Lifestyle intervention in obese infertile women

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Introduction

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In 2000, the World Health Organisation declared obesity a pandemic and one of the most important current public health problems.[1] Globally, the prevalence of obesity has doubled since the 1980s. It is estimated that globally 600 million adults were obese in 2014, mounting to 13% of the adult population.[2] The World Health Organisation (WHO) defines overweight as a body-mass index (BMI) of ≥ 25 kg/m^2 and obesity as a BMI of ≥ 30 kg/m^2, with a further division into Obesity Class I (BMI 30.00-34.99 kg/m^2), Obesity Class II (BMI 35.00-39.99 kg/m^2) and Obesity Class III (BMI ≥ 40.00 kg/m^2). For the Netherlands, data on prevalence of overweight and obesity from 2012, shows that 6% of Dutch women aged 20 to 29 years and 10% of those aged 30 to 39 years were obese (Figure 1). Furthermore, 26% of women aged 20 to 29 years and 37% of women aged 30 to 39 years were overweight.[3]

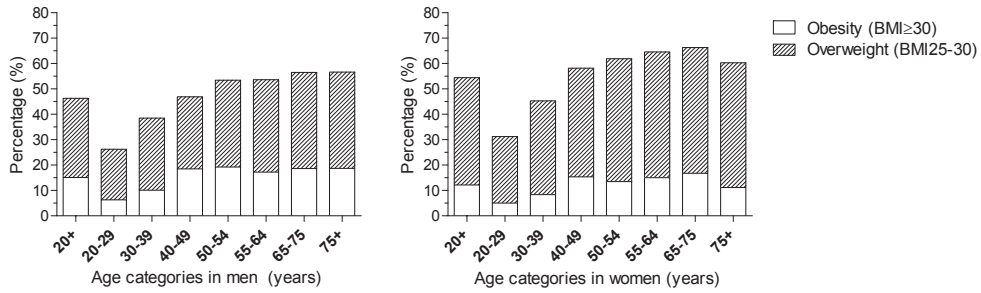

Figure 1. Overweight and obesity in The Netherlands by gender and age category in 2012 adapted from Gezondheidsmonitor volwassenen GGD'en, CBS and RIVM.

Overweight and obesity are caused by a long-lasting imbalance between energy intake and energy expenditure.[4] The increasing amount of readily available energy-dense processed foods and lower physical activity levels are likely to be important drivers of the obesity pandemic.[5] In general, obesity is more common among people with a lower level of education.[6]

Obesity is a major risk factor for several non-communicable diseases, such as cardiovascular disease, diabetes, some types of cancer and musculoskeletal disorders such as osteoarthritis.[2] Moreover, health-related quality of life in obese individuals tends to decrease with higher degrees of obesity.[7,8] Because of its association with these diseases, obesity is a financial burden to societies leading to an estimated 0.7% to 2.8% of a country's total health care expenditure.[9] In the United States the incremental healthcare costs per year for an obese individual were estimated to be $1901 (2014), equivalent to $149 billion per year at the national US level.[10]

1.1 Aetiology of obesity

Over the past four decades, substantial changes have occurred in the global food system. More processed, affordable and effectively marketed food is produced than ever before, promoting overconsumption of foods and decreasing the time-cost of food.[5] In addition, the need for physical activity has been reduced. It has been estimated that over the last 50 years, occupation-related energy expenditure has decreased by more than 100 kilocalories per day (which equals 4-5% of the total daily energy intake).[11] This decrease in energy expenditure and subsequent positive energy balance has been calculated to increase average weight in American men from 77 kilograms in 1960-1962 to 90 kg in 2003-2006, which closely resembles actual mean weight in men of 92 kg in an United States cohort in 2003-2006. In addition, the amount of moderate-to-vigorous physical activity, such as brisk walking or cycling, is inversely associated with obesity in a cohort study of 5083 American adults.[12] Men and women with low levels of moderate-to-vigorous physical activity had a 2.7 times (95% confidence interval [CI] 2.0-3.6) and 2.8 times (95% CI 2.2-3.7) increased risk of obesity compared to individuals with high levels of moderate-to-vigorous physical activity. In addition, in this study, obesity was more strongly related with moderate-to-vigorous physical activity than either television time or sedentary time. Furthermore, genetic polymorphisms, genetic disorders, neuroendocrine diseases, low birth weight, certain types of medication, sleep deprivation, cessation of smoking and psychological factors may all contribute to progressive weight gain and finally obesity.[13]

1.2 Pathophysiology of obesity

Obesity implies an excess storage of fat. Excess dietary glucose and fat is first and foremost stored in adipose tissue as lipids, mostly in the form of triglycerides.[4] From an evolutionary point of view, lipid deposition in adipose tissue is advantageous since it promotes survival in periods of energy depletion and allows efficient storage of energy.[14] In humans and other mammals there are two types of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT). WAT stores excess energy as triglycerides and consists of subcutaneous and visceral fat depositions. BAT has the ability to convert stored energy from the diet into body heat.[15] BAT was thought to be primarily important in new born infants to maintain body temperature and to regress during aging, but the presence of metabolically active brown adipose tissue has recently been documented in healthy adults.[16,17] WAT into BAT conversion could prove to be a new pathway in the treatment of obesity, chronic cold exposure is the most effective activator for WAT to BAT conversion and many other endogenous, drugs and nutritional factors are currently being investigated.[18]

Subcutaneous fat accumulation of white adipocytes is predominantly seen on the hips and thighs and poses little metabolic risks.[19] Intra-abdominal (often referred to as visceral or central obesity) adipose tissue accumulation, on the other hand, is related to increased cardiometabolic risks.[19,20] It has been described that preferential visceral accumulation of fat more frequently occurs in smokers, people with a genetic susceptibility to visceral obesity and people with a neuroendocrine profile associated with a maladaptive response to stress.[19] Furthermore, the triglyceride surplus in people with visceral obesity also tends to be deposited at other undesirable sites, such as the liver, the heart and the skeletal muscle.[19]

Adipose tissue (i.e. adipocytes) is not a passive tissue that merely stores fat, it is an active endocrine organ that modulates the release of a large number of cytokines and bioactive mediators, such as interleukin-6 (IL-6), tumour-necrosis factor-α (TNF-α), leptin and adiponectin.[21-23] The release of cytokines, by adipocytes and macrophages within adipose tissue leads to a low-grade inflammation in individuals with central obesity.[22,24] Triglycerides in adipocytes are hydrolysed and subsequently released as free fatty acids in the peripheral circulation leading to high levels in obese individuals.[22] Leptin is a hormone that primarily acts in the hypothalamus, signalling sufficiency of energy storage, suppressing appetite and increasing energy expenditure.[25] Leptin levels in obese individuals are generally high, as a consequence of relative leptin resistancy.[26] Adiponectin is a modulator for free fatty acid metabolism; its correlation with the presence of obesity is still under debate.[27]

The combination of elevated levels of free fatty acids and the presence of inflammatory cytokines contributes to impaired insulin signalling and insulin resistance in obese individuals.[22] Furthermore, a high influx of fatty acids and cytokines from adipocytes through the portal system into the liver distorts hepatic metabolism and leads to increased hepatic glucose production.[19,28] The consequences of the obesity-associated increased levels of free fatty acids, cytokines and the impaired insulin metabolism on cardiometabolic and reproductive health will be discussed further in paragraph 3 and 4.

1.3 Obesity and cardiometabolic health

Cardiovascular disease (CVD) is the leading cause of death globally.[29] Increased bodyweight in overweight and obese individuals leads to an increased risk for cardiovascular disease and type II diabetes mellitus (DM) through a complex interplay of pathways. Obesity is a prominent risk factor for CVD, along with age, smoking, male gender, hypertension, dysfunctions in glucose metabolism (insulin resistance and diabetes), high low-density lipoprotein (LDL) levels and genetic risk factors.[19,21] Obesity is a direct and indirect risk factor for CVD, since it affects blood pressure, lipid profile and glucose metabolism.[21,30]

Visceral obesity, is associated with insulin resistance and this could eventually lead to type II DM. Type II DM is characterised by hyperglycaemia, insulin resistance and relative deficiency in insulin secretion. Insulin is the key hormone that regulates glucose and lipid homeostasis, it is secreted in response to a meal by pancreatic beta-cells to promote the uptake of glucose and synthesis of glycogen, fat and proteins.[31]

The co-existence of risk factors for both CVD and type II DM is commonly called metabolic syndrome. These risk factors include visceral obesity, hyperglycaemia, dyslipidaemia and hypertension. Insulin resistance and the subsequent hyperinsulinaemia and hyperglycaemia may lead to vascular endothelial dysfunction, abnormal lipid profiles, hypertension and vascular inflammation. All these factors promote the development of atherosclerotic CVD and type II diabetes.[32] The most commonly used criteria for the diagnosis of metabolic syndrome are the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATPIII) criteria.[33,34] Metabolic syndrome is present when 3 of the 5 following criteria are met; 1) waist circumference > 102 cm in men and > 88 cm in women, 2) triglyceride ≥ 1.7 mmol/L, 3) HDL-cholesterol < 1.0 mmol/L in men and < 1.3 in women, 4) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg and 5) fasting glucose ≥ 6.1 mmol/L.

1.4 Obesity and reproductive health

Obesity impairs reproductive health in both men and women in several ways.[35] Obesity decreases the chance to conceive naturally and after infertility treatment. Obesity is also associated with anovulation and it increases the risk of miscarriage.[36,37] Besides the negative impact of obesity on reproductive outcomes, obesity also carries an increased risk of maternal and neonatal complications during pregnancy and is associated with reduced health of the offspring. The negative influence of obesity on reproductive health will be explained further in the following paragraphs.

1.4.1 Natural conception

Obese women have an increased risk of subfecundity compared to lean women. In a Danish birth cohort study, obese women with a normal weight male partner had a 18% chance of subfecundity, compared to a 12% chance in normal weight women with a normal weight male partner (adjusted OR 1.7, 95% CI 1.5-2.0).[35] Furthermore, it is known that obese infertile women with ovulatory cycles have a lower chance of pregnancy per cycle. The probability of a natural conceived ongoing pregnancy within one year declined linearly by 4% per kg/m^2 in women with a BMI ≥29 kg/m^2.[36] In a cohort study of 500 couples, a decreased chance of conception was found in couples were both male and female partners had obesity class II compared to lean couples (adjusted OR 0.4, 95% CI 0.2-1.0). Furthermore, an increased waist

circumference of the female partner, as a measure of visceral adiposity, was associated with a longer TTP in the unadjusted model (OR 0.6, 95% CI 0.5-0.9), but not in the adjusted model (OR 0.8, 95% CI 0.6-1.1).[38]

1.4.2 Anovulation

Anovulation is clinically characterised by oligomenorrhea or amenorrhea and classified into hypogonadotrophic hypogonadism (WHO class I), normogonadotrophic anovulation (WHO class II) and hypergonadotrophic hypogonadism (WHO class III).[39,40] WHO class II anovulation is further classified in WHO class II anovulation due to polycystic ovary syndrome (PCOS) and non-PCOS class II anovulation. The relative risk of a chronic anovulatory disorder is significantly increased in women with increased BMI at age 18, as shown in Table 1.[41]

Table 1. Relative risk of an anovulatory disorder in obese women as shown by Rich-Edwards et al.[41]

BMI (kg/m^2)	Relative risk anovulatory disorder
24-25.9	1.3 CI 1.2-1.6
26-27.9	1.7 CI 1.4-2.1
28-29.9	2.4 CI 1.8-3.1
30-31.9	2.7 CI 1.9-3.8
≥32	2.7 CI 2.0-3.7

Adjusted for age at menarche, current age, year of birth, ethnicity, frequency of physical activity, smoking, alcohol use, diabetes and use of oral contraceptives

PCOS is the most common subtype of anovulatory disorders and has a prevalence of 6 to 8% in an unselected population of women of reproductive age.[42] The diagnosis of PCOS is commonly based on the revised Rotterdam 2003 criteria according to which 2 out of 3 of the following criteria should be present to diagnose PCOS; 1) oligo- and/or or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism and/or 3) polycystic ovaries. Other aetiologies, such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome should be excluded.[43] Clinical symptoms of PCOS may include reproductive (infertility, pregnancy-related risks), metabolic (obesity, insulin resistance, type II diabetes and cardiovascular disease) and psychological (anxiety, depression, impaired quality of life, body image and eating disorders) features.[44]

Obesity and insulin resistance are associated with PCOS, women with PCOS have an increased prevalence of obesity (relative risk, RR 2.8, 95% CI 1.9-4.1).[45,46] It is likely that a bidirectional relationship between obesity and PCOS exists, in which obesity is secondary to PCOS and obesity further increases the severity of the reproductive and metabolic symptoms of PCOS.[47]

1.4.3 Conception after infertility treatment

It is difficult to generalise the impact of obesity on the success of infertility treatment due to the various infertility diagnoses and range of treatments. Ovulatory obese and overweight women undergoing intrauterine insemination (IUI) using gonadotropin stimulation or an aromatase inhibitor (such as letrozole) require higher doses of gonadotropins and produce fewer follicles for a given dose. The clinical pregnancy rate in IUI is not significantly different among women in the different BMI categories.[48-50] Zaadstra et al. found that women with a waist-hip ratio ≥0.8 had a significantly decreased pregnancy rate after artificial insemination with donor sperm compared to women with a waist-hip ratio < 0.8, independent of bodyweight.[51]

It has been shown that BMI affects the live birth rate in women with PCOS undergoing ovulation induction (OI) with either clomiphene, metformin or both, in a factor analysis of a large RCT by Legro et al.[52] Independently of treatment arm, women with a BMI < 30 kg/m^2 had a significantly higher rate of live births compared to women with a BMI ≥ 30 kg/m^2 ($P < 0.001$). BMI was also a significant confounder in the rates of live birth in another RCT by Legro et al. in women with polycystic ovary syndrome, which compared treatment with clomiphene to letrozole.[53] In a systematic review by Mulders et al., obese women with normogonadotrophic anovulation needed a higher dose of gonadotropin during OI (mean difference 771 units, 95% CI 700-842), had increased cycle cancellation rates (OR 1.9, 95% CI 1.1-3.1) and decreased ovulation rates (OR 0.4, 95% CI 0.3-0.6) compared to women with a normal weight. Obesity was not associated with pregnancy rates, though insulin resistance was, with insulin resistant women having a decreased pregnancy rate (OR 0.3, 95% CI 0.1-0.8).[54]

Multiple cohort studies have been published on the effects of increasing bodyweight and success of IVF (*in vitro* fertilization) and ICSI (intracytoplasmic sperm injection) treatments. In a retrospective cohort study in the United States, including 494,097 IVF cycles from women between 2008 and 2013, obese women had a lower chance of having a live birth compared to normal weight women (adjusted RR 0.9, 95%CI 0.86-0.88).[55] Similar findings were described in a previous cohort study and systematic review.[37,56]

In summary, most studies show that obese women respond less well to clomiphene and letrozole and gonadotropins for ovulation induction and require higher dosages of medication, this leads to lower pregnancy rates in ovulation induction. In artificial reproductive techniques (ART), such as IVF and ICSI, increased BMI is associated with decreased chances of pregnancy.

1.4.4 Mechanisms through which obesity causes decreased pregnancy chances

Several hypotheses have been formulated regarding the mechanisms through which obesity could decrease chances of conception in natural cycles or after infertility treatment. These mechanisms include reduced oocyte and embryo quality, reduced endometrial receptiveness and increased chance of miscarriage in obese women. A retrospective cohort study of 426 IVF/ICSI cycles by Metwally et al., reported lower mean embryo grade (grade 2.3± 1.4 versus 2.0 ± 0.6, P = 0.02), lower embryo utilisation rate (defined as the number of embryos transferred and frozen in relation to the number of embryos available) (31 ± 3.9 versus 49 ± 2.9, P = 0.01) and less cryopreserved embryos (0.2 ± 1.2 versus 1.1 ± 2.2, P = 0.04) in obese women compared to women with a normal BMI. This effect was only present in women < 35 years old.[57] Similar results were shown by Zhang et al., in a Chinese cohort study.[58] However, sample sizes in both cohorts were relatively small, precluding definitive conclusions. It is likely that the interaction between BMI and oocyte and embryo quality is multifactorial. Elevated androgen levels, insulin resistance, LH hypersecretion, mitochondrial dysfunction and increased levels of adipokines, cytokines and leptin could all play a role and influence folliculogenesis and oocyte maturation and hence embryo quality.[59-63]

The effects of obesity on endometrial receptiveness can be investigated in studies on pregnancy chances in ovum donation cycles. By doing so, two important determinants of achieving a pregnancy can be separated, namely the embryo and endometrium. In a systematic review by Jungheim et al. in 2013, the authors found no negative effect of obesity in ovum donation cycles, with a relative risk of 0.9 (95%CI 0.7-1.3) of live birth in obese recipients compared to recipients with a normal BMI.[64] This systematic review did not include a cohort study by Bellver et al., who analysed 9 587 first cycles of ovum donation with donors having a normal weight.[65] Live birth rates in recipients according to BMI were 39% (< 20kg/m^2), 38% (20-24.9 kg/m^2), 35% (25-29.9 kg/m^2) and 28% in women with a BMI > 30 kg/m^2 (P < 0.001). Embryo parameters and miscarriage rates were similar in all BMI groups. The authors conclude that obesity impairs the reproductive outcome of oocyte donation, probably as a result of reduced endometrial receptivity. Factors underlying poor endometrial receptiveness in obese women are hypothesized to be endocrine dysfunction and alterations in cytokine expression (such as TNF-α).[57] In another study –not included in the sytematic review by Jungheim et al.- the authors analysed 45 163 embryo transfers from both autologous and ovum donation transfers according to the recipients' BMI.[66] They concluded that a higher BMI in recipients was associated with increased failure to achieve a clinical pregnancy in autologous transfers (aOR of failure to achieve a clinical pregnancy 1.1, 95% CI 1.1-1.2 in Obese Class I) and that this risk was overcome when using donor oocytes (aOR of failure to achieve a clinical pregnancy 1.0, 95% CI 0.8-1.2 in Obese Class I). Therefore,

this study does not support the presence of endometrial dysfunction in obese women.[66] The risk of miscarriage in obese women is increased and this could further contribute to the lower live birth rate observed in obese women undergoing ART. A systematic review by Rittenberg et al. on the effect of BMI on IVF treatment outcome showed that there was a significantly higher miscarriage rate (RR 1.3, 95% CI 1.2-1.4 and RR 1.4, 95% CI 1.2-1.7) following IVF/ICSI treatment in women who were overweight or obese, compared to women with a normal BMI.[37] Lashen et al. showed that obese nulliparous women have an increased risks of an early miscarriage and recurrent miscarriage with ORs of 1.2 (95%CI 1.0-1.5) and 3.5 (95% CI 1.0-12) respectively, compared to women with a normal BMI.[67]

In conclusion, the mechanisms through which overweight or obesity are able to cause decreased pregnancy rates are manifold and complex. Decreased oocyte and embryo quality, altered endometrial receptiveness and an increased miscarriage rate in obese women are among the most widely investigated hypotheses, but no definite conclusions on causal pathophysiological pathways can be made up until now.

1.4.5 Male reproductive health

In a systematic review investigating the effects of paternal obesity on reproductive potential, obese men were significantly more likely to experience infertility compared to couples with a normal weight male partner OR 1.7 (95% CI 1.5-1.8). Furthermore, the chance of a live birth after IVF or ICSI was decreased when the male partner was obese (OR 0.7, 95% CI 0.4-1.0), however the majority of studies included in this review did not adjust for maternal BMI, which could lead to biased results.[68] Additional evidence for the association between obesity in males and decreased fertility is found in a systematic review and meta-analysis showing an increased rate of azoospermia or oligozoospermia in obese class I and II (OR 1.3, 95% CI 1.1-1.6) and obese class III men (OR 2.0, 95% CI 1.6-1.6) compared to normal weight men.[69] Moreover, Ramlau-Hansen et al. stratified their analysis for maternal and paternal BMI on the occurrence of subfecundity in a large Danish birth cohort study of 64 167 pregnant women. Obesity in men with a normal weight female partner is associated with aOR 1.5 (95% CI 1.3-1.8) for subfecundity.[35]

Several pathophysiological mechanisms have been postulated regarding the relationship between obesity and sperm parameters and infertility in men. Obese men have increased amounts of peripheral fat tissue leading to an increased conversion by aromatase in this fat tissue of male steroids to oestrogens. This leads to a relative hypogonadotrophic hyperoestrogenic hypogonadism and hence decreased spermatogenesis.[70] Furthermore, studies report a decreased level of sex hormone-binding globulin in obese men, likely caused by hyperinsulinaemia, this further increases the negative feedback on spermatogenesis.[69]

1.4.6 Maternal complications

There is a large body of evidence showing that obese women are at an increased risk of complications during pregnancy. Gestational diabetes and hypertensive disorders of pregnancy are two of the major and most prevalent obstetric complications. Rates of gestational diabetes are three to four times higher and rates of gestational hypertension and preeclampsia approximately three times higher in women with obesity compared women with a normal weight.[71]

The relationship between BMI and obstetric complications was studied in a large prospective cohort in an unselected obstetric population by Weiss et al.. The study was performed in the United States, 16 102 women were included, of which 1473 were obese class I and 877 were obese class II and III.[72] This cohort study showed increased risk of gestational diabetes, pregnancy-induced hypertension, preeclampsia, Caesarean section in obese class I, II and III as compared to women with a normal weight (Table 2). Furthermore, morbidly obese women are at an increased risk of operative vaginal delivery, postpartum atonic haemorrhage and infections compared to normal weight women.[71-74] Women with PCOS, irrespective of BMI, have a further two times increased risk of gestational diabetes and 1.5 times increased risk of pregnancy-induced hypertension compared to women without PCOS.[75]

Table 2. Relationship between BMI and obstetric complications, adapted from Weiss et al.[72]

Complication	Obesity class I aOR (95% CI)	Obesity class II and III aOR (95% CI)
Gestational diabetes	2.6 (2.1-3.4)	4.0 (3.1-5.2)
Pregnancy-induced hypertension	2.5 (2.1-3.0)	3.2 (2.6-4.0)
Preeclampsia	1.6 (1.1-2.3)	3.3 (2.4-4.5)
Caesarean section	1.7 (1.4-2.2)	3.0 (2.2-4.0)
Operative vaginal delivery	1.0 (0.8-1.3)	1.7 (1.2-2.2)

Adjusted for age, ethnicity, education, marital status, parity, use of assisted reproductive technology, gestational age at delivery and birth weight.

The Institute of Medicine issued recommended amounts of weight gain during pregnancy (gestational weight gain) in 2009.[76] Women with a normal weight are recommended to gain 11.5 to 16 kg during pregnancy, overweight and obese women are recommended to gain 7 to 11.5 kg and 5 to 9 kg respectively. Excessive gestational weight gain is weight gain during pregnancy in excess of these recommendations.[76] Forty-six percent of obese pregnant women and 38% of normal weight women have excessive gestational weight gain in a US cohort.[76] A Swedish cohort study among 298 648 singleton pregnancies

showed that the rate of an adverse maternal or neonatal outcome increases with increasing gestational weight gain.[77] Furthermore it is known that excess gestational weight gain is associated with gestational diabetes, hypertensive disorders of pregnancy, preterm birth and Caesarean section.[78] On the longer term there is an increased risk of postpartum weight retention and obesity in the mother.

1.4.7 Offspring health

Maternal overweight and obesity also affects the health of the foetus. Maternal obesity and subsequent insulin resistance results in exposure of the foetus to a hyperglycemic and hyperinsulinemic environment, leading to increased foetal growth and foetal body fat mass.[79] In a systematic review by Yu et al. in 2013, children born to obese mothers had an increased risk of being large-for-gestational-age (LGA) (OR 2.1, 95%CI 2.0-2.2), having a high birth weight (OR 2.0, 95%CI 1.8-2.2) and having macrosomia (OR 3.2, 95%CI 2.4-4.4).[80] Conversely, children born to obese mothers had lower risks of being small-for-gestational-age (OR 0.8, 95%CI 0.8-0.8). Similar findings were found by Liu et al. in another systematic review in 2016, the children of overweight or obese mothers had a higher risk of LGA, macrosomia, admission to the neonatal intensive care unit and being stillborn.[81]

The relation between maternal obesity and preterm birth is less unambiguous. A systematic review by McDonald et al. including 84 studies, totalling 1 095 834 women, showed that the risk of preterm birth, when corrected for publication bias, was significantly higher in overweight and obese women (RR 1.2, 95%CI 1.1-1.4) compared to normal weight women. However this effect was not seen when the authors did not correct for publication bias (RR 1.1, 95% CI 0.9-1.3).[82] In a systematic review by Torloni et al. only women with class II obesity, BMI ≥ 35 kg/m^2 had an increased chance of preterm birth (aOR 1.3, 95% CI 1.1-1.6).[83] Women with class III obesity had an even higher increased risk of preterm birth compared to women with a BMI between 30 and 40 kg/m^2 (RR 1.2, 95%CI 1.1-1.3).[84]

Associations have been found between increasing maternal bodyweight and increased risk of congenital anomalies, such as neural tube defects, cardiovascular anomalies, limb reduction anomalies and orofacial clefts.[85-87] Folate deficiency, presence of diabetes and impaired fasting glucose levels could be the mechanisms for the increase risk of congenital anomalies in obese women, but definitive conclusions cannot be made.[88] Furthermore associations have been found between maternal BMI and perinatal death. In a systematic review and meta-analysis by Aune et al., increased risks of stillbirth (RR 1.2, 95%CI, 1.1-1.4) perinatal death (RR1.2, 95%CI 1.0-1.4) and infant death (RR 1.2, 95%CI 1.1-1.3) were found for every 5-unit increase in maternal BMI compared to women with a BMI of 20 kg/m^2.[89] The increased risk of maternal complications during pregnancy, increased inflammatory

responses and endothelial dysfunction, decreased sensibility of the mother for foetal movements and increased risk of foetal macrosomia in obese women could all explain the association between BMI and increased risk of perinatal death.[89]

It has been shown that excessive gestational weight gain influences neonatal health, as it increases birth weight and the rate of LGA.[90] Faucher et al. showed in a systematic review that excessive gestational weight gain is associated with an increased rate of preterm birth (aOR 1.5, 95% CI 1.1-2.2).[91] Furthermore, in the long-term, excessive gestational weight gain is associated with childhood obesity.[78] Maternal obesity is a risk factor for less favourable breastfeeding outcomes, such as less frequent initiation of breastfeeding and shorter duration of breastfeeding.[92] The lower rate of breastfeeding in obese mothers could be one of the mediating factors for the increased rate of childhood obesity, however studies investigating this topic report different results.[93]

A large body of evidence indicates that early life events, such as exposures in utero, influence susceptibility to chronic diseases later in life.[94] A systematic review and meta-analysis revealed that children of obese mothers have an OR of 3.1 (95% CI 2.7–3.5) of childhood overweight or obesity.[80] Gademan et al, showed in a cohort study including 1727 children born at term in Amsterdam, between 2003 and 2004 from non-diabetic mothers, that every unit increase in prepregnancy BMI leads to a 1.2 (95% CI 1.1-1.2) increased risk of childhood overweight at age 5 to 6 years.[95] In the Helsinki Birth Cohort Study, 2003 individuals were evaluated at the mean age of 62 years. Higher maternal BMI was associated with less favourable body composition in the offspring and there was a significant interaction between birth weight and maternal BMI on offspring body fat percentage.[96] Furthermore, maternal obesity is associated with an increased risk of premature death in adult offspring.[97] Nicholas et al. postulate a "two-hit hypothesis" in which exposure to maternal obesity leads to programming of obesity in the offspring.[98] The first hit occurs in the periconceptional period and results in increased fat mass, mostly in visceral fat depots in female offspring. There are also programmed changes in the insulin signalling and fatty-acid metabolism in the liver and skeletal muscle in the offspring. The second hit occurs with exposure to maternal obesity in later gestation, leading to an increased subcutaneous fat mass, an increase in leptin expression in fat depots and central leptin resistance in postnatal life.[98] These periconceptional and gestational programmed changes lead to a greater susceptibility for obesity later in life.

1.4.8 Costs of infertility treatment

Whether a woman's increased BMI has impact on the subsequent costs of infertility investigations and treatment is under debate. Koning et al. estimated that in a hypothetical cohort of 1000 women, the reduced probability of achieving a successful pregnancy and

the increased risk of complications during pregnancy was associated with increased costs in overweight and obese women. The authors estimated that the cost per live birth was 100% higher in obese anovulatory women and 70% higher in obese ovulatory women compared to their normal weight counterparts. [99] On the other hand, Pandey et al. found higher costs of infertility diagnostics and treatments in women with a normal weight, as compared to obese women in a retrospective cohort study in Aberdeen, Scotland.[100] In this cohort, women with a high BMI were less likely to receive invasive investigations or procedures, such as laparoscopy and IVF treatments. Furthermore, the probability of a live birth tended to decrease with increasing BMI, leading to lower pregnancy associated costs. This might reflect current practice in some countries, where invasive diagnostic procedures or treatments in obese women are not offered or reimbursed until sufficient weight loss has been achieved.[101-103] In addition, there is evidence that couples who exhibit less healthy lifestyle behaviours are less likely to seek help for their infertility problems, which could consequently decrease resource use and total costs in this population.[104]

1.4.9 Maternal obesity and costs

Due to the increased risk of pregnancy complications and worse perinatal outcomes, pregnancies in obese women are associated with higher costs. Costs of 484 singleton pregnancies were compared in a retrospective setting in Wales by Morgan et al.[105] When adjusting for maternal age, parity, ethnicity and comorbidities, mean total costs of healthcare utilisation and direct healthcare costs were 23% higher among overweight women and 37% higher among obese women compared to women with a normal weight.[105] A Scottish retrospective cohort study by Denison et al. investigated health service costs of 124 280 singleton deliveries according to maternal BMI. They found a 45% and 88% increase in the number of admissions and a 9% and 12% increase in the duration of hospital stay in obese class I-II or obese class III women respectively compared to normal weight women.[106] This led to an increase of additional maternity admission costs of approximately £450 (unadjusted) for an obese woman (with mean cost of admissions in a normal weight woman being approximately £2100). After adjusting for sociodemographic factors and adverse outcomes associated with BMI, the increase in costs was approximately £200 in obese women, showing that roughly 50% of the increase in costs is caused by the additional risk of complications during pregnancy in obese women.

1.5 Lifestyle interventions for obesity

Lifestyle interventions are the recommended first-line treatment for overweight or obese individuals.[107,108] Cornerstone of lifestyle interventions is that the total energy intake should be less than the energy expenditure. Lifestyle interventions generally consist of a change

in diet, an increase in exercise and behavioural modification. The NICE guideline for obesity, which is supported by the Dutch guideline for diagnosis and treatment of obesity, recommends a diet with a 600 kilocalories (kcal) deficit than that is needed to stay the same weight, or reducing energy intake by reducing fat content of the diet in combination with support and intensive follow-up.[108,109] Weight loss of 300-500 grams per week should be achieved by such an energy deficit.

The Dutch Standard for healthy exercise (Nederlandse Norm Gezond Bewegen), published in 2008, advices at least 30 minutes of moderate intense activities a day for at least five times a week.[110] In addition, it is recommended that behaviour change strategies are included in the intervention to increase physical activity levels and improve eating behaviours. Guidelines recommend that healthcare providers screen for overweight and obesity and opportunistically advice patients to lose weight, also in patients without any obesity-associated co-morbidities.[108]

1.5.1 Lifestyle interventions to achieve weight loss

Weight loss is usually achieved with any low-carbohydrate or low-fat diet and the type or brand of the diet does not materially change the amount of weight loss that can be achieved.[111] Dietz et al pooled average weight loss recorded from intervention trials of dietary programmes of 12 months or longer in a systematic review.[112] The results are shown in Table 3. The amount of weight loss was largely similar between dietary programmes, although the average weight reduction was greatest with a Weight Watchers programme.

Table 3. Average weight loss according to dietary programme, adapted from Dietz et al. [112]

Dietary programme	Average weight reduction after 12 months (kg)
Low glycaemic	-4.0
Low carbohydrate, high protein	-5.5
Low fat, high protein	-4.1
Mediterranean	-4.4
Weight Watchers	-7.0

Although lifestyle interventions might induce a moderate amount of weight loss on the relative short term, weight maintenance is a problem on the longer term and crucial to maintain the beneficial effects of weight loss.[113] Dombrowski et al. performed a systematic review and meta-analysis of RCTs regarding long term maintenance of weight loss using non-surgical interventions.[113] They analysed RCTs wherein initially obese adults who achieved ≥5% weight loss were included with long term follow-up of weight maintenance

(≥12 months). The weight reduction during the initial weight loss phase averaged -10.8 kilograms in 42 studies. After 18 months, the difference between participants receiving a behavioural intervention versus the control group was -2.0 kg (95% CI -2.7 to -1.2 kg). The authors conclude that a behavioural intervention targeting diet and physical activity are moderately effective in slowing the regain of weight in obese adults after initial weight loss for up to 24 months.

Even though at the group level a moderate amount weight loss can be achieved during a lifestyle intervention, many individuals fail to complete or adhere to a lifestyle intervention programme. Not only long term adherence to lifestyle modification is important, also drop-out or non-completion affects the efficacy of lifestyle interventions, since it is know that dropout of a lifestyle intervention is associated with less weight reduction.[114] Moroshko et al. aimed to investigate predictors of dropout in weight loss interventions, the dropout rate in the included studies varied from 9 to 90%.[114] In addition, dropout rates may be different in RCTs compared to regular care, a retrospective study studying 383 patients visiting an outpatient clinic for obesity treatment reported a 77% dropout rate one year after the first evaluation.[115] In conclusion, short term weight loss is often achieved by weight loss programmes, long term weight loss and completion rates of interventions should remain focus of attention.

1.5.2 Preconception lifestyle interventions in obese infertile women

Due to the deleterious effects of obesity on fecundity, outcomes after infertility treatment and the course of pregnancy, lifestyle interventions are recommended in obese women trying to achieve pregnancy. Guidelines recommend that optimal control of obesity begins before conception and that benefits of postponing pregnancy in women to achieve preconception weight loss should be balanced against the risk of declining fertility with advancing age.[102,116,117] However, evidence that lifestyle interventions increase fertility and decrease complications during pregnancy is limited.

Sim et al. performed a systematic review investigating the effect of weight loss in overweight or obese women undergoing ART on their subsequent pregnancy outcome.[118] The authors included 11 studies in their review, of which seven studies investigating preconception dietary interventions (excluding very low energy diets), two studies investigating very low energy diets and three studies investigating non-surgical medical procedures (such as an intragastric balloon procedure) or bariatric surgery in the review. All seven studies on dietary interventions reported weight loss and four studies reported significantly increased pregnancy rates and/or live birth rates compared to a control group. Studies also reported normalisation of menstrual pattern, a reduction in the number of ART cycles to achieve

pregnancy a less cycle cancellations. Furthermore, there was an increase in the number of natural conceptions in women who lost more weight. However, the study quality of the studies that were included in this systematic review was poor, only two studies were RCTs (including in total 87 patients), seven were cohort studies and two were case reports.

The two RCTs included in the systematic review were performed by Sim et al. in 2014 and Moran et al. in 2011. Sim et al. randomised 27 women to a 12-week intervention including diet, exercise and behavioural support and randomised 22 women to the control group.[119] Women lost 6.6 kg and 1.6 kg ($P < 0.001$) in the intervention and control group respectively. At 12 months after the intervention, 12/27 (44%) women achieved a live birth in the intervention group and 3/22 (14%) women in the control group ($P = 0.02$). Moran et al. performed a pilot RCT including women with a BMI between 28 and 45 kg/m^2, undergoing IVF treatment. Women were randomised to a lifestyle intervention consisting of dietary and exercise advice (including one meal replacement) or to the control group, consisting of standard advice on appropriate diet.[120] In total 18 women in the intervention group and 20 women in the control group were analysed. Women in the intervention group lost 3.8 kg and women in the control group 0.5 kg ($P < 0.001$). Seven of 18 women in the intervention group had a live birth and 5 of 20 women in the control group ($P = 0.48$). The authors of the systematic review concluded that well performed RCTs are therefore necessary to investigate if a lifestyle intervention preceding infertility treatment improves reproductive outcomes.

In conclusion, few RCTs, with small sample sizes, have been performed to investigate whether a preconception lifestyle intervention program improves reproductive outcomes in obese infertile women. The RCTs that have been performed show that weight loss is feasible in this patient group, whether this weight loss influences reproductive outcomes is unclear. Furthermore, dropout is also a problem in this patient population, with 24% of obese infertile women not able to complete a lifestyle intervention program.[121]

In addition, few studies have been performed regarding preconception lifestyle intervention and/or weight loss in obese women and the subsequent effects on maternal and neonatal outcomes during or after pregnancy and childbirth. Villamor and Cnattingius examined the association between interpregnancy weight change of the first and second pregnancy and risk of adverse pregnancy outcomes in the second pregnancy in 151 025 women using data from the Swedish Birth Register.[122] The authors did not find a significant difference in the rate of gestational hypertension or gestational diabetes in overweight women who lost > 1 kg/m^2 before the next pregnancy, but there was a lower rate of LGA (aOR 0.8, 95%CI 0.7-1.0) in these women. The authors show that weight gain between pregnancies was detrimental

in women within all weight groups even in women with normal BMI. Furthermore, it has been shown that neonatal mortality is lower in overweight women who reduced their interpregnancy weight with 2 or more units BMI compared to women who remained at a stable weight (adjusted RR 0.5, 95% CI 0.3-0.9).[123]

1.5.3 Lifestyle interventions for women with PCOS

Characteristics of PCOS such as hyperandrogenism, insulin resistance and hyperinsulinaemia generally are worse in obese women compared to normal weight women with PCOS.[124,125] It has been shown that weight loss in anovulatory obese women can lead to resumption of ovulation, especially in case of intra-abdominal fat loss.[126] The mediating mechanism is presumably a decrease in insulin resistance and a subsequent decrease in the hyperandrogenaemia.[126,127] Therefore guidelines recommend lifestyle intervention for obese women with PCOS as the first management option, however evidence is limited.[127] A Cochrane review on lifestyle interventions in women with PCOS by Moran et al. in 2011, showed that there were no studies assessing important reproductive outcomes, such as live births, miscarriages or resumption of ovulation.[128] Lifestyle interventions did however provide benefits for secondary outcomes, such as a decrease in testosterone, hirsutism, weight, waist circumference and fasting insulin levels.

A recent secondary analysis of RCT data by Legro et al. showed that women who were randomised to a 16-week lifestyle intervention preceding ovulation induction with clomiphene citrate (n = 48), compared to immediate ovulation induction (n = 187), had significantly increased cumulative ovulation rates (RR 1.4, 95%CI 1.1-1.7) and a significantly increased live birth rate (RR 2.5, 95%CI 1.3-4.7) after four cycles of ovulation induction.[129]

1.5.4 Lifestyle interventions during pregnancy

A systematic review of randomised trials by Thangaratinam et al., published in 2012, reviewed the effects of lifestyle interventions during pregnancy in obese women on maternal and neonatal outcomes.[130] The authors identified 44 RCTs including 7278 women and evaluated three types of interventions: diet and physical interventions or a mixed approach. Overall, there was a 1.4 kg gestational weight gain reduction with any intervention compared to the control group. All types of interventions reduced the risk of preeclampsia (RR 0.7, 95% CI 0.6-0.9) and shoulder dystocia (RR 0.4, 95% CI 0.2-0.7), but did not reduce the risk of other important maternal and neonatal outcomes. Dietary interventions were most effective in reducing gestational weight gain (-3.8 kg, 95% CI -2.5 to -5.2 kg) and were associated with improved pregnancy outcomes, such as a 33% reduced risk of preeclampsia (RR 0.7, 95% CI 0.5-0.9), a 61% reduced risk of gestational diabetes (RR 0.4, 95% CI 0.2-0.7) and a reduction in pregnancy-induced hypertension (RR 0.3, 95% CI 0.1-0.9) and preterm delivery (RR 0.7,

95% CI 0.5-1.0). Birth weight and the rates of SGA and LGA were not significantly different in women who received lifestyle intervention during pregnancy. Though physical activity alone was associated with a 60-gram reduction in birth weight (95% CI, -120--10).

Oteng-Ntim et al. also published a systematic review and meta-analysis on lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome. They identified 13 RCTs and six non-randomised studies, investigating 1228 women from randomised studies and 1534 women from non-randomised studies. They found that a lifestyle intervention reduced gestational weight gain (-2.2 kg, 95% CI -2.9 to -1.6 kg), but they did not identify a difference in prevalence of adverse maternal or neonatal outcomes in women who received a lifestyle intervention during pregnancy compared to women in the control group.[131] Discrepancies between this meta-analysis can and the meta-analysis by Thangaratinam et al. can probably be explained by the different number of studies included in both meta-analyses and the included number of women.

After publication of these reviews several well-executed RCTs were published further investigating the effects of lifestyle interventions during pregnancy in obese women. The LIMIT RCT, published in 2014, investigated the effects of a dietary and lifestyle intervention (n = 1108) in pregnant women with a BMI > 25 kg/m^2 compared to women receiving regular care (n = 1104). The main outcome parameter was being large-for-gestational-age. The risk of being LGA was not significantly different between groups, nor were any other maternal or neonatal outcomes.[132] The UPBEAT RCT, published in 2015, investigated the effects of a behavioural intervention in obese pregnant women on the incidence of gestational diabetes and LGA. The authors randomly assigned 783 women to the intervention group and 772 women to standard care. The incidence of gestational diabetes and LGA was not different between groups.[133] The RADIEL study was published in 2016 and did report a 39% reduction of gestational diabetes in obese women or women with previous gestational diabetes receiving an individualized lifestyle intervention programme (n = 155) compared to standard care (n =138).[134]

The number of cost-effectiveness analyses of lifestyle intervention during pregnancy is limited and studies use a variety of outcome measurements. Dodd et al. performed an economic evaluation of the LIMIT RCT, in which pregnant women (gestational age 10-20 weeks) with a BMI ≥25 kg/m^2 were randomised to a lifestyle intervention or to standard care. The authors found that the costs of the lifestyle intervention were compensated by savings associated with improved neonatal outcomes. The probability that the intervention was cost-effective for preventing a child with a birth weight > 4 kg was 85% using a threshold value of $20,000.[135] Kolu et al. evaluated 399 women with at least one risk factor for gestational

diabetes using data of a RCT (the NELLI study). The authors showed that with a probability of 87% that each gram of additional birth weight avoided 7 euros of costs.[136] Oostdam et al. performed a similar economic evaluation in 121 women at risk for gestational diabetes, with the aim to investigate whether an exercise program during pregnancy is a cost-effective intervention for preventing gestational diabetes.[137] The authors found that the intervention was not cost-effective regarding blood glucose levels or infant birth weight.

1.5.5 Determinants of successful lifestyle change

As described previously, not all patients participating in a lifestyle intervention will achieve weight loss and roughly a quarter of patients will discontinue the intervention. Certain characteristics or determinants of participants of a lifestyle intervention can be associated with successfully changing lifestyle or on the contrary discontinuing a lifestyle intervention. Future intervention programs could be adapted or focused on certain patient groups if these determinants of successful lifestyle change are known. The most widely studied determinants of successful lifestyle change are behavioural and psychological constructs. Teixeira et al. aimed to review prospective predictors of weight loss, and found that less previous dieting and a self-motivated, autonomous style with high levels of self-efficacy were the most consistent predictors of successful weight loss.[138] However, the authors note that a review on determinants of successful lifestyle change is difficult because a large heterogeneity exists in studies assessing these determinants.

1.6 Other methods for treating obesity

1.6.1 Weight loss medication

In the Netherlands, orlistat, a pancreatic lipase inhibitor, is the only registered and approved medication to induce weight loss.[107,139] The Dutch Society for General Practitioners and the Dutch Health Institute do not recommend prescription of orlistat to obese patients for trying to achieve weight loss. Reasons for this are that orlistat induces only modest weight loss, long term follow-up is not available and 30 to 40% of patients discontinue orlistat due to side-effects.[139]

1.6.2 Bariatric surgery

Bariatric surgery is an alternative method of achieving weight loss, which is both effective and sustainable.[140] Bariatric surgery is associated with significant risks, such as thromboembolisms, anastomotic leakage, haemorrhage and pneumonia and these occur in about 10% of cases, mortality is however low (0.1 to 1.1%).[107] In addition, it is a costly therapy with life-long consequences and therefore it is not suitable for the treatment of obesity on the population level, but in can be a solution for individuals. Therefore, in The

Netherlands, obese patients can only qualify for bariatric surgery if their BMI is ≥ 40 kg/m^2 or if their BMI is between 35 and 40 kg/m^2 and at least one obesity-associated comorbidity is present. Other interventions such as a comprehensive lifestyle intervention should have been tried, but have failed to induce significant weight loss.[107]

Multiple systematic reviews of the literature have been performed concerning the consequences of bariatric surgery preceding pregnancy. Yi et al. performed a systematic review and included 11 articles in the review, the authors found a decreased rate of gestational diabetes (OR 0.3, 95% CI 0.2-0.7) and hypertensive disorders (OR 0.4, 95% CI 0.2-0.8) in women who previously underwent bariatric surgery. The authors also found a decreased ratio of macrosomia (OR 0.4, 95% CI 0.2-0.7) and a higher rate of SGA (2.2, 95% CI 1.3-3.7) in women who previously had bariatric surgery.[141] Maggard et al. found, in a systematic review, that rates of gestational diabetes (0% vs 22%, P < 0.05) and preeclampsia (0% vs 3.1%, P < 0.05) were lower in women with previous bariatric surgery compared to obese women in a matched control group who did not have a history of previous bariatric surgery.[142]

A cohort study by Johansson et al., investigated 627 693 singleton pregnancies in women who had previously undergone bariatric surgery. Bariatric surgery was associated with a lower risk of gestational diabetes (2% vs 7%, OR 0.3, 95%CI 0.1-0.5) and LGA (9% vs 22%, OR 0.3, 95%CI 0.2-0.4) as compared with control pregnancies that were matched for presurgery BMI and other confounders. In contrast, pregnancies after bariatric surgery were associated with a higher risk of SGA (16 vs 8%, OR 2.2, 95%CI 1.6-3.0) and shorter gestation (mean difference -4.5 days, P < 0.001).[143]

It is advised that women delay pregnancy until at least one year after bariatric surgery, after the rapid and catabolic phase of weight loss has ceased.[144] Furthermore, pregnant women who previously underwent bariatric surgery are at risk for deficiencies of micronutrients such as folate, thiamin, vitamin A, D and E, phylloquinone, calcium and iron, depending on the type of surgery.[145] A systematic review of the literature showed the most common neonatal complications associated with micronutrient deficiencies were visual complications, intracranial haemorrhage, neurological and developmental impairments and neural tube defects.[145] However, the authors described the quality of the evidence as low. Despite low evidence, the authors propose additional screening in women who underwent bariatric surgery during the preconception period and during pregnancy.

1.7 Aims and outline of the thesis

The aim of this thesis is to perform an in-detailed analysis of several aspects of a lifestyle intervention preceding infertility treatment when compared to prompt infertility treatment in obese infertile women. The results and data of the LIFEstyle study, a randomized controlled trial in obese infertile women on lifestyle intervention preceding infertility treatment compared to immediate infertility treatment, play a central role in this thesis and the main results are presented in **Chapter 2**. All chapters presented thereafter use data of the LIFEstyle study. Since in the LIFEstyle study a heterogeneous population of obese infertile women were included, the aim of **Chapter 3** is to evaluate the effects of the lifestyle intervention in the LIFEstyle study in subgroups of obese infertile women. The predefined subgroups of women were based on age, body-mass index, ovulatory status and waist-hip ratio**. Chapter 4** presents an in-detailed economic analysis comparing lifestyle intervention preceding infertility treatment to prompt infertility treatment. The economic analysis includes various scenarios using different effectiveness measurements and subgroups of women to estimate in which scenario lifestyle intervention preceding infertility treatment can be cost-effective. **Chapter 5** provides an in-depth analysis of the effects of a lifestyle intervention on cardiometabolic health and quality of life on the short term. In **Chapter 6** the effects of periconceptional weight loss, independent of randomisation arm of the LIFEstyle study, on maternal and neonatal outcomes are investigated. By doing so the biological effects of weight loss, instead of participating in a lifestyle intervention could be studied. The aim of **Chapter 7** is to identify determinants of successful lifestyle change. Successful lifestyle change was defined as successful weight loss, adaptation of energy intake and improvement in the number of steps taken daily. **Chapter 8** provides an overview and summary of the main results of this thesis, the possibilities and recommendations for future research.

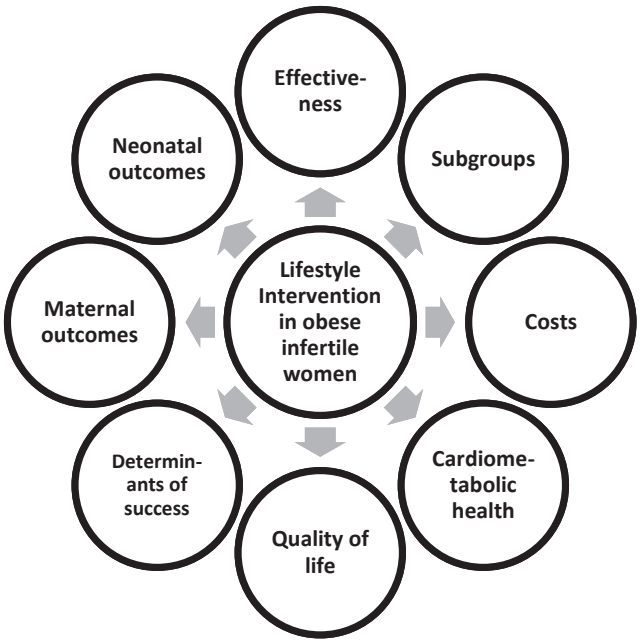

Figure 2. Graphical presentation of central concept and detailed aspects of this thesis

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