Obesity and IVF outcome

The hope of improvements through weight reduction

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When you talk, you are only repeating what you already know.
But if you listen, you may learn something new.

Dalai Lama

Abstract

Background: Female obesity is associated with decreased live birth rate (LBR) after in vitro fertilization (IVF) and adverse maternal and perinatal outcomes are increased in obese women compared to normal weight women after spontaneous conceived pregnancies. If the same applies in pregnancies achieved after IVF is scarcely investigated. Publicly funded IVF clinics in Sweden have BMI limits that women must meet to be accepted for IVF.

Aim: To assess if weight reduction prior to IVF can increase LBR and cumulative live birth rates (CLBR) in obese women. To explore the women's views of having participated in a randomized weight reduction trial prior to IVF and further, to investigate the association between obesity and CLBR and maternal and perinatal outcomes after IVF.

Methods:
Paper I: A randomized controlled trial (RCT) including 317 infertile obese women, comparing a weight reduction intervention for 16 weeks prior to IVF to immediate IVF, to assess LBR in the two groups.

Paper II: A two-year follow-up to assess CLBR, and whether the weight reduction achieved in the RCT remained.

Paper III: A qualitative interview study, using thematic content analysis, to explore the women's experiences and views of the RCT. Ten women from the intervention group and seven women from the control group participated in the interviews.

Paper IV: A nationwide population-based register study including 126 620 fresh IVF cycles and subsequent frozen embryo transfers (FET) stratified by body mass index (BMI). The fresh cycles were performed between 2007 to 2019 and the main outcome was CLBR. In addition, 58 187 singleton deliveries, achieved after fresh or FET, were included to assess maternal and perinatal outcomes stratified by BMI. The transfers were performed between 2002 to 2020 and the primary outcomes were hypertensive disorders of pregnancy (HDP) and preterm birth less the 37 weeks.

Results:
Paper I: Despite a substantial weight reduction in the intervention group, mean 9.10 kg, no significant difference in LBR could be shown between the weight reduction and IVF group compared to the IVF only group, 29.6% respective 27.5% (difference 2.1%, confidence interval 12.9 to –8.6). In the weight reduction and IVF group a higher frequency of children born after spontaneous conception was noted.

Paper II: The CLBR was similar in the two groups and the women in the weight reduction and IVF group had regained the weight they had lost.

Paper III: The women were happy about the invitation to participate in the RCT. They described the weight reduction treatment as tough, and the support during the weight loss as crucial. They were against a strict BMI limit and wished to be evaluated individually.

Paper IV: The CLBR decreased in overweight and obese women compared to normal weight women and adverse maternal and perinatal outcomes increased with severity of obesity.

Conclusion: Weight loss in obese women prior to IVF did not increase LBRs, nor CLBR after two years. Most interviewed women had a positive attitude to an offer of weigh reduction treatment prior to IVF. They wished to be assessed individually and not solely on the basis of their BMI. Overweight and obesity are associated with decreased CLBR and adverse maternal and perinatal outcomes after IVF.

Keywords: Infertility, IVF, obesity, weight reduction, live birth, patient's views, maternal outcome, perinatal outcome.

Svensk sammanfattning

Bakgrund: Flertalet observationsstudier har visat att kvinnor med övervikt och obesitas har högre risk för komplikationer i samband med graviditet och förlossning jämfört med normalviktiga kvinnor. Barn födda av obesa kvinnor har också en högre hälsorisk jämfört med barn födda av en normalviktig kvinna. De har till exempel ökad risk att födas stora för tiden och de har en ökad risk för missbildningar. För infertila överviktiga och obesa kvinnor som genomgår provrörsbefruktning (in vitro fertilisering = IVF) har man sett en minskad chans till ett levande fött barn jämfört med normalviktiga kvinnor som genomgår IVF. Kvinnor med övervikt och obesitas har också en ökad risk för missfall och ökade risker för obstetriska komplikationer. På grund av dessa orsaker har offentligt finansierade IVF-kliniker i Sverige Body Mass Index (BMI) gränser som kvinnan måste följa för att få tillgång till IVF.

Syfte: Att undersöka om viktminskning innan IVF för infertila kvinnor med obesitas kan förbättra chanserna till ett levande fött barn jämfört med kvinnor som genomgår IVF direkt utan viktminskning. Vi ville också undersöka hur de kvinnor som deltog i studien upplevde sitt deltagande samt få information om deras åsikter vad gäller BMI-gränser samt erbjudande om viktminskning innan IVF. Vidare ville vi undersöka sambandet mellan BMI och andelen levande födda barn efter IVF samt sambandet mellan BMI och komplikationer under graviditet och förlossning efter IVF.

Metoder:
I delarbete I genomfördes en randomiserad kontrollerad studie (randomized controlled trial = RCT) där 317 kvinnor slumpmässigt fördelades till att antingen genomgå en viktminskningsbehandling med lågkaloridiet under 12 veckor innan IVF eller att starta IVF direkt.

I delarbete II genomfördes en observationsstudie två år efter att kvinnorna blev inkluderade i RCT:n. Kvinnorna fick bland annat svara på om de fått barn efter den randomiserade studien och ge information om deras nuvarande vikt.

Delarbete III var en kvalitativ studie där 17 kvinnor intervjuades, 10 från gruppen som genomgått viktreduktionsbehandling och 7 från gruppen som gjorde IVF direkt. En tematisk innehållsanalys genomfördes för att kunna återspegla de teman som framkommit i data från intervjuerna.

Delstudie IV var en nationell populationsbaserad registerstudie som inkluderade 126 620 startade, färska IVF-behandlingar, som genomfördes i Sverige mellan 2007 och 2019, och efterföljande frysåterföringar (frozen embryo transfer = FET) stratifierat i olika BMI-grupper. Huvudutfallet var kumulativ födelsefrekvens hos överviktiga och obesa kvinnor jämfört med normalviktiga kvinnor. Vidare undersöktes också sambandet mellan BMI och risken för komplikationer hos mor och barn efter behandlingar genomförda mellan 2002 och 2020 som ledde till födsel i enkelbörd, totalt 58 187 födslar. Huvudutfallet var högt blodtryck under graviditet och havandeskapsförgiftning samt risken för att barnet föddes tidigare än 37 veckor.

Resultat:

Delstudie I: Studien kunde inte visa att födelsefrekvensen var högre hos de kvinnor som gick ner i vikt innan IVF jämfört med de kvinnor som inte gick ned i vikt, 29,6% respektive 27,5% (skillnad 2,1%, 95% konfidensintervall 12,9 till -8,6). Det var dock en högre andel av kvinnor som fick barn efter en spontan graviditet i gruppen av kvinnor som gick ner i vikt. Kvinnorna i viktreduktionsgruppen gick i medeltal ner 9,10 kg.

Delstudie II: Studien visade att det inte var någon skillnad mellan grupperna gällande andelen kvinnor som fått barn efter två år. Beräknat kumulativt hade 57,2% i viktreduktionsgruppen fått barn jämfört med 53,6% i gruppen som gjorde IVF direkt (odds ratio 1,16, 95% konfidensintervall 0,74 till 1,52). Flertalet av kvinnorna i viktreduktions-gruppen hade gått upp i vikt igen och medelvärdet för BMI var likvärdigt i de bägge grupperna.

Delstudie III: Den tematiska innehållsanalysen visade att de intervjuade kvinnorna var glada över att ha blivit tillfrågade om att delta i RCT:n. De kvinnor som gick ner i vikt beskrev viktreduktionsbehandlingen som tuff och att stödet de fick var väldigt bra men också nödvändigt för att klara av behandlingen. De flesta kvinnor uttryckte att de var emot en strikt BMI-gräns och de önskade individuella bedömningar innan IVF oavsett BMI.

Delstudie IV: Studien fann ett tydligt samband mellan BMI och chansen att få barn och antalet komplikationer hos mor och barn i graviditeter uppkomna efter IVF. Den kumulativa födelsefrekvensen minskade gradvis med ökande BMI hos överviktiga och obesa kvinnor jämfört med normalviktiga kvinnor. Vidare ökade andelen komplikationer gradvis hos mor och barn under graviditet och förlossning efter IVF, med svårighetsgraden av övervikt och obesitas.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Einarsson S, Bergh C, Friberg B, Pinborg A, Klajnbard A, Karlström PO, Kluge L, Larsson I, Loft A, Mikkelsen-Englund AL, Stenlöf K, Wistrand A, Thurin-Kjellberg A. **Weight reduction intervention for obese infertile women prior to IVF: a randomized controlled trial**. Hum Reprod 2017 Aug 1;32(8):1621-1630.

II. Kluge L, Bergh C, Einarsson S, Pinborg A, Mikkelsen Englund AL, Thurin-Kjellberg A. **Cumulative live birth rates after weight reduction in obese women scheduled for IVF: follow-up of a randomized controlled trial.** Hum Reprod Open. 2019 Dec 10;2019(4):hoz030.

III. Kluge L, Holter H, Bergh C, Thurin-Kjellberg A. **Women's experience and long-term perspective: a qualitative substudy of a randomized controlled trial on weight reduction prior to in vitro fertilisation**. Reproductive, Female and Child Health. 2023; 2: 143-151.

IV. Kluge L, Källén K, Thurin-Kjellberg A, Wennerholm UB, Bergh C. **The association between body mass index and live birth and maternal and perinatal outcomes after in-vitro fertilization: A national cohort study**. Accepted for publication in Frontiers in Endocrinology, section Obesity, August 18, 2023.

Contents

Abbreviations

ART	Assisted reproductive technology
ASRM	The American Society of Reproductive Medicine
BMI	Body mass index
CLBR	Cumulative live birth rate
e.g.	Exempli gratia, ”for example”
FAS	Full analysis set
FET	Frozen embryo transfer
FSH	Follicle stimulating hormone
GEE	Generalized estimating equation
GnRH	Gonadotrophin-releasing hormone
hCG	human chorionic gonadotropin
HDP	Hypertensive disorders of pregnancy
IVF	In vitro fertilization
ICSI	Intracytoplasmic sperm injection
ITT	Intention to treat
IU/L	International units per liter
LBR	Live birth rate
LGA	Large for gestational age
LH	Luteinizing hormone
OHSS	Ovarian hyperstimulation syndrome
PCOS	Polycystic ovary syndrome
PGT	Preimplantation genetic testing
QEWP-R	Eating and weight patterns-revised
Q-IVF	The National Quality Registry for Assisted Reproduction
RCT	Randomized controlled trial
SDI	Standard dietary intervention
SDS	Standard deviation score
SET	Single embryo transfer
SGA	Small for gestational age
VLED	Very low energy diet
WHO	World Health Organization

Introduction

Fertility

The desire to have a child is usually strong in most individuals. Studies among university students have shown that around 90-95% wish to have children in the future[1] [2]. This will usually not be a problem as most women and men are fertile, meaning that they will conceive within a year of unprotected intercourse. A German study showed that after six months of pregnancy attempt around 80% will conceive and in the following six month another 10% will have achieved a pregnancy[3]. Another study, only including women under the age of 34, showed even higher rates, where 90% had conceived within six months[4].

Male fertility

The reproductive function of men can be assessed with a sperm sample analysis. The World Health Organization (WHO) has established thresholds for basic sperm parameters, table 1. The reference values have been set after analysis of sperm samples from men who achieved a pregnancy within 12 months. A man with a sperm sample below the limits does not necessarily have a problem with fertility[5]. Men often retain their fertility from puberty throughout life[6].

Table 1. Reference values, semen parameters[5].

Semen parameter	**Reference value**
Semen volume (mL)	≥1.4
Sperm concentration (x10^6/mL)	≥16
Total sperm number (x10^6)	≥39
Total motility, %	≥42
Progressive motility, %	≥30

Female fertility

Female fertility starts after puberty with the onset of ovulation and menstruation and ends at menopause. In the United States in 1999-2002, the mean age for the first menstruation was 12.3 years but varied depending on ethnic background and BMI[7]. At puberty the girl has around 300 000 to 500 000 oocytes (eggs) in her ovaries, "the ovarian reserve". There is a progressively decrease of the oocytes, due to atresia of the follicles and ovulation, and at menopause at around 50 years of age, approximately 1000 oocytes remain. However, female fertility starts to decline already at 30 years of age and then progressively deteriorates for every year being low after the age of 40. This has been shown in a study exploring success rates after donor sperm inseminations[8] and studies investigating the association between age and live birth rate (LBR) after in vitro fertilization (IVF)[9] [10], where higher age is associated with lower LBR. Higher female age is also associated with an increased risk of miscarriage[11].

Menstrual cycle

A prerequisite for the woman to be fertile is that she has an ovulatory cycle. The menstrual cycle is complex and involves a series of events regulated by hormones from hypothalamus, the pituitary gland, and the ovaries, the so called hypothalamic-pituitary-ovarian axis. A normal ovulatory cycle is usually 26 to 35 days long and starts at the first day of the menstruation when the follicular phase begins. During the follicular phase the pulsative release of gonadotropin-releasing hormones (GnRH) from hypothalamus stimulates the pituitary gland to release follicle stimulating hormone (FSH), which stimulates a cohort of follicles in the ovaries to grow. The growing follicles produces estradiol, and the rising estradiol level stimulates the growth and proliferation of the endometrial lining. When the estradiol level is high the luteinizing hormone (LH) surge is induced, and the ovulation is triggered. Usually only one follicle will reach maturity and ovulate. After ovulation the luteal phase begins. The ovulating follicle transforms to a corpus luteum which produces progesterone and prepares the endometrium for a possible implantation. In absence of an implantation the corpus luteum degenerates and the levels of progesterone and estradiol decreases, and a new cycle begins with menstruation[12], figure 1.

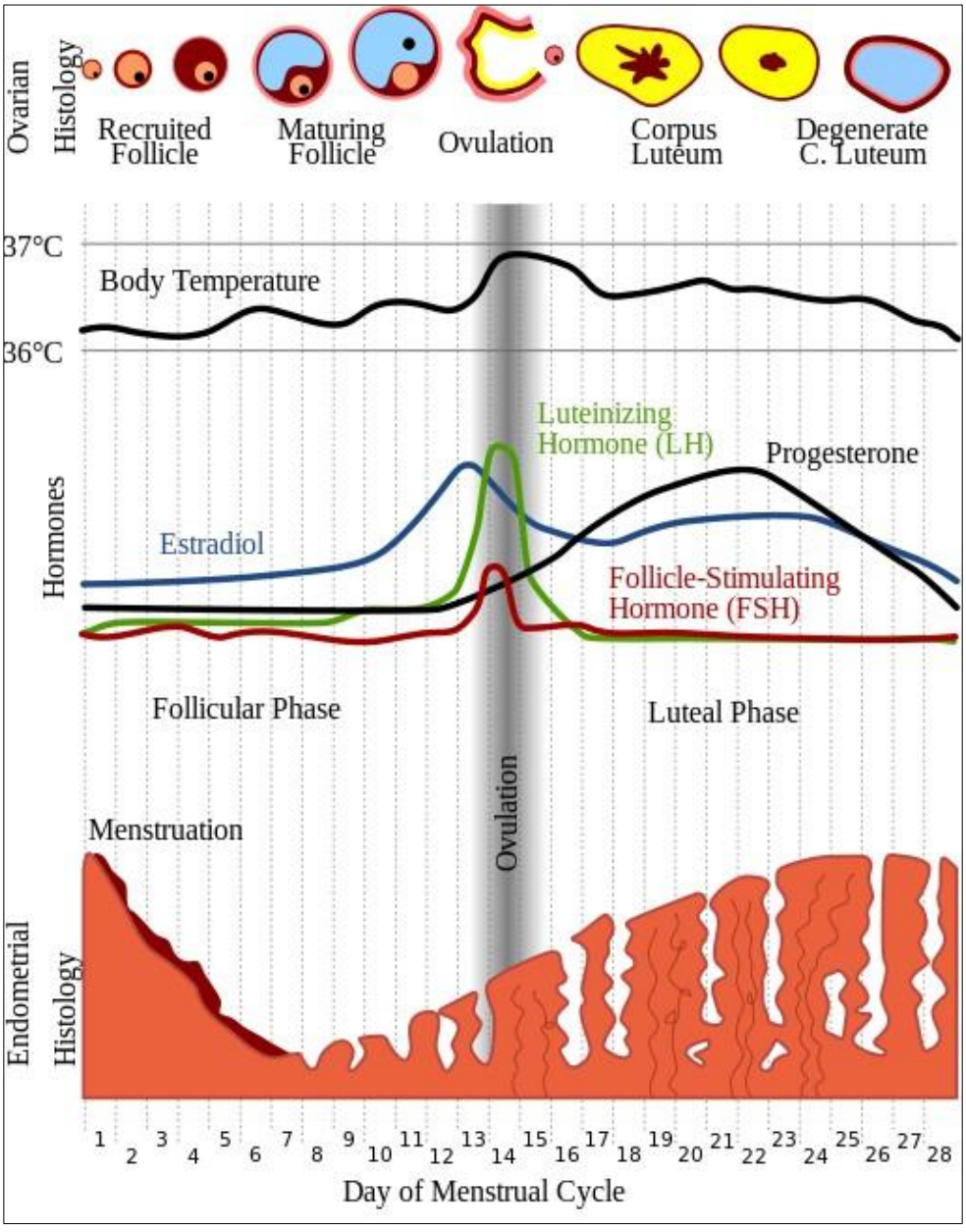

Figure 1. The menstrual cycle.

Infertility

The accepted definition of infertility is when a woman and a man have failed to conceive after one year of regular unprotected intercourse. According to the World Health Organization (WHO), it is estimated that around one of six couples have experienced infertility during their life[13]. In a survey in Britain including around 8000 women and 5700 men between 18 and 74 years of age, it was shown that approximately 10% of the men and 12% of the women had ever experienced infertility and about 53% of the men and 57% of the women had sought medical care due to infertility[14].

The cause of infertility cannot always be explained, which applies to approximately 15% of infertile couples, and is then called unexplained infertility. In around 85% a cause is found and is in about one third due to female factors, one third to male factors and in one third the infertility is caused by a combination of female and male factors.

Female infertility

A common female factor for infertility is ovulatory dysfunction which is often caused by polycystic ovary syndrome (PCOS). PCOS is an endocrine heterogenous disorder characterized by polycystic ovaries, hyperandrogenism and irregular menstruation or amenorrhea due to anovulation. During pregnancy, women with PCOS are at increased risk for miscarriage, hypertensive disorders and gestational diabetes[15]. Another common factor negatively affecting female fertility are blocked fallopian tubes which is often caused by sexually transmitted diseases. Other medical factors affecting fertility are endometriosis and uterine abnormalities such as polyps and myomas[16].

Male infertility

The cause of male factor infertility cannot be found in 30-50% of the cases, but several medical conditions, such as genetic or chromosomal abnormalities, varicocele, post-inflammatory conditions, and systematic diseases can lead to impaired sperm parameters or azoospermia (no sperms in the ejaculate). Azoospermia is mostly caused by primary testicular dysfunction but can also be caused by obstruction of sperm transport[17].

Infertility evaluation

In Sweden you can, as a heterosexual couple, apply for a publicly funded fertility evaluation if you have tried to conceive for one year without getting pregnant. An evaluation includes medical and sexual history and physical examinations. Investigations in women includes a sonography of the uterus to exclude abnormalities and a sonography of the ovaries to evaluate the ovarian reserve. A hysterosalpingosonography (HSS) is also performed to check if the fallopian tubes are open. Blood tests are taken, including hormones affecting ovulation. In men a sperm sample is analyzed. If the sperm sample show a low sperm count, usually a new sperm sample is analyzed and possibly also further investigations with hormone tests and genetic testing. In cases of azoospermia, a surgical procedure can be performed under local anesthesia to examine if sperms can be aspirated from the epididymis by percutaneous epididymal sperm aspiration (PESA) or from the testicle by testicular sperm aspiration (TESA), testicular sperm extraction (TESE) or microscopic testicular sperm extraction (micro TESE). Depending on the result of the infertility evaluation, the couple can be recommended; to try to conceive for another couple of months, surgery in case of, for example, a myoma or a polyp or fertility treatment (ovulation induction, insemination, or IVF) with their own or donated gametes.

IVF

Development in IVF

First child

After pioneering steps by Patrick Steptoe and Robert Edwards, later awarded the Nobel prize 2010, the first child after IVF was born in the United Kingdom in 1978[18]. Since then, the technique has been developed enormously and is today widely used. Today over 2.5 million IVF cycles are performed worldwide each year resulting in 500 000 deliveries. Globally, more than 10 million children have been born after IVF.

The first child born in Sweden after IVF was delivered at Sahlgrenska University Hospital in 1982, and now more than 5000 children are born yearly in Sweden as the result of treatments with IVF.

Oocyte donation

After start of IVF 1978, new developmental steps have continuously been introduced.

One such step was oocyte donation. The first child born after an oocyte donation was born in 1983[19]. The method made it possible for women with primary ovarian failure, chromosomal anomalies, or poor oocyte quality to carry and give birth to a child. Nowadays the method is part of standard IVF practice for the initial indications but is to a large extent used internationally by women of advanced reproductive age[20].

Cryopreservation

Another important step is the technique with cryopreservation of embryos[21 22]. The method of freezing, storing and thawing embryos made it possible to increase the chance of having a child also in subsequent cycles without having to perform another oocyte retrieval. The first child born after a frozen embryo transfer (FET) was born in 1984[22]. The embryos were initially frozen on day two to three after oocyte retrieval at cleavage stage, with a technique called slow freezing. Nowadays embryos are usually frozen on day five to seven, at blastocyst stage by vitrification, which is an ultra-rapid freezing method.

Intracytoplasmic sperm injection (ICSI)

Further pioneering step was the introduction of ICSI, which made it possible to treat male infertility[23]. IVF and ICSI are methods used to fertilize the oocytes retrieved after a controlled ovarian hyperstimulation. In IVF the oocytes will be mixed with spermatozoa in culture medium and the oocyte will be fertilized after natural selection. When ICSI is performed a single sperm will be selected for each oocyte and injected to the cytoplasm of the oocyte. Men with poor sperm quality were previously referred to treatments with donated sperms, but with ICSI they have an opportunity to have a child with their own gametes. In 1992 the first child was born after ICSI. Today ICSI is the fertilization method used in about 70% of all treatments in the world[24], in Sweden the corresponding rate was almost 50%, in 2020[25].

Preimplantation genetic testing (PGT)

PGT is another method developed using IVF technology, which makes it possible to avoid a serious genetic disorder or a chromosomal abnormality being inherited from the prospective parents to the child. A biopsy of the embryo is performed at cleavage stage or blastocyst stage, and the cell/cells removed from the embryo are analyzed for the specific genetic disorder or chromosomal abnormality before an embryo

transfer is made. This method is an alternative to other prenatal testing, such as chorion villi biopsy or amniocentesis, and often a termination of the pregnancy, if the fetus has inherited the disorder. The first child after PGT was born in 1989[26].

Single embryo transfer (SET)

Further important step in IVF was the change in routine, in many countries, implementing the SET strategy. SET has decreased the adverse outcomes enormously, both in mothers and children, related to multiple pregnancies which was very common after IVF in the past. In a case series by Vilska et al., in 1999, it was found that pregnancy rates after elective SET was similar to those after double embryo transfer[27]. A large Swedish RCT in 2004, found no substantial difference in LBR after a fresh SET and if not pregnant also one FET compared to one fresh double embryo transfer. The multiple birth rate was 33.1% in the double embryo transfer group compared to 0.8% in the SET group[28].

Antagonist protocol

The introduction of the antagonist protocol has had an impact on the safety of IVF treatments. There are mainly two different protocols for controlled ovarian hyperstimulation; the long agonist protocol and the short antagonist protocol which is the most commonly used treatment today. The protocols differ in their way to prevent premature ovulation. In the agonist protocol a GnRH agonist is used for downregulation, and in the antagonist protocol the ovulation is inhibited with GnRH antagonist injections. The antagonist protocol has some advantages, such as fewer side-effects and shorter treatment duration. However, the most important advantage is the possibility to trigger ovulation with a GnRH agonist injection, thereby inducing an endogenous LH surge. Such a strategy is particularly useful when development of many follicles and risk of ovarian hyperstimulation syndrome (OHSS). Agonist triggering has been shown to almost eliminate OHSS, a potentially life-threatening complication[29].

Uterus transplantation

Another very advanced method that has been developed, but is not yet part of standard IVF practice, is uterus transplantation. For women with an absolute uterine infertility, (being born without a uterus or having a non-functional uterus) where previously the only possibility to have a biological child has been surrogacy, uterus transplantation has made it possible for women to conceive after IVF. The first child born after a uterus transplantation was born at Sahlgrenska University hospital in 2014[30].

Swedish legislation and guidelines

The law regulating IVF treatment in Sweden is included in The Genetic Integrity Act (2006:351) which has been updated several times. For treatments when donated sperms or oocytes are used regulations are more detailed and a more thorough investigation is required compared to when the couples' own gametes are used. For all treatments it is required that no infectious diseases can be transmitted to the women or the child. Prior to treatment the women, male partner and in case of a donor of sperms or oocytes, also the donor, must be tested for hepatitis B and C, anti-HBc, HIV, HTLV I+II and syphilis. In public clinics, women's age should be below 40 when the treatment is started, and the male partner should not be older than 56. Usually, three IVF treatments are offered in publicly funded clinics.

Developmental steps in Sweden include:

- Oocyte donation is allowed since 2003.
- Treatment of same sex couples (lesbians) since 2005.
- Since 2016, single women have access to fertility treatment.
- Since 2019, it has been permitted to carry out a treatment where both donated oocytes and sperm are used. Donation of an embryo is also allowed.
- The period an embryo can be stored in a freezer is extended 2019, from five to ten years.

Q-IVF

In 2007 the Swedish National Quality Register of Assisted Reproduction (Q-IVF) was established[31]. Since then, individual data with full identification on IVF treatments and their outcomes are reported to the register, both from publicly funded and private clinics. The register presents updated data online available for IVF clinics and yearly aggregated reports publicly available at Q-IVF homepage. The register enables research and follow-up of mothers, fathers and children born after IVF.

Between 1982 and 2006, aggregated data of IVF-treatments was reported to the Swedish National Board of Health and Welfare.

Follow-up of children born after IVF and their mothers

Compared to children born after spontaneous conception higher rates of adverse outcomes have been reported in children born after IVF, such as low birth weight and being born preterm. This is largely due to multiple pregnancies occurring after the transfer of more than one embryo[32 33]. However, also in IVF singletons higher risks are reported, including higher rate of birth defects[34-37]. The reasons for the elevated risk are not known but seems to be related to both the IVF technique and parental characteristics[38].

Different methods in IVF have also been compared, for example, children born after FET are at increased risk of being born large for gestational age (LGA) and born with macrosomia (birth weight >4000 gram), but have a lower risk of being born small for gestational age (SGA) and being born preterm compared to children born after a fresh embryo transfer[37 39]. Concerning long term data, for example (e.g.), neurodevelopment, autistic disorders and cardiovascular diseases, most studies have shown reassuring results. A few large register studies have indicated some increased risks for certain diseases[40]. In a recent Swedish register study on childhood cancer, no overall higher risks were found for children born after IVF while children born after FET had a slightly higher risk[41]. Increased obstetric risks are also observed in mothers, in particular higher rates of hypertensive disorders of pregnancy have been noticed in pregnancies achieved after FET[39 42].

Live birth after IVF

Success rates after IVF have usually been reported as live birth either per started cycle, per oocyte retrieval or per embryo transfer. However, embryo transfer policy has changed during the last years due to several reasons. FET has increased, firstly because of the introduction of SET, thereby leaving more surplus embryos for freezing, and secondly sometimes all embryos are frozen to avoid OHSS. Thus, reporting LBR after first embryo transfer, either fresh or frozen, better reflects the success rates after IVF and has therefor recently been introduced in Sweden and Q-IVF as a new method of reporting results. Another way to define success rates after IVF is CLBR, which includes all transfers after one oocyte retrieval, a fresh embryo transfer and subsequent FET. This way of reporting results after IVF has been suggested beneficial from the patient´s perspective as it summarizes the chances of a having a child after one oocyte retrieval. A large Swedish registry study showed that the CLBR have increased over time, accompanied by a higher rate of blastocyst

transfers performed every year. The CLBR was 27% in 2007 and increased to 36.3% in 2017[43] and 43.2% in 2019[31].

Several factors have an impact on success rates after IVF, particularly female age where higher age, is associated with lower LBR due to diminishing ovarian reserve and deterioration of oocyte quality[9 10 43 44]. Studies have also shown that number of oocytes retrieved have an impact on LBR, where fewer oocytes are associated with decreased LBR[45 46]. Other predictors are e.g., years of infertility, parity, and number of previous failed cycles.

Further, another factor that has an impact on fertility and IVF outcome is obesity.

Obesity

Classification and prevalence

According to WHO, overweight and obesity is defined as "abnormal or excessive fat accumulation that presents a risk to health"[47]. The most used measurement to assess if a person is of normal weight, overweight or obese is body mass index (BMI). BMI is calculated by dividing the weight in kilograms by the height in meters squared (kg/m^2). The classification of different BMI levels is shown in table 2.

Table 2. BMI classification according to WHO.

BMI classification	
BMI kg/m^2	**Category**
<18.5	Underweight
18.5-24.9	Normal weight
25.0-29.0	Overweight
30.0-34.9	Obesity class I
35.0-34.9	Obesity class II
≥40.0	Obesity class III

BMI is a widely used measurement because of its simplicity, and it is useful in measuring obesity at a population-level[47]. At an individual level BMI has some limitations as it does not consider an individual's muscle and bone mass or fat distribution. Other measurements as hip-to-waist ratio and waist circumference that

measures central obesity, have been shown to better predict some health risks associated with obesity[48].

Globally the percentage of adults living with obesity has nearly increased three times between 1975 and 2016[47]. According to the World Obesity Federation the estimated number of individuals over 20 years of age with obesity in 2020 were 813 million, approximately 16% of all adults (18% of women and 14% of men). Obesity is more common in older ages. In children and adolescents aged 5-19 years, 9% are estimated to be obese[49].

Being obese is associated with increased risk for several diseases such as diabetes, cardiovascular disease and cancer, and in addition it has a negative effect on female fertility[50]. In the United States in 2020, the rate of women with pre-pregnancy overweight were 27.2% and 30.1% had pre-pregnancy obesity. These data are self-reported and recorded in the women´s birth file[51]. The percentage of women in Sweden with overweight and obesity in early pregnancy was 28.4% respective 16.8% in 2021[52]. The rate of women with obesity in different parts of the world differs significantly, being under 5% in a few countries to over 30% in several countries, figure 2.

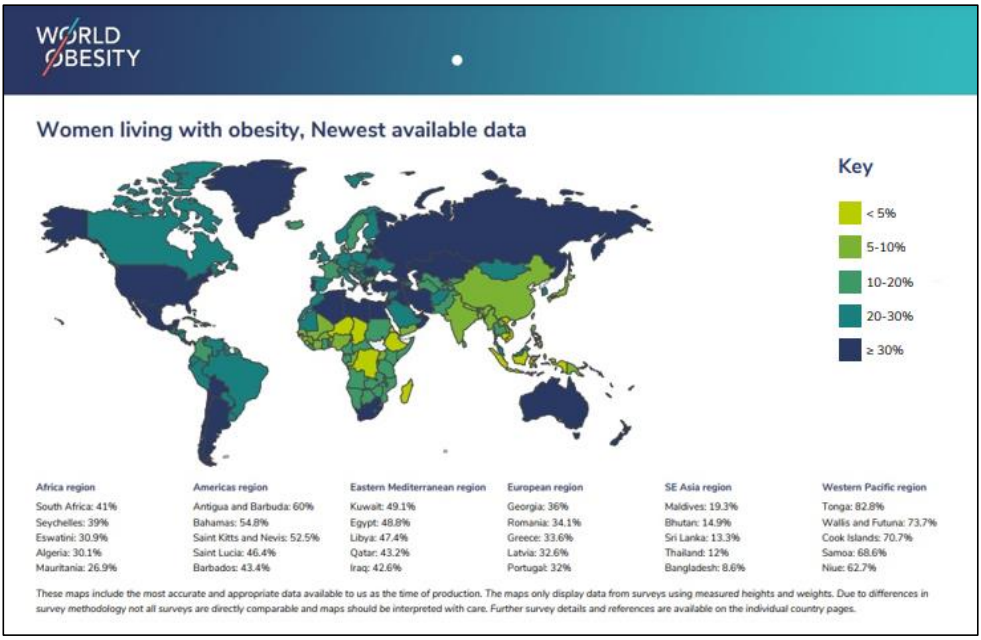

Figure 2. Prevalence of obesity in women.
Published with permission from the World Obesity Federation https://data.worldobesity.org/ 230329

Weight reduction treatments

To lose weight and then maintaining the lower weight has been shown in several studies to be difficult to accomplish. According to a review by Nordmo et al. most individuals regain pre-treatment weight after a weight reduction intervention where no further follow-up by health care is performed[53]. Studies have also shown that it is common with weight cycling, meaning that an individual have made several successful attempts in losing weight but then always regained the weight[54 55].

In a systematic review by Franz at al. different weight loss methods were compared. Interventions consisting of energy reduced diets and/or medication for weight loss, led to weight loss during the first six months of treatment, thereafter the weight loss plateaued. The largest weight loss, but also the most rapid weight regain, was observed in very low-calorie diet interventions. The mean weight loss was 17.9 kg at six month and after 36 month the remaining weight loss was 5.6 kg. Diet interventions with or without exercise and diet and/or medication interventions resulted in a mean weight loss of 5.0 to 8.5 kg after six month and at 36 months 3 to 4 kg of the weight loss was maintained[56].

An ongoing follow-up after weight loss have been shown to promote weight maintenance[57], but also factors, such as continuous self-monitoring, exercise, eating breakfast and capacity for handling cravings increases the chance to maintain a lower weight[58 59].

As a weight loss of 5 to 7% has been shown to reduce risks e.g., of high blood pressure and diabetes, even a smaller weight loss and weight maintenance after weight loss is beneficial to promote health[56 57].

An effective but also more invasive method to lose and maintain a lower weight is bariatric surgery. In publicly funded clinics in Sweden individuals with a BMI over 40 kg/m^2, or 35 kg/m^2 in combination with a co-morbidity such as diabetes, are accepted for surgery. Different procedures can be performed, and examples of two commonly used methods are sleeve gastrectomy where 80% of the stomach is removed, and the Roux-en-Y Gastric Bypass where a larger part of the stomach is bypassed. A systematic review showed a maintained weight loss of 18.8% after five years for individuals who had performed a sleeve gastrectomy, and for individuals who had performed a Roux-en-Y Gastric Bypass the maintained weight loss was 25.5%[60].

Obesity, fertility, and pregnancy outcome

Obese women have impaired fertility compared to normal weight women. The reason for this is not fully understood but due to the excess adipose tissue in obese individuals, higher levels of leptin and adipokines are secreted from the adipocytes (fat cells) leading to disturbances of the metabolism and to chronic low-grade inflammation. Due to the chronic inflammations and impaired function of other cells in the body obese individuals have an elevated risk for insulin resistance leading to hyperinsulinemia. Higher levels of fatty acids are also seen in individuals with obesity[61 62]. These factors can have an impact on reproductive outcome in obese women in different ways. Studies have shown that time to pregnancy is prolonged in obese women[63 64] which can be caused by a perturbation of the hypothalamic-pituitary-ovarian axis leading to a higher prevalence of menstrual disturbance in obese women[61 62]. In pregnancies achieved after spontaneous conception a higher rate of adverse maternal and perinatal outcomes are observed in obese women compared to normal weight women. Obese women have an increased risk for miscarriage[65], HDP, gestational diabetes and cesarean section[62 66 67], and children born to obese women are at increased risk for birth defects, stillbirth, being born preterm and LGA[68-71].

In pregnancies achieved after IVF, the LBR is decreased in overweight and obese women compared to normal weight women[72-74]. A systematic review and meta-analysis showed that the relative risk of live birth was 0.85 (95% confidence interval (CI) 0.82 to 0.87) when comparing obese women to normal weight women[73]. As in pregnancies achieved after a spontaneous conception the miscarriage rate is increased in overweight and obese women after IVF[65 75]. The adverse maternal and perinatal outcomes shown to be increased in overweight and obese women in pregnancies achieved after spontaneous conception are less investigated in IVF pregnancies. A few studies have shown an increased risks for preterm birth less than 37 weeks and infants being born LGA[76-78].

Obesity, fertility, and weight reduction

In a sub-study of a recent RCT in obese women who planned a pregnancy, a weight reduction treatment with a very low energy diet (VLED) was compared with standard dietary intervention (SDI) for 12 weeks, to investigate time to pregnancy. The study showed that a substantial weight loss in the VLED group compared to the SDI group, mean difference 9.8 kg, significantly reduced time to pregnancy. In the VLED group the mean time to pregnancy was 51 days compared to 140.5 days in the SDI group.

The pregnancy rate in the VLED group (50/85, 59%) was significantly higher than in the SDI group (32/79, 41%)[79]. This is in line with earlier studies showing that menstruation and ovulation can be normalized and spontaneous pregnancy rates increased after a weight loss of 5-10%[80].

Retrospective studies in women who have performed a bariatric surgery prior to pregnancy have shown that some of the adverse maternal and perinatal outcomes present in obese women, such as gestational diabetes, HDP and children being born LGA are decreased, while other adverse outcomes such as SGA and preterm birth are increased[81 82].

Due to the increased risks, noted in observational studies, for complications during pregnancy and childbirth in overweight and obese women, and the decreased live birth rate in obese women undergoing IVF, several fertility clinics have set BMI limits that women must meet to be accepted for treatment[83 84]. Aside from smaller studies[85 86], not powered for live birth, on weight reduction treatment before IVF, two large RCTs have been performed[87 88]. A Dutch trial randomized 577 obese women to a lifestyle intervention for six months prior to fertility treatment (ovulation induction, insemination, or IVF) or to prompt fertility treatment. Primary outcome was LBR of a healthy singleton at term within 24 months after randomization. The intervention group who had a mean weight loss of 4.4 kilos had a lower LBR of a healthy singleton at birth compared to the control group who lost 1.1 kilos, 27.1% respective 35.2% (rate ratio 0.77, CI 0.60 to 0.99). However, when including ongoing pregnancies achieved during the study period, no significant difference in the primary outcome between the groups was found. A higher rate of spontaneous conception was noted in the intervention group, 26.1% compared to 16.2% in the control group. No follow-up of weight maintenance was perfomerd[87]. The second large RCT, published in 2022[88], will be presented in the discussion.

Despite the lack of evidence of improved results in obese women losing weight before fertility treatment, BMI limits persists. Most publicly funded fertility clinics in Sweden have a limit of 35 kg/m^2, while a few clinics have a limit of 30 kg/m^2. The American Society of Reproductive Medicine (ASRM) have on the other hand changed their recommendations, and in the committee opinion from 2021, it is stated that obesity should not be the only reason to deny an obese woman IVF treatment. In the situation where anesthesia during oocyte retrieval cannot be undertaken safely due to obesity, IVF treatment can be denied[89].

Aim of the thesis

- To investigate if women with obesity class I (BMI 30.0-34.9 kg/m^2) who were randomized to a weight reduction program before IVF had an increased chance to a live birth compared to obese women who performed IVF without such intervention.

- To assess cumulative live birth rates two years after inclusion in the randomized weight loss trial and to explore if the weight reduction was maintained.

- To explore the women's experiences and perspectives of participating in the randomized controlled trial.

- To investigate the association between BMI and cumulative live birth rates and perinatal and maternal outcomes after IVF in a large cohort of IVF patients.

Material and methods

In this thesis four papers are included. Four different methodological designs were used: A randomized controlled multicenter trial, an observational prospective cohort study reporting a two-year follow-up of the RCT, a qualitative interview study, and an observational retrospective population-based register study. An overview of the papers and study designs are shown in Table 3.

Table 3. Overview of the papers included in the thesis.

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Study design	Randomized controlled trial	Observational prospective cohort study	Qualitative interview study	Observational retrospective population-based register study
Study period	2010-2016	2012-2018	Sep-Dec 2020	2002-2020
Sample size	305	276	17	126 620 cycles 58 187 deliveries
Data collection	eCRF, health records	Questionnaires, eCRF	Interviews	Register-data
Primary outcome	Live birth rate	Cumulative live birth rate. Weight maintenance	N/A	Cumulative live birth rate. HDP and preterm birth <37 weeks
Purpose of qualitative analysis			Explore women´s experiences and views	

eCRF = electronic case report form, HDP = Hypertensive disorders of pregnancy,
N/A = Not applicable

Setting

The Nordic RCT (Paper I) and the pre-planned two-year follow-up (Paper II) was initiated at Sahlgrenska University Hospital to evaluate if a weight reduction could increase live birth rate in obese women after IVF. The RCT was a collaboration between nine reproductive medicine clinics and five obesity clinics. Initially four

clinics in Sweden were planned to include all patients within three years, but since the inclusion took longer time than expected, also four clinics in Denmark and one on Iceland were involved. The first woman was included in October 2010 and the last in January 2016. The participating IVF and obesity clinics in Sweden were located at Sahlgrenska University Hospital in Gothenburg, Skåne University Hospital in Malmö, Karolinska University Hospital in Stockholm and Örebro University Hospital. In Denmark participating IVF clinics were located at Rigshospitalet in Copenhagen, Herlev Hospital, Hvidovre Hospital, all part of the Copenhagen University Hospital and Holbaek Hospital. The women randomized to weight reduction treatment in Denmark was supported by the Department of Nutrition, Exercise and Sport in Copenhagen. In Iceland the participating clinic was ART Medica in Reykjavik.

The nine IVF clinics were all involved in the two-year follow-up of the RCT, which was performed between October 2012 and January 2018.

The interviews in the qualitative study (Paper III) were intended to be held at Sahlgrenska University Hospital or in the patient's home, if that was preferred by the woman. However due to the coronavirus pandemic, this changed. Only two interviews were held at Sahlgrenska, two via a phone call and the majority, 13 interviews, were held digitally via Zoom. The interviews were conducted between September and December 2020.

The nationwide register study (paper IV) included IVF treatments performed between 2002 and 2020, and the study was conducted during 2020-2022 when the ethical permit was received, and data was retrieved from several registers:

- The Swedish National Quality Register of Assisted Reproduction (Q-IVF)[31]. For data on IVF treatments performed between 2007 and 2020.
- MBR-IVF; a research data set stored at the Swedish Medical Birth Register, (MBR)[90] containing data on IVF treatments performed between 1982 and 2006, resulting in births.
- MBR[90 91] for maternal and perinatal outcomes.
- The National Patient Register (NPR)[92 93], for data on infertility diagnosis.
- Statistics Sweden (SCB)[94], for data on country of birth and educational level.
- The Swedish Neonatal Quality Register (SNQ)[95 96] for perinatal outcomes.
- The Swedish Cause of Death Register (CDR)[97 98] for data on neonatal and maternal death.

The unique Swedish personal identification number makes it possible to cross link data from the registers. Crosslinking was performed by The Swedish National Board of Health and Welfare[99] and pseudonymised data, with serial number instead of personal identification number, was sent to the researchers. The Swedish National Board of Health and Welfare stores a key for 3 years that contains the personal identification number, enabling updates of the data for use in longitudinal studies.

Participants

Paper I

The women eligible to be included in the RCT and a following two-year follow-up (paper I and paper II) were scheduled for their first, second or third IVF, had obesity class I (BMI 30.0 -34.9 kg/m^2), were between 18 to 38 years of age and were willing to be allocated to one of the two groups; weight reduction and IVF or IVF only. If the woman was planned for oocyte donation, preimplantation genetic testing, had diabetes mellitus, poor knowledge in Swedish, binge eating disorder or if partner had planned testicular retrieval of sperm, she could not be included due to exclusion criteria.

All women with obesity class I, were screened for eligibility by a study nurse or a doctor at each reproductive clinic. They were identified either in the referral to the clinic, at their first visit or when they were planning their second or third IVF-treatment.

As studies have shown that a low-calorie diet can have a negative effect on a binge-eating disorder all women willing to participate, were screened for the condition by filling out the Questionnaire on Eating and Weight Patterns-Revised (QEWP-R)[100] before randomization into the trial. If the questionnaire indicated that the woman suffered from a binge eating disorder, she was not randomized.

Diabetes mellitus type 1 was another exclusion criterion, fasting Glucose and HbA1c (average blood sugar during the past three month) was measured in blood after randomization to screen for this condition.

The thyroid function was also tested with a thyroid-stimulating hormone (TSH) blood test. If any dysfunction was detected the IVF treatment was postponed until the woman was treated.

If the woman were eligible and willing to participate, she was randomized to one of two groups:

- Weight reduction and IVF
- IVF only

The computerized randomization aimed to divide the women included into two similar groups, balancing for factors that are known to have an impact on IVF outcome. Optimal allocation was applied according to Pocock's minimization technique for sequential randomization[101] taking account the following variables:

BMI (kg/m^2; continuous)
Age (<30 years of age at inclusion/≥30, and as continuous variable)
Diagnosis of PCOS (yes/no)
Parity (0/>0)
Tubal factor (yes/no)
Smoking (yes/no)
Fertilization method (IVF/ICSI)
Waist (cm; continuous)

In all, 962 women were screened for participation and approximately one third, 317 women, agreed to participate. Over a third of the screened women could not be included due to exclusion criteria and approximately a quarter of eligible women declined to participate. For 60 screened women, there were other reasons, such as staff members neglecting to ask the patient to participate in the study.

Of the 317 women randomized, 160 were allocated to the weight reduction and IVF group and 157 to immediate IVF, see flow chart 3.

Paper II

At the time for inclusion in the RCT, the women were informed about the two-year follow-up as a part of the trial. Two years after randomization in the RCT, a questionnaire was sent by regular post with a prepaid return envelope included. In case of non-response, a new questionnaire was sent as a reminder. If still no response, we tried to reach them via a phone call. Out of the 305 women in the full analysis set (FAS) population (See Statistical analysis, and Figure 3) from the RCT, 276 women (90.5%) participated in the follow-up.

The follow-up aimed to investigate the long-term impact of performing a weight reduction treatment prior to IVF regarding CLBR in comparison to women who had performed IVF without weight reduction treatment. In this study CLBR was defined as at least one child born alive, between randomization and the two-year follow-up, after fertility treatment or spontaneous conception. A follow-up of the children born after the IVF treatment in the RCT was also included.

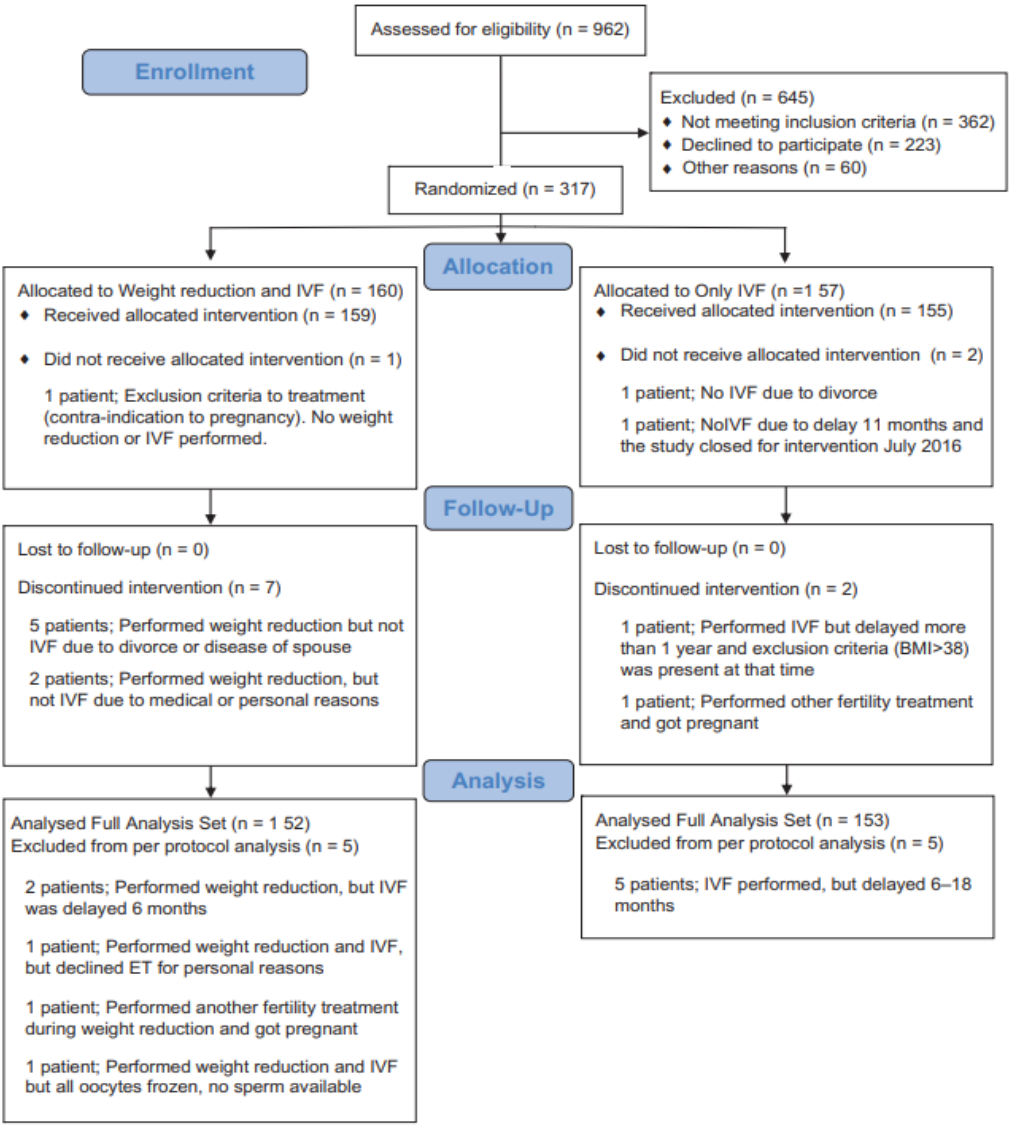

Figure 3. Flow chart of eligibility, randomization, and follow-up.

Paper III

In the interview study, 25 consecutive women who had been randomized in the RCT at Sahlgrenska University Hospital six years earlier were invited to be interviewed about their experiences and attitudes of the trial. For practical reasons only women from this site were invited as the intention was to conduct the interviews face to face, by one researcher. We invited five women at the time by sending them a letter with information regarding the purpose of the interview study. We called them after about one week to give them an opportunity to ask questions and to inquire if they were willing to participate. An interview was scheduled if the woman could consider participating and if so, the woman also returned a signed informed consent by post. Of 25 invited women, 17 agreed to be interviewed. Of these women ten had participated in the weight reduction and IVF group in the RCT and seven in the control group. Of the eight non-participants who were invited to be interviewed, two were unreachable, three cancelled the interview (reasons unknown), and three women gave other reasons (spontaneous pregnancy, other fertility treatment than IVF and long time had passed since the RCT).

The interviews were held between September and December 2020.

Paper IV

In the register study, we analysed CLBR and maternal and perinatal outcomes in association with BMI, in a complete national cohort of IVF patients. Two sub-populations were investigated, see table 4.

All women who performed IVF between 2007 and 2020 were identified in Q-IVF[31], and treatments performed between 2002 and 2006 were identified in MBR-IVF[90]. The MBR-IVF only includes information on IVF treatments resulting in deliveries; hence, CLBR could not be analysed for treatments performed between 2002-2006.

Subpopulation 1: For the analysis of CLBR, 150 847 started IVF/ICSI cycles (*n*=66 568 women) and subsequent FET were identified. In 24 427 cycles BMI was missing giving a total number of 126 620 analysed cycles.

Subpopulation II: For the analysis of maternal and perinatal outcomes, 60 095 treatments (fresh or frozen transfers) (*n*=50 651 women) leading to a singleton delivery were identified. BMI was missing in 1065 (3.2%) deliveries; hence, these treatments were excluded, giving a total number 58 187 deliveries analyzed.

In both subpopulations, treatments with PGT, women treated with donated eggs and oocyte freezing (fertility preservation) were excluded. In subpopulation 2, also treatments leading to a multiple birth were excluded due to higher rates of complications in these pregnancies.

Table 4. Overview of subpopulation 1 and 2.

	Subpopulation 1	**Subpopulation 2**
Treatments included	All fresh IVF/ICSI cycles and FET performed*	IVF/ICSI and FET performed, leading to a singleton delivery*
Year of treatment	Fresh cycles 2007 to 2019, FET until 2020	Fresh and FET 2002 to 2020
Size of population in the analysis	126 620 fresh IVF/ICSI cycles and subsequent FET	58 187 singleton deliveries
Primary outcome	Cumulative live birth rate	Hypertensive disorders of pregnancy. Preterm birth less than 37 gestational weeks

IVF = in vitro fertilization, ICSI = intracytoplasmic sperm injection, FET = frozen embryo transfer
*Treatments with donated eggs and preimplantation genetic testing were excluded.

Intervention and exposure

Weight reduction treatment

The women randomized to weight reduction treatment received support from either a dietician or a nurse at the obesity clinic. The treatment consisted of a low-calorie diet consisting of powdered meal replacements (Modifast), approximately 880 kilocalories per day, for 12 weeks. The diet aimed at a weight loss of 15-25 kilos, and to reach a BMI as close to normal (18.5-24.9 kg/m^2) as possible. During the period with low-calorie diet the women were scheduled for visits at the obesity unit at baseline, week two, five, eight and twelve. At each visit the wellbeing of the women were assessed and the weight measured. If a woman did not manage to adhere to the low-calorie diet, due to side effects, she received an individualized diet to lose weight for the time remaining until the IVF treatment. After the 12 weeks of low calorie-diet, or earlier if a woman had reached a BMI below 25 kg/m^2, a weight stabilization phase was initiated. Solid food was re-introduced, and a mild hypo-caloric diet aimed to stabilize the women´s weight within ±two kilos. Further visits were scheduled at week 15 and 18 and thereafter monthly visits for up to a year after randomization was offered to promote weight maintenance. Regardless of how much weight the woman lost, the IVF treatment was started after 12 plus two to five weeks, depending on her menstrual cycle.

IVF treatment

The standard IVF treatment in Sweden at the time of planning this study, was the GnRH agonist protocol and therefore that protocol was chosen for the RCT. The women started on the first day of the period or from luteal phase with a two week down regulation of the pituitary using a GnRH agonist nasal spray. Thereafter all women injected themselves with recombinant FSH (Gonal-F), at an individual dose for around ten days, until at least three follicles had developed to ≥17 mm. The ovulation induction was triggered with recombinant hCG (Ovitrelle), 36 hours before oocyte retrieval. The oocytes were retrieved under transvaginal ultrasound guidance, using sedation and local anesthesia. Depending on the quality of the sperm sample, given from partner at the day of oocyte retrieval, IVF or ICSI was performed to fertilize the eggs. On day two or three after oocyte retrieval, according to local routine, one cleavage stage embryo was transferred. Double embryo transfers were only allowed in the case of no good quality embryos present (defined as day two; 4-6 blastomeres, <20% fragmentation and no multinucleated blastomeres). Surplus embryos were frozen on cleavage or blastocyst stage. Vaginal progesterone was given as luteal phase support until pregnancy test, which was taken 14 days after embryo transfer. In case of a positive pregnancy test (Serum hCG >5 IU/L), an ultra-sound was performed in pregnancy week seven to confirm a clinical pregnancy and to determine if it was a single or a multiple pregnancy.

BMI

In the register study the main exposure was maternal BMI categorized according to the WHO classification as underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), class I obesity (30.0–34.9 kg/m²), class II obesity (35.0–39.9 kg/m²) and class III obesity (≥40.0 kg/m²). For subpopulation 1, we retrieved data on BMI, in relation to each fresh cycle, from Q-IVF and for subpopulation 2, BMI was retrieved from the first prenatal visit (data from MBR) or from Q-IVF if missing from MBR.

Outcomes

Paper 1

LBR was the primary outcome in the RCT. A live birth was defined as at least one child born alive regardless of gestational age or whether it was a pregnancy achieved after the IVF treatment or a spontaneous conception. Only one fresh embryo transfer

or the first FET, in the case of all embryos having been frozen due to medical reasons, was included.
The secondary outcomes were:

- Dietary related: Weight change from randomization until oocyte retrieval, rate of women lowering their BMI by at least five units or reaching normal BMI (<25 kg/m^2).
- IVF related: Number of cancelled cycles, total dose of gonadotropin, number of oocytes retrieved and rate of OHSS.
- Embryological measurements: Number of good quality embryos and number of frozen embryos.
- Pregnancy related: Rate of biochemical pregnancies, ectopic pregnancies, clinical pregnancies, miscarriages, live births after spontaneous pregnancy and multiple births.

Paper II

The two primary outcomes in the two-year follow-up were CLBR and the women´s weight at follow-up. CLBR was in this study defined as at least one child born alive, after a spontaneous conception or after fertility treatment, between randomization and the two-year follow-up.
The secondary outcomes were:

- Number of children born since the RCT.
- Number of fertility treatments performed since the RCT (IVF/ICSI and FET).
- Follow-up of children born in the index cycle in the RCT and data on children born after the RCT were also assessed.

Paper III

Qualitative outcome
The qualitative interview study aimed to attain a deeper knowledge of the experience and views of participating in a randomized controlled trial on weight reduction prior to IVF.

Paper IV

In the register study, in subpopulation 1, CLBR was the primary outcome, which in this study was defined as at least one live born child per started fresh IVF cycle,

including one fresh and/or all frozen embryo transfers within one year, until one delivery with a live birth or until all embryos were used, whichever occurred first[102]. The secondary outcomes in subpopulation 1 were:

- Live birth per fresh embryo transfer, live birth per first embryo transfer (fresh or frozen) and live birth per started fresh IVF cycle.
- Miscarriage among clinical pregnancies (A clinical pregnancy was defined as ultrasonographic visualisation of one or more gestational sacs).
- Multifetal pregnancy rate.

The primary outcome in subpopulation 2 was: diagnosis of HDP (classified as gestational hypertension, preeclampsia, or eclampsia), and preterm birth less than 37 gestational weeks.
The secondary outcomes in subpopulation 2 were e.g.:

- Maternal: Gestational diabetes, emergency caesarean section, postpartum haemorrhage and shoulder dystocia.
- Perinatal: Stillbirth or neonatal death, Apgar score less than 7 at 5 minutes, birth trauma, admission to a neonatal intensive care unit for more than four days and major birth defects.

Statistical and qualitative analysis

Statistics (Paper I, II and IV)

Power calculation: The power calculation in the RCT was based on a study by Kahnberg et al., 2009[103], showing a live birth rate in women with obesity of 12.5% (7/56) and for women of normal weight, a live birth rate of 26.3% (81/308)[103]. To be able to show a difference in live birth of 13%, from 12% to 25% (significance 5% power 80%), between the two groups, at least 152 patients had to be included in each group. The reason for choosing this study for the power calculation was the lack of available BMI data in IVF treatments at the time of planning the RCT. A rather large difference (12% to 25%) in live birth rate was also considered to be required if this kind of intervention should be an option in daily praxis, for obese women planning IVF. No loss of follow-up was expected but the sample size was increased to 316 in total to compensate for possible dropouts.

The main analysis was performed in the FAS population, a population as close to the intention-to-treat (ITT) approach as possible. The ITT method means that all randomized subjects are included in the analysis and analyzed in the group they were

allocated in, while the FAS population excludes a few. Women who achieved a spontaneous pregnancy or had at least one follow-up variable and had started the IVF treatment were included in the FAS. Women excluded from the FAS population were, e.g., women who divorced or had medical or other personal reasons and because of this, did not do the IVF treatment. Hence, they did not intend to get pregnant for the time being, and therefore the effect of the treatment could not be evaluated in those women.

A per protocol analysis was performed as well, which included all women randomized, who completed the study and who did not significantly deviate from the protocol. For the primary variable LBR and for selected secondary variables, two pre-planned sub-group analyses were performed; one in women completing the dietary program and reaching normal weight or lowering BMI by at least five units, and another one in women with PCOS.

An overview of the statistical analyses performed in the RCT, the two-year follow-up and the register study are shown in table 5.

Table 5. Statistical methods.

Statistics	**RCT**	**Two-year follow-up**	**Register study**
Descriptive continuous variables, measures	SD, median, minimum, and maximum	SD, median, minimum, and maximum	
Descriptive categorical variables, measures:	Number and percentage	Number and percentage	Number and percentage
Analyses of dichotomous variables	Fishers exact test Multivariate logistic regression	Fishers exact test	Generalized Estimating Equation (GEE) models
Analyses of ordered categorical variables	Mantel-Haenszel Chi Square test	Mantel-Haenszel Chi Square test	
Analyses of non-ordered categorical variables	Pearson´s Chi Square test	Pearson´s Chi Square test	
Analyses of continuous variables	Mann-Whitney U-test	Mann-Whitney U-test	
	ANCOVA	Fisher´s non-parametric permutation test	

RR = risk ratio, aRR = adjusted risk ratio, CI = confidence interval

For the primary and selected secondary variables in the RCT, complementary analysis was performed in the FAS population where adjustments were made for differences in baseline variables. For continuous variables adjustment were performed by ANCOVA and for dichotomous variables, by multivariate logistic regression.

For the primary variable, live birth, and for important secondary variables, risk differences and risk ratios with 95% CI and exact 95% CI for the estimated proportions were calculated. All significance tests were two sided and conducted at the 5% significance level.

When approximately 60% of the women had been included in 2014, an interim analysis was performed by an experienced researcher and statistician, uninvolved in the RCT. The intention was to detect if there were large differences between the groups with regard to baseline variables at randomization and live birth rate. It was recommended by the data safety and monitoring board that the RCT should continue.

The main analysis of CLBR in the two-year follow-up was performed on the FAS population from the RCT. After amendment to the ethical committee, we had the possibility to access medical records at respective IVF clinic, to find out whether the non-participating women had had a child or not. Of the 29 non-participating women six women in the weight reduction and IVF group and three women in the IVF only group had achieved a live birth in the RCT. We assumed that the other 20 non-participants had not succeeded in having a child after the RCT. It was, according to a post hoc power calculation, possible to detect a 15% difference in CLBR between the groups. The statistical methods used are shown in table 4.

To analyze the association between BMI and the outcomes in the register study, Generalized Estimating Equations (GEE) were used to obtain crude risk ratios and adjusted risk ratios with 95% confidence intervals, adjusting for dependence within each woman.

In subpopulation I, adjustments were made for, the woman's age (years, continuous), year of treatment (continuous), the woman's educational level (≤9, 10–12, ≥13 years), the woman's country of birth (Sweden/Other European/Outside Europe), fertilisation method (IVF/ICSI), number of previous IVF children (continuous) and number of previous failed started fresh IVF cycles (continuous).

In subpopulation 2, adjustments were made for maternal age (continuous), year of treatment (continuous), parity (0/≥1), maternal educational level (≤9, 10–12, ≥13 years), maternal country of birth (Sweden/Other European/Outside Europe), maternal smoking (yes/no), fertilisation method (IVF/ICSI), and type of embryo transfer (fresh/frozen).

Qualitative analysis (Paper III)

In the interview study thematic content analysis was used, according to Braun and Clarke, 2006[104], to analyse the data. A co-worker outside the research team transcribed the interviews verbatim. The interviewing author checked the transcribed data for accuracy and then interesting aspects were identified separately by two authors. NVivo software program was used when the data was coded by the two authors together, and thereafter sorted into potential main and sub-themes. The relationship between the codes and the themes were visualized with a mind map. Thereafter, the process of reviewing the themes began. The entire dataset and the coded data were re-read, to ensure that no themes were missing and that the themes were representative of the data. The main and sub-themes were named and revised during the final stage. Selected quotations and an analytic narrative clarify the themes in the results.

Methodological considerations

We used a randomized controlled setting with concealed allocation of the participants to explore if a weight reduction treatment in obese women prior to IVF would increase the live birth rate compared to a control group who performed IVF immediately. The advantages of a RCT are that the randomization provides two comparable groups by balancing for confounding factors, known and unknown, and allows any differences in outcomes between the groups to be attributed to the intervention.

When planning the trial, the initiating researchers discussed which kind of weight reduction treatment that would be suitable, and they chose the low-calorie diet after recommendation from specialists at the obesity unit. The reason for this was an expected weight loss of one to two kilogram per week, and a woman with obesity class I could possibly reach normal weight within 12 weeks. Couples who are scheduled for IVF treatment have usually tried to conceive during a long time and it

was not reasonable to think that they would have wanted to postpone the IVF treatment much longer, which the choice of another weight reduction method would have entailed. For this reason, a life-style intervention with physical exercise was opted out, due to an expected smaller weight loss in the same amount of time. Bariatric surgery was also discussed, however, to be eligible for this treatment in Sweden BMI must be ≥40 kg/m^2 and it is also recommended not to get pregnant during the first year after surgery. Hence, this method was neither an option.

For the two-year follow-up study a questionnaire was chosen as it was easy for the women to fill out. To get an exact measure of the women's weight it would have been necessary for all women to come to the clinic for the follow-up. However, such approach was considered to reduce the participation rate and was therefore not a suitable method. When we received the responses of the questionnaires, we became aware of the difficulty in measuring weight in this group of women who may have recently given birth or were pregnant. The weights of pregnant women were not included in the analysis.

In the interview study the interviews were held six years after randomization in the RCT which can be considered a long time for a follow-up study. The reason to why we made the interviews after six years was that, after approximately three years into the two-year follow-up, we thought it would be of interest also to explore the impact of the weight reduction treatment in an ever longer perspective. We had an intention to include the women in the RCT, to assess cumulative live birth rate and weight maintenance. We received an ethical permit to conduct the six-year follow-up and to interview around 20 women. Questionnaires was sent out from Sahlgrenska University Hospital to women included at all Swedish sites, but due to a low response rate, the inclusion was ended but the interviews were performed as intended.

To capture the women's views and experiences of the RCT, a qualitative hypothesis generating study design was used. The RCT gave us information about the impact of weight reduction on live birth rate, but the interviews increased our knowledge about the RCT from a different perspective. In comparison to quantitative research the generalizability and external validity is however limited. The in-dept data collected from the interviews can form the basis for further quantitative research, for example by questionnaires, to determine whether the opinions expressed also apply to a larger number of patients.

Ethical considerations

The randomized controlled trial (Paper I), including the two-year follow-up (Paper II), were approved by the Regional Research Ethics Committee in Gothenburg (Dnr: 292-10) and by The Committees on Health Research Ethics in the Capital Region of Denmark (H-2-2012-127) and by Vísindasiðanefnd (Bioethics) in Island (13-139-S1). The interview study (Paper III) was approved by the Regional Research Ethics Committee in Gothenburg (Dnr: 740-17) and the register study (*Paper IV*) by The Swedish Ethical Review Authority (Dnr: 2020-07126). Prior to the RCT and the interview study the women received both written and oral information and they all signed an informed consent.

In the RCT, an age limit was set as an exclusion criterion as age has a negative impact on LBR. It was not considered ethically acceptable to possibly delay IVF treatment for four months to lose weight for women older than 38 years.

Another exclusion criterion was binge eating disorder. If a woman, according to the QEWP-R[100] had a binge eating disorder, she could not take part in the RCT. She would have been referred to an eating disorder specialist and allowed to start IVF treatment without being part of the trial.

Further, a follow-up program was included for women who were randomized to weight reduction treatment, aiming to help the women to maintain the lower weight. They were able to receive dietary advice monthly during one year after inclusion in the trial.

In the interview study, questions would be asked about whether the women had become a parent or not and concerning obesity. These topics may be perceived as sensitive and could possibly lead to psychological stress, especially in women who were still childless. For this reason, an information letter was sent to inform the women about the study and that we intended to call them within two weeks, to inquire whether they were willing to participate. If they did not want to participate, they could contact us by email and thus avoid the phone call and any further questions in the subject.

The register study includes sensitive information regarding BMI and outcomes after IVF. All data retrieved from The National Board of Health and Welfare was pseudonymised, however the personal integrity could still be affected. Patients have

a possibility to withdraw their personal data from national quality registers, such as Q-IVF, this is however very rare. The health registers held by the National Board of Health and Welfare are mandatory, such as the Medical Birth Register.

Results

Paper I

After randomization in the RCT, the two groups had similar baseline characteristics regarding mean BMI (≈33 kg/m^2), age (≈32 years), duration of infertility (≈39 month), parity, number of previous treatments and cause of infertility. A difference in termination of pregnancies was seen; 7.9% in the weight reduction and IVF group had had an abortion compared to 20.3% in the IVF only group.

The women allocated to weight reduction treatment prior to IVF lost a substantial amount of weight, figure 4. The mean weight change, from randomization until oocyte retrieval was 9.10 kg. The difference in weight change was large within the group, 54.6% of the women lost more than 10% of initial body weight, 19.1% lost more than 5% and 26.3% lost less than 5%. The women in the IVF only group had gained 1.19 kg.

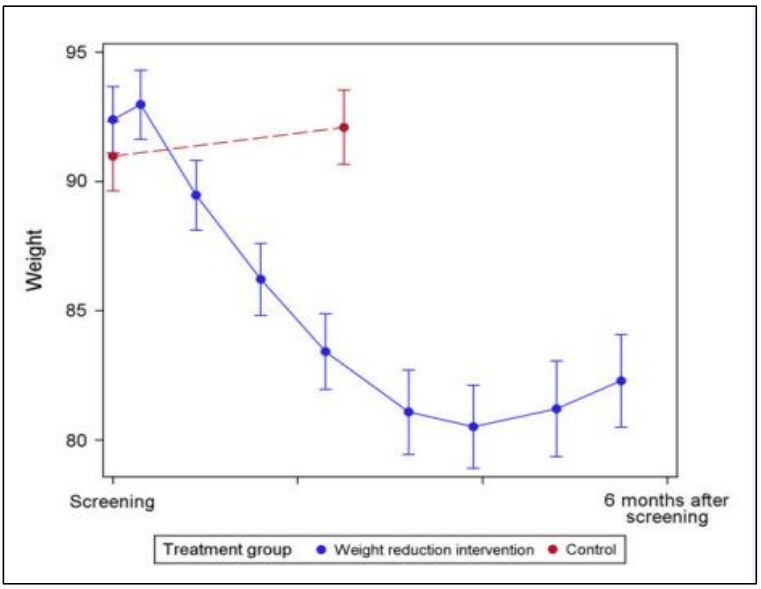

Figure 4. Weight change in the two study groups, from randomization to oocyte retrieval.
The first dots, blue and red, represent weight at randomization, the second blue dot; weight at first visit at the obesity unit followed by week 2, 5, 8, 12 15, the penultimate blue dot and the second red dot represents the oocyte retrieval and the last blue dot week 18 in the weight reduction treatment.

The LBR after IVF and spontaneous pregnancies, was high in both groups, but no significant difference between the groups was shown. In the weight reduction and IVF group the LBR was 29.6% (45/152) compared to the IVF only group, 27.5% (42/153) (difference 2.1%, 95% CI 12.9 to -8.6, *p*=0.77).

In the weight reduction and IVF group a higher proportion of children born after spontaneous conception was noted. A summary of the secondary outcomes in each treatment group are shown in table 6.

Table 6. Summary of outcomes according to treatment group in the RCT.

Variable	**Weight reduction and IVF group** (*n*=153)	**IVF only group** (*n*=152)	***p*-value**
Spontaneous pregnancy leading to live birth	16 (10.5%)	4 (2.6%)	<0.005
Number of oocytes retrieved per patient	8.56 (5.28) 7.00 (1.00; 25)	9.00 (5.85) 8.00 (0.00; 32)	0.63
Number of embryo transfers performed	105 (77.25)	122 (81.9%)	0.46
Number of frozen embryos	1.32 (1.66) 1.00 (0.00; 8.00)	1.64 (2.56) 1.00 (0.00; 15.00)	
Miscarriage gestational weeks 6-12	8/66 (12.1%)	4/56 (7.1%)	
Miscarriage gestational weeks 12-22	0 (0.0%)	1/56 (1.8%)	
Live birth (including spontaneous pregnancies)	45 (29.6%)	42 (27.5%)	

For categorial variables n (%) is presented.
For continuous variables mean (SD/median (min; max) is presented.

A per protocol (PP) analysis was performed to evaluate the effect of the treatment in women who had followed the protocol without any major deviations. From the FAS-population, five women from each group were excluded from the PP-analysis, mostly due to postponement of the treatment with over six months. The result of the PP-analysis followed the same pattern as the analysis of the FAS-population, with no significant difference in LBR between the groups.

Two subgroup analyses were performed for the primary efficacy variable live birth. The first compared the women in the IVF only group to women in the weight reduction and IVF group who had reached a BMI of ≤25 kg/m^2 or who had lowered the BMI with more than five points. In the weight reduction and IVF group the live

birth rate was 7/38 (18.4%) compared to 42/153 (27.5%) in the IVF only group (p=0.53).

The second sub-groups analysis compared women with PCOS in the two groups regarding LBR. The LBR in women with PCOS in the weight reduction and IVF group was 11/40 (27.5%) compared to 9/41 (22%) in the IVF only group (p=0.75)

Paper II

Of the 305 women who were included in the FAS population in the RCT, 276 women, 90.5% participated in the two-year follow-up. The baseline characteristics, recorded when they were randomized in the RCT, was similar in both groups except a difference in termination of pregnancy which was higher in the IVF only group.

CLBR

No difference in the primary outcome CLBR (defined as at least one child born, after fertility treatment or spontaneous conception, between randomization in the RCT until the two two-year follow-up) could be shown. The CLBR in the weight reduction and IVF group was 57.2% (87/152) compared to 53.6% (82/153) in the IVF only group (odds ratio 1.16, 95% CI 0.74 to 1.52, p=0.56). Additional live births since the RCT were 42/137 (30.7%) in the weight reduction and IVF group and 40/139 (28.8%) in the IVF only group. Of these additional live births, nine in each group was achieved after a spontaneous conception. In the weight reduction and IVF group 19 ongoing pregnancies was reported and, in the IVF only group there was 16 ongoing pregnancies, table 7.

Weight maintenance

The second primary outcome in the two-year follow-up was weight maintenance in the weight reduction and IVF group. The women in the weight reduction an IVF group had a mean weight gain of 8.57 kg compared to a mean weight loss of -1.2 kg in the IVF only group, table 8, figure 5.
A significant difference between the groups was shown regarding number of women with a BMI <30 kg/m^2. In the weight reduction and IVF group 23.1% had a BMI under 30 kg/m^2 compared to 10.9% in the IVF only group (p=0.019), table 8.

Table 7. Summary of outcomes in the FAS population at the two-year follow-up.

Variable	Weight reduction and IVF group	IVF only group	*p*-value OR 95% CI
Cumulative live birth rate*	87/152 (57.2)	82/153 (53.6)	0.56 1.16 (0.74 to 1,52)
No. of participants in the follow-up	137	139	
Additional live birth rate	42/137 (30.7)	40/139 (28.8)	
Way of conception			
IVF/ICSI	20/42 (47.6)	20/40 (50)	
FET	11/42 (26.2)	9/49 (22.5	
Spontaneous pregnancies	9/42 (21.4)	9/40 22.5)	
Other fertility treatment or unknown	2/42 (4.8)	2/40 (5.0)	
Ongoing pregnancies	19	16	
Expecting first child in the study	10/137 (7.3)	7/139 (5.0)	
Expecting second child in the study	9/137 (6.6)	9/139 (6.5)	
Cumulative live birth rate/ongoing pregnancy rate	97/152 (63.8)	89/153 (58.2)	0.34 1.28 (0.8 to 2.01)

FAS = Full analysis set, FET = frozen embryo transfer, OR = odds ratio
For categorial variables n (%) is presented.
For continuous variables mean (SD/median (min; max) is presented.
*Cumulative live birth rate defined as at least on child born alive. Calculated in all FAS patients 152/153.

Table 8. Weight changes at two-year follow-up, excluding ongoing pregnant women at the time for the follow-up.

Variable	Weight reduction and IVF group	IVF only group	*p*-value
Weight change (kg) from last assessment in the RCT until 2-year follow-up*	8.57 (9.55) 8.40 (−33.50; 30.60)	-1.18 (7.05) -0.60 (−29.10; 16.60)	0.0001
BMI (kg/m^2) at 2-year follow-up*	32.5 (3.5) 33.2 (22.7; 39.1)	33.1 (3.0) 33.3 (23.7; 42.2)	0.44
No. of women with BMI <30	27 (23,1)	13 (10.9)	0.019
No. of women with BMI ≥30-<34.9	52 (44.4)	70 (58.8)	0.044
No. of women with BMI ≥35	37 (32.5)	36 (30.3)	0.895

For continuous variables mean (SD) median (min; max) is presented. For categorial variables n (%) is presented. For comparison between groups, the Fisher´s Exact test (lowest I-sided *p*-value multiplied by 2) was used for dichotomous variables and the Mann-Whitney U-test vas used for continuous variable.
*Missing weight data of two patients in the weight reduction and IVF-group and four patients in the IVF only group.

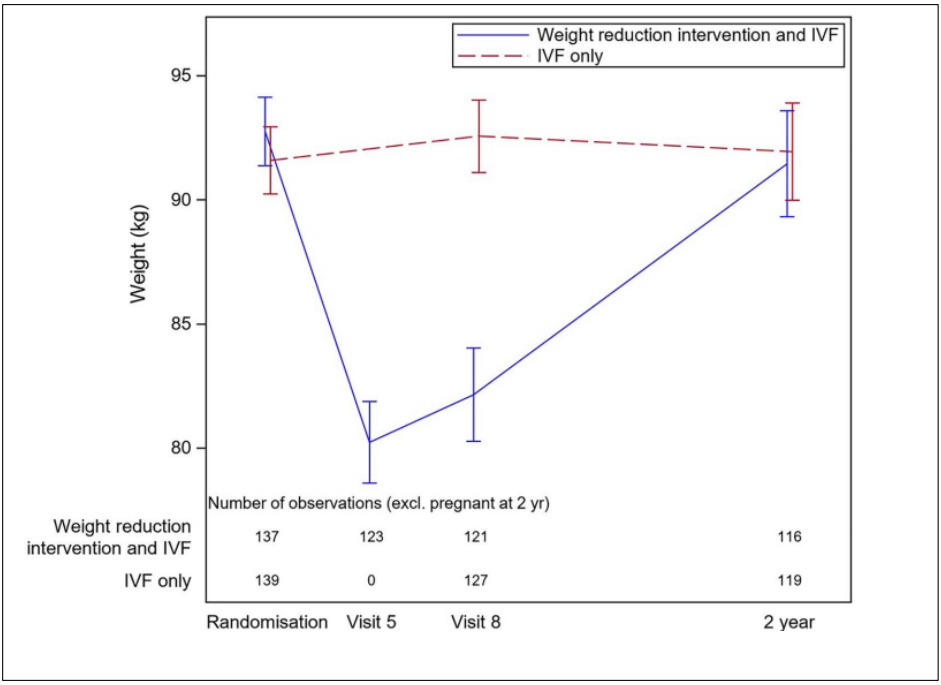

Figure 5. Weight of women from randomization until 2-year follow-up.

Visit 5 = week 15 of the diet. Visit 8 = oocyte retrieval. Missing data visit 5, on 14 patients in the weight reduction and IVF group. Missing data visit 8, on 16 patients in the weight reduction and IVF group and 12 patients in the IVF only group. Excluding ongoing pregnant women at the 2-year follow-up. Missing data, at the 2-year follow-up on two patients from the weight reduction and IVF group and four patients from the IVF-only group.

Follow-up of the children

Weight standard deviation score (SDS) of children born after the IVF in the RCT was analyzed at the two-year follow-up. For the children born of mothers participating in the weight reduction and IVF group the weight SDS was 0.218 (1.329) (mean, standard deviation) and for children born of mothers participating in the IVF only group the weight SDS was -0.005 (1.271). No significant difference was found (mean difference 0.327; 95% CI -0.272 to 0.932).

Paper III

In the interview study two main themes were identified during the analysis and five related sub-themes, see table 9. The different themes are presented with illustrative quotations from the interviewed women. Depending on which group the women were allocated to in the randomized controlled trial, the quotations are labeled with a number and an I or a C (intervention and control).

Table 9. Overview of main and sub-themes.

Pros and cons related to trial participation	**Message to healthcare**
Opportunity for myself	To be judged by a number
The challenge with weight loss and keeping it off	To be offered weight reduction
The value of the study – for me and others	

Pros and cons related to trial participation

The women described a positive reaction when being informed about the study. Most of them felt that it was a win-win situation; to receive help in losing weight and possibly increase the chance for a pregnancy or to start IVF immediately. At the time for the study the reproductive clinic at Sahlgrenska University Hospital had about a six-month waiting period.

> *I just felt that of course I wanted to do it. I took all the chances I could to increase the chance of getting pregnant. It was like, "Yes, why not?" If I didn't get pregnant, we would in any case have got something for nothing. (8 I)*

Some of the women also mentioned that a weight reduction would have an impact on future health in a positive direction, and this was another reason for participating in the trial.

Most of the women interviewed expressed a wish to be randomized to the weight reduction and IVF group.

The women who participated in the weight reduction treatment described the 12 weeks with low-calorie diet as a though challenge. They described the support received as very important in managing the low-calorie diet. Because of side-effects of the diet, a few women abandoned the low-calorie diet and received dietary advice

instead. Most of the women were happy with the weight reduction they had achieved, however, they all had difficulties maintaining the lower weight. Different reasons were mentioned for their weight gain, either lack of support after the initial weight loss treatment or focusing on a new treatment or getting pregnant.

> *Well, I went up after…, I went up a bit between every.., hormone treatment, during that time… I did. You see…, I did quite well really until I got pregnant, OK. It was really hard. Because I went down…, I don't remember, was it 25 kilos perhaps. A lot in a short time, which I thought was really great, but then I put on 30 when I was expecting S and they were very hard (kilos) to lose. (2 I).*

Almost all of the women expressed a value of having participated in the trial, either for themselves, that they were given the opportunity to lose weight or for others who may benefit from the results in the future.

Message to healthcare

Different opinions were expressed regarding BMI limits set by IVF-clinics in Sweden. A strong view was however, that obese women should be allowed to come to an initial consultation, compared to now, when the referral will be denied if a woman exceeds the BMI limit. They wished to be assessed as individuals in a meeting with a clinician, and not only judged by their BMI.

> *Yes, but I think that BMI is a pretty crude tool. I think that someone with a BMI of 31 say, perhaps has a problem with…and that affects other things like what the ovaries look like …but that can mean that someone with a BMI of 31 perhaps needs help just as much as someone with a BMI of 37. And I think that perhaps BMI cannot be the only measurement, but there should be a form of individual assessment. (15 I)*

The opinion in just over half of the interviewed women was that it was correct to set a BMI limit, with some flexibility, for access to IVF treatment. The remaining women were doubtful or against it but at the same time they understood the medical considerations for the set limit. Those who were in favor for a limit expressed the importance of creating the best conditions before the IVF treatment.

Almost all women had a positive attitude towards an offer of weight reduction treatment before IVF, despite the fact that no more children were born in the weight reduction and IVF group. They expressed that they would have preferred to receive support in losing weight and possibly achieving a spontaneous conception rather than

having to do IVF. The higher rate of live births after spontaneous conception in the weight loss and IVF group was perceived as encouraging.

Paper IV

Live birth rate

In subpopulation 1 in the register study, the association between BMI and LBR was assessed in almost 130 000 fresh cycles and subsequent FET performed in Sweden during a period of 14 years, starting at 2007. This population were divided into six BMI categories. In 2.4 % of the cycle's women were underweight, in 62% of normal weight, in 26% they were overweight, and in 8.7%, 1.1%, 0.05% they had obesity class I, II respective III.

The main outcome, CLBR decreased with severity of obesity and so did other assessments of LBR.

In subpopulation 2 the association between BMI and maternal and perinatal outcomes were assessed in fresh and FET, performed during a period of 19 years (from 2002), resulting in almost 60 000 singleton deliveries. The percentages of deliveries in which women were underweight in this population was 2.2 %, in 64.7% they were of normal weight, in 24.4% overweight and in 7.5%, 1.0% and 0.1% of the deliveries the women had obesity class I, class II respective class III.

Maternal outcomes

A significant association was found between BMI and the primary maternal outcome HDP. The rate of women with HDP increased with severity of obesity.

Perinatal outcomes

A significant association was found between BMI and the primary perinatal outcome preterm birth less than 37 weeks. The rate of women with preterm birth less the 37 weeks increased with severity of obesity. Also, secondary perinatal outcomes were affected in a similar way.

Discussion

Main findings

In the large RCT no difference in LBR could be found, despite a substantial weight loss in the intervention group. Neither were there any differences in CLBR after two years, and the women in the weight reduction and IVF group had regained the weight lost in the RCT. The interviewed women were in general positive to the RCT. They expressed a wish for individual evaluations and support if weight loss were advocated. In the registry study a progressive decrease in LBR and CLBR was noticed by increasing BMI, and perinatal and maternal outcomes were negatively affected by increasing BMI.

Weight reduction prior to fertility treatment

In a period of five years and four month, 962 women were screened for eligibility to participate in our Nordic RCT[105]. Of these women, 362 had an exclusion criterion and for 60 women other reasons was noted. Of the remaining 540 eligible women, 317 agreed to participate and 223 women declined, showing how difficult it is to include individuals in these kinds of trials. In our RCT the drop-out rate in the weight reduction and IVF group was low, only seven out of 159 women. However, in a review by Mutsaerts et al. exploring the drop-out rates in lifestyle interventions in obese infertile women, 24% discontinued weight loss interventions[106] .

The women receiving the weight reduction treatment in our Nordic RCT had an initial mean BMI of 33.1 kg/m^2, and they lost a mean of 9.10 kg from randomization until the last recorded weight, usually measured at oocyte retrieval, or before a spontaneous conception. The low-calorie diet (880 kcal/day) was chosen to reach a large weight loss in a short amount of time, and to reach a BMI as close to normal as possible. Even though 29 (19.1%) women lost 5% to 9.9% of initial body weight and 83 (54.6%) women lost over 10%, the mean BMI after the weight reduction treatment was 29.85 kg/m^2. Thirty-eight (24%) women lowered their BMI with five BMI units or reached a BMI ≤25 kg/m^2, which highlights the challenge in reaching a normal BMI, even with professional support.

Two additional large RCTs, one Dutch[87] and one American[88], have been performed investigating the live birth rates after weight reduction prior to fertility treatment. Other interventions were chosen in those trials, resulting in fewer kilos lost. In these trials, 22% respective 16.5% of the women dropped out of the intervention. In the Dutch trial 577 women with a median BMI of 36 kg/m^2 were randomized to a lifestyle intervention for six months or to start fertility treatment instantly. The lifestyle intervention aimed to lower the initial body weight with 5-10%, by reducing their daily calorie intake by 600 kcal and by increasing daily physical exercise. The goal was reached by 37.7% of the women in the lifestyle group. The mean weight loss after six months was 4.4 kg[87].

In the American RCT, 370 women with a mean BMI around 39 kg/m^2 were randomized to a 16-week weight loss program with exercise, anti-obesity drugs and a diet consisting of meal replacements, vegetables, and fruits (a total of 1200 kcal/day) aiming to lose 7% of initial body weight or to a standard lifestyle, only encouraged to increase exercise for 16 weeks. The goal was almost met, 6.6% (mean 7.3 kg) of initial body weight was lost in the weight reduction group, reducing their BMI from 39.2 kg/m^2 to 36.6 kg/m^2, compared to the control group who lost 0.3 kg. It was also shown that the weight loss program improved biochemical and biometric parameters, such as leptin, triglycerides, insulin, and blood pressure[88].

No randomized controlled trial has yet been performed in infertile obese women performing a bariatric surgery prior to IVF. However, retrospective studies have been performed in women who have undergone a bariatric surgery and thereafter also an IVF treatment[107 108]. In one of those studies[107], 83 women who had a history of bariatric surgery, had lost mean 41.8 (±16.7) kg, a weight loss that would be extremely difficult to achieve with a diet or a change in lifestyle. The women had a BMI over 40 kg/m^2 before surgery and lowered their BMI from having obesity class III to being overweight.

LBR after weight reduction prior to fertility treatment

Despite the large weight loss achieved in the weight reduction and IVF group in our Nordic RCT, no difference in LBR was found compared to the group of women who performed IVF without losing weight, 29.6% respective 27.5% (difference 2.1%, 95% CI 12.9 to – 8.6, p=0.77)[105]. We had assumed that the rate of live birth in the

IVF only group would be much lower, but it was surprisingly high and in line with the mean LBR after IVF in Sweden at the time[31].

The Dutch and the American RCTs also failed to show an increased rate of a live birth, after weight loss interventions before fertility treatment, compared to the control group. In the Dutch RCT the chance of a live birth of a healthy singleton at term, within 24 months from randomization, the primary outcome of that study, was even lower after a lifestyle intervention prior to fertility treatment (ovulation induction, intrauterine insemination, IVF) compared to the control group, 27.1% respective 35.2% (Rate ratio 0.77, 95% CI 0.60 to 0.99). However, after including women with ongoing pregnancies, who gave birth after the study end, no difference in live birth rate was found[87].

In the American RCT, where the primary outcome was a healthy live birth after up to three cycles of ovarian stimulation with clomiphene citrate and thereafter insemination or a spontaneous conception, no difference between the groups was found. The LBR was 12.2% in the weight reduction group and 15.2% in the control group (Rate ratio 0.81, 95% CI 0.48 to 1.34). Despite improvements in biochemical and biometric parameters in this study, no improvement in reproductive outcome was noticed[88].

In these three RCTs[87 88 105], which are the only large RCTs conducted to investigate the effect of weight reduction on LBR after fertility treatment, the results are not complete comparable due to different methods chosen for both weight loss treatment and fertility treatment and in addition different initial BMI for participants. However, regardless of which method chosen, none of the interventions were able to improve LBR by weight reduction. These results are confirmed in a recent individual participant data meta-analysis, including 8 randomized trials and 1715 women[109].

The rate of women achieving a live birth after spontaneous conception in our Nordic RCT[105] was higher in the weight reduction and IVF group compared to the IVF only croup, 10.5% and 2.6% respectively. Previous studies have found that weight loss can be beneficial for spontaneous conception[79 80], but the increased rate, noticed in our study, may also have been a direct consequence of that the women who lost weight had four months longer time to conceive. However, the duration of infertility was over three years in both groups at randomization, suggesting that the weight loss itself probably had an impact. The same applied for the Dutch trial where higher rates of births after spontaneous conceptions were noted in the lifestyle group[87].

In the two-year follow-up of the Nordic RCT, no difference in CLBR could be found between the groups, being 57.2% in the weight reduction and IVF group and 53.6% in the IVF only group. When including ongoing pregnancies in the CLBR, the percentage difference was 5.6% between the weight reduction and IVF group compared to the IVF only group, 63.8% respective 58.2%, however the difference was not statistically significant (p=0.34, odds ratio 1.28, 95% CI 0.8 to 2.01)[110].

Observational studies comparing outcomes after IVF in women who had undergone bariatric surgery with a control group, matched by post-bariatric BMI level, found no difference in CLBR between the groups[107 108]. This suggests that a large weight loss, which is possible to achieve after bariatric surgery, could have a positive impact on CLBR. One of the studies also compared CLBR in women who had undergone bariatric surgery to women with BMI over 35 kg/m^2 and found a difference in CLBR between the groups, being 22.9% in the bariatric surgery croup and 12.0% in the high BMI group. The result, however, did not reach statistical significance, only 83 women were included in each group[107].

Weight maintenance

In the two-year follow-up after the RCT, the current weight of the women was examined. In both groups the mean BMI at the follow-up was similar to when they were randomized in the RCT. Thus, the women in the weight reduction and IVF group had regained the weight lost during the intervention in the RCT. This is in line with results from several studies showing that it is a challenge to keep the weight off and that weight regain is very common[56 111]. However, compared to the women in the IVF only group a higher rate of women in the weight reduction and IVF group had a BMI under 30 kg/m^2 at the follow-up. For these women, the study may have contributed to better health, which is valuable on a personal level. In both groups more than 30% of the women had a BMI above 35 kg/m^2 at the follow-up which may be due to that some of the women had recently been pregnant and not returned to their pre-pregnancy BMI. It has been shown that obese women are at higher risk for excess gestational weight gain[112].

Studies have found that weight maintenance is promoted by an ongoing clinical follow-up and counseling to encourage healthful behavior[57 113 114]. In the Nordic RCT the women in the weight reduction group had the possibility for continuous support by a dietician or a nurse for one year after randomization, this was however only

utilized by 48% of the women (27%; 1 to 3 visits, 21%; 4 to 7 visits)[110]. The reasons for this are not fully known, but the women in the interview study mentioned reasons such as not being encouraged to continue with further check-ups, that they became pregnant or that they were focusing on a new IVF treatment. It is well known that weight maintenance is difficult to achieve and for this group of women, who was also focused on getting pregnant, it was perhaps even harder. However, despite the weight gain, most women in the interview study expressed that they felt satisfied with having tried to improve their chances by losing weight prior to IVF[115].

Observational studies

Live birth rate

The register study showed that increased BMI is associated with decreased LBR which is in line with findings from other studies investigating the association between BMI and LBR after IVF[72 73 77]. The LBR in 239 127 IVF cycles were explored in a large retrospective cohort study from 2016. They found that the live birth per started cycle after IVF was 31.4% in normal weight women, 29.8% in overweight women and 28.0%, 26.3%, 24.3% in women with obesity class I, II and III respectively[72]. A progressive decrease with increasing BMI by 1.6% to 2% between BMI classes. Thus, a difference of 3.4% between obese and normal weight women and much less than was anticipated in our power calculation for the RCT.

In two studies investigating the association between BMI and CLBR in combination with age, it was found that CLBR declined with elevated BMI[9 116]. However, in women over 38 years of age, age had a more pronounced impact on CLBR than increased BMI. Goldman et al., 2019, showed that women of 33 years of age with normal BMI had a CLBR of 56% compared to women of the same age with obesity class III who had a CLBR of 37%, a difference of 19%. The respective percentages for women of 39 years of age was 25% and 23%, a difference of only 2%[9]. Both studies concluded that woman's age must be considered before a possible weight loss is recommended that could potentially improve the outcomes after IVF[9 116].

Maternal and perinatal outcomes

The register study found that women with overweight and obesity had a significantly increased risk for adverse maternal and perinatal outcomes, which is in line with several other studies examining outcomes after spontaneous conception[65-69 71 117],

and with some small Chinese studies reporting similar results in pregnancies after IVF[76 118 119]. The risk for adverse outcomes such as miscarriage, HDP, preterm birth, children being born LGA, major birth defects and perinatal death, are increasing with severity of obesity[65-69 71 117].

A previous Swedish observational study compared the maternal and perinatal outcomes in women who had had a bariatric surgery (*n*=596) to matched controls (*n*=2356) with a similar pre-bariatric surgery BMI. The mean weight loss was 37 kg in the bariatric surgery group. They found that the women in the bariatric surgery group had a significantly decreased risk for gestational diabetes and of having children born with macrosomia or LGA, but an increased risk for children being born SGA. The study found higher rates, although not significantly, of the combined outcome stillbirth or neonatal death in women who had had a bariatric surgery, 1.7% compared to 0.7% in the matched controls (odds ratio 2.39, 95% CI 0.98 to 5.85)[82].

A systematic review and meta-analysis confirmed the results found in that study and also showed a decreased risk for hypertensive disorders of pregnancy and an increased risk for preterm birth in women who had undergone bariatric surgery compared to women with a similar pre-bariatric surgery BMI. They found no difference in stillbirth or neonatal death between the groups[81]. These studies suggests that a large weight loss reduces some of the negative maternal and perinatal outcomes in obese women, but instead adds other negative effects[81 82].

The reasons why obesity negatively affects LBR after IVF, and also maternal and perinatal outcomes are not well known. Some of the proposed mechanisms behind the elevated risks are related to higher levels of metabolic and inflammatory markers in individuals with obesity, such as adipokines, increased insulin resistance, alterations in placental function and excessive weight gain which is more common in obese women compared to normal weight women[62 112]. It has also been suggested that both the quality of the oocytes[120] and the endometrium[121] are affected by the chronic low-grade inflammation present in women with obesity. One study found that the LBR in obese oocyte recipients was decreased compared to normal weight oocyte recipients, which might be due to an altered uterine receptivity[121]. Another study showed that increasing BMI may have a negative effect on the oocyte as the LBR in oocyte recipient decreased with increasing donor BMI[120].

Patients' perspectives

The views of the women who participated in the interview study[115] gave another perspective to the results found in the RCT and the two-year follow-up. From a clinical perspective the weight reduction treatment prior to IVF was futile, as the live birth rate was similar in both groups, and the women in the weight reduction and IVF group regained the weight they had lost during the RCT. However, the opinions of most of the women were that it could still be of value to offer a supported dietary intervention to motivated obese women to perhaps increase the chance of a spontaneous pregnancy, but also to improve general health.

Some of the women mentioned that future health was one of the reasons why they chose to participate in the trial. It has been shown that health is an important reason to why women decide to lose weight[122].

When BMI limits for access to IVF treatment were discussed, different opinions were expressed, and a bit surprisingly, the view of half of the women were that it made sense to have a limit. However, they wished that individual aspects should be taken under consideration, and the limit should not be strict. A few women were against a BMI limit, and some were uncertain. However, most women said that they understood that the limits were set due to medical concerns.

In a recently published interview study regarding restrictions to fertility treatment due to high BMI, similar opinions were expressed. Several participants in that study regarded the limits as unfair and discriminatory. Others, however, were satisfied with being informed about the risk associated with obesity and could understand why a limit was set. They also expressed, as the women in our interview study, that individual considerations should be made, and a limit should not be due to one single biometric value[123].

In the updated committee opinion from 2021, the ASRM[89] state that an individual fertility evaluation should be performed, and the woman/couple should be informed about the risks associated with obesity on IVF outcome. However, denying fertility care only due to a high BMI is not recommended. An IVF treatment should only be denied if the oocyte retrieval under anesthesia, as it is performed in the USA, cannot be performed safely.

General discussion

Why does RCTs in obese women fail to show an improvement in live birth rates by weight loss while numerous observational studies suggest a deterioration in live birth by increasing BMI? A possible explanation is that the power calculations in the three RCTs described, were based on the assumption that a large difference (13%-15%), in LBR or a live birth of a healthy singleton could be found, between women who lose weight, and a control group. However, Provost et al.[72] found in their large observational study that the difference in LBR per started cycle, is not as great as assumed, but rather 3.4% between women with obesity class I and normal weight women[72]. This means that all three RCTs were underpowered. Much larger trials would have been necessary to detect such a small difference. Another contributing explanation is that the weight loss achieved was not large enough. Even though the women in our Nordic RCT lost mean 9.10 kg they still had an average BMI of 29.85%. The women in the other two RCTs lost even less weight[87 88]. However, as mentioned earlier, observational studies have shown that women who have lost large amounts of weight after bariatric surgery have a similar chance of a live birth as women with similar post-bariatric BMI[107 108]. Other reasons for the discrepancy between RCT and observational studies are the role of confounders, running in observational studies. This means that there might be other parameters of today unknown origin and thus not adjusted for, which might have affected the outcome.

Regarding the increased risks for adverse maternal and perinatal outcomes observed in women with overweight and obesity in observational studies, the RCTs were too small to be able to detect if the weight loss achieved had any impact on these outcomes. However, the aforementioned observational studies in women who have undergone bariatric surgery, found that a very large weight reduction improved some of the adverse outcomes, such as rate of HDP, cesarean section and gestational diabetes and LGA while other adverse outcomes were increased. Thus, it is possible that even minor weight loss may have a positive effect on adverse outcomes in women with overweight and obesity. The risk for stillbirth or neonatal death, the most serious complications, was not reduced, despite the large weight loss[81 82].

Strengths and limitations

The main strength of this thesis is that the four included studies represent four different study designs to address a common issue: one RCT, one observational study, one qualitative study and one registry study. From a pedagogical and PhD student perspective this should be regarded as optimal.

The strength of paper I is the study design, being a RCT, performed in nine clinics in the Nordic countries which enables generalizability. Another strength is that many women achieved a large weight loss with the low calorie-diet, exceeding the weight loss achieved in the other two RCT discussed earlier[87 88]. However, the weight loss was not as large as anticipated, only 25% of the women reached a BMI under 25 kg/m^2 or lost five BMI units which is a limitation. The RCT aimed to show a difference of 13% in LBR between groups, based on the power calculation, but also because a large difference was considered to be necessary for patients to perceive the time-consuming and demanding weight loss treatment as meaningful. However, later, and larger studies have suggested much smaller difference in LBR between normal weight and obese women[9 73 124].

A further limitation in the RCT is that the women in the IVF only group started the IVF treatment as soon as possible compared to the weight reduction and IVF group who started the treatment four months later, which gave that group the opportunity to conceive spontaneously during a longer time.

In the two-year follow-up of the RCT, 90.5% of the women included in the RCT participated, which is a strength. A limitation is the design of the study being a questionnaire follow-up. There is a risk of response bias. The questionnaire included a sensitive question concerning the women´s current weight, a systematic review has showed that self-reported weight, in women of reproductive age, was often lower than measured weight, however not to such a degree that it is likely to affect clinical studies[125].

In the interview study we chose to consecutively invite women to participate in the study from both groups, without any selection concerning if they had a child or not. This was however not known to us in several cases. Of the women participating in

the interviews most of them had a child, which may have influenced their positive attitude and could be considered being a limitation.

The register study has several strengths. It includes a large national population, covering IVF cycles performed during several years. The possibility to cross-link the data from Q-IVF[31] with several other national registers made it possible to investigate LBR and maternal and perinatal outcomes after IVF in relation to female BMI.

Registers have limitations such as missing data. In the analysis of LBR, data on BMI was missing in 16% of IVF cycles, especially in the first years, when BMI was not routinely recorded. This is the main limitation in the register study.

Conclusions

A mean weight loss of 9.10 kg in women with obesity class I, did not increase the chance to a live birth after IVF in comparison to women who performed IVF without losing weight. However, the rate of children born after spontaneous conceptions was higher in women who lost weight.

Two years after inclusion in the RCT, CLBR was found to be similar in both groups, and the women in the weight reduction and IVF group had regained pre-study weight.

Although no difference in LBR was found, most of the interviewed women saw a value in having participated in the RCT. They advocated individual infertility assessments and not being judged solely by BMI. In general, they had a positive attitude to a weight reduction treatment with support prior to IVF.

The register study found that, compared to normal weight women, overweight and women with obesity have a reduced CLBR and are at increased risk for adverse maternal and perinatal outcomes after IVF.

Future perspectives

How should fertility clinics take care of women with obesity?

It should be noted that most women with obesity are fertile. The proportion of obese women, in 2021, who were enrolled in Swedish maternity care was 17% (19,363 women)[126] and most of these women had conceived spontaneously. The health risks of obesity, which affect a large part of the population, must be dealt with by society in a broad perspective. Perhaps could fertility clinics, as part of public care, help motivated women and men to a healthier life instead of denying them care with a BMI limit?

In a recent Danish study[127], women and men with obesity were invited to participate in a lifestyle intervention for 6 months, prior to fertility treatment. The clinic had, at the time being, six months waiting time, and the women and men were contacted soon after they had been referred to the clinic. They invited individuals until their pre-defined number of 45 participants were included. The lifestyle intervention, consisting of calorie restrictions and increased physical activity, was completed by 21 women and 17 men. Three women and four men discontinued the intervention. The mean weight reduction after six months was 5.4 kg (95% CI -7.5 to -3.3), and one year after inclusion 4.4 kg of the weight reduction was maintained. In this study, four participants were found to have undiagnosed type 2 diabetes, for which they started medication.

For 27 women (23%) in our Nordic RCT[105] who had a BMI below 30 kg/m^2 at the two-year follow-up[110] and for the participant in the above-mentioned Danish[127] study who managed to maintain most of the weight lost even after one year, the studies probably have had a positive impact on their health.

Should a weight loss treatment with support be offered before IVF even though the three large RCTs could not show that a weight reduction had an impact on LBR, and it is unknown if a diet or a change in lifestyle have an impact on maternal and perinatal outcomes? Since at least some individuals are motivated to lose weight and that the weight loss is sustained by at least a part and further, that women, especially those with anovulation, may benefit from losing weight as ovulation is

promoted[79 80], this seems reasonable. Moreover, an offer of a weight loss treatment was also a wish of the women in the interview study[115].

However, if a woman does not wish to lose weight at the time being, she may have tried several times and failed, should she be denied IVF if not making another try of losing weight or if she tries but does not succeed? Especially given the lack of evidence that a minor weight loss, which is what the women in the three RCTs achieved, improves outcomes after IVF. Opinions have been raised, by ASRM[89] and others[128-130], against having a BMI limit for fertility treatments. Aspects mentioned against a limit are that women with other conditions, such as diminishing ovarian reserve, advanced reproductive age, and women with medical conditions such as diabetes, have access to fertility treatment despite decreased LBR and elevated maternal and perinatal risks. They refer to ethical principles of not discriminating against a particular group of individuals[89 128-130]. In Sweden and in several other countries, certain restrictions exist, at least at publicly funded clinics, referring mainly to safety reasons[83 84].

However, the routine in Sweden of denying access to infertility evaluation solely because of the woman's BMI may be questioned. Other causes, besides BMI, also have an impact on the outcomes after fertility treatments, e.g., the women's age and the ovarian reserve. Even obese women with a BMI above the set limit should be allowed to come to a first assessment. At this appointment, women with obesity should be informed of the increased adverse maternal and perinatal outcomes found in women with obesity and of the available data on the effect of weight reduction before IVF. Individual consideration should be taken, before weight loss is recommended.

If a woman with obesity wishes to proceed with fertility treatment without losing weight, maybe she should be allowed to? This decision may be based on the present lack of evidence of improved outcomes after RCTs[109]. A decision should be taken in agreement between IVF physician and the patient in order to satisfy the patient's needs and to ensure the safety of mother and child.

Fertility clinics with a waiting time could implement the strategy used in the Danish study[127], so that women who wish to lose weight can take advantage of that period and not lose time. However, it is also important to include continuous follow-up after weight loss treatment to promote weight maintenance and thereby future health. A collaboration between fertility clinics and weight loss clinics is desirable.

New drugs, have in recent years been approved for treatment of obesity, these have been shown to be effective even in a longer perspective[131]. A recently published RCT[132] compared a lifestyle intervention in combination with Semaglutide to lifestyle intervention and placebo and showed that the mean weight loss after two years was 16.1 kg in the Semaglutide group compared to 3.2 kg in the placebo group. The weight loss plateaued at around 60 weeks and were thereafter maintained up to study end at two years. However, the drug cannot be taken during pregnancy and treatment must be stopped two months before conception. The drug is not yet subsidized in Sweden for the treatment of obesity but may become a supplement to life-style interventions for individuals with obesity in the future.

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