positive energy balance – which probably have had evolutionary advantages in times when food was scarce, but nowadays contribute to obesity. Any mutation in these hormones, or their receptors, could lead to obesity. One example is binge-eating disorder caused by mutations or polymorphism in the MC4R gene coding for the receptor that receives the transmitted signals of leptin.[15]

In the 1960's J.V. Neel outlined the 'thrifty gene' hypothesis. Genes that predispose to obesity would have had a selective advantage in populations that frequently experienced starvation. People who possess these genes in today's obesogenic environment might be those that 'overreact' — that not merely become slightly overweight but become extremely obese[16].

"Barker's hypothesis" Barker stated the hypothesis that undernutrition in utero permanently changes the body's structure, function and metabolism in ways that lead to coronary heart disease in later life. The association between low birth weight and coronary heart disease has been confirmed by longitudinal studies around the world.[17] However, the Barker's hypothesis has been extended and available evidence suggests that poor maternal and paternal periconceptional nutrition can increase the risk of metabolic syndrome in offspring, through epigenetic imprinting.[18] There are also other illustrations of epigenetic imprinting, such as a study where women exposed to smoking during foetal life were at higher risk of developing gestational diabetes and obesity.[19] Another is the finding that maternal exposure to the pesticide DDT was associated with increased obesity risk among middle-aged women[20].

Consequences of obesity

Obesity is a major threat to physical health, with recognised fatal and non-fatal comorbidities such as type 2 diabetes mellitus (T2DM), coronary heart disease, stroke, high blood pressure, sleep apnoea, osteoarthritis, and several forms of cancer (breast, colorectal, liver, endometrium). This has negative effects on longevity, disability-free life-years, quality-of-life, and productivity.[21]

Reduced levels of adiponectin contribute to the development of T2DM, but adipose tissue also produces tumour necrosis factor alpha (TNF-α), an inflammatory mediator that reduces insulin sensitivity and is also thought to be involved in the development of T2DM, with increased insulin-resistance. Other immunoregulatory mediators like interleukin-6 (IL-6) are also secreted, contributing to considering obesity as an inflammatory state in the body.[22]

A multi-cohort study measured the loss of disease-free years attributable to major noncommunicable diseases in obese adults compared with those who were normal weight. Individuals lost 3–4 more disease-free years if they were mildly obese and 7–8 more disease-free years if they were severely obese.[23]

Stigma of obesity

As stated in a recent International Consensus statement,[3] "individuals affected by overweight and obesity face a pervasive form of social stigma based on the typically unproven assumption that their body weight derives primarily from a lack of self-discipline and personal responsibility." This is related to discrimination, - in childhood the risk for poor peer relations and high rates of bullying, as well as in adulthood with undermined opportunities for employment, career progression, and income for people with obesity.[3] In a Swedish study, treatment-seeking young adults (18-25 years) had doubled relative risks for mental distress, depression, anxiety and suicidal behaviour compared to individually matched population controls.[24] Health-related quality of life (HRQL) as investigated by Sullivan et al[25] in the Swedish Obese Subjects study was found to be worse in the severely obese than in several other groups of patients with chronic conditions. High levels of obesity-related psychosocial problems in everyday life and dysfunction in social interaction were also observed. On a societal level, a higher proportion of overweight and obesity in a population leads to greater use of health services, resulting in higher treatment costs for the many obesity-related diseases than in a less obese population, coupled with productivity losses due to staff working while sick, to unplanned absences and loss of productivity from premature deaths.[21]

Treatment

Treatment of obesity has a long history, and during the last decades attempts to develop methods for weight loss have been intensified.

Prevention programmes

Since the Global Burden of Disease Study 2010[26] identified that dietary factors are the most important factors that undermine health and well-being in several parts of the world, there have been efforts made to change public health policy in the same way that has led to progress in tobacco control and cardio-protective diets with decreased deaths caused by cardiovascular diseases and smoking-related diseases. Results, that are now threatened by rises in BMI.[21] One such attempt is the European Food and Nutrition Action Plan 2015-2020[27] and the action towards banning trans fats.[28] Prevention programmes are still not yet fully implemented, and have so far been unsuccessful.

Dietary intervention

Life-style interventions combining diet and exercise can give a substantial weight loss, with observable effects on diabetes within months.[29] Patients are counselled to reduce their caloric intake to create a deficit of around 500 kcal/day, but weight loss varies highly due to heritable factors.[30] Among the most popular diets is the highly effective Mediterranean diet which consists of 50% carbohydrates, 20% protein and 30% fat while prioritizing fruits, vegetables, healthy fats, nuts, and fish.[31]

No specific diet plan has proven more effective, as long reduction of energy intake occurs. Recently, for example, intermittent fasting has grown in popularity. Lowe et al. examined the effects of time-restricted eating (a form of intermittent fasting where food consumption is limited to a particular time window in every 24 h) in people with overweight or obesity, and found that time-restricted eating did not have a significant effect on weight loss or a range of metabolic parameters.[32]

It is well known that losing weight through a change in diet is very challenging, most people regain weight because of the physiological responses to weight loss, such as increased hunger and slower metabolism. Massive weight loss, as in the Biggest Loser competition has been found to be associated with metabolic adaptation, and more worrying, this metabolic slowing persists independently of weight regain.[33]

Medical Management

The list of medications for weight loss is relatively small, and although it offers treatment options for the physician, it needs to be emphasized that the most effective non-operative means of achieving sustained weight loss is through behavioural changes in energy intake and expenditure.

The list of medications includes GLP-1 agonist Liraglutide, lipase inhibitor Orlistat, 5-HT agonist Lorcaserin, sympathomimetic and antiepileptic Phenterminetopiramate and opioid antagonist and antidepressant Naltrexonebupropion, - all of which have potential adverse effects and average weight loss varies between 2,5 – 8,9 kgs.[34]

Most studies are however short-term and with high levels of drop out.

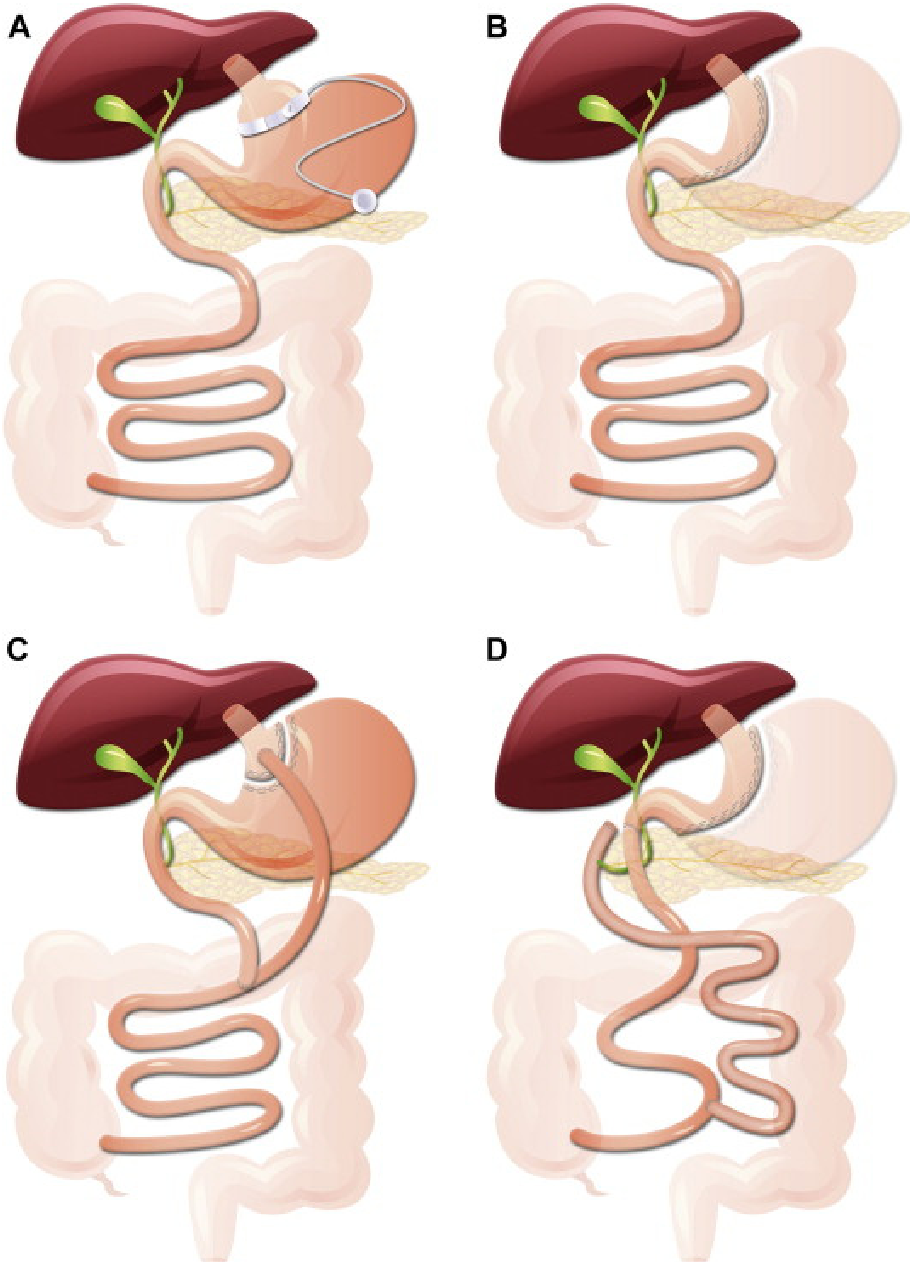

Figure 3. Bariatric surgery techniques A=adjustable gastric band B=sleeve gastrectomy C=Roux-en-Y gastric bypass D=biliopancreatic diversion. Reprinted from Canadian Journal of Cardiology, Vol 31 (2), Marie-Ève Piché, Audrey Auclair, Jany Harvey, Simon Marceau, Paul Poirier, How to Choose and Use Bariatric Surgery in 2015, Pages No 153-66., Copyright (2015), with permission from Elsevier.

Bariatric surgery

Bariatric surgery, being the most effective treatment for obesity, has developed and increased during the last decades. The surgery can be divided into restrictive and malabsorptive procedures, or a combination of both described as hybrids.[35] Restrictive surgeries limit the food intake by reducing the stomach size and include adjustable gastric band (AGB) Fig 3A and sleeve gastrectomy (SG) Fig 3B. The AGB is an implanted inflated band device in the upper part of the stomach. The band is connected to a subcutaneous reservoir port where saline is injected for its adjustment. The patient achieves appetite control and satiety as the upper pocket fills up quickly and the band slows the passage of the food. Due to long-term side effects the AGB is largely abandoned. In SG nearly 80% of the stomach along the greater curvature is removed, creating a narrow tubular stomach while leaving the pylorus structurally intact. The sleeve gastrectomy is increasing in popularity since it does not involve intestinal rearrangement and thus preserves normal intestinal nutrient flow. A recently introduced technique is minimally invasive endoscopic sleeve gastroplasty,[36] but there are not yet any long-term studies.

Fig. 3C The Roux-en-Y Gastric Bypass (RYGB) operation bypasses ~95% of the stomach and upper gastrointestinal tract by creating a small gastric pouch just under the oesophagus, then anastomosing the mid- to distal jejunum directly to the small pouch. The remainder of the stomach and the proximal intestine remain in the body with intact nerve and blood supply. They are excluded from nutrient flow but drain via the duodenum to the jejunum. Thereby, nutrients from the small gastric pouch are brought together with bile acids and digestive enzymes. This leads to increased signalling of satiety, a changed eating-pattern, but also malabsorption of iron and vitamins.[35] Another potential adverse effect is severe hypoglycaemia, often associated with symptoms of dumping syndrome, which occurs as a result of the rapid gastric emptying seen after RYGB.[37]

The biliopancreatic diversion (BPD) malabsorptive procedure, later modified including the duodenal switch (BPD-DS) Fig. 3D was the first method introduced and yields a very good and sustained weight loss. It involved a gastric restriction with a SG, and then the duodenum is transected approximately 4 cm distal to the pylorus and anastomosed to a 250 cm alimentary limb of ileum. The biliopancreatic limb, which consists of the distal duodenum, jejunum, and proximal ileum, contains the biliopancreatic secretions attaches to the alimentary limb approximately 100 cm from the ileocecal valve. The BPD-DS therefore has a greater malabsorptive component than the RYGB.[35]

In contrast to dietary interventions and medical management, bariatric surgery (specifically RYGB and SG) results in substantial weight loss that is maintained over time. Typically, around 75% of excess weight is lost after one year, and health related quality of life is improved.[38] The weight loss has also proven sustainable with good effects after 10 and 20 years of follow-up.[39-41]

RYGB is an effective treatment for some people with type 2 diabetes and is associated with improvements in other obesity-related complications, including risk of cardiovascular disease.[41] Carlsson et al. found that bariatric surgery prolonged average life expectancy by 3 years compared with non-surgical obesity treatment.[42] With increasing numbers of procedures annually, the mortality rates have dropped over the years,[43] and it is now considered a safe and low risk procedure, on par with the risks for cholecystectomy.

Eligibility for bariatric surgery includes BMI ≥ 40, or BMI ≥ 35 with comorbidities in which surgically induced weight loss is expected to improve the disorder (such as metabolic disorders, cardio-respiratory disease, severe joint disease, obesity-related severe psychological problems).[44]

Bariatric surgery, though effective at reducing body weight and related comorbidities, and improving quality of life is still invasive and associated with complications, thus not seen as an easy way out by patients. In a qualitative study, the "tipping point" for the decision to proceed with bariatric surgery was patients' own perception of worsening health issues and low energy levels limiting activities.[45]

Young Women and Fertility

Although pointed out as the potential "winners" in individualistic and neoliberal Western societies, being a young woman of today is not easy. There is hard pressure on this group to make the "right choices", with demands from society and peers on everything from looks to career, sexual-life and childbearing.

Psychosocial health

Young women are generally a vulnerable group. Recent Swedish statistics from 2018, showed that one third of women aged 16-29 years self-reported mental distress. Mild or severe anxiety and hospitalization due to self-injury is over-represented among young women.[2] This trend starts already in early adolescence. When examining school-aged children in Europe and North America regarding health complaints such as headache, stomach-ache, backache, depressed mood, irritability, nervousness, sleeping difficulties and dizziness, the investigators found a robust pattern of increasing gender differences across age with 15-year-old girls as a group at increased risk for health complaints across all countries.[46]

Societal demands

The period between late teens and through the twenties has been conceptualized as emerging adulthood in industrialised or post-industrial countries. Changes in educational patterns and delayed marriage and parenthood, lie behind that it is no longer normative to settle into long-term adult roles during this period. While not having entered the enduring responsibilities of adulthood, these years are now a period of exploration of possible life directions in love, work, and worldviews. However, social class, educational and occupational opportunities limits the extent to which young people can experience their late teens and twenties as a volitional period.[47] Wiklund et al.[48] explored the stressors of young women in a Swedish qualitative study. Their results revealed that multiple and intersecting discourse-shaped stressors and demands connected to essential life spheres contribute not only to experiences of distress but also to feelings of constraint. Stressors of modernity included striving to experience as much as possible, get an education, and to create a good life before settling down. There were also stressors of gendered o rders, “To please and care for others” “Being responsible and taking responsibility” and the “Problematic female body and self” and the authors concluded that gendered individualism and healthism proved to be essential in understanding the young women’s experienced stress.

Body image

In comparison with young men, young women seem to consider health a more difficult project involving managing and monitoring practices associated with eating and exercise to maintain an "appropriate" body shape.[49] Body, and body image represent integral part of self-image and identity.[50] However, unrealistic ideals of beauty in the media are an important source of social comparison, and a possible cause of body dissatisfaction.[51] An Australian self-report questionnaire study also revealed a significant association between higher body dissatisfaction and higher ratings of peer stress, lower self-esteem, and greater body importance for both female and male adolescents.[52]

Sexuality

The median age at first sexual intercourse was 15 years in a Swedish study from 2011.[53] Girls were more sexually experienced than boys, as were students in vocational programmes compared to their theoretical peers.[53] A good sexual life is important, and has previously shown protective benefits, such as greater mental health satisfaction,[54] and higher levels of relationship and emotional satisfaction.[55] Of women aged 16-29 years, 57% report that they are content with their sexual life, as compared to 63% among 30-44 year old women.[56] A Swedish qualitative study showed that young women's ideal images of sexual situations were characterized by sexual pleasure on equal terms, implying that no one dominates and both partners get pleasure.[57] However, young women face several obstacles, and a functioning sexual life is not self-evident. There is a high prevalence of pain and/or discomfort associated with sexual intercourse among young women,[58] and almost half of those continue to have vaginal intercourse despite pain, prioritizing the partner's enjoyment before their own, indicating that young women take a subordinate position in sexual interactions.[58] In the national study “Sexual and reproductive health and rights 2017” (SRHR 2017) from the Public Health Agency of Sweden, young women and men were the most frequent users of the Internet for sex-related activities such as looking for information, reading sexually arousing texts, or looking for a partner.[56] Another aspect of being exposed and compared on the internet, is that a poor evaluation of, and behaviour towards body image has shown to be detrimental to women's sexual functioning, and dissatisfaction with one's body has been found to predict decreases in desire and arousal.[59] Common cultural stereotypes promote women’s submission to men, especially within intimate heterosexual relationships. Mirroring these stereotypes, women possess nonconscious associations between sex and submission. These associations predict impaired ability to reach orgasm among women.[60]

Fertility

Oocytes and the ovarian reserve

Women are born with all their reproductive cells, oocytes, or informally – eggs. The oocytes are part of a follicle, which is filled with fluid containing hormones and growth factors and has surrounding cell layers. During the 16th week of gestation, the foetal ovary is formed with its peak number of about 7 million primordial follicles.[61] Originating from germ cells, oogonia have undergone the first step of meiosis and developed into primary oocytes. Thereafter, there is a continuous degeneration of primordial follicles, by birth there are 700 000 – 2 million, and at onset of puberty only around 400 000 primordial follicles remain. This is the ovarian reserve, which continues to diminish with age.

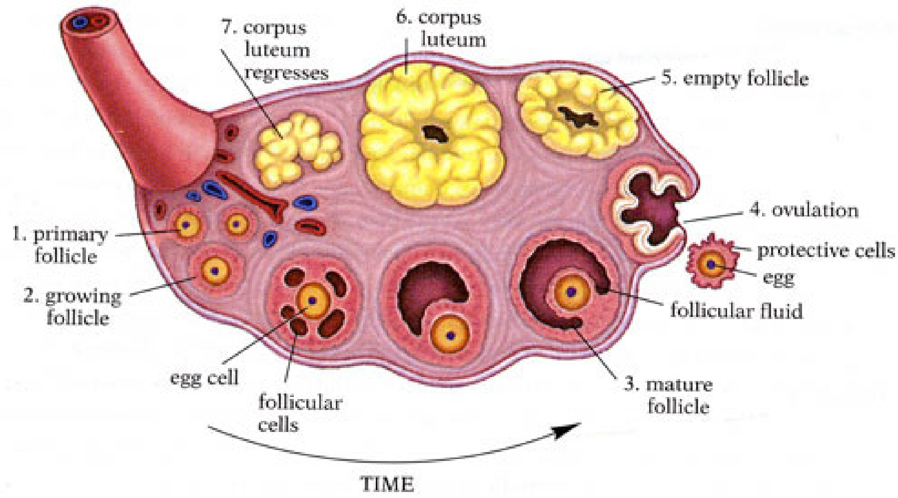

Figure 4. Ovary and follicular development.
Attribution: Anatomy of the ovaries Kimanh Nguyen, CC BY-SA 3.0, via Wikimedia Commons.

Follicular development and the menstrual cycle

Menstrual cycles start at puberty, with the purpose of producing a single female gamete and an endometrium prepared to receive a fertilized embryo. Gonadotropin releasing hormone (GnRH) stimulates the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary. The recruitment and maturation of oocytes begin. Although most primordial follicles are still held in a dormant state, they are continuously recruited to join the early growing cohort (initial recruitment). This is a gonadotropin-independent process, which leads to growth from a size of 0.15 mm to 1.0 mm, and takes about 70 days. There is a rapid growth to 5 mm's and FSH in the luteal phase in the previous cycle stimulates the differentiation into antral follicles.

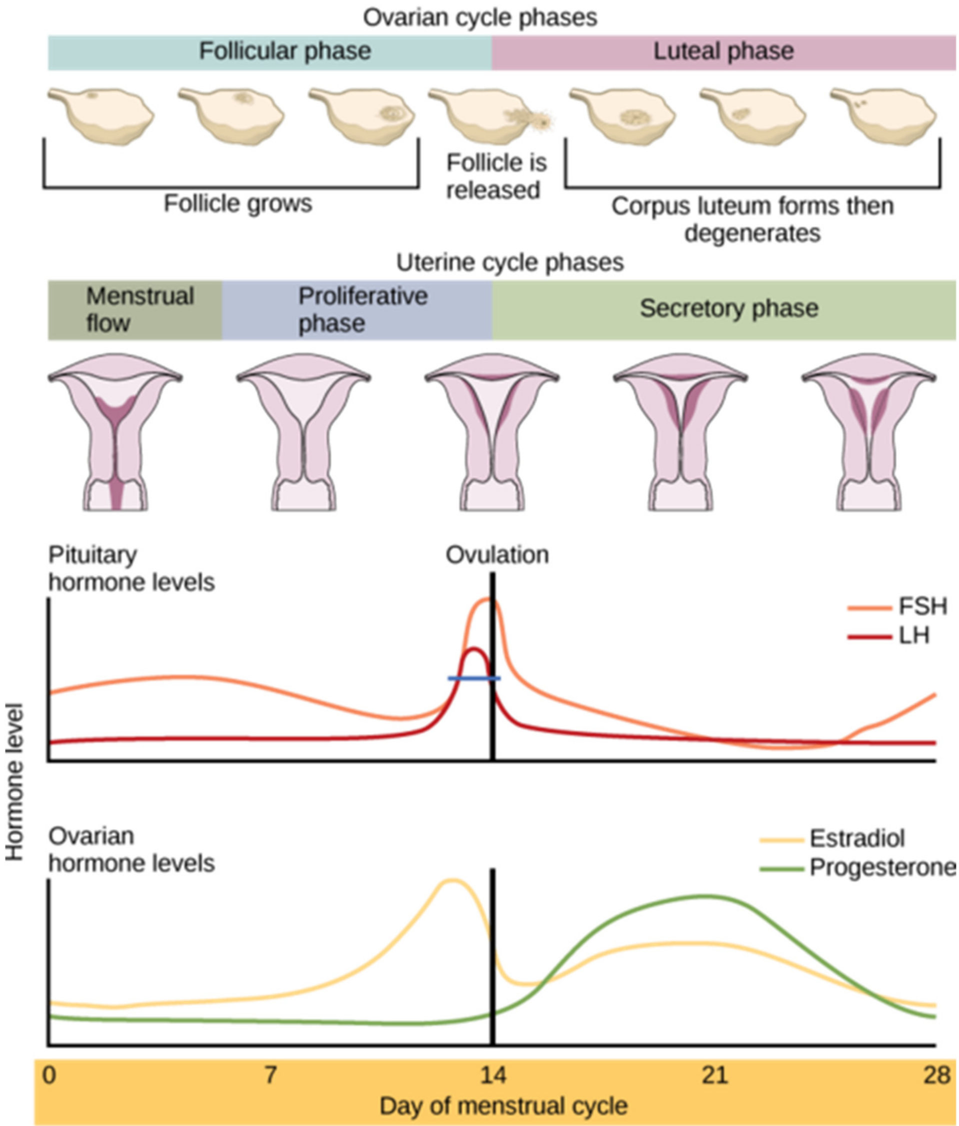

Figure 5. The menstrual cycle
Attribution: CNX OpenStax, CC BY 4.0, via Wikimedia Common

As the FSH level rises in in the late luteal phase and the first days of the menstrual cycle, there is a recruitment of follicles sized around 5 mm. These follicles are FSH sensitized and rapidly increase their number of covering granulosa cells (primary follicles). Around the oocyte, the zona pellucida forms, separating it from the surrounding granulosa cells. Stimulated by FSH and LH, the granulosa cells produce increasing levels of oestrogen, and the antrum is formed in these secondary follicles.

Meanwhile, oestrogen stimulates the endometrium to grow. In every new cycle a limited number of follicles are recruited from this cohort of small growing follicles (cyclic recruitment), followed by a final selection around day 6 (depending on the number of FSH-receptors) for dominance of a single follicle, while the rest are deemed to atresia at earlier stages.[62] The dominant follicle produces high levels of oestrogen, which inhibits FSH and triggers the LH peak that leads to ovulation, generally around day 14 of the cycle. The meiosis that has been in arrest since foetal life, continues during the maturation but is completed first when the oocyte is fertilized. After ovulation, the follicle collapses and forms the corpus luteum where the granulosa- and theca-cells now starts producing oestrogen and progesterone, where the latter causes maturation of the endometrium to receive the fertilized oocyte. The corpus luteum is viable for 11-13 days, but its degeneration is prevented if hCG from an early pregnancy is present. If not, the falling levels of progesterone and oestrogen cannot support the endometrium anymore, and a menstruation is initiated.

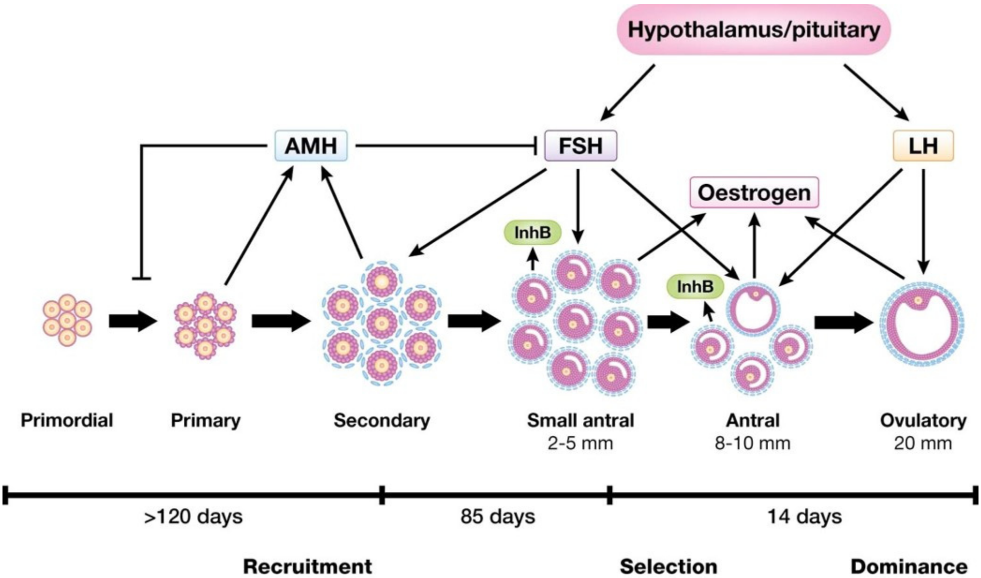

Figure 6. Folliculogenesis.
AMH = anti-Müllerian hormone; InhB = inhibin B.
Reprinted from Reproductive BioMedicine Online, Volume 31 Issue 4, Richard Fleming, David B. Seifer, John L. Frattarelli, Jane Ruman, Assessing ovarian response: antral follicle count versus anti-Müllerian hormone, Pages 486-496 (October 2015), with permission from Elsevier

AMH

Anti-Müllerian Hormone (AMH) is a dimeric glycoprotein and a member of the transforming growth factor beta (TGF-β) family. Granulosa cells in antral and pre-antral follicles produce AMH. Acting as a gatekeeper, AMH both inhibits recruitment of primordial follicles, as well as reduces oestrogen production and FSH sensitivity in growing follicles, thereby contributing to the selection of a dominant follicle.[63] See Fig 6. Thus, the circulating level of AMH reflects the number of growing follicles and can be used to assess the ovarian reserve. Peak concentrations of AMH are seen at age 24.5 years.[62] Levels thereafter decline with age, on average by 5,6% per year,[64] until unmeasurable at menopause. Although representing the number of growing follicles, AMH is not related to oocyte quality or live birth.[65] However, AMH can be used to monitor ovarian response in fertility treatment, [66] in order to make ovarian stimulation well tolerated and effective.

Infertility

Prevalence

Infertility, defined as the inability to conceive after 12 months of unprotected intercourse, without any other reason such as breastfeeding or postpartum amenorrhea, is estimated to affect 3.5 - 16.6 % of reproductive age couples worldwide. [67] In the Swedish Sexual and Reproductive Health and Rights 2017, 3% are involuntarily childless, whereas 5% in all age brackets do not want children. [56] Infertility is stated to be a public health problem according to WHO, and the United Nations has included infertility and its treatment as part of Sexual and Reproductive Human Rights.

Aetiology in the female

It is generally said that infertility is caused by 1/3 to female factors, 1/3 to male factors and 1/3 a combination of both female and male factors or unknown factors.

Ovulatory disorders are common, affecting up to ¼ of all infertile women.[61] However, infertility rates have increased in the last century, mainly due to problems associated with increasing maternal age and postponing childbearing.[68] The woman's age is the single most important predictive factor for the chance of a live birth. At higher age, a decreased ovarian reserve, and an increase in chromosomal abnormalities due to aneuploidy, results in failed implantation and/or increased miscarriage rate. In 2019 the mean age for women in Sweden having their first child was 29.6 years,[69] and fertility declines progressively after age 30-32.[61]

Other factors of importance for infertility also increases with age, such as myomas and endometrial polyps that disturb the uterine environment. Pelvic infections and endometriosis are other examples, where both can compromise tubal patency. Lifestyle factors such as smoking, alcohol-intake, and tea/coffee consumption as well as overweight are known to negatively affect time to pregnancy.[70]

Treatment

Of those with infertility, 76% seek medical care.[67] Ovarian stimulation with ovulation-inducing fertility drugs include clomiphene citrate and aromataze inhibitors such as letrozole, and exogen gonadotropins. Sometimes treatments include intrauterine insemination, in natural cycles or with ovarian stimulation. The efficiency of these treatments varies with the underlying cause of infertility. The most effective treatments encompass techniques involving direct manipulation of oocytes outside of the body, known as assisted reproductive technology (ART).

ART

Fertility treatments by assisted reproductive technologies (ART) including In Vitro Fertilization Treatment (IVF) and Intracytoplasmic Sperm Injection (ICSI) are widely available within the tax-financed health care system in Sweden. The treatments are based on stimulation of the ovaries with supraphysiologic doses of gonadotropins (FSH) to achieve growth of several ovarian follicles. The aim is to obtain several oocytes to fertilize in the laboratory.

Injections containing recombinant FSH (rFSH) or urinary-derived gonadotropin (hMG) are administered for 10±2 days. Only follicles that have reached the mature state of FSH dependency are possible to recruit. Vaginal ultrasound examination is used to monitor follicle size. There are two different treatment protocols to prevent premature ovulation: one using GnRH-agonists for down-regulation of the pituitary starting on day 21 of a previous cycle and continuing until ovulation induction, the other blocks the pituitary with GnRH-antagonists. When three or more follicles reached mature size, ovulation is induced with an injection of hCG similar LH. Oocyte pick-up (OPU) is undertaken by ultrasound guided transvaginal puncture 36 hours after the hCG injection.

Procedures for fertilization are IVF, where the oocytes and spermatozoa are mixed, and fertilization occurs after natural selection. The other technique is ICSI, where a single sperm is injected to into an oocyte. After embryo culture of 2-5 days, one embryo with the best characteristics is transferred to the womb of the woman. Surplus embryos can be frozen for later thawing and transfer. Luteal phase support with vaginal progesterone is administered for 14 days, starting from the day of the oocyte pick-up.

Outcomes of ART are reported as Live Birth Rate (LBR) per started cycle or per OPU, predominantly used in Sweden. Worldwide, clinical pregnancy rate (CPR) per started cycle or per OPU is also common. Treatment cancellations are common both before OPU and before transfer, thus these measurements give lower rates than the CPR or LBR per transfer. In the Swedish National Quality Register for Assisted Reproduction (Q-IVF) the average LBR per started cycle in 2016 was 22%, all age groups included.[71] In the yearly ART surveillance from the United States a total of 197,706 ART procedures with the intent to transfer at least one embryo resulted in

65,964 live birth deliveries giving a 33% LBR, with a multiple birth rate of 31.5%.[72] ART has been associated with adverse birth outcomes, such as preterm birth after fresh blastocyst (day 5) transfer,[73] and large-for-gestational-age offspring after frozen embryo transfer.[74]

Obesity in Young Women

Prevalence

The prevalence of obesity is increasing in children and adolescents, as well as young women worldwide. Since 1975, the prevalence of obesity has nearly tripled,[75] and in the WHO European Region, now one in three 11-year-olds is overweight or obese[76]. In Sweden, data from 2018 show that 7% of women aged 16-29 years are obese, and the number has increased to 14% in the age group 30-44 years.[77]

Psychosocial health

Poor mental health is more common in young obese women, depressive and anxiety disorders are overrepresented. In a Swedish study, treatment-seeking young adults (18-25 years) had doubled relative risks for mental distress, depression, anxiety, and suicidal behaviour compared to individually matched population controls[24]. Stigma and negative body image might increase mental distress in this group. Unrealistic ideals of beauty in the media are an important source of social comparison, and a possible cause of body dissatisfaction among certain boys and girls[51].

Studies on bariatric surgery candidates have also shown a high prevalence of psychopathology and personality disturbance, and that they differ from other obese women in splitting, impulsivity, and difficulties in intimate partnerships[78 79]. In a study on obese women with PCOS, a link between body dissatisfaction, distorted self-perceived body image, sexual dysfunction, and depression was suggested[80].

Sexual health in obese women

Compared to women of healthy weight severely obese women engage in fewer romantic and sexual behaviours.[81 82] Subgroups of severely obese females engage in higher rates of sexual risk behaviours with unplanned pregnancies and sexually transmitted infections.[81 82] It is not uncommon that these women receive no birth control information from physicians and they are less likely to take contraceptives.[81 82] Female sexual dysfunction is more common, and higher BMI is associated with greater impairments in sexual quality of life, with obese women and gastric bypass surgery candidates reporting worse data.[83]

Obesity-related infertility

It is important to remark that all obese women are not infertile. However, obese women have an increased risk of experiencing problems related to fertility. Previously, obesity-related infertility has been considered caused by anovulation and hyperandrogenism. However, these are features of polycystic ovary syndrome (PCOS), the prevalence of which is around 6.5 – 8%.[84] Non-syndromic obesity is much more prevalent than PCOS and seems to have another pathophysiology of the reproductive impairment. There is some evidence that endometrial factors play a considerable role. Obese women seem to have an altered gene expression during the implantation window of natural cycles, which is even more pronounced in women also presenting with PCOS.[85] Further support is the association between lower implantation rates and increasing BMI, as studied in obese donor egg recipients.[86 87] Oocyte quality is also affected, as shown in studies where increasing oocyte donor BMI is associated with a reduction in clinical pregnancy and live birth rates.[88].

Time to pregnancy

Obese women have an almost three-fold probability to suffer infertility as compared with women of a BMI within the normal range.[89] In a study on life style factors affecting fertility, obesity was associated with a doubled time to pregnancy.[70] These findings were confirmed in a large retrospective cohort study from 7,327 US couples, where women with higher BMI had a longer time to pregnancy than their normal weight counterparts. The association also remained when the analysis was restricted to women with regular menstrual cycles.[90]

Miscarriage

There is evidence that obesity may increase the general risk of miscarriage, [91] and even more so in the case of recurrent miscarriage.[92] In a Danish internet-based study of 5,132 women planning pregnancy there was a hazard ratio for miscarriage of 1.23 in obese women compared to non-obese controls.[93] In a recent prospective cohort analysis of more than 18,000 nulliparous Chinese women there was an 1.5 increased risk for miscarriage, even though the authors defined obesity at the Asian level of a BMI $\geq$ 27.5.[94] In an observational study on 372 women with recurrent pregnancy loss, obese women had an increased risk of euploid miscarriage risk as compared with non-obese controls.[95]

Endocrine changes

As previously described, the body's state of energy metabolism is regulated and communicated by the complex leptin-ghrelin system. Although many of the mechanisms remain to be elucidated, it is well known that there is a connection between reproduction and the body's state of energy metabolism. Better explored is the anorectic situation, where excess levels of ghrelin inhibit gonadotropins via GnRH.[96] Pulsatile release of GnRH from the hypothalamus is the central driver of the reproductive hypothalamus – pituitary - ovarian axis (HPO axis), and many of the neurones that link directly or indirectly to the GnRH neurones also have compounds that are involved in appetite control, such as NPY, αMSH, oxytocin, galanin, and galanin-like peptide - all of which can either be stimulated or down regulated by the metabolic hormones leptin, insulin and ghrelin.[96]

Anovulation

Chronic anovulation can be diagnosed in patients with oligomenorrhea (defined as less than eight periods per year, or cycles exceeding 35 days) or amenorrhea (absence of menstruation for more than three months without pregnancy).[84] Obesity causes an endocrine milieu characterized by insulin resistance, which appears to be related to anovulation. Chronic insulin stimulation, like in the situation of overeating, also causes upregulation of the LEP gene, and nearly all obese individuals have elevated leptin levels.[97] Chronic elevated leptin levels could lead to down-regulation of this receptor in the brain.[97]

Obese women generally present with lower serum LH,[98] in contrast to PCOS women who have elevated LH-levels. This indicates another hormonal mechanism where obesity itself affects the pituitary via GnRH. The ovaries, on the other hand, are not subject to leptin resistance and the high circulating leptin levels caused by obesity inhibit both granulosa and thecal cell steroidogenesis which could also interfere with ovulation.[99]

Obese patients have lower levels of growth hormone (GH), which could also affect the ovaries, since GH stimulates the growth of small follicles and prevents atresia, as well as its collaboration with gonadotropins to stimulate further follicular growth.[100]

High levels of insulin lead to low levels of sex hormone-binding globulin (SHBG), hyperandrogenaemia and high levels of free insulin-like growth factor 1 (IGF-1).[101] Adipose tissue synthesizes androgens and can also convert androgens to oestrogens in addition to storing both these hormones in an inflated steroid pool. This leads to a condition of "relative functional hyperandrogenism".[100] The ovaries are not affected by insulin resistance though, but remain sensible to insulin – which stimulates the theca cells to produce androgens, both through a direct effect and by upregulating the sensitivity to LH.[100] The excess ovarian androgens can produce premature follicular atresia, leading to anovulation. Low levels of SHBG, further increases androgen excess and an overproduction of oestrogens, that in its turn leads to even higher levels of LH. Increased LH can arrest follicular growth at earlier stages, as well as promote early luteinisation of granulose cells and damage oocyte quality.[100]

PCOS

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age[84], and defined by the Rotterdam criteria as fulfilling two out of the three criteria:

1. Oligo- or anovulation,
2. Clinical and/or biochemical signs of hyperandrogenism,
3. Polycystic ovaries and exclusion of other etiologies.[102]

The exact aetiology and pathophysiology of PCOS is still not known. However, it has been shown that the thecal cells in PCOS patients have an intrinsic ability to produce excess androgens,[84] contributing to the clinical signs of hirsutism, alopecia, and acne. Biochemically, hyperandrogenaemia is assessed by total testosterone (T), sex hormone binding protein (SHBG), followed by calculation of the free androgen index (T/SHBGx100).[84] Other androgens, such as androstenedione and the adrenal androgen dehydroepiandrostenedione (DHEAS) could sometimes also be useful for diagnostics.

PCOS patients are at risk of developing a vicious circle of excess recruitment of primordial follicles by androgens and causing a larger pool of AMH-secreting follicles. The AMH-gatekeeper then exceeds its physiological purpose and leads to follicular arrest.[103]

There is a relationship between AMH, androgens and insulin resistance that can be seen in women with PCOS, but also in women without this diagnosis, although women with PCOS have a higher rate of AMH per antral follicle.[104] AMH has, however, previously been reported to have a weak negative correlation to BMI in women with PCOS, but not in women without this diagnosis.[105, 106] Anovulation is maintained and worsened by obesity in accordance with the endocrinological aberrations described under the previous heading, and so is also the inherited metabolic syndrome with androgen associated adipose tissue and risks of type II diabetes, hyperlipidaemia, hypertension and cardiovascular disease.[84]

ART treatment in obese women

Infertility treatments are negatively affected by obesity. Gonadotropin use is related to body weight and subsequently higher doses are needed.[107] Compared to their normal weight counterparts, overweight and obese women with a diminished ovarian reserve (FSH>10 IU/L day 3) have lower AMH levels and fewer oocytes retrieved. [108] Although some conflicting evidence has been reported,[109] most studies have shown poorer outcomes of in vitro fertilization in obese women. Obesity has been associated with increased cycle cancellation rates, lower oocyte recovery, implantation failure, pregnancy loss and overall lower live birth rates, as summarized in a large systematic review[110] and meta-analysis that included 33 studies with a total of 47,967 IVF/ICSI cycles.[111] Interestingly, in the mentioned meta-analysis,[111] a subgroup analysis of overweight women revealed lower clinical pregnancy and live birth rates and also higher miscarriage rate compared with women with normal weight. This is in analogy with findings that BMI is an independent prognostic factor for IVF results.[112] The largest cohort study, from the United States, including 239,127 fresh IVF cycles, also showed progressive worsening of outcomes in groups with higher BMIs.[113] However the absolute decline in pregnancy rates was rather small, 31.4% LBR in women with a normal BMI, as compared with 26.3% and 24.3% in women with a BMI of 35 - 39.9 and 40-44.9 respectively.

Pregnancy outcomes in obese women

Independently of previous fertility treatment, almost all risks related to pregnancy are higher in obese women. The risk of miscarriage has already been discussed.[93] Some others are that, pregnant obese women have an increased risk for gestational diabetes, which increases with BMI. In a large population-based study from the United States,[114] women with obesity class I had a doubled risk of gestational diabetes compared with women of normal weight. Likewise, the same study showed a tripled risk of preeclampsia, comparing the same weight classes. Related to the risk of gestational diabetes in the mother, is the risk of foetal macrosomia, however this risk persists among obese women even without gestational diabetes,[115] and even though the absolute risk increase is low, maternal obesity is also linked to congenital malformations.[116] Obesity is associated with an increased frequency of caesarean sections, and preterm birth, defined as delivery prior to 37 weeks, is also more common in obese women, with a doubled risk in women with obesity class II.[114] Other well-known risks are wound infections, thrombosis and the overall neonatal morbidity.

Non-surgical weight loss and fertility outcomes

Hoping to reverse the situation with the negative effects of obesity upon female fertility, several strategies for weight-loss have been investigated. Weight-loss by diet in obese women with PCOS, has shown conflicting results regarding AMH levels. In one study on overweight and obese women with PCOS and reproductive dysfunction, a 20-week weight loss intervention resulted in improvements in reproductive function but no change in AMH levels. In other studies weight loss in obese PCOS women seem to lower AMH and androgen levels as well as restoring regular cycles.[117 118]

Non-randomized studies of obese anovulatory women undergoing nonsurgical weight loss programs with diet and exercise have also shown improvements in menstrual function, as well as improved live birth rates.[119 120] Likewise, a small, randomized control trial of 49 women undertaking ART treatment showed that those receiving an intensive 12-week life style intervention had a significantly higher live-birth rate than controls (44% vs 14%).[121]

However, these results have been difficult to repeat in larger RCTs, the largest being a study of 577 women assigned to either a six months lifestyle intervention or prompt infertility treatment, which did not result in higher rates of a vaginal birth of a healthy singleton at term within 24 months.[122] A Scandinavian RCT including 317 women with obesity class I randomized to either 12 weeks of a low calorie liquid formula diet or prompt IVF treatment resulted in a large weight loss but did not either affect live birth rates, although a higher rate of spontaneous conception was seen in the weight loss group.[123]

When it comes to pharmacotherapy, the results are modest, and studies hampered by high dropout rates. Metformin and orlistat both seem to increase ovulation frequency in obese anovulatory women,[124] but metformin before or adjacent to IVF treatments has not shown to increase live birth rates.[125] Treatment with the recently introduced GLP-1 receptor agonist liraglutide in overweight PCOS women has shown significant weight loss, alongside with improved ovarian parameters and bleeding patterns.[126] However, the possible effects in obese women with infertility are not yet well studied.

Bariatric surgery and obesity-related infertility

Bariatric surgery induces significant weight-loss, and variable outcomes relating to female fertility have been studied, although the original studies in this field are still few. In line with the improved overall quality of life, also sexual function seems to improve.[127] Menstrual cycles are regularized[128] with resolved anovulation, especially in PCOS patients.[129 130] Androgens in PCOS patients are also lowered.[131] Whole cycle and peak LH increases in women who have undergone bariatric surgery compared to preoperative levels, indicating partial recovery of luteal functioning.[132]

The evidence for resolution of infertility after bariatric surgery is limited to retrospective chart reviews or questionnaire data, and case-series.[133-139] One case-series study stated lower miscarriage rates,[134] whereas a larger questionnaire-based study found higher miscarriage rates postoperatively.[136] Effects are difficult to evaluate due to small numbers of patients in the studies, and there is still little evidence that bariatric surgery improves the chance of conception or reduces the rate of miscarriage. [140 141] Infertility is not an indication for bariatric surgery and lifestyle modification is the first-line treatment for obesity.[142] However, around 13% of female bariatric surgery candidates in a US sample had previously been diagnosed with PCOS by a health care provider, and 30% of the women under 45 years of age considered future pregnancy important.[137]

There are few studies concerning the impact of bariatric surgery on IVF outcomes. These studies are also case reports, including women with a known fertility history and known IVF outcome after bariatric surgery. In a case series of five IVF patients with previous bariatric surgery four women delivered a term singleton, and IVF was suggested to be a safe and effective fertility treatment for these women.[143]

One case report described empty follicle syndrome that could be resolved by changing the route of hCG administration from subcutaneous to intramuscular. The authors concluded that the abdominal skin redundancy after bariatric surgery may alter the absorption of subcutaneously administered medications.[144]

In another study of seven patients that underwent IVF treatment both before and after bariatric surgery, the number of gonadotropin ampoules required during stimulation was lower, but there were no between-cycle differences in peak oestradiol level, number of oocytes retrieved, or percentage of mature oocytes.[145]

On the other hand, in a sample of 29 women with prior bariatric surgery, there was a significant decrease in the number of follicles, oocytes retrieved and metaphase II oocytes compared with the two control groups of normal and obese BMI.[146] The largest study on IVF outcomes after bariatric surgery included 40 obese women with previous IVF failure and subsequent bariatric surgery.[147] In this group in their following cycles gonadotropin units and stimulation length decreased and 14 of the 40 women had a live birth.[147] Thus, IVF results do not seem to be impaired by bariatric surgery, even though there might be specific challenges.

Pregnancy after bariatric surgery

Many of the adverse pregnancy outcomes related to obesity are reduced after bariatric surgery, reaching levels lower than those in obese women who have not undergone surgery, or even to the same levels of adverse events as in nonobese women.[148 149] The effect of bariatric surgery on adverse pregnancy outcomes seems dependent of the control group used for comparison, and also the type of bariatric surgery procedure, with malabsorptive procedures generating doubled risks of

SGA.[149 150] The risk of hypertensive disorders of pregnancy is lower, but the risk of preeclampsia is similar to that of women matched for pre-surgery BMI.[149]

The risk of gestational diabetes (GDM) is reduced after bariatric surgery. The meta-analysis by Kwong et al[149] included around 2.8 million subjects, of whom 8346 were women with prior bariatric surgery, and the risk of GDM was reduced with 80% compared to women matched on pre-surgery BMI. The risk for large for gestational age is reduced by 30 percent compared with control women matched for pre-surgery BMI.[149]

Although bariatric surgery may lower obesity-associated risks of preterm birth,[151] the surgery can also itself be an independently associated risk factor. Preterm birth was increased with an OR of 1.35 (CI 1.02 to 1.79) in the study of Kwong et al.[149] However in a large Swedish cohort study it was shown that even though the risk of moderately preterm birth was increased, there was no significant association between previous bariatric surgery and very preterm birth (<32 weeks of gestation) nor medically indicated preterm birth.[152]

It is recommended to delay pregnancy by twelve to 18 months after bariatric surgery, due to nutritional concerns during rapid weight loss. However there is little evidence to support this recommendation.[141]

Caesarian delivery rates are similar in women who have undergone bariatric surgery when compared to women of matched pre-surgery BMI.[149 150] Perinatal morbidity and mortality have been discussed, but the largest studies so far[150 153] have not found any statistically significant differences in outcomes such as low Apgar score, perinatal morbidity or perinatal death. Birth defects do not either seem to be increased in offspring to women with previous bariatric surgery,[149] and in a Swedish study on 3000 women with previous RYGB the risk was lower compared with women matched for pre-surgery BMI.[154]

Rationale

Due to the negative effects of obesity on female fertility many clinics worldwide apply BMI cut-offs for access to fertility care.[155] In Sweden cut-offs vary between <30 and <35. Women with a BMI above the cut-off are currently recommended weight loss by diet and life-style changes. Many women with obesity and infertility seek gynaecological advice. As previously described, several interventions have been studied to alleviate the effect of obesity on infertility, but the results have not matched expectations.[155] When the first study of this thesis was initiated in 2012 there was little evidence regarding the effect of bariatric surgery on female fertility [141 151] and few high-quality studies for guidance. However, reviews were abundant, possibly as a sign of great interest in the field.

As the obesity epidemic continues, there is a growing demand for bariatric surgery and increasing numbers of women of fertile age are seeking treatment. According to data from the Scandinavian Obesity Surgery Registry, in the year of 2012 some 7,900 bariatric surgery procedures were performed, 75% of the patients were women, out of which 49% were of fertile age.[43]

The available evidence such as regularized menstrual cycles and resolved anovulation, points in a favourable direction regarding fertility. Whether these findings are motivators for young women to go through bariatric surgery, has not previously been investigated though. The mechanisms of improved fertility after bariatric surgery could also be related to psychological aspects and body image as well as sexual function, although the studies are few.

There is conflicting evidence regarding the effect of BMI and BMI changes on AMH, but if AMH levels decline, this leaves room for further questions regarding the improved fertility. Even though AMH levels might not be connected to time-to-pregnancy in those without infertility, there is a relationship between AMH levels, oocyte yield and subsequent live birth rate in IVF treatments. However, the effect of bariatric surgery on ART results is still not well studied.

More knowledge about the effects of bariatric surgery on female fertility is needed to counsel patients regarding the management of obesity-related infertility, and to develop future evidence-based treatment guidelines for this increasing group of patients.

Aims

The overarching aim of this thesis was to investigate patients' expectations and the effects of bariatric surgery on female fertility in terms of changes in body image, sexuality, sex hormones and IVF results, along with exploring patients' experiences of surgery.

Specific aims

AIMS

- to explore the motives behind young women's wishes to go through a major surgical procedure, and their expectations on future fertility.
- to evaluate changes in serum levels of AMH and sex-hormones following weight loss first achieved by very low-calorie diet (VLCD) and then the more pronounced weight-loss after bariatric surgery.
- to explore how women perceive the effects of bariatric surgery on quality of life, focusing on sexual health and fertility.
- to investigate if outcomes of IVF differ between women with a history of bariatric surgery compared with non-operated control women matched for a BMI corresponding to post-surgery BMI.

Material and Methods

Study design

This thesis includes three studies reported in four papers (Table 3). The studies have different methodological designs. Study I resulted in two papers: paper I was a qualitative hypothesis generating study, while paper III involved a qualitative study supported by questionnaire-data with a follow-up cut-off time of 18 months. The study population in Study I was enrolled at Aleris Obesity prior to bariatric surgery. Study II was an observational prospective cohort study which resulted in one paper, with a study population Study III was an observational case-control study based on nation-wide registers for bariatric surgery (Scandinavian Obesity surgery Registry, SOReg) assisted reproductive techniques (National Registry for Assisted Reproduction, Q-IVF) and the Medical Birth Registry (MBR) and resulted in one paper. The women included in the study underwent their IVF/ICSI treatments between January 1st 2007 and December 31st 2017.

Table 3.
Overview of the general design of the project.

STUDY	DESIGN	DATA COLLECTION	PARTICIPANTS	PAPER	ANALYSIS
I	Qualitative	Interview data	12 women scheduled for bariatric surgery	I	Thematic analysis, Mann-Whitney U-test
II	Observational prospective cohort study	Questionnaires at surgery and blood samples before, at surgery, at 6 and 12 months postoperatively	Clinical prospective cohort of 48 women who underwent bariatric surgery	II	Wilcoxon test for paired data, Mann-Whitney U-test
I	Qualitative	Interview data, and questionnaires collected before and 18 months postoperatively	18-month follow-up of 11 women.	III	Thematic analysis and Wilcoxon test for paired data.
III	Observational register-based case-control study	Register-data. Linkage of SOReg, Q-IVF and MBR.	308 cases operated with bariatric surgery before going through ART compared with 1381 controls.	IV	Independent T-test, Mann-Whitney U-test, Logistic regression.

Study Participants

The participants of study I (papers I and III) were included between April 2016 through March 2017. Eligible were Swedish-speaking women without previous children, aged 20-35 years and accepted for bariatric surgery (both privately and publicly funded) at Aleris Obesity, Skåne. Patients eligible for publicly funded surgery should have an obesity duration of > 5 years and BMI > 40, or BMI > 35 with one or more comorbidity.

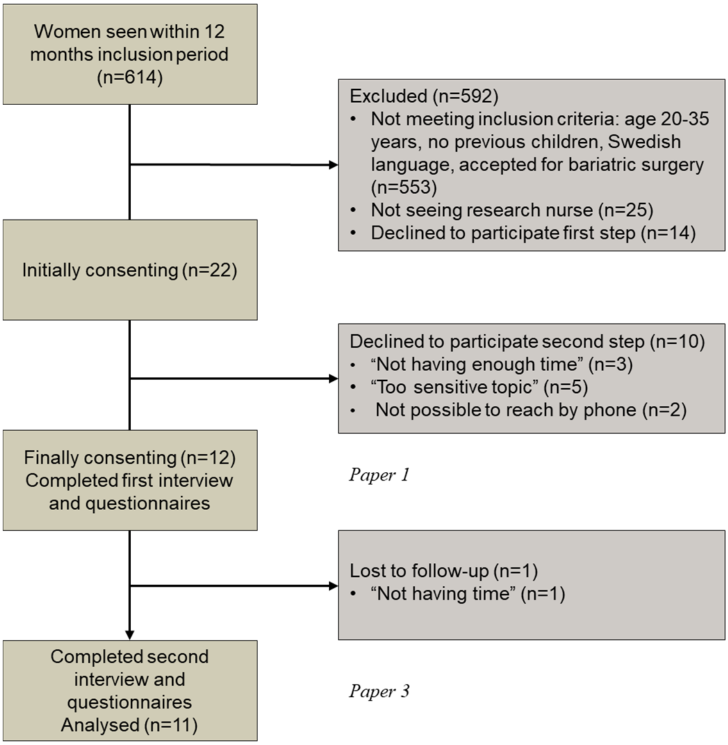

Figure 7. Inclusion of participants study I.

Privately funded bariatric surgery is offered to patients with BMI > 30 and at least one serious attempt to weight-loss. The patients were consecutively identified and invited (n=22) at the scheduling visit at the bariatric centre by the research nurse. See Fig. 7. Participants' characteristics are shown in Table 4. The participants were compared to the reference group scheduled for bariatric surgery, using anthropometric data and the questionnaires Short Form 36 (SF-36) and the Obesity problems scale (OP-9) that are part of the bariatric centres reporting to the national quality register SOReg.[43] The SF-36 is a validated generic instrument for measuring quality of life (QoL), independently of underlying conditions; measurements are divided into domains representing various aspects of life. Values from these domains are then joined together into two compound scores, physical and emotional; higher values in the test indicate a better QoL.[156] The OP-9 scale is a psychometrically valid disease-specific instrument designed to measure obesity-related problems in nine different domains; a higher value indicates more obesity-related problems.[157] See Table 5.

Table 4.
Participants' characteristics study I.

VARIABLE	PARTICIPANTS (N=12)
Obesity duration	
Since childhood	2
Since teens	6
Since 20s	4
Ethnicity	
Swedish ancestry	9
Other	3
Highest level of education	
Secondary school	9
University	3
Occupation	
Employed	6
Unemployed	4
Student	2
Comorbidities	
Knee- and backpain	9
Psychiatric disorders	8
Sleep apnea	1
Incontinence	1
Gastroesophageal reflux	1
Funding of surgery	
Private	2
Public	10
Fertility	
In a romantic relationship	5
Menstrual irregularities	7
Previous pregnancy[a]	5[a]
Previous difficulty to conceive, of those	6
- legal abortion in history	2
- miscarriage in history	1
No difficulty to conceive, of those	6[a]
- legal abortion in history	1
- miscarriage in history	2
- never tried to get pregnant	4

[a]One woman had both a legal abortion and a miscarriage in her history.

Table 5. Comparison of participants with reference group, study I.
Reference group = reference group scheduled for surgery

VARIABLE	COMPARISON		
	REFERENCE GROUP	PARTICIPANTS IN THIS STUDY	*P* VALUE
n	238	12	
Age, y; mean (SD)	28.0 (4.4)	27.4 (2.8)	.3834
BMI; mean (SD)	41.0 (6.3)	41.6 (5.6)	.5962
Compound score SF-36, physical; mean (SD)	36.6 (12.7)	30.7 (14.0)	.2002
Compound score SF-36, emotional; mean (SD)	32.4 (14.0)	33.6 (18.4)	.7028
Op-9; mean (SD)	82.2 (19.8)	80.2 (20.7)	.8068

Paper 3

At follow-up, 18 months after surgery, one participant declined participation due to lack of time. See Fig 7. Ten of the participants had undergone laparoscopic gastric bypass surgery and one participant had had a laparoscopic gastric sleeve surgery. BMI reductions are shown in Table 6. None of the participants had gone through plastic surgery. Life changes had occurred post-surgery, as shown in Table 7.

Table 6. Anthropometric data, study I.
at baseline and 13 months after operation

ANTHROPOMETRIC DATA median (range)	PREOPERATIVELY	POSTOPERATIVELY	*P*-value
Body weight, kg	117 (84—148)	83 (55—90)	.008
BMI, kg/m^2	41.9 (32.8—49.5)	29.1 (22.0—33.2)	.008
Waist circumference, cm	118 (96—135)	92 (68—104)	.028

Table 7. Participants' characteristics at follow-up, study I.
18 months postoperatively.

VARIABLE	PREOPERATIVELY	POSTOPERATIVELY
No.	12	11
Age, median (range)	27 (23—32)	29 (25—34)
Ethnicity		
Swedish ancestry	9	8
Other	3	3
Highest level of education		
University	3	3
Secondary school	9	8
Occupation		
Employed	6	9
Unemployed	4	2
Student	2	0
In a romantic relationship	5	10
New partner	0	7
Menstrual irregularities	7	0

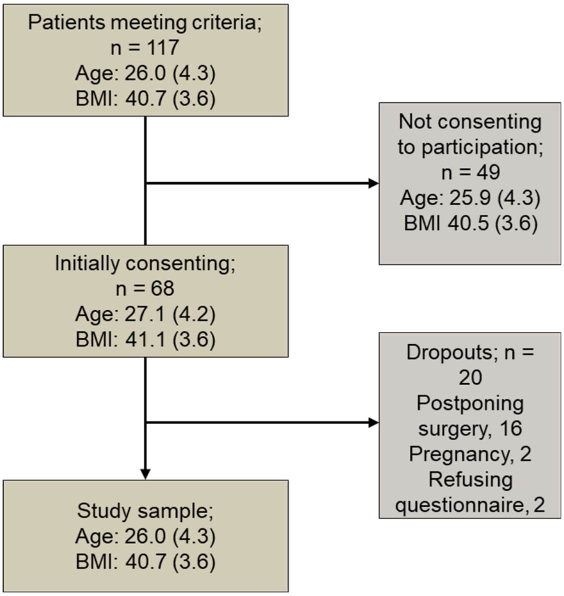

Figure 8. Inclusion of participants study II;
mean (SD)

The inclusion period of study II (paper II) was between October 2012, and September 2013. Swedish-speaking women aged 18-35 years, were invited to participate after being referred for publicly funded bariatric surgery based on the criteria of the European guidelines[44] at Aleris Obesity Skåne. All patients had attempted, but failed, conservative weight loss programs. Exclusion criteria included diabetes, ongoing steroid medication, or participation in other studies. In total, 404 women in the appropriate age group were referred for laparoscopic RYGB during the study period. Of these, 117 consecutive women met the study criteria and were invited to participate by the research nurse and 68 initially accepted. There were no differences between those 68 and the 49 who refused to participate, neither in terms of age (27.7 vs. 26.5 years; n.s.) nor BMI (42.2 vs. 40.9 kg/m2; n.s.) See Fig 8.

For study III (paper IV), data on women undergoing ART treatment after bariatric surgery were collected by linking the Scandinavian Obesity Surgery Registry (SOReg) to the Swedish National Quality Register for Assisted Reproduction (Q-IVF). Between January 1st 2007 and December 31st 2017 n =30 436 women aged 18-45 years having gone through bariatric surgery were identified via SOReg. SOReg was established as a national registry in 2007 and its coverage of performed bariatric surgery has gone up from 80% in 2008 to more than 99 % since 2010.156 All women treated with IVF during January 1st 2007 to December 31st 2017, except those using donated germ cells, were identified via Q-IVF. Q-IVF, was established 2007 and has a coverage close to 100% including both private and public clinics, since reporting fertility treatments to the registry is mandatory.[158] Combining these two registers, women (cases) n = 310, having gone through both BS and IVF during the actual time periods were identified. From the Q-IVF, we aimed at retrieving 5 controls per case, matched for age in years and months at treatment, and BMI-class according to WHO at treatment, but for some cases we could not reach the desired number of controls (see Fig. 9).

After matching and exclusion of non-matched cases, secondary cycles, and cases with bariatric surgery after IVF, the study population consisted of 153 bariatric surgery cases and 752 non-operated controls contributing with 905 first fresh cycles and 418 frozen transfers. Linkage to the Swedish Medical Birth Register (MBR) (covering 98-99% of all births in Sweden[159]) was performed in order to obtain status of previous parity, and matching was made to previous births (yes or no).

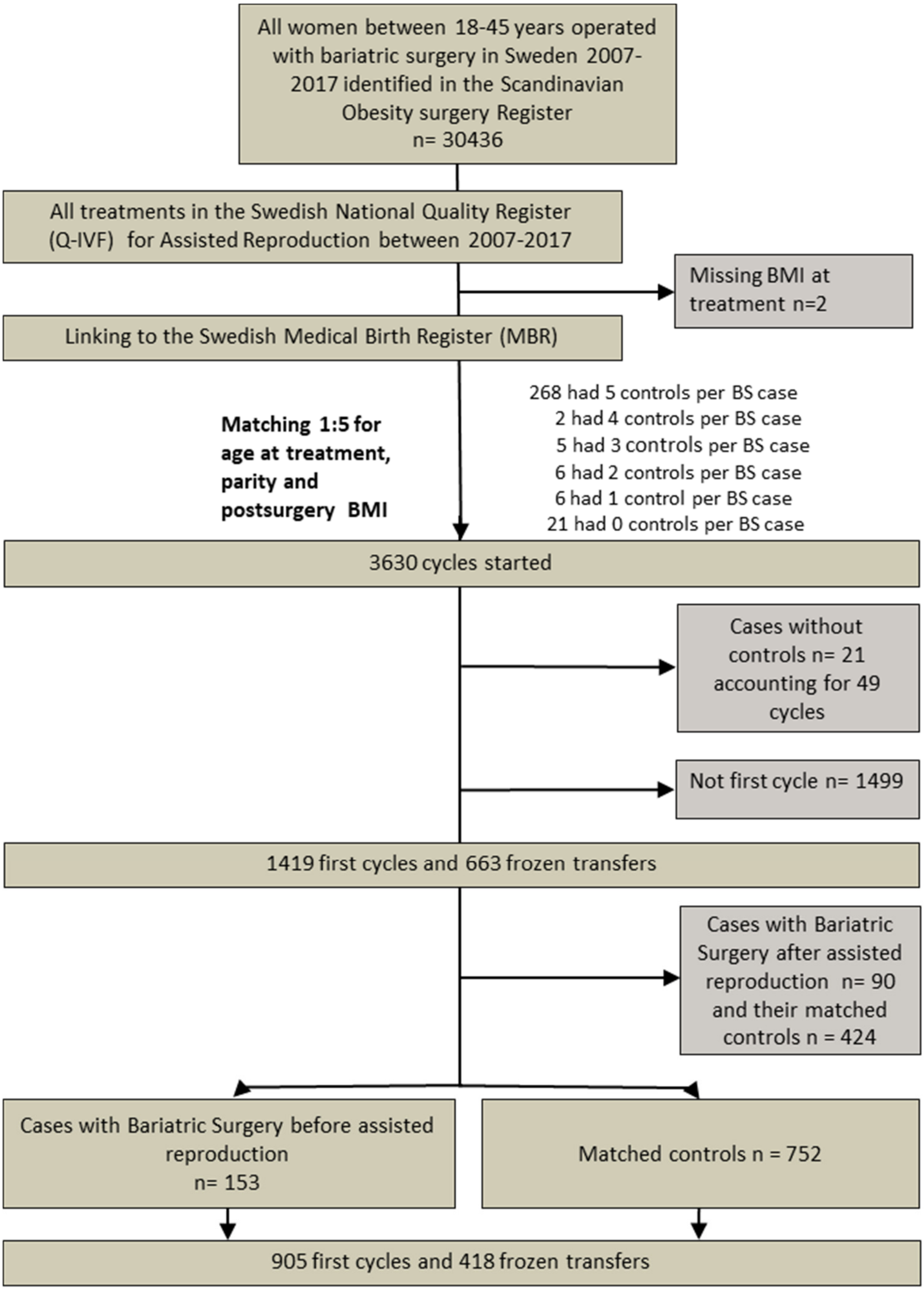

Figure 9. Register linkages and the selection of women with prior bariatric surgery and controls, respectively.

Exposure

Bariatric surgery

In paper I all participants were planned for bariatric surgery, and all participants in papers II-IV had/had had bariatric surgery. During the study period, the most common procedures were Roux-en-Y Gastric Bypass (RYGB) and Sleeve Gastrectomy (SG), When patients were accepted for surgery, a target weight for operation was set, in order to reduce liver size.[160] This pre-surgery target weight corresponded to a 5% reduction of total body weight and was achieved using a VLCD, starting 3-4 weeks prior to surgery. In study II all participants were laparoscopically operated with RYGB, as previously described by Aghajani et al.[161] This major rearrangement of the upper gastrointestinal tract is illustrated in Fig 10. In study I all patients had RYGB, except one that had laparoscopic sleeve gastrectomy, see Fig 3B page 20, and in study III, 142 cases were operated with RYGB and eleven were operated with SG.

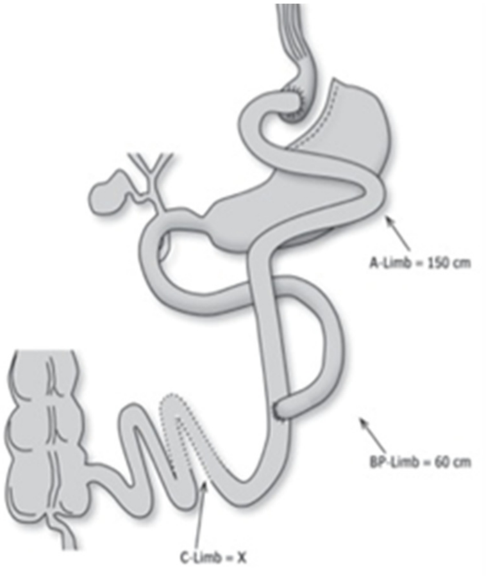

Figure 10. Schematic drawing of upper gastrointestinal anatomy after a Roux-en-Y Gastric Bypass. A-limb = alimentary limb; BP-limb = biliopancreatic limb; C-limb = common channel, x denotes that its length was not measured.

Data collection

In study I data was collected on two occasions; preoperatively (interview and questionnaires) and 18 months postoperatively (interview and questionnaires) Recruitment was in two steps. First, an invitation letter including a written consent to participate was handed out by our research nurse to women (n=22) who fulfilled inclusion criteria. Second, if the women consented to participate, they were contacted and booked for an interview. At the interview they got the questionnaires, filled them out and handed them back along with the signed informed consent form. The follow-up was carried out 18 months from inclusion, when the participants were contacted by phone as previously agreed, and eleven participated in the follow-up interview and filled out the questionnaires. Interviews were conducted either at the hospital, or if the participants so preferred, in their own home. Preoperatively 5/12 preferred the hospital, versus 3/11 postoperatively. The lengths of the first interviews were 38 to 95 min (mean 54 min), and the follow-ups were a bit shorter since the background questions were already covered. All interviews were audio-recorded and transcribed verbatim. Short field notes were taken regarding the setting of the interview.

In study II the participants were followed until one year after surgery. There were four visits during the study: (1) Baseline (BL). A preoperative visit, at which baseline blood samples were collected, the women were examined for height and weight. The mean (SD) length of time between baseline visit and operation was 55 (28) days. (2) At operation: Blood samples and body weight data were collected the day before surgery, and the questionnaire was filled out. (3) Six months postoperatively: Only blood samples were collected. (4) Twelve months postoperatively: Blood samples were collected. The women visited their bariatric surgeon for follow-up and postoperative weight was measured.

In study III, register-data was obtained after approval from the Ethics Board and the Swedish National Board of Health and Welfare. All linkages were possible via the unique personal identification numbers assigned to all individuals in Sweden.

Evaluated parameters

Interview data

In Study I, a semi-structured interview guide was used. The interview guide was developed from clinical knowledge and previous research and covered the following topics: decision-making to have bariatric surgery, psychological aspects on reproduction, fertility, expectations on surgery and future fertility, and information.

Examples of questions from the first interview were: Tell me why you are choosing bariatric surgery? How is your physical health? Have you got any other health issues? Are you menstruating? Is there today anything you avoid doing because of your weight? Are you in a relationship right now? How is your libido? Have you ever, during life, considered becoming a parent? Have you previously been pregnant? Do you want to get pregnant? What are you hoping that will change after the surgery? What do you think about the effects of the surgery on the possibility to get pregnant? What do you think about the effects of the surgery on a possible future pregnancy? Has health care (staff) affected your decision to go through surgery?

In the follow-up study, Study III, the interview guide was derived from the guide used in Study I and contained the following themes: Health after bariatric surgery including self-reported weight loss, psychological aspects of reproduction, fertility, expectations of surgery and future fertility, and information.

Examples of questions were: How is your physical health? Are you menstruating? Did you have any fears related to go through the surgery and life afterwards? Were your fears realized? What do you think about the effects of the surgery on relationships? Do you think the surgery has affected your sexual life? Has it become better or worse? What do you think about the effects of the surgery on the possibility to get pregnant?

The interviews started with a broad question about the current situation, about plans (first interview) and experiences (follow-up). The participants were encouraged to speak freely as topics were introduced, and if necessary, questions from the interview-guide were posed. The interviewer emphasized that no right or wrong answers existed, and that the main interest of the research was the personal experience.

Questionnaires

HADS & FSFI

Before the interviews in study I, the participants completed the Hospital Anxiety and Depression Scale (HADS) and the Female Sexual Function Index (FSFI) questionnaires (Paper III). The HADS is a 14-item self-report screening scale that consists of a seven-item anxiety subscale and a seven-item depression subscale, each item is scored from 0 to 3. The HADS depression subscale is assessed by the sum of the scores of the depression items, and the HADS anxiety subscale is assessed by the sum of the scores of the anxiety items. Cut-off points to assess both subscales are: 0–7: Normal; 8–10: Doubtful; and 11 or more: Clinical problems. The scale performs well in assessing the symptom severity and identifying cases of anxiety disorders and depression in the general population and has been evaluated in a Swedish setting, where mean values for women aged 30-39 were 4.61 for anxiety and 3.77 for depression.[162]

The FSFI is a multidimensional self-report instrument for assessing important aspects of sexual function in women. It has 19 items, scoring 0 to 5 or 6, and covering six key domains of female sexuality: desire, arousal, lubrication, orgasm, satisfaction, and pain where higher scoring indicates better function/less pain.[163] Swedish healthy women with a mean age of 30.9 had a mean score of 31.57 in the validated version of FSFI[164] that we used.

SF-36 & OP-9

The Short Form-36 is a generic instrument for measuring quality-of-life (QoL) independently of underlying conditions; measurements are divided into domains representing various aspects of life. Values from these domains are then joined together into two compound scores, physical and emotional; higher values in the test indicate better QoL.[156] The Obesity Problems scale (OP-9) is a disease-specific instrument designed to measure obesity-related problems in nine different domains; a higher value indicates more obesity-related problems.[157] These validated questionnaires provided background information on participants for comparison with the reference group scheduled for surgery.

Questionnaire Study II

At the time of surgery in study II, all patients filled out a questionnaire with five questions regarding 1) current contraception, 2) length of menstrual cycle, 3) previous difficulties to conceive, 4) if having been diagnosed with PCOS, and 5) experience of hirsutism.

Biochemical measurements

In study II, blood samples were drawn independently of menstrual cycle day at primary health care centres and transported to the Department of Clinical Chemistry, Skane University Hospital in Malmö, fresh, or aliquoted and frozen at -20°C according to laboratory guidelines. Androstenedione, Dehydroepiandrosterone sulfate (DHEAS) Estradiol, FSH, LH, Sex Hormone-Binding Globulin (SHBG) and Testosterone were analysed by two-step Electro Chemi Luminiscence Immunoassay (ECLI) on Cobas® from Roche Diagnostics. AMH was analysed by two versions of the AMH Gen II ELISA kit from Beckman Coulter, using a conversion factor based on internal data (see Fig 11) in analogy with a previously reported algorithm.[165]

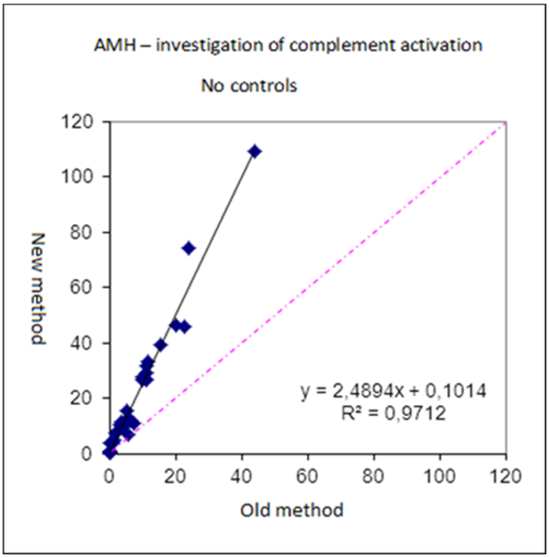

Figure 11. Routinely treated assays –
Complement interference seems to be negligible, hence this correlation was used to transform values. N=35

IVF treatment

The primary outcome for study III was the live birth rate (LBR) after the first IVF cycle, defined as the presence of at least one live birth after the fresh and subsequent frozen embryo transfers of the first IVF cycle. Deliveries of multiple pregnancies were counted as one live birth.

Secondary outcomes were cancellation rates, number of oocytes retrieved, number of frozen embryos, rate of pregnancy loss and cumulative live birth rate, defined as all live births after the first cycle including fresh and frozen embryo transfers. Pregnancy loss was defined as biochemical pregnancies, extrauterine pregnancies, spontaneous abortion before 22 weeks of gestation or legal abortions. All outcomes of IVF were retrieved from the Q-IVF.

Birth outcomes

Birth outcomes included gestational age, birth weight, small-for-gestational age (SGA), preterm birth (PTB) and mode of delivery. SGA was defined as those infants with a birth weight less than the 10th percentile.[166] PTB was defined as <37 completed weeks of gestation. All birth outcomes were retrieved from the Medical Birth Register (MBR).

Analyses

Qualitative analysis

The interview data were analysed inductively using thematic analysis in accordance with the methods of Braun and Clarke.[167] This method was chosen because the approach was explorative, with the aim of increasing knowledge about individual expectations and motivations, and experiences of bariatric surgery 18 months postoperatively. ATLAS.ti was used to facilitate qualitative data analysis.

For Paper I, 35 diverse initial codes were created, and these were organized into four broad themes: A) better self-image B) gynaecological health, C) healthy pregnancy and D) emotional aspects, with a total of 17 underlying categories. In the next stage of the analysis, the four themes were restructured into three main themes: 1) A better me, 2) A fertile me, and 3) A pregnant me, which in total had 11 subcategories. Thereafter, the research group agreed upon a final understanding of the themes and subcategories. *To get back on track* was identified as a master theme, affecting the three underlying sub-themes labelled *A better me*, *A fertile me* and *A pregnant me*.

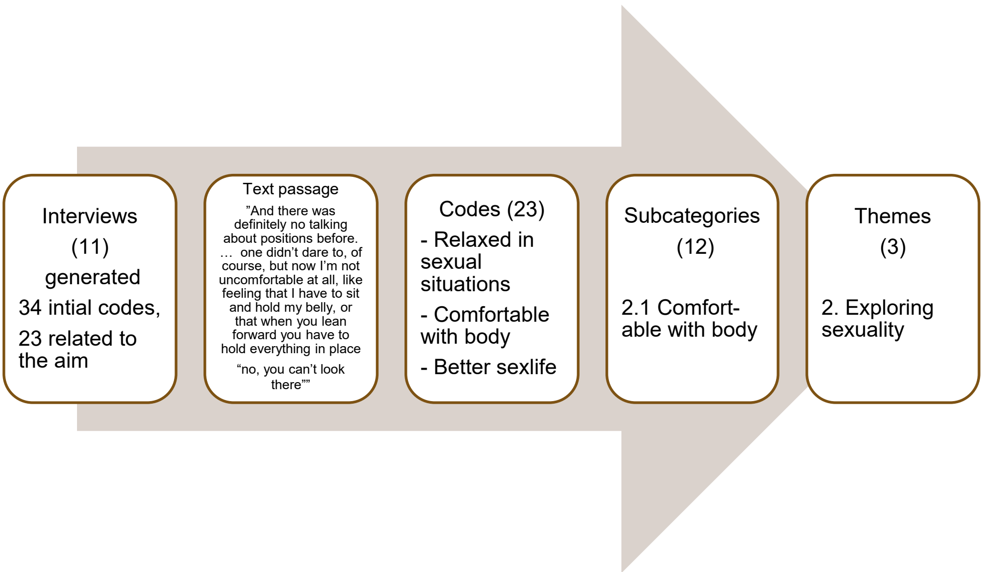

Figure 12. The data analysis; example of coding organized into subcategories and main themes.

For Paper III, 34 diverse initial codes derived from the eleven interviews where 23 were related to the aim, see an example of the coding in Fig. 12. These codes were organized into four broad themes: A) Worthy of love, B) Find love, C) Explore sexuality and D) Maybe a parent, with a total of 17 underlying categories. In the next stage of the analysis, the four themes were restructured into three main themes: 1) Being worthy of love, 2) Exploring sexuality, and 3) Considering parenthood. In total, these three had 12 sub-categories. The authors agreed on a final understanding of the master theme *A new beginning* and three underlying themes *Being worthy of love*, *Exploring sexuality* and *Considering parenthood.*

Statistical analyses

Data were expressed as mean ± SD, median (range) or as percentages. Anthropometric and questionnaire data in study I were stored in a proprietary database with access only for the authors. SF-36 and OP-9 questionnaire data were retrieved from the SOReg central registry and analysed using Mann–Whitney *U*-test since normal distribution could not be presumed.

For the biochemical assays, intra-individual variation for the different time points was calculated using the Wilcoxon test for paired data. For comparison of pre-operative and 12 months postoperative AMH levels, the former were reduced by 5.6% to compensate for age-related decline.[64] Mann-Whitney *U*-test was used to analyse differences between subgroups, and linear regression was used to examine associations. Mixed model was used to adjust for confounders. HADS and FSFI questionnaire data were analysed using the Wilcoxon-test for paired data.

For comparison of IVF- and birth outcomes, groups of data were assessed for distribution using the Kolmogorov-Smirnov test. Demographics and treatment outcomes were explored using Independent t-test for comparison of means of normally distributed quantitative variables since there was a variable number of matched controls. Likewise, Mann-Whitney U-test was used for non-normally distributed variables. Categorical variables were compared with the Chi-square test. Chance of birth in first cycle, the risk of SGA and PTB were explored through logistic regressions, generating odds ratios and 95 % confidence intervals. Age and BMI are known risk factors for lower birth rates after IVF, and previous childbirth increases chances of success. These confounders were accounted for by the matching of the study. A Directed Acyclic graph revealed that year of treatment should be included as a confounder to adjust for potential cohort effects. Adjusted odds ratios (aOR) were calculated including the matching variables age at treatment, parity, BMI intervals and treatment year intervals.

Two-tailed p-values were used, and the level for statistical significance was set at $p < 0.05$.

Analyses were performed using Winstat for Excel® (Kalmia, NY, USA), IBM SPSS Statistics, ver. 23, 24, (IBM Corp., Armonk, NY, USA), STATA and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical considerations

We followed the ethical principles for medical research involving human subjects as stated in the Helsinki declaration and developed by the World Medical Association.[168] All women in studies I and II received both oral and written information about the purpose of the studies. Written informed consent was obtained from all participants.

In the two prospective studies, all participating women were informed about the research and the current knowledge gaps regarding the impact of bariatric surgery on fertility.

In study I participants were invited to share their thoughts on the sensitive topics of fertility and sexuality in both questionnaires and interviews. Psychological discomfort and anxiety could occur when confronted with these topics. The participants received information about the possibility of psychological support from a licensed psychologist in case discomfort related to the study would occur. However, it could also be perceived as positive to share experiences regarding disease and healthcare, knowing that this information is useful for the development of future healthcare policies.

In study II, along with the basic tests for bariatric surgery that routinely included blood samples, the hormonal assays were added. There were no extra visits nor extra blood samples for the study to avoid inconvenience or harm to the participants. Questions regarding fertility and menstrual dysfunction could possibly cause discomfort, but on the other hand having the question regarding fertility brought up while still being in their reproductive years could also be an advantage.

Study III involved de-identified data regarding sensitive information related to bariatric surgery, IVF treatments and birth outcomes. Linkages of registers was done by the National Board of Health and Welfare, and data were delivered with unique but unidentifiable numbers. Information about enrolment in National Quality Registers is available at the actual health care providers, and patients who do not consent have the possibility of withdrawal. Information about the studies is provided on the homepages of the Quality Registers, in this case Q-IVF and SOReg.

All three studies were approved by the Regional Ethical Review Board in Lund, Sweden. Study I #2016/50, Study II #2012/482 and Study III #2018/1140.

Results

Motives and expectations

The overall master theme in Study I/Paper I was labelled *To get back on track*, and affected all underlying sub-themes. See Table 8. Quotations presented are identified by a number indicating participant (1-12).

Table 8. The data analysis; master theme, main themes and underlying categories.

TO GET BACK ON TRACK		
"I want to get back on my feet first and I want to be comfortable with my body before I…, I look at it this way, that if I'm not content then I can't be a role model to my child. … Because they see more than you think. I'd rather be done there. I am dreaming of having children, but it's just not now." **(Participant 8)**		
Main themes	Categories	Quotations
1. A better me	1.1 Self-image 1.2 Self esteem 1.3 Relationship 1.4 Sexuality 1.5 Not an easy way out	*"I don't like to be the way I am now, for example, that I'm like, overweight. … I've got an ideal body. It's just hiding, somewhere in here, right now."* (Participant 3)
2. A fertile me	2.1 Gynaecological problems 2.2 To achieve pregnancy 2.3 To qualify for pregnancy	*"…when you lose weight you get your period and then when you get your cycle going and, like, regular then you'll have a baby. You can have children. That's no problem."* (Participant 11)
3. A pregnant me	3.1 A healthy pregnancy 3.2 Pictures of pregnancy after bariatric surgery 3.3 A healthy parent	*"Because I know that you still can get pregnant. Yes. … Because otherwise…, like if I couldn't get pregnant… then I 'd never have the surgery. Because that's my biggest dream in life. That's just having children. So…"* (Participant 12)

The master theme *To get back on track* can be seen as the hope that all of the participants had in common, viz. that surgery would improve their lives in several areas, not only physically. All participants had decided to go through surgery because they wanted to achieve a change in their lives. Independently of having previous experience of not being obese, the participants expressed how they wanted to return to normality, describing obesity as an obstacle to move forward with their lives and to have a family.

1. A better me

The participants described a feeling of how life was set on pause since they had become obese. They talked about being inhibited both psychologically and physically, and that this would turn back to normal when they lost weight, described as “the real me” is in there, somewhere.

2. A fertile me

Gynaecological problems such as polycystic ovary syndrome, menstrual irregularities and endometriosis were spontaneously mentioned as contributing to the urgency of losing weight. The participants considered obesity to be the most probable underlying mechanism to these problems. For most of the participants the main purpose of the operation was not to achieve pregnancy, but all of them saw the picture of improved possibilities to get pregnant as another positive and important part of having bariatric surgery. Of the participants that were in a relationship, some already had found out that they needed help from hormonal stimulation, In Vitro Fertilization IVF or insemination. Since there are BMI limits to publicly funded IVF, the operation was also seen as a mean to qualify for treatment.

3. A pregnant me

All participants described a wish of having children in a more, or less, close future, and that having a family was very important to them. None of them had heard anything negative about pregnancies after bariatric surgery. The participants knew that obesity causes high-risk pregnancies, and that this meant a risk for mother as well as child. None of the participants was worried that bariatric surgery would affect future pregnancies negatively. The fact that friends and family members which already had gone through the operation had delivered successfully afterwards, was encouraging enough.

Changes in serum levels of AMH and sex hormones

All women in Study II/Paper II were treated with RYGB without complications and were all discharged on the first or second postoperative day (mean postoperative stay 1.04 days). Weight loss was substantial, as described in Table n.

The questionnaire was answered by 46 women. Normal menstrual cycles were reported by 18 women, three women had short cycles than <21 days, and 23 were oligo- or amenorrhoeic. Based on the answers of the questionnaire the women were categorized as "suspected PCOS" (n = 10) if they previously had been given this diagnosis, or if they fulfilled two out of the three Rotterdam criteria.[102] Previous fertility problems were stated by eleven women (24%), eight women had never tried getting pregnant. During the first postoperative year six women got pregnant.

Table 9.
Demographics

PARAMETER	BASELINE (n=48)	OPERATION after VLCD (n=44-45)	12 MONTHS postop. (n=41-43)
Age in years, mean (SD)	26.5 (4.3)		27.7 (4.3)
Height (cm)	169.0 (5.3)		
Weight (kg)	117.2 (12.9)	110.3 (12.3)	75.5 (11.4)
BMI in kg/m^2, mean(SD)	40.9 (3.6)	38.6 (3.5)	25.4 (6.4)
Excess Body Weight, mean (SD)	45.4 (10.7)	38.8 (10.0)	4.5 (10.3)
% Excess Body Weight Loss, mean (SD)			92.5 (20.1)
Smoking			
Yes	10		
No	37		
Previous diagnosed/"Suspected PCOS"	10		
Contraception, Progestogen-only methods	16		
Contraception, Combined Oral Contraceptives	2		

Excess Body Weight = kg's over BMI 25

Median AMH levels were significantly higher after the initial weight-reduction before surgery, 35.0 pmol/L as compared with 30.0 pmol/L at baseline (BL). Median AMH at six and twelve months postoperatively were significantly lower compared with BL, 19.5 and 18.0 pmol/L respectively (P=0.001 for both comparisons).

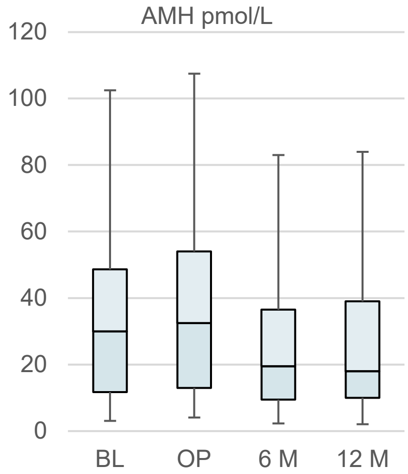

Figure 13. AMH levels in pmol/L
BL = Baseline, OP = At operation after VLCD, 6M = 6 months postoperatively, 12M = 12 months postoperatively

The AMH concentration at twelve months postoperatively was significantly lower ($p<0.0005$) than could be explained by the 5.6% annual decline in AMH levels. See Fig. 13. Lower AMH levels were seen in 29 of 41 (71%) patients, their mean BL AMH was 36 and their mean age was 27 years. Increased AMH levels were seen in twelve patients, their mean BL AMH was 27 pmol/L and their mean age was 25 years.

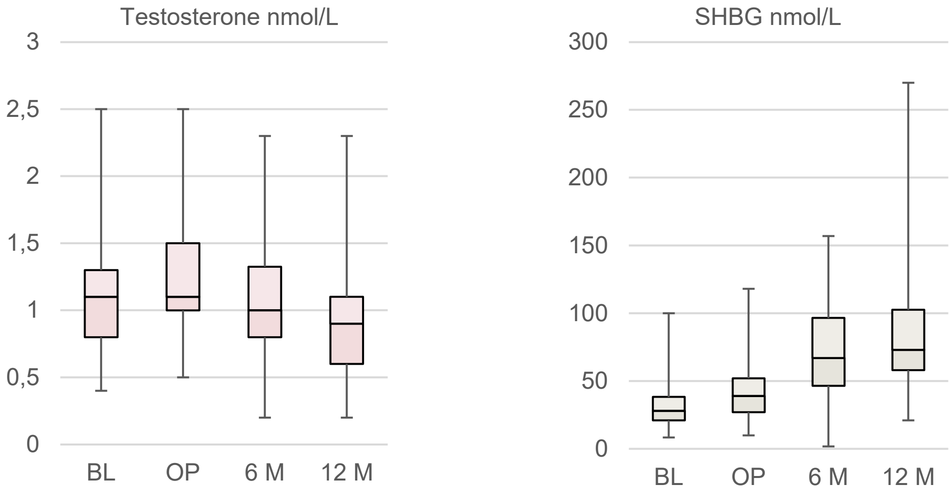

Figure 14. Testosterone and SHBG levels in nmol/L BL = Baseline, OP = At operation after VLCD, 6M = 6 months postoperatively, 12M = 12 months postoperatively

There was no difference between the group of patients with suspected PCOS, and those without, neither in terms of change in AMH nor in weight reduction, p=0.6 and p=0.7, respectively. See Table 10. Free androgen index (FAI) also exhibited significant alterations related to the obesity treatment. See Table 10 and Fig 14.

Table 10.
Hormonal assays

HORMONES Median (range)	**BASELINE (n=48)**	**OPERATION after VLCD (n=44-45)**	**6 MONTHS postop. (n=41-44)**	**12 MONTHS postop. (n=41-43)**
AMH pmol/L	30.0 (3.1-102.5)	35.0 (4.1-160.0) [b]	19.5 (2.0-83.0) [ab]	18.0 (2.0-84.0) [abc]
Expected AMH in pmol/L according to age related decline, i.e. -5.6%				33.0 (3.9-151.0)
Testosterone nmol/L	1.1 (0.4-2.5)	1.1 (0.5-2.5)[b]	1.0 (0.2-2.3) [ab]	0.9 (0.2-2.3)[ab]
SHBG nmol/L	28.0 (8.4-297.0)	39.5(10.0-199.0) [b]	67.0 (1.8-157.0) [ab]	73.0 (21.0-270.0) [ab]
FAI	0.035 (0.027-0.153)	0.038 (0.004-0.131)	0.015 (0.001-0.611)[b]	0.012 (0.001-0.040)[b]
LH IU/L	6.1 (0.1-20.0)	5.9 (0.1-41.0)	5.9 (0.1-21.0)	5.3 (0.1-18.0)
FSH IU/L	5.5 (0.9-13.0)	4.8 (1.3-10.0)	4.2 (0.1-15.0)	4.3 (0.1-12.0)
Estradiol pmol/L	142.0 (20.0-1950.0)	312.5 (100.0-2378.0) [b]	314.0 (20.0-15780.0)[b]	306.0 (20.0-3719.0) [b]
Androstenedione nmol/L	6.0 (2.1-24.7)	6.1 (0.8-16.3)	4.2 (1.8-14.5)[ab]	3.8 (1.3-9.3) [ab]
DHEAS µmol/L	5.3 (2.1-12.0)	6.0 (1.9-13.0) [b]	4.3 (1.2-9.6) [ab]	4.5 (1.5-12.0) [ab]

MIXED MODEL WITH NO ADJUSTMENT	**MIXED MODEL WITH ADJUSTMENT FOR CHANGE IN BMI**
Op vs. BL, difference = 8.8, p = 0.017	Op vs. BL, difference = 7.5, p = 0.013
Month 6 vs. BL, difference = -7.0, p = 0.002	Month 6 vs. BL, difference = BMI data missing
Month 12 vs. BL, difference = -8.0, p = 0.001	Month 12 vs. BL, difference = -11.7, p < 0.001
Subgroup-analysis, Mean effect on AMH:	Adjustments for smoking and use of oral contraceptives are redundant as these covariates do not vary during follow-up.
Smoking +6.82, p = 0.315	
Progestogen-only pill -5.09, p = 0.621 Combined Oral Contraceptives -4.29, p = 0.714	Association Change AMH BL to Month 12 postop. and the change of BMI, β=-0.8; p=0.1

[a] significant as compared with Operation
[b] significant as compared with Baseline
[c] significant as compared with Expected AMH

FAI = Free Androgen Index

Perceived effects of bariatric surgery on quality of life, sexual health and fertility

In the follow-up of study I /Paper III, *A New Beginning* was identified as the master theme, affecting the three underlying main themes, see Table 11.

Table 11. The data analysis; master theme, main themes and underlying categories.

A NEW BEGINNING		
"Now I feel a bit more like the X that maybe I didn't see in the mirror, but the one that I've always felt like. Especially when it comes to activities. I never dared go snowboarding for example, I never dared that. I never dared to step in front of a ski renter and tell my weight to adjust the bindings properly,…. A bit crazier and finding ways to have fun." **(Participant 1)**		
Main themes	Categories	Quotations
1. Being worthy of love	1.1 Reflected appraisal 1.2 Finding myself 1.3 Active and outgoing 1.4 Finding a partner 1.5 Continuous body improvement	*"Definitely. I've found my other half now. I have. So that's a lot. He's comfortable with me, and I'm comfortable with him. He's not judging. You can notice that he likes me and the way I look."* (Participant 8)
2. Exploring sexuality	2.1 Comfortable with the body 2.2 Daring to make demands 2.3 Improved sexual functioning 2.4 Lacking desire	*"… and then not being afraid of saying what you want and so on. So just, … really, to be comfortable with yourself leads to a thousand other things around sex that makes it a much, much better experience and makes it more pleasant, and makes it, like, easier to have orgasms"* (Participant 10)
3. Considering parenthood	3.1 The body seems ready 3.2 Planning for children 3.3 The uncertain fertility	*"And people are complaining about their..., I love my period"* (Participant 4)

The master theme *A New Beginning* represents the optimistic views on changes that had already taken place, or that were hoped for in a close future. The changes were related to self-image regarding all the three subthemes *Being worthy of love*, *Exploring sexuality* and *Considering parenthood*.

1. Being worthy of love

The participants described how they were now much more satisfied with their own body and appearance. Self-esteem felt improved, and inhibitions were lowered. The majority were in a romantic relationship (10/11).

2. Exploring sexuality

Most of the participants described a more active and satisfying sex life than before surgery. Internal factors, such as being more comfortable in a sexual situation and enhanced self-esteem allowed them to demand more of their partners. The participants talked about feeling relaxed about guiding the partner to better sex, and the stimulation needed to reach climax. Factors such as increased energy levels and endurance, also contributed to a more active sex life.

3. Considering parenthood

One of the participants had already become a parent, and a second was pregnant. The other participants said that they wanted to have children in the future, but not all of them felt ready to get pregnant, depending on other factors than weight loss though. Having regular cycles was considered very positive, as a marker of female fertility. Several of the participants planned to postpone pregnancy until two years after surgery, on the advice of healthcare staff. Still, some were feeling stressed about fertility, and said they still did not feel certain they would conceive when they felt ready.

The qualitative findings above, were supported by questionnaire data.

Mood

Scores for depression 18 months postoperatively were significantly lower than preoperatively, 6.5 vs 2, p= 0.007. Preoperatively, six out of 12 participants scored 8 or higher as in Doubtful regarding depression, but postoperatively no participant scored over 7 (Normal). Scores for anxiety were lower postoperatively, 10 (Doubtful) vs 7 (Normal) although not significant p = 0.137. Preoperatively, seven of 12 participants scored 8 or higher (Doubtful or Clinical problems) for anxiety and postoperatively 5 of 11 participants scored 8 or higher as seen in Table 12.

Female sexual functioning

The total FSFI score was significantly improved from a median of 23.3 to 29.1, p = 0.012. The participants scored significantly higher on most domains of the FSFI, except for Orgasm, where there was no significant difference, see Table 12 and Fig.15.

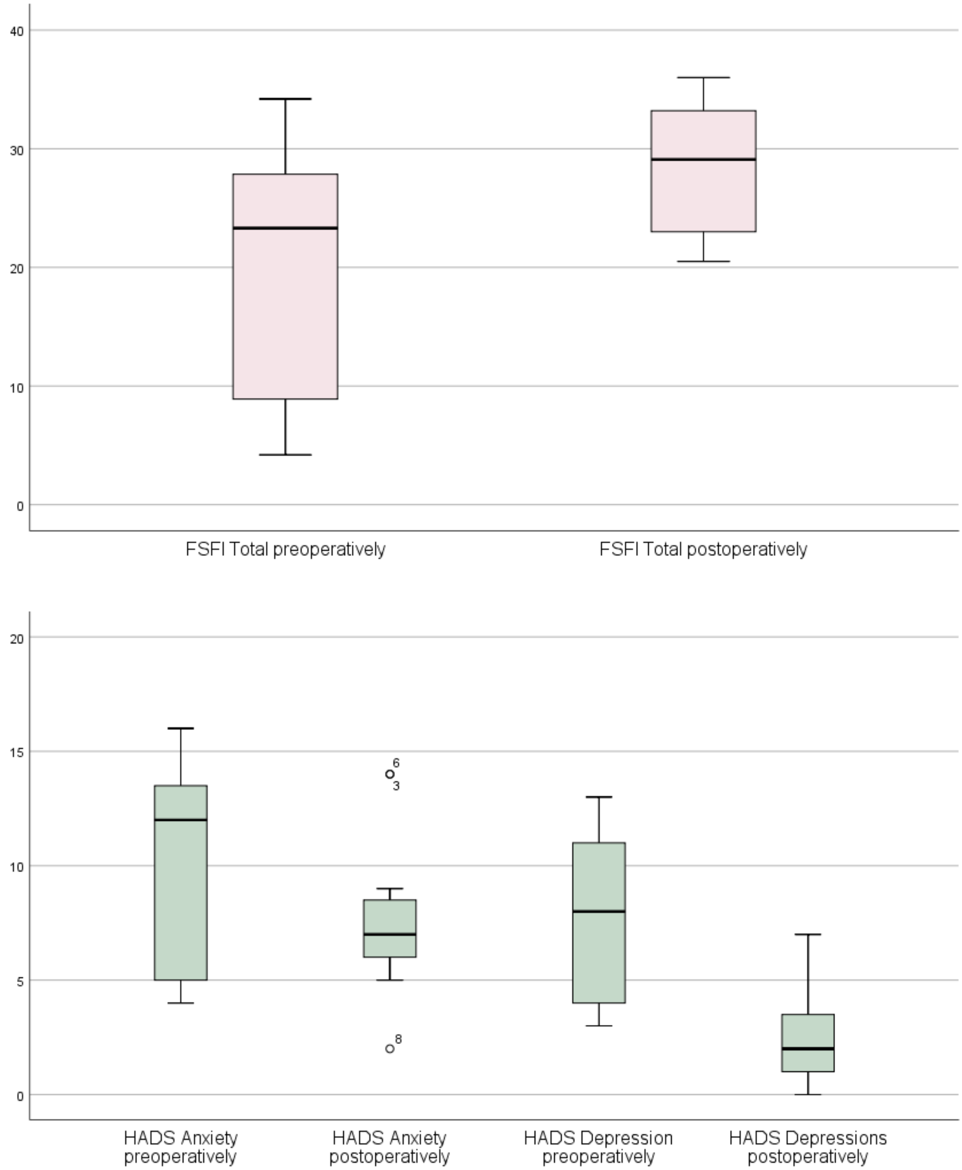

Figure 15. FSFI total scores and HADS scores for anxiety and depression.
FSFI = Female Sexual Function Index; HADS = Hospital Anxiety and Depression Scale. *P*-values are found in table 12.

Table 12.
Comparison of questionnaire data preoperatively vs 18 months postoperatively

VARIABLE	N Valid	N Missing	Median	Minimum	Maximum	*P*
HADS						
Anxiety pre	12	0	10.0	4.0	16.0	.137
Anxiety post	11	1	7.0	2.0	14.0	
Depression pre	12	0	6.5	3.0	13.0	.007
Depressions post	11	1	2.0	0.0	7.0	
FSFI						
Desire pre	11	1	2.4	1.2	4.8	.014
Desire post	11	1	3.6	2.4	6.0	
Arousal pre	11	1	4.5	0.0	5.7	.018
Arousal post	11	1	5.4	3.3	6.0	
Lubrication pre	11	1	4.8	0.0	6.0	.028
Lubrication post	11	1	5.4	3.3	6.0	
Orgasm pre	11	1	4.8	0.0	6.0	.106
Orgasm post	11	1	4.4	1.6	6.0	
Satisfaction pre	11	1	2.8	1.2	6.0	.025
Satisfaction post	11	1	5.2	3.2	6.0	
Pain pre	11	1	3.6	0.0	6.0	.027
Pain post	11	1	6.0	1.2	6.0	
FSFI Total pre	11	1	23.3	4.2	34.2	.012
FSFI Total post	11	1	29.1	20.5	36.0	

IVF after bariatric surgery

Demographics for cases and controls are presented in Table 13. The mean BMI was comparable; 28.4 among the bariatric surgery patients and 28.1 in the matched controls. Mean age was 32.7 years for bariatric surgery patients and 33.0 years for the controls. There was no significant difference in parity, with 80.4 % of bariatric surgery patients being nulliparous, as compared with 83.0 % in the controls.

The IVF results are shown in Table 14. Cancellation rates before the first cycle were comparable, and oocyte retrieval was performed in 141 cases and 699 controls. The number of retrieved oocytes was significantly lower in the BS group, 7.6 vs 9.0 (p=0.011), as was the number of frozen embryos 1.0 vs 1.5 (p=0.007). Eight cycles were excluded since the treatment was done for other reasons, such as oncological egg freezing and not intended for transfer. There was no significant difference in cumulative live birth rates.

Table 13.
Descriptive characteristics of the patients in the exposed and non-exposed groups

	Bariatric surgery patients (n = 153)	**Non-operated matched controls (n = 752)**	**Between group comparisons *P-value*[a]**
Age at treatment, mean (SD)	32.7 (4.4)	33.0 (4.6)	.438
Age classes total valid	153 (100)	752 (100)	
< 25	4 (2.6)	17 (2.3)	
25 – 30	35 (22.9)	169 (22.5)	
30 – 35	67 (43.8)	307 (40.8)	
36 – 37	25 (16.3)	135 (18.0)	
38 – 39	15 (9.8)	73 (9.7)	
40 – 41	4 (2.6)	34 (4.5)	
> 42	3 (2.0)	17 (2.3)	
Nulliparous n (%)	123 (80.4)	624 (83.0)	.442
BMI, mean (SD)	28.4 (3.7)	28.1 (4.1)	.471
BMI classes total valid n (%)	153 (100)	752 (100)	
< 18.5	0	0	
18.5 -25	31 (20.3)	146 (19.4)	
25 - 30	67 (43.8)	314 (41.8)	
30 - 35	49 (32.0)	272 (36.2)	
35 - 40	6 (3.9)	20 (2.7)	
> 40	0	0	
ART Treatment year total valid n (%)	153 (100)	752 (100)	
2007 - 2009	3 (2.0)	50 (6.6)	
2010 - 2012	24 (15.7)	249 (33.1)	
2013 - 2015	41 (26.8)	190 (25.3)	
2016 - 2017	85 (55.6)	263 (35.0)	

[a] Independent t-test was used for comparison of means of quantitative variables and chi-square test was used for comparison of categorical variables.

Table 14.
IVF Outcomes

	Bariatric surgery patients	Non-operated matched controls	Between group comparisons *p*-value[b]
First cycles intended for transfer	153	744	
IVF outcomes			
Cycle cancelled before oocyte retrieval (of first cycles); n (%)	12 (7.8)	53 (7.0)	.728
Oocyte retrievals; n	141	699	
Number of retrieved oocytes; mean (SD)	7.6 (5.2)	9.0 (5.7)	.005
Number of frozen embryos after first fresh cycle; mean (SD)	1.0 (1.7)	1.5 (2.4)	.032
Transfers in first fresh cycle; n (%)	117 (76.5)	570 (76.6)	0.970
Number of embryos transferred in first fresh cycle, mean (SD)	0.82(0.5)	0.84 (0.5)	0.603
Pregnancy rate per started first fresh cycle; n (%)	44 (28.8)	226 (30.4)	0.691
Pregnancy loss[c] first fresh cycle; n (%)	10 (6.5)	67(9.0)	0.321
Live birth rate after first fresh cycle; n (%)	34 (22.2)	159 (21.4)	0.815
Pregnancy rate per first fresh embryo transfer; n (%)	44 (37.6)	226 (39.6)	0.706
Pregnancy loss per first fresh embryo transfer; n (%)	10(8.5)	67 (11.8)	0.316
Live birth rate per first fresh embryo transfer n (%)	34 (29.1)	159 (27.9)	0.798
Total numbers of, fresh and frozen, embryo transfers in first cycle; n (%)	166/1310 (79.8)	904/1310 (82.0)	0.447
Cumulative pregnancy rate in first cycle; n (%)	62 (40.5)	365 (49.1)	0.062
Cumulative pregnancy loss in first cycle; n (%)	17 (11.1)	119 (16.0	0.138
Cumulative live birth rates in first cycle; n (%)	45 (29.4)	246 (33.1)	0.395
Cumulative pregnancy rate *per transfer* in first cycle; n (%)	62 (37.3)	365 (40.4)	0.464
Cumulative live birth rate *per transfer* in first cycle; n (%)	45 (27.1)	246 (27.2)	0.978

[b] Independent t-test or Mann-Whitney U-test were used for comparison of means of quantitative variables and chi-square test was used for comparison of categorical variables.

[c] Pregnancy loss was defined as biochemical pregnancies not leading to a viable pregnancy, extrauterine pregnancies, spontaneous abortion before 22 weeks of gestation and legal abortions.

We also investigated birth outcomes of the first IVF cycles, excluding multiple pregnancies, as shown in Table 15. There was a lower mean birth weight, 3190 g compared with 3478 g in controls (p=0.037), but no difference in frequency of SGA or preterm birth. Adjusted outcomes by presence of bariatric surgery before IVF are shown in Table 16. There was no association between live birth in first cycle and bariatric surgery, adjusted odds ratio (aOR) 1.04 95% confidence interval (CI) (0.73, 1.51), neither was there any association between bariatric surgery and preterm birth aOR 0.73 CI (0.34, 1.64).

Table 15.
Perinatal outcomes, only singletons.

	Bariatric surgery patients n=44	Non-operated matched controls n=241	Between group comparisons *P*[d]
Gestational age; weeks, mean (SD)	38.3 (2.8)	38.9 (3.1)	.254
Preterm birth[e]; n (%)	5 (2.4)	26 (2.4)	.969
Birth weight; grams, mean (SD)	3190 (690)	3478 (729)	.037
Small for gestational age[f]; n (%)	0	6 (2.5)	.242
Vaginal delivery; n (%)	21 (47.7)	126 (52.3)	.578

Table 16. Odds ratios (OR) with 95% CI for outcomes by presence of bariatric surgery before IVF
Cumulative first cycles (fresh and frozen embryo transfers included), stimulation for oncological egg freezing excluded, n=1513.

	Bariatric surgery patients n=153	Non-operated matched controls n=744	Crude OR (95% CI)	Adjusted[g] OR (95% CI)
Live birth in first cycle	**45**	**246**	**0.96 (0.67, 1.38)**	**1.04 (0.73, 1.51)**
Preterm birthe	**8**	**29**	**0.98 (0.37, 2.56)**	**1.0 (0.38, 2.78)**
Small for gestational age[f]	**0**	**6**	**N.A.**	**N.A.**

[d] Independent t-test was used for comparison of means of quantitative variables and chi-square test was used for comparison of categorical variables.

[e] Preterm birth was defined as <37 completed weeks of gestation.

[f] Small for gestational age was defined as those infants with a birth weight less than the 10th percentile.

[g] Adjustments were made for age at treatment, parity, BMI intervals and treatment year intervals.

Discussion

The studies in this thesis were conducted with the aim to increase knowledge about bariatric surgery in nulliparous women, and what to expect regarding outcomes related to infertility. While the emphasis lies on obesity-related infertility, it needs to be highlighted that most overweight and obese women do not need help to achieve a pregnancy, and that spontaneous conception still is the norm.

In paper I, the study participants constituting of obese childless women had high expectations on fertility outcomes and childbearing after bariatric surgery. This generated the hypothesis that fertility is an important motivator to go through bariatric surgery in this group of patients. In paper II we found that AMH, as a measure of ovarian reserve, significantly decreases after bariatric surgery. Hyperandrogenism is corrected as demonstrated by a lower free androgen index, which could contribute to increased fertility by regularisation of menstruations and ovulations. The women who underwent bariatric surgery in the follow-up in paper III described a transformation into being more comfortable with themselves that affected all areas of life, including sexual life, which was supported by lower levels of depression and improved sexual function as expressed by FSFI-scores. In IVF treatments, paper IV, fewer oocytes were retrieved in women who had undergone bariatric surgery compared to non-operated women matched on post-surgery BMI, although this did not seem to impact the live birth rates, which were comparable. However, the children that were conceived with IVF after bariatric surgery had a significantly lower birth weight.

Expectations on future childbearing

Our participants in study I described that there was a shared common knowledge among bariatric surgery patients that the operation increases fertility. Although the master theme was *To get back on track*, with the hope that surgery would improve several areas in life, it also included improved fertility and greater prospects of becoming a parent in the future.

However, making the choice to go through bariatric surgery was not an easy one. The results in Study I are consistent with Wysoker's[169] findings of bariatric surgery described as the last resort and also provide a more in-depth understanding of the motives behind the choice of bariatric surgery among young childless women. Our participants described the stigma of obesity resulting in a negative body image and low self-esteem leading to social avoidance, which was also shown in a British study.[170] The social avoidance is supported by previous findings showing that obese women engage in fewer romantic and sexual relationships.[81 82] The participants expressed a wish to become more active and outgoing, making it possible to meet a partner and form a family. In a study by Gosman et al.[137] 30% among reproductive-aged women considered future pregnancy important at the time of bariatric surgery. In our participants, a strong belief that bariatric surgery increases fertility was based on stories from family, friends, and acquaintances. This belief was further fortified by the information given from the bariatric surgeons that fertility could be regained when menstrual irregularities dissolve. Indeed, in Study I some of the participants sought privately funded bariatric surgery because of a BMI <40, but with hopes of improved fertility. The expected improved fertility was among the main motivators for several of the women in the study. This has previously not been studied, however Pournaras[171] in a Letter to the Editor, reported that subfertility was the main reason for undergoing bariatric surgery to 7.4% of women 18–45 years old in a British sample. The hypothesis generated in study I is that improved fertility is a motivator to go through bariatric surgery.

Lower serum levels of AMH

Lower AMH levels are usually regarded as a marker of reduced ovarian reserve, and a shorter reproductive life span.[62] In study II, the main findings were that serum levels of AMH and testosterone, as well as the FAI, exhibited alterations related to the obesity treatment. AMH levels increased after calorie restriction before bariatric surgery (from 30.0 to 35.0 pmol/L) and all three hormonal markers were then reduced below base-line values at both six (19.5 pmol/L) and twelve months postoperatively (18.0 pmol/L). For AMH this reduction was seen in 71% of the participants and was significantly lower than the expected physiological 5.6% annual decline.[64] This finding was in line with the first study by Merhi et al.[172] and before our study was published, this decline was also confirmed in other studies.[173-175] By the use of the questionnaire regarding already known diagnosis of PCOS, menstrual history, clinical signs of hyperandrogenism and the results of the hormonal assays, we tried to evaluate the percentage of women with PCOS in our sample and found ten women classified as “suspected PCOS”. There was no difference in AMH decline between these women and the rest of the sample in our study. This might indicate that the post-operative decline in AMH was not due to resolution of PCOS only. Furthermore, it was not restricted to high basal levels of AMH. The decline in AMH independently of suspected PCOS or not, was in accordance with studies where the PCOS diagnosis was confirmed and used for group comparison before and after bariatric surgery.[173-175] At the initiation of the study, there was also some evidence that AMH might be negatively correlated to

BMI in women with PCOS,[105 106] but we did not find any association between changes in BMI and AMH.

Research has evolved, however the theory presented in paper II, that a lower AMH is related to improved insulin sensitivity is still uncertain. Some studies have shown a relationship between AMH, insulin resistance and androgens,[104] while others show no relationship between insulin resistance and AMH.[118 176] Negative effects of Leptin on the follicular steroidogenesis might be another explanation.[99] However, there still seems to be a relationship between AMH and androgens.[118 177] Probably, in study II, the weight loss leads to the hormonal effects of less hyperandrogenaemia, and this, in turn, to the resolution of a high degree of follicular arrest. Then, the lower AMH levels probably would not be related to a lowered ovarian reserve, or a shorter reproductive lifespan in our patients. Women with PCOS benefit from lower AMH values, since high levels are associated with anovulation.[103] However, in an IVF-context, AMH is related to the number of retrieved oocytes and a higher cumulative live birth rate.[178]

Lower Free Androgen Index

The reduction in testosterone levels in study II was significant compared to baseline (1.1 to 0.9 nmol/L). The levels of SHBG simultaneously increased significantly (28.0 to 73.0 nmol/L). This was in accordance with a previous study on patients with PCOS going through bariatric surgery, who found normalisation of testosterone and SHBG after six months.[179] The FAI in our study, was hence significantly lowered from 3.5 to 1.2. These changes related to lowered androgens were also prevalent in the entire sample, and not only to women with suspected PCOS. Although not investigated in our study, it has previously been demonstrated that lower levels of androgens are also related to improvements in menstrual regularity and improved ovulation.[131] Another Swedish study,[180] investigated the effect of RYGB in 100 women, and found that bariatric surgery normalised levels of sex-hormones, improved sexual function, HRQL and psychological well-being. They also found correlations between lower testosterone and improved sexual behaviour and improved general health.

Improved sexual function and lower levels of depression

In paper III (follow-up of study I), we compared the FSFI questionnaire data preoperatively and 18 months postoperatively and found a significantly improved sexual function even though the sample was small (11 women). The median FSFI-score improved from 23.3 to 29.1, findings that are in line with other larger studies, [127 180 181] The HADS questionnaire data showed lower levels for the HADS-D dimension from 6.5 preoperatively, to 2.0 postoperatively, indicating significant improvement in the level of depression scores. Several studies have previously shown decreased levels of depression and improved psychological general well-being after bariatric surgery.[129 180 181] Improvements in sexual life after bariatric surgery have previously been linked to a decrease in BMI, as well as decreased body image dissatisfaction,[182] and increased self-esteem.[181] Similarly, in a study on women with PCOS, data from FSFI, Body Shape Questionnaire, Figure Rating Scale, HADS-A and HADS-D as well as anthropometric indices showed correlations, suggesting a link between body dissatisfaction, negative self-perceived body image, and depression and impaired sexual function.[80] Our study participants also contributed with in-depth interview data pointing in the same direction. They highlighted the improved self-esteem as crucial for increased satisfaction with their sexual life. In the qualitative analysis in the follow-up of study I, we found the themes *Being comfortable with the body*, related to improved body image, as well as *Daring to make demands* related to a higher self-esteem and sense of worth.

A new beginning

After bariatric surgery, the women described many changes in their lives that were related to the weight loss, and the ensuing enhanced self-esteem. The master theme in paper III was *A new beginning*. The overall setting around the participants was positive, and the master theme represents both changes that had already taken place, and those that were hoped for. Previously, a transformation after bariatric surgery has been reported,[183] similar to our study. All three sub-themes, *Being worthy of love*, *Exploring sexuality* and *Considering parenthood* were related to self-image. The physical body is important to identity in both positive and negative ways,[52 184] and a perception of body control might contribute to feelings of empowerment after bariatric surgery.[185]All but two participants were now employed. Out of eleven participants, ten were in a relationship, seven of those with a new partner. These changes are in line with quantitative findings on alterations in relationship status in a Swedish study-population, showing significant changes in both marriage and divorce.[186] The stigma of obesity can undermine opportunities for employment, career progression and relationships.[3] Changes described above related to work and love can be connected to the societal expectations on young women of emerging adulthood.[47 48] Being able to fulfil these expectations might be part of the general well-being reported by the women. In study I the women had expectations on a return to normality, which seem to be matched in the follow-up 18 months post-surgery.

Improved fertility?

A central goal in the self-image of the study participants in study I was parenthood. In the follow-up, regularised menstruations were appreciated and taken as a marker of improved fertility. Although advised to postpone pregnancy by 12-18 months, one woman was now pregnant, and another had already delivered a healthy baby. Previous studies on obese women have shown a link between high BMI, sexual behaviour and adverse sexual health outcomes including more unplanned pregnancies.[82] After we finished the inclusion to study I, Menke et al.[187] published a study on the prevalence of contraceptive use and conceptions among 710 women of median age 34 years, with seven years of follow-up after bariatric surgery. In the first postsurgical year, 4.3% of women tried to conceive, although recommended a delay of 18 months, and 42% did not use any contraception.[187]

None of our studies were designed to evaluate spontaneous conception rates, but the improvements in sexual function in study I, and lower androgen levels in study II, both support a possible improved fertility. Other studies have previously shown that bariatric surgery improves ovulation, particularly in PCOS patients.[129] Another large, register-based UK-study[130] found that bariatric surgery reduced the prevalence of menstrual dysfunction by 12%, and PCOS by 15%. Another factor that can be negative to fertility, T2DM was reduced by 54%.[130]

By year two, in the above-mentioned study by Menke et al.[187] 13.1% of the women tried to conceive, and the conception rate was 53.8 per 1,000 woman-years across the follow-up of median 6.5 years. There was an 8.5 increased adjusted relative risk of early conception for those being married or living as married and rating future pregnancy as important preoperatively. In another paper referring to the same study,[188] the authors reported that out of the 8.0% nulliparous women with a preoperative history of infertility, over half reported postoperative pregnancy plans as 'important'. These women also had a higher postoperative early (before 18 months) conception rate 115.4 versus 33.9 /1,000 woman-years. They also had a higher risk of unprotected intercourse.

The finding of a higher risk of unprotected intercourse in nulliparous women and early conception, could be related to the theme *The uncertain fertility* in our study I/paper III, where the women talked about feeling stressed of not being certain that they would conceive when they felt ready. The sum of the growing body of evidence, is pointing towards a resolution of obesity-related infertility issues by bariatric surgery. However, there are still no large-scale studies that definitely can conclude that fertility is improved after bariatric surgery, and to clarify the role of bariatric surgery for infertility further investigation is needed.[188]

IVF after bariatric surgery

In the national register-based case-control study (III), we compared outcomes of IVF for all women operated with bariatric surgery with non-operated control women matched for a BMI corresponding to post-surgery BMI and found no negative effects of previous bariatric surgery. However, the hypothesis that lower AMH levels seen after bariatric surgery in study II, could adversely affect the treatment proved to be partly right. The number of retrieved oocytes, and subsequently frozen embryos, were significantly lower. Independently of this, the CLBR was comparable between the bariatric surgery group and the matched controls. Previous smaller studies[145-147 189] have also pointed towards similar outcomes. Possibly, other mechanisms, such as the improved glucose control after bariatric surgery, could compensate and favour implantation as well as reduce risks of birth defects and pregnancy loss.[154 190]

The birth weight was significantly lower in the bariatric surgery group, although the mean gestational length was not significantly shorter, neither was there any increased prevalence of preterm birth (PTB). The majority in the bariatric surgery group had been operated with RYGB, which has previously been reported to be associated with an increased risk of SGA.[149 150] However, SGA is a rare outcome, and there was not enough power in our study to detect changes in the prevalence.

The largest study for comparison, a retrospective multicentre cohort study by Grzegorczyk et al.[189] had two matched groups for comparison in a study on IVF outcomes after bariatric surgery in 83 operated women, one with 83 women matched on pre-surgery BMI, and another with 166 women matched on post-surgery BMI. Even though the CLBR in the group matched on pre-surgery BMI was 12 .0% versus 22.9% in the bariatric surgery group, the difference did not reach statistical significance.[189] However, in large materials there is a significantly reduced probability for live birth rate in morbid obesity (aOR 0.73) typically corresponding to pre-surgery BMI, compared to overweight or post-surgery BMI (aOR 0.94).[113] In our study, we excluded multiple pregnancies, whereas in the study of Grzegorczyk et al.[189] they were included, and that study also found a lower birth weight.

Live birth rate has been shown to be related to AMH, although not within the highest levels of this hormone.[178] A larger proportion of women with PCOS and the related high AMH levels, could rather benefit from the decrease associated with bariatric surgery (study II). Both IVF and bariatric surgery are associated with an increased frequency of PTB in offspring[73 191], however, we did not detect any increase of PTB in our bariatric surgery group compared to controls.

Bariatric surgery for PCOS?

Lower birth weight, SGA and PTB are known to be associated with bariatric surgery[153 191] and the proposed mechanism has been the reduced intake of nutrients in the mother. On the other hand, it is conceivable that the bariatric surgery group differs from the obese controls in other ways. There could, for instance, be a larger fraction of women with PCOS in the bariatric surgery group and the risk of adverse birth outcomes could then rather be related to this condition than the surgery itself.

Excluding this type of explanations is always a risk when studying associations in large materials such as registers.

In a study on pregnancy and perinatal outcomes in women with PCOS that had had bariatric surgery, the birth weight was lower than in non-PCOS controls.[192] PCOS has also been related to adverse neonatal outcomes following frozen-thawed embryo transfers.[193] However, PCOS has also been associated with PTB in population-based studies, where epigenetic changes in the placenta has been a hypothesized mechanism.[194] Thus, PCOS women might be those who benefit the most from bariatric surgery. Although the aetiology of PCOS is not well understood, recent research findings suggest that PCOS originates, at least in part, in foetal life where elevated androgens and/or obesity in the mother affect the offspring by altered gene expression.[195] Hence, the weight reduction and lowered androgens associated with bariatric surgery, could perhaps be key to reduce the transmission of PCOS and the inherent risk of the metabolic syndrome.

Bariatric surgery for infertility?

As shown, bariatric surgery has several positive effects related to fertility and general well-being. It is also associated with reduced risks of obesity-related morbidities.[41 42] After surgery it is generally recommended to postpone pregnancy by 12-18 months, but concerning women in their later reproductive period this recommendation must be balanced against the declining fertility.[142] When assessing the ovarian reserve, AMH levels might be elevated due to other hormonal mechanisms hence giving a too optimistic picture of the fertility potential in severely obese women. Thus, for women with pre-operative AMH values in the low normal range it may be advantageous to start trying to conceive as soon as weight loss has been induced. If infertility treatment is needed, IVF results become comparable to those for non-operated women with a BMI corresponding to the post-surgery BMI. Taken together, for obese women willing to go through a surgical procedure, the positive effects of bariatric surgery make it a viable option for improving the possibility to conceive.

Methodological considerations

In study I, we chose to work in a different paradigm; the interpretive, as opposed to the positivistic. Instead of testing hypotheses generated by medical doctors, we chose to start with a hypothesis generating qualitative study, where the hypothesis emerged from a group of patients by their shared knowledge. The advantage of the qualitative research approach is that it can capture individual experiences and perceptions. In contrary to quantitative research in the positivistic paradigm, the external validity and the generalizability of the results are limited. However, they form a solid ground for future quantitative research, such as questionnaire-based studies. The semi-structured interview guide and the inductive thematic analysis according to the methods of Braun and Clarke[167] that were used in study I, papers I and III, collected in-depth data. This made it possible to gain knowledge about motivators, expectations and later, experiences related to fertility, as this had not been studied previously.

Almost half of the 22 invited women declined participation, probably due to the sensitive nature of the study, but also because of the time-consuming participation. This made the study rather small, also in qualitative terms, however, data saturation was met after twelve interviews, and related to the difficulties in recruiting participants we settled with this number. The sampling could have been done by other means, such as snowball-sampling.[196] However, our convenience sampling involved inviting nearly all nulliparous women scheduled for surgery, and since the study included a follow-up after surgery – participants inviting friends and acquaintances, would probably only have reached the same women. The study had selection bias, as all our participants expressed that they wanted to have children in the future, we do not know whether fertility and future pregnancy was less important to the invited women who declined to participate. Future child wish is not an uncommon finding in nulliparous women planning bariatric surgery, as shown in quantitative studies.[137] Self-selection can also bias participants that are more open-minded regarding questions about sexuality. In other aspects the participants were well representative of the Swedish population's ethnicities and including a wide range of fertile age and could also be compared to the reference group in terms of anthropometric data, obesity problems and QoL.

A team constituting of a gynaecologist, a psychologist and a bariatric nurse analysed the data and built the model together. To enhance credibility further by triangulation, the participants could have given feedback on the coding, but we declined from this since they already contributed with a considerable amount of their time.

Another, quantitative strategy could have been to use questionnaires, but this approach could also introduce bias, related to the eligibility for surgery. The participants were aware of the criteria to qualify for the surgery, and when asked for the reasons to choose bariatric surgery, the accepted comorbidities were their first answers.

The questionnaires that we did use were subordinate in the study and merely a support to the qualitative findings. They are also a means to compare our participants with other studies' samples. Both the FSFI and the HADS are validated questionnaires which have been extensively used in medical research. However, there are other questionnaires regarding sexuality that are more easily accessible for the participant to fill out, but we chose FSFI for comparability with other studies.

The results of the FSFI questionnaire could be biased by the included participants, however, the results were similar those of other studies.

In the prospective cohort study II, it would have been advantageous with a gynaecological examination and the use of vaginal ultrasound for a proper diagnose of PCOS. Ideally, we could have followed the patients at all study points by vaginal ultrasound to be able to correlate the AMH levels also to antral follicle count. However, these suggestions were not logistically possible, nor covered by our ethical permission. It could be argued that many women could benefit from a gynaecological examination, but many obese women also avoid gynaecological care[82] and could have declined participation for this reason. Instead, we tried to include as many participants as possible by offering minimal inconvenience to the participants by following the routine visits and further gained a low drop-out rate. One of the strengths as compared to previous reports on the same issue indeed was the larger study population. We also had a longer follow-up period than the only earlier study on AMH changes following bariatric surgery.[172] Furthermore, to reduce selection bias related to fertility, we did not exclude those who became pregnant during the first year after surgery. The change in laboratory methods of AMH during the study may be a limitation but could be overcome by establishing a conversion factor, in the manner previously published.[165] We adjusted the AMH results for the confounders we had data on, smoking, contraceptives divided into combined-oral and progestogen-only, and change in BMI. However, we lacked follow-up data for smoking and contraceptives. We could have analysed other hormonal assays known to affect sex hormones, such as TSH. In this study, there could also be selection-bias regarding the patients who chose to participate, possibly having some previous experience of infertility. For both prospective studies I-II, selection-bias could also apply for loss to follow-up, although the drop out rate was low in both studies.

Study III is a national population-based register-study with retrospective data, although prospectively collected. A strength of all studies in this thesis, is the known exposure of bariatric surgery, as opposed to e.g., patients taking anti-obesity medications. The SOReg has since 2010 a coverage of more than 99% of surgeries performed in Sweden. Regarding the outcomes, Q-IVF covers almost 100% of IVF treatments in Sweden, since reporting of fertility treatments to the registry is mandatory.[71] Likewise, the MBR covers 98-99% of all births in Sweden.[159] Using registers minimizes the risk of bias, and using Swedish data, factors related to socioeconomic status and the health related effects of this, are also decreased since both bariatric surgery and IVF are offered within the public health-care system. External validity and generalizability are high with treated women of different ages in a national sample including all IVF clinics.

Studying a large time-period to gain power has disadvantages such as changes in the techniques of both bariatric surgery and IVF. However, we chose a time-period where IVF practices and results have changed little. Sleeve gastrectomy is the restrictive surgery technique that was introduced during the study-period although most (142/153) surgeries were RYGB. A retrospective register-study has some inherent disadvantages since the available data is restricted to the register's content on exposure, outcomes, and confounders. A weakness of the study is the lack of infertility diagnosis, which is not possible to access since the Q-IVF register does not contain this information. The quality of the data in the registers also affect the variables that can be studied. Sometimes when data are collected, certain questions might be forgotten, omitted, or not reported because the woman is unwilling to report e.g., pre-pregnancy weight and then data are missing not-at-random, which can cause bias. When introducing new variables in the registers, there is often a latency before there is sufficient coverage, but this is not an issue since the data are missing at random. In other cases, data are missing completely at random for mishaps, which also has little impact on the estimates. In our study, combining several registers, we could in most cases obtain the missing data from another register. E.g., if a woman did not report the BMI in Q-IVF or pre-pregnancy weight in the MBR, BMI was obtained from the post-operative follow-up in SOReg, and if the time frame was too long, the case was excluded. However, the Q-IVF has very little missing data because the outcome variables clinical pregnancy rate and live birth rate, are reported and validated on a regular basis. If data are incomplete, or missing, the IVF clinics are informed, so that the data can be completed. This further strengthens our results because the main outcome did not have any missing values. We did not compare the results with those for a group matched on pre-surgery BMI. This could possibly have enabled us to show improvements in outcomes for the bariatric surgery group. Most publicly funded IVF clinics in Sweden have BMI limits in the range between 30 and 35, hence, it would be almost impossible to find matching controls without introducing other biases, such as socioeconomic factors allowing for privately funded IVF but also contributing to healthier women independently of higher BMI. Lastly, although including all bariatric surgery patients having subsequently used IVF from a complete national sample, the study did not reach sufficient power to detect potential smaller differences in live birth rates, nor regarding differences in rare birth outcomes.

Conclusions

Young obese childless women seeking bariatric surgery seem to have high expectations on future childbearing, considering the operation a means to achieving normality including improved fertility.

Hormonal imbalances are corrected after bariatric surgery, with a lowered free androgen index. However, AMH levels decreased below the expected normal age-related decline.

After bariatric surgery, young women report improved quality-of-life, psychological well-being and sexuality which seem related to improved body image and self-esteem.

Improved psychological and sexual quality of life outcomes as well as correction of hormonal imbalances could contribute to increased fertility after bariatric surgery.

When needing IVF, there was no negative effect of bariatric surgery. There was no difference in live-birth rate after IVF for women with previous bariatric surgery compared to non-operated control women matched for a BMI corresponding to post-surgery BMI, but the mean birth weight of the infants was lower in the bariatric surgery group.

Future perspectives

The findings of these studies highlight the importance of further research on the fertility outcomes of bariatric surgery. Study I identified improved fertility as a motivator to go through bariatric surgery, however there are few studies on this topic.[137 171] For generalizable results regarding women's motivations to go through bariatric surgery it would be beneficial to make a large internet-based questionnaire study where treatment-seekers could rank their motivations. Data from different parts of the world would be preferable.

To avoid leaving obese patients with infertility in a state of limbo, there is a need to harmonize treatment guidelines. The BMI cut-offs for IVF treatment could be elevated to <35. By approving infertility as a comorbidity for bariatric surgery along with the BMI 35, publicly funded bariatric surgery would give patients another treatment option than the lifestyle changes they have already tried. But to balance beneficial effects against risks,[153 191] information is also needed regarding to which extent bariatric surgery improves fertility. There are positive findings in studies like ours. Likewise, the study of Menke et al.[188] suggests an association with previous infertility and increased spontaneous conception rates. Still, hard evidence is lacking on whether bariatric surgery improves fecundity.[188]

One way to study whether fertility is improved, could be to evaluate treatment seeking patterns in a population-based register-study with details on infertility diagnoses, surgery, and infertility treatments.

Although preferable to meta-analyses, a randomized intervention study for obese women needing ART might still be out of reach, both regarding the ethical part, as well as the numbers needed to study clinically relevant increases in live birth rate and birth outcomes. Future studies need also to focus on comparing the outcomes of fertility after bariatric surgery stratified on underlying causes of infertility. It would be advantageous to have more data on comorbidities, including PCOS. Long-term follow-up of children born to mothers with pre-conceptional bariatric surgery is warranted to investigate whether bariatric surgery could reduce risks of obesity, the metabolic syndrome and PCOS in the offspring.

The women in our register-based study on assisted reproduction did not reach a normal BMI although operated with bariatric surgery. Many of them remained overweight or obese, and possibly, the effects of obesity on fertility are not all reversible either. However, other effects such as the improvements in quality-of-life, psychological well-being and sexuality add to the positive effects. Still, childhood obesity is dramatically increasing with subsequently more young adults and women of childbearing age being obese. In terms of fertility awareness, obesity causes several diseases at a young age. This interferes negatively with fertility, but whether these effects are well known in the broader society is unclear. There is an ethical problem though, whether to worry the obese about infertility or not, since most of them would not have any problems related to fertility at all.

However, taken together, the negative health effects of obesity force us to think about prevention in a much larger scale, and at an earlier point in time. One way forward could be increased physical activity from an early age. Physical education has gained less importance in the Swedish school system, but interestingly a study showed that daily physical education throughout compulsory school was followed by higher duration of physical activity also in young adulthood, four years after termination of the intervention.[197] Teaching health-related behaviour seems to be an important contribution to slowing down the obesity epidemic, instead of the present focus on calorie-restriction when the damage is already done.

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Female fertility and bariatric surgery

While patients trying to lose weight sometimes hit a wall referring to a weight loss plateau, the subtitle of this thesis refers to another wall. To reduce later obstetric risks, fertility clinics frequently use BMI cut-offs for access to fertility treatments – which in the eyes of the patient is another wall. Weight loss is truly difficult to achieve. Is bariatric surgery a means to improve female fertility and getting past that wall?

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