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Lifestyle and Reproductive Health among Women prior to Conception

LANA SALIH JOELSSON



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Abstract

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Health and lifestyle is of great importance when women intend to become pregnant, as well as during pregnancy. It is crucial that people seeking for infertility are aware of which lifestyle changes they can undertake to enhance the likelihood of treatment success. The overall aim of this project was to investigate the extent to which women comply with recommendations for lifestyle changes during the time they try to conceive and during early pregnancy and the impact of lifestyle risk factors on treatment results in sub-fertile women. Lifestyle factors and mental health at baseline and lifestyle changes women made while they were trying to conceive were assessed by a study-specific questionnaire. Both pregnant women and non-pregnant sub-fertile women in the mid-Sweden region were included. The level of pregnancy planning was associated with planning behavior. Only one-third of all pregnant women took folic acid one month prior to conception, 17% used tobacco daily and 11% used alcohol weekly three months before conception. In the sub-fertile non-pregnant women cohort, 13.2% used tobacco daily, 13.6% drank more than three cups of coffee per day, and 11.6% consumed more than two glasses of alcohol weekly. Among sub-fertile women, one-third were overweight or obese. Pregnant women who conceived with Assisted Reproductive Technology (ART) reported lower rates of anxiety and depression symptoms compared to sub-fertile women. They also showed no difference in depression and anxiety symptoms compared to women who conceived naturally. Among sub-fertile women undergoing their first IVF treatment cycle, an independent as well as a cumulative effect of smoking and BMI on the number of aspirated oocytes and the proportion of mature oocytes was observed, especially among women with low ovarian reserve. In conclusion, approximately half of the women in our studies retained habits with negative effects on fertility. This is worrying because the harmful consequences of negative lifestyle factors are well established. These negative lifestyle factors are easy to detect and adjust at an early stage in the assessment process and might allow for optimization of fertility treatment and pregnancy outcomes.

Keywords: lifestyle, pregnancy, infertility, in vitro fertilization, smoking, obesity, alcohol

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Dedication
To my mother and father for making me be who I am!

List of Papers

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

- I. Stern J, Salih Joelsson L, Tydén T, Berglund A, Ekstrand M, Hegaard H, Aarts C, Rosenblad A, Larsson M, Kristiansson P. Is pregnancy planning associated with background characteristics and pregnancy planning behaviour? *Acta Obstetrica et Gynecologica Scandinavica* 2016; 95:182-189.
- II. Joelsson LS, Berglund A, Wångren K, Lood M, Rosenblad A, Tydén T. Do subfertile women adjust their habits when trying to conceive? *Ups J Med Sci* 2016;121:184–91
- III. Joelsson LS, Tydén T, Wanggren K, Georgakis MK, Stern J, Berglund A, A Skalkidou. Anxiety and depression symptoms among subfertile women, women pregnant after infertility treatment, and naturally pregnant women. *Eur Psychiatry* 2017;45:212-9.
- IV. L. S. Joelsson, E. Elenis, K. Wångren, A. Berglund, A. Nyman, C. E. Cesta, S. L. Mumford, R. White, T. Tydén, A. Skalkidou. Investigating the effect of lifestyle risk factors upon number of aspirated and mature oocytes in vitro fertilization cycles; interaction with antral follicle count. (Manuscript)

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Abbreviations and Symbols

ART	Assisted Reproductive Technology
IVF	In Vitro Fertilization
BMI	Body Mass Index
IOM	Institute of Medicine
WHO	World Health Organization
PCC	Preconception care
TTP	Time to pregnancy
IT	Information Technology
AMH	Anti-Mullerian Hormone
ICSI	Intra-Cytoplasmic Sperm Injection
IUI	Intra-Uterine Insemination
FET	Frozen Embryo Transfer
SWEPP	Swedish Pregnancy Planning Study
UppStART	Uppsala-Stockholm ART study
SAB	Spontaneous Abortion
SPSS	Statistical Package for the Social Sciences
HADS	Hospital Anxiety and Depression scale
EPDS	Edinburgh Postnatal Depression scale
SBU	Statens Beredning för medicinsk och social Utvärdering
GnRh	Gonadotropin-Releasing hormone
FSH	Follicle-Stimulation Hormone
hMG	Human Menopausal Gonadotropin
AFC	Antral Follicle Count
R 3.4	Language and environment for statistical computing and graphics
MII	Metaphase II stage oocytes
IQR	Interquartile Range
IRR	Incidence Rate Ratio
OR	Odds Ratio
CI	Confidence Interval
“n”	Number
PR	Prevalence Ratio
χ^2 -test	Chi-squared test

Preface

*“THE SECRET OF CHANGE IS TO FOCUS ALL OF YOUR ENERGY,
NOT ON FIGHTING THE OLD, BUT ON BUILDING THE NEW*

-Socrates

It is not a secret that lifestyle factors are incredibly important for maintaining **optimal health** throughout life. For women of childbearing age, **good nutrition** is important for **preparing** the body for the **demands** of pregnancy. Moreover, pushing for health-promoting lifestyle changes is one of the most important ways to help couples struggling to have a healthy child. It is never too late to **start moving** away from unhealthy lifestyles, but we also know that it is difficult to change old habits and furthermore it is not easy to admit that you have unhealthy lifestyle habits in the first place.

Since I started working at the Fertility Clinic ten years ago and during my last years of my specialist education I was often confronted with health-promoting challenges posed by my patients. This dissertation is the result of questions generated from these challenges, which I felt were important to investigate further. So, what **problems** are we facing, how big are the problems, what should be done? What can we as healthcare professionals do to make the patients in question to **understand** that they have problems they need to address? And further, that they have to take the **lead and make the changes** themselves.

This is the first large-scale **Swedish project** focusing on **lifestyle behaviors** among women **prior to conception**. To our knowledge, this is also the first project to demonstrate a possible interaction between BMI and smoking in relation to the ovarian reserve when exploring their effect on the proportion of mature oocytes per number of aspirated oocytes in **IVF cycles**. Our project is also unique in taking lifestyle risk factors into consideration as a confounder when assessing the association of infertility with depression and anxiety.

I have now also realized that there are still many questions, in addition to the ones discussed in my dissertation which need answers. This makes my dissertation more like a **starting point** than an end.

Introduction

Reproduction

Reproduction can be considered as the motor of evolution [1]. There is no life if there is no reproduction and this is globally applicable to for all living organisms. Consequently, throughout history people have struggled with reproduction and threats to reproduction; either problems of unwanted reproduction or the inability to reproduce despite a strong wish to do so. Fertility is the natural capacity to give life. Building a family has a strong social impact in all cultures worldwide, and fertility is of great importance for both women and men.

Most aspects of reproduction, such as sexuality, miscarriage, legal abortion, infertility, childbearing and delivery are also influenced by strong social attitudes, regulations and even laws.

Pregnancy planning and preconception care (PCC)

Most commonly, pregnancies are described as planned or unplanned based on the willingness of the couple for the pregnancy and its timeliness. (i.e. earlier or later than desired)[2]. Optimizing preconception health requires the pregnancy to be planned. The period before conception is increasingly regarded as significant for the health of pregnant women and future generations. Factors such as diet and nutritional status, which are modifiable before conception, have an influence on the intrauterine environment and fetal development. Consequently, the preconception period is seen as a critical period where interventions can lead to both short term benefits, by reducing pregnancy complications and adverse birth outcomes and long term health gains, as emphasized in the WHO Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013–2020 [3].

Since the release of the Institute of Medicine (IOM) report on preventing low birth weight in 1985, researchers have been calling for a new prevention paradigm—preconception care (PCC)—to reduce or eliminate adverse birth outcomes [4–6] Preconception care is defined as “any intervention provided to women and couples of childbearing age before pregnancy, regardless of pregnancy status or desire, to improve health outcomes for women, newborns and children” [7].

Adverse reproductive outcomes can affect the child's health and quality of life during infancy, childhood and later in life [8–10]. Preconception counseling targeted at the mother, father, and family can reduce maternal and infant morbidity and mortality. Negative birth outcomes may also affect family life if they require psychosocial and family adjustments and are associated with increased family costs and costs for society [8]. Many adverse reproductive outcomes are associated with maternal and paternal risk factors that can be modified before conception through primary prevention [11–13].

There is a fair degree of consensus among experts on professional guidelines about what a preconception care program should entail. It includes folic acid supplementation for all women to prevent neural tube defects [14,15] and reduce preterm birth [16] and congenital heart defects [17]; smoking cessation, reducing alcohol consumption, achieving or maintaining normal weight, and screening for infections [18]. By eliminating risk factors and optimizing their health status, women can have healthier pregnancies and reduce the risk of maternal and childhood mortality and morbidity [3,19].

PCC is not a new concept but has been gaining momentum over the last two decades [11]. Although the concept of PCC has been recommended for many years, healthcare professionals do not provide it and most women do not ask for it [20]. There is a lack of homogeneous guidelines, recommendations and services for preconception healthcare in European countries [20–22]. Additionally, studies of women's knowledge of preconception health focus mainly on the intake of folic acid to prevent neural tube defects [20], and not on other modifiable risk behaviors associated with maternal and infant health and pregnancy outcomes. Strategies are needed to promote preconception health interventions tailored to the needs of a specific country or specific target groups [23–25].

Infertility and sub-fertility

“Infertility is defined as the inability to reach a viable pregnancy within a year when having a normal frequency of sexual intercourse and no contraceptives.” [26]. There are many definitions of infertility. The concept of subfertility is also commonly used referring to any form of reduced fertility with prolonged period of unwanted non-conception [28].

Fecundity, is the biological ability of a couple to conceive [29] and *time to pregnancy* (TTP) can be considered as a marker for it [30]. The monthly conception rate of normal fertile couples is ~20% [31]. However, fecundability steadily decreases with increasing age of the female partner [32,33] and approximately 15% of fertile age couples suffer from infertility, which corresponds to 60 - 80 million couples worldwide [34,35].

Causes of infertility

Infertility can be attributed to any abnormality in the female or male reproductive system [36]. The most common causes of female infertility are ovulation disorders (e.g. polycystic ovary), tubal disorder, uterine factors and endometriosis [37–39]. A couple is diagnosed as having unexplained infertility when no reason for infertility has been identified in either partner after having conducted all standard infertility tests [40,41]. Male infertility most commonly occurs when there are deficiencies in the semen, such as low semen quality or low sperm count [42]. Causes and frequencies of infertility are shown in Figure 1

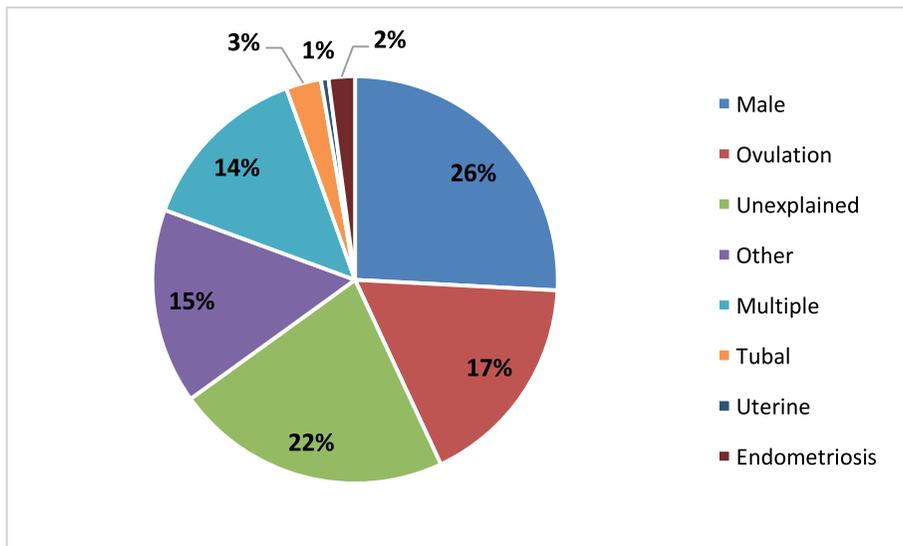


Figure 1: Causes of infertility [34]

Infertility may often have complex etiologies. In addition to the well-known risk factor of age and delaying childbirth it has been suggested that besides clinical diagnosis, lifestyle factors such as: female obesity, smoking and psychological stress [43–47] some specific genotypes [48] and micronutrient deficiencies may be associated with infertility [49].

The impact of age on reproductive health

Age is a crucial factor for female fertility [32,33]. In recent years, the number of women giving birth for the first time at the age of 35 or later has increased considerably [43]. As in many other European countries, there have also been demographic changes in Sweden such as postponed childbearing and less stable relationships [50,51]. The mean age of first-time mothers has increased from 24 years to 29 years over the past four decades [52].

Postponing childbirth to an age when female reproductive capacity is lower entails the risk of involuntary childlessness. Female fertility peaks at the age of 22 and subsequently decreases until around the age of 38, where after it falls more rapidly until menopause. It has long been known that with increasing chronological age, female fecundity decreases [53].

Several factors are presumed to play a role in women's decisions to delay childbirth including improved educational and career opportunities, changes in contraception use, economic cycles, and marriage patterns [54,55]. Delayed childbearing is even more pronounced among women with postgraduate education and in 2014, almost 3 out of 10 women attending antenatal care in Sweden were 35 years or older [52,56]. In general women overestimate their own reproductive capacity and underestimate the risk of future childlessness with the continuous postponement of pregnancies [57].

Older women who do get pregnant run a higher risk for complications in both the mother and the child [58]. Risks for the mother include gestational diabetes, preeclampsia, multiple pregnancy, increased likelihood of caesarean section and postpartum hemorrhage [59–61]. Also for children born to older mothers there is an increased risk for chromosomal deviations [62,63], premature birth or being small for gestational age [60,61]. Pregnancies among older women are also more likely to end in spontaneous abortion, extra uterine pregnancy or stillbirth [62]. Finally, the number of oocytes that can be collected in Assisted Reproductive Technology (ART) and fertility preservation decreases with age [57] and the chance of a live birth after a cycle of in vitro fertilization (IVF) also decreases with age [64,65].

Lifestyle factors and reproductive health

According to the existing studies, it is acknowledged that besides genetic predisposition, lifestyle has a significant influence on the physical and mental health of human beings. An individual may not be born with a disease but may be at a high risk of acquiring it, a concept referred to as genetic predisposition or susceptibility [66]. Understanding genetic predisposition and its possible interaction with lifestyle modifications that might either exacerbate or decrease the risk for disease development is necessary for the public to make informed choices. Today, significant changes in lifestyle have occurred within a short time span. Malnutrition, but also overeating, an unhealthy diet, smoking, alcohol consumption, drug abuse, stress, sleep deprivation etc., all represent unhealthy lifestyles. Besides, emerging new technologies such as the internet and virtual communication networks, provide new opportunities for knowledge and connection, but could also represent a major challenge that threatens the physical and mental health of individuals [67].

The relevance of personal behavior and lifestyle-related factors that may adversely affect fertility and reproductive outcomes has increasingly been discussed over the last ten years [68,69]. Many lifestyle factors such as the age

at which to start a family, nutrition, weight, exercise, sleep [70], psychological stress, environmental and occupational exposures, and others can have substantial effects on fertility; lifestyle factors such as cigarette smoking, illicit drug use, and alcohol and caffeine consumption can negatively influence fertility while others such as preventative care may be beneficial [71–74].

Lifestyle factors and nutritional status have been shown to be related to the reproductive function both in the preconception period and during pregnancy and may impact on growth, development and later health outcomes of the fetus [74]. However, these issues might be particularly important for women seeking treatment for infertility [43,75]. Studies looking at the combined effect of several lifestyle factors, including obesity, smoking and drinking, have found increased risks of delayed conception, preterm labor, low birth weight and fetal growth restriction that are greater than the sum of the expected effects of the individual factors [76]. Consequently, since these factors often occur together, the suggestion of a synergistic effect merits further investigation [74,77]). Other negative factors include an unhealthy diet, the over-use of other drugs, harmful infections such as sexually transmitted infections, exposure to environmental hazards, psychological distress and an adverse medical history [72,78].

The European Society of Human Reproduction and Embryology (ESHRE) Guideline Development Group recommends fertility staff to consider providing women with information about the impact of lifestyle habits and supporting them in making necessary changes [79]. Some counseling about lifestyle is generally included in initial consultations in fertility clinics. In Sweden, brochures and handouts about lifestyle are generally available at fertility clinics, but this information is only passively available. Effective strategies and support for making healthy changes are not routinely offered.

Tobacco

Women represent the fastest growing part of the cigarette smoking population [80]. Almost 14% of the women used tobacco three months before the current pregnancy in Sweden in 2013. However, the proportion of pregnant women who smoke during registration in maternal health units has declined from over 31% in 1983 to nearly 6% in 2013[52]. Smoking impairs every step of the natural reproductive process such as folliculogenesis, steroidogenesis, embryonic development and transport as well as implantation [81]. Cigarette smoking contains compounds that are suspected to cause reproductive damage and possibly affect hormone activity [82–84]. Toxic substances such as cotinine and cadmium have been found in follicle fluid both in active and passive smokers. Nicotine may act as a mutagen and possible oocyte toxin [85]. Studies have also shown that tobacco smoking causes a reduction in the ovarian reserve and a lower anti-Mullerian hormone (AMH), short irregular menstrual cycles, ovarian insufficiency, and dysmenorrhea [82,84,86]. A high accumulation of

active smoking was associated with a prolonged time to pregnancy in both current and previously regular smokers compared with non-smokers [87].

Furthermore, it has been shown that both active and passive smoking may reduce women's chances for successful ART cycles by more than 40%, whereas the risk of not conceiving during IVF/ICSI is estimated as four times higher in women who have smoked for >5 years [88,89]. Smokers have lower odds for a live birth per cycle, lower odds for clinical pregnancy per cycle, higher odds for miscarriage and higher odds for ectopic pregnancy [90,91]. Fuentes et al., 2010 reported a reverse linear correlation between cotinine levels in the follicle fluid and the number of oocytes retrieved from IVF treatment [92].

Tobacco smoking during pregnancy is associated with a series of negative pregnancy outcomes including placental abruption, miscarriage, premature birth and low birth weight [93,94].

Therefore, stopping smoking is essential to halt the negative effect on ovarian function and increase the chances of spontaneous pregnancies.

Obesity

The initiation and maintenance of reproductive functions are related to an optimal body weight in women. The worldwide epidemic of obesity and related morbidity significantly affects fertility and reproduction in both men and women. In Sweden an increasing trend of overweight pregnant women has been observed; particularly, in 2011, it was estimated that 38% of pregnant women were overweight or obese [95]. Several studies indicate that obesity increases the probability of menstrual disorders and infertility [72,96] and predisposes women to miscarriage, poor pregnancy outcomes and impaired fetal well-being [97].

Body mass index (BMI) is a calculated measurement that combines a person's weight and height and is used as an objective marker to classify underweight, overweight and obesity in adults [98]. Currently, a person is classified as overweight at a BMI of ≥ 25 kg/m² and obese when BMI is ≥ 30 kg/m² (moderate obesity ≥ 30 ; severe obesity ≥ 35 ; morbid obesity ≥ 40). The recommended BMI range is between 20 and 25 kg/m² [74].

Reduced fertility in obese women is a result of the cumulative effects on the hypothalamic pituitary ovarian axis, the quality of the egg cells and endometrial receptivity [99] as well as psychological and social factors [100]. Obesity leads to prolonged time to pregnancy in both men and women and increases the risk of miscarriage in women [97,101,102]. The negative influence of obesity on conception is also manifested in results obtained by those turning to ART [103]. Studies have shown two main effects of BMI on IVF results; on the egg cell environment and/or the endometrial environment [102,104,105]. Increasing BMI is associated with decreasing ovarian response to follicle stimulating hormone, resulting in fewer oocytes collected in a given

IVF cycle [106]. It also carries an increased risk of early miscarriage [107]. Similar observations have also been demonstrated in egg donation studies where it has been shown that the chance of successful implantation and pregnancy decreases significantly with obesity in women using donated egg cells [108]. Kort *et al* showed that a 10% weight loss improves the chance of pregnancy in both assisted fertilization and natural fertilization [109]. In addition, other studies have shown that this weight loss level improves adiponectin which is associated with infertility in obese patients [99]. Lifestyle changes that lead to weight loss are likely to be important, but even without weight loss, physical activity can benefit overweight women [110].

Furthermore, maternal obesity (BMI of 30 kg/m² or above) is associated with increased risks for pregnancy complications such as preeclampsia and gestational diabetes, increased risks of infant mortality, preterm births as well as complications during delivery [111–113]. Recent data from a review and meta-analysis also indicated that healthcare providers should be aware of the fact that obese women who become pregnant are more likely to experience elevated antenatal and postpartum depression than normal weight women [114,115].

Alcohol

Although it is well established that excess alcohol consumption influences both female and male fertility, the exact cut-off level of risk consumption has not yet been identified [75]. Similarly, the exact mechanism of how alcohol affects fertility remains unclear, possibly because of the diversity of alcoholic beverages and the difficulty in determining a threshold consumption frequency.

Moderate alcohol use (≥ 5 drinks/ week) during pregnancy has been associated with nearly a four-fold increase in risk of a first trimester spontaneous abortion (SAB) [116]. Moreover, three or more episodes of binge drinking (≥ 5 drinks/episode) have also been associated with an increased risk of fetal death (≥ 22 weeks' gestation) and ≥ 5 drinks/week associated 3 times greater risk of fetal death (at ≥ 28 weeks) [117].

Regarding ART cycles, studies are scarce. Klonoff-Cohen *et al* found that one standard drink (12g alcohol)/day or more was associated with fewer oocytes retrieved [118]. Rossi *et al* showed that women consuming more than 4 drinks/week had a 16% decrease in the odds of a live birth, but this was not associated with increased odds of SAB [119]. A more recent study demonstrated that lower quality embryos were found among women consuming more than two alcoholic drinks daily compared to women consuming less [120]. Therefore, prevention of alcohol consumption among women of reproductive age should be promoted to safeguard their fertility and future motherhood.

Caffeine

In the general population, caffeine intake during the pregnancy planning period has been associated with a decreased chance of a live birth [43]. Thus, people trying to conceive are recommended to limit their caffeine intake to the equivalent of less than two cups of coffee per day [121,122]. A coffee cup contains 100-130 mg caffeine depending on the cup size, as well as the coffee range and cooking method. Tea, coke and chocolate contain caffeine in smaller amounts. Studies on the effect of caffeine intake on female fertility are few [123,124]. Pauli et al. have indicated that IVF patients who consume caffeine might have lower live birth rates [125]. They have consequently hypothesized that reducing caffeine intake before IVF would decrease the number of immature oocytes retrieved. However, the mechanism via which caffeine exerts its effect on fertility remains unknown.

High maternal caffeine intake (350-699 g/day) during pregnancy is associated with higher risk of miscarriage and also with the risk of low birth weight infants [126,127]. WHO recommend people trying to conceive are recommended to reduce their caffeine intake to less than two cups of coffee per day [128].

Some caffeinated drinks can affect fertility through mechanisms that do not include caffeine. Soda drinks, for example, may cause subfertility due to increased risk of insulin resistance, metabolic syndrome and weight gain [129,130].

Psychological distress

Today, the ability to control fertility is often taken for granted, both in the medical profession and by the general public. The advent of safe and effective methods of contraception have made control possible in only one direction; but conversely, fertility control to achieve pregnancy, is not as obvious [131]. Most couples in their childbearing years are accustomed to thinking in terms of preventing pregnancy, whereas conceiving and having a child is taken for granted. Failure in reproduction may result in numerous negative psychological effects in infertile couples including loss of self-esteem, impaired dignity, threat of the sense of masculinity and femininity, decrease in marital satisfaction as well as psychological stress [132,133].

Expensive and tedious infertility treatments as well as uncertainty and disappointment due to treatment failures are other important threats for the quality of life of infertile couples [134]. In many cases, couples realize they are infertile only after repeated attempts at becoming pregnant. The stress of the non-fulfillment of a desire for a child has been associated with emotional squeal such as anger, depression, anxiety, marital problems and feelings of worthlessness [135]. The infertility itself and the medical investigation that is usually a time-consuming and protracted process may evoke many feelings.

The causal link behind the association between psychological distress and infertility remains unclear. Various psychological factors have been shown to affect reproductive ability. Proposed mechanisms involve the pathophysiology of the depressed state, such as elevated prolactin levels, disruption of the hypothalamic- pituitary-adrenal axis, and thyroid dysfunction [136]. Possibly this is also because a high percentage of infertility causes remain unexplained despite medical advances [137]. Data suggest that stress and reproduction ability are interrelated; however, the direction of that association is unclear. Lynch et al. [78] showed an association between salivary stress biomarkers and prolonged time to pregnancy in infertility. In vitro fertilization (IVF) patients report higher levels of anxiety and depressive symptoms than matched fertile controls [138,139]. Other studies have shown that anxiety and depression are associated with infertility and negative results of ART [140–142].

Until now the scientific discussion of psychological aspects of pregnancies after IVF gives contradictory results. The heightened emotional state and anxiety from a long, arduous and uncertain journey seems to remain, certainly in the early stages of pregnancy and for some couples also in the later stages, even after reaching the final destination, namely parenthood. The absence of a national policy regarding antenatal booked visits following assisted conception, has created a practice gap in the care of women following successful infertility treatment [143]. Few studies have investigated how couples having conceived after fertility treatment experience their pregnancy and if there is need for customized antenatal care for women following successful fertility treatment.

Treatment of infertility

Treatment of infertility depends on the etiology. Hormonal disorders can sometimes be treated with hormone therapy (e.g. ovarian hormone stimulation, ovulation induction). Artificial reproductive technology (ART) treatments include intra-uterine insemination (IUI), in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and frozen embryo transfer (FET).

IVF/ICSI treatment can be quite an extensive procedure that requires several weeks of hormonal treatment with sprays and injections. After hormonal treatment, a minor procedure is required, in which ova are picked from the ovaries of the woman in order to be fertilized outside the body and then transferred back into the uterus after 2-5 days. The possibility of transferring frozen embryos (FET) decreases the burden for the woman as it requires much less intervention [144]. The results from IVF/ICSI have steadily improved since the beginning in the early 1980s. The probability of becoming pregnant per embryo transfer is now 32-33% per treatment cycle and about 28% for FET [145,146]. IVF is a symptomatic treatment and not a curative one, i.e. the disease that causes the infertility is not cured.

The use of ART, though often perceived to be discretionary and expensive, has important economic implications. Different countries pursue different policies regarding which treatments, if any, are publicly funded. For example, in France, IVF is fully reimbursed by the social security system, whilst in Belgium, Denmark and Norway the state bears most, but not all, of the cost of IVF. In Sweden, IVF/ET treatment costs at public clinics are fully reimbursed within the state, while costs for treatments performed at private clinics are not reimbursed. However, up to three IVF attempts are allowed in public clinics. The costs for drugs are reimbursed to 95% irrespective of whether it is for a publicly or privately performed cycle [147]. All residents of Sweden have access to public healthcare so, from an international perspective, access to reproductive treatment is good. There are nineteen IVF clinics in Sweden of which Twelve are private and six are public. All public clinics and one private clinic also have university status.

Aims

The overall aim of the project was to investigate the extent to which women comply with the lifestyle recommendations while trying to conceive and during early pregnancy and also to study the impact of lifestyle risk factors on treatment results among sub-fertile women.

The project includes 4 studies. The specific aims of each study in this thesis are:

- Study I** To investigate if women attending antenatal care have planned their pregnancies and what pregnancy planning behavior women engage in. Additionally, to investigate the association between different background characteristics and pregnancy planning level.
- Study II:** To investigate lifestyle habits and lifestyle adjustments among sub-fertile women trying to conceive in relation to their background characteristics.
- Study III:** To investigate the prevalence of anxiety and depression symptoms among sub-fertile women seeking infertility treatment, and to compare these to women who conceived after infertility treatment and women who conceived naturally.
- Study IV:** To investigate the cumulative effect of lifestyle risk factors on reproductive outcomes after a completed fresh In Vitro Fertilization (IVF) cycle and test a possible interaction with antral follicle count.

Materials and Methods

Design and setting

The following table describe the design and settings of the four studies included in the thesis:

Study	Design	Assessment of variables	Sample Characteristics	Statistics
I	Multicenter cross sectional- <i>“Swedish Pregnancy Planning study” (SWEPP)</i>	Questionnaire	3389 women registering at 153 antenatal clinics	Kruskal-Wallis H test Pearson’s χ^2 test Multinomial logistic regression
II	Multicenter cross sectional- <i>“Lifestyle study”</i>	Questionnaire	466 women at their first visit to 10 fertility clinics	t- tests, Pearson’s χ^2 -test, Multinomial logistic regression
III	Multicenter cross sectional based on 2 different prospective cohorts – <i>Lifestyle study, “SWEPP” study</i>	Questionnaire	485 women at their first visit to fertility clinics. 3389 women registering at 153 antenatal clinics.	t- tests, Pearson’s χ^2 -test, logistic regression
IV	A Cohort study based on 2 different prospective cohorts- <i>Lifestyle study, UppStART study</i>	Questionnaire + Medical records	242 women starting their first IVF cycle from study II (hypothesis generating cohort). 432 women starting their first IVF cycles from the UppStART study cohort (validation cohort)	Quasi-poisson regressions (both univariable and multivariable)

Swedish Pregnancy Planning (SWEPP) study (Study I)

Procedure and participants

The study enrolled pregnant women ($n = 5493$) who consecutively visited any of the 153 antenatal clinics in ten counties in central and northern Sweden between the period September 2012 and July 2013. A total of 5 796 women were registered at the clinics, and out of the 5 493 women who received written and oral information from a midwife and who were invited to participate, 90% agreed to participate. A total of 61% of all women approached completed the study ($n = 3389$), 98% used the Swedish questionnaire. Figure 2 shows a flowchart of the study procedure.

During the recruitment period the midwives listed the number of women approached and their responses (accepted/declined) and they also recorded contact information for all participants. A reminder was sent by text message or email to those who had not returned the questionnaire within two weeks. Swedish-speaking women were offered a questionnaire to fill in at the clinic or at home and to return it by post in a prepaid envelope. The signed form for consent, which was returned with the completed questionnaires, was separated to be archived securely and safely immediately upon receipt. Participating non-Swedish-speaking women gave written consent and were offered a translated questionnaire (in English or Arabic) by post or a telephone interview (all other languages). For the interview, professional interpreters used a structured interview guide including twenty-nine of the questions in the questionnaire. Non-Swedish-speaking non-responders received a reminder and a new copy of the questionnaire by post and several attempts were made to reach the women for telephone interviews.

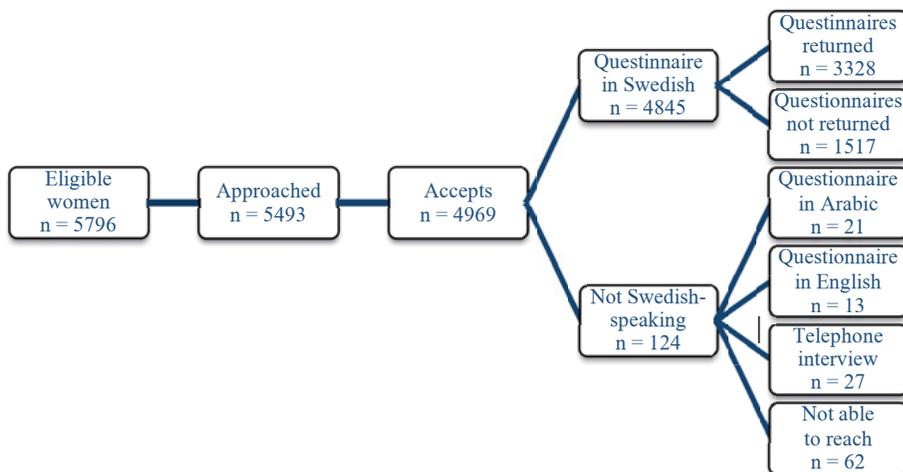


Figure 2: Flowchart of the study procedure (Following publication of the study, it was noted that one of the patients had answered the questionnaire twice, **hence the inconsistency** in the number of patients from the original article)

Instruments

A draft questionnaire was developed in dialogue with the research team including both experienced researchers and clinicians. The study-specific questionnaire was designed for pregnant women registering at antenatal clinics in mid-Sweden region; questions were thereafter adapted for sub-fertile women at their first visit to a fertility clinic in the same region.

The questions covered pregnancy planning for the current pregnancy. Most questions were designed as multiple-choice questions. A pilot study had been conducted among 270 [148] pregnant women, and revisions were made based on the results and feedback. The final questionnaire consisted of 148 items.

A single item was used for measuring the main outcome, level of pregnancy planning. The item was developed to nuance the dichotomized measurement planned/ unplanned while posed in a way that could be used routinely in the clinical setting and it has previously in Sweden and Denmark [22,148].

Data analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) (version 20, IBM, Armonk, NY, USA) for studies I-III.

The differences between the five *levels of pregnancy planning* regarding pregnancy planning behavior were analyzed using Kruskal-Wallis H test for ordinal variables and Pearson's chi-square test for categorical variables.

The following variables were separately addressed at a univariate level: age, level of education, household income, occupation, immigrant background, relationship duration, obstetric history, somatic diagnoses, psychiatric diagnosis and partner's age.

To analyze the *effect of background variables on pregnancy planning*, a multinomial logistic regression was used in which pregnancy planning categorized as planned (highly or quite), neither planned nor unplanned or unplanned (highly or quite) was the outcome variable. All variables that were statistically significantly ($p < 0.05$) associated with pregnancy planning were thereafter included in a multivariate regression analysis model. Results are presented as odds ratio (OR) with 95% confidence intervals.

Lifestyle study (Study II)

Procedure and participants

Eligible women ($n = 782$) were asked to participate at their first visit to one of ten fertility clinics in the central region of Sweden. The time of this first visit to the clinic is defined as the "Baseline year". Data collection started in May 2013 and ended in March 2015 with a planned follow-up after two years (study IV). Midwives gave oral and written information about the study to women who met the inclusion criteria which were: to be able to read and write in Swedish and; having no previous known infertility diagnosis. However, in nineteen cases, women were excluded from the study either because they reported having a female partner or did not answer the question about lifestyle changes while they tried to conceive. Those who agreed to participate received the questionnaire to complete at the visit to the clinic or at home and in that case returning it by mail in a prepaid envelope. During the study period, the midwives listed all registrations, the numbers of women approached, and their response (accepted/declined). A reminder was sent by text message or email to those who had not returned the questionnaire within two weeks. The signed form for consent, which was returned with the completed questionnaire, was separated to be archived securely and safely immediately upon receipt. Of the 782 eligible women, 747 (95.5%) agreed to participate in the study and 466 women (62.4%) completed the study. (Figure 3 shows a flow chart of the study procedure)

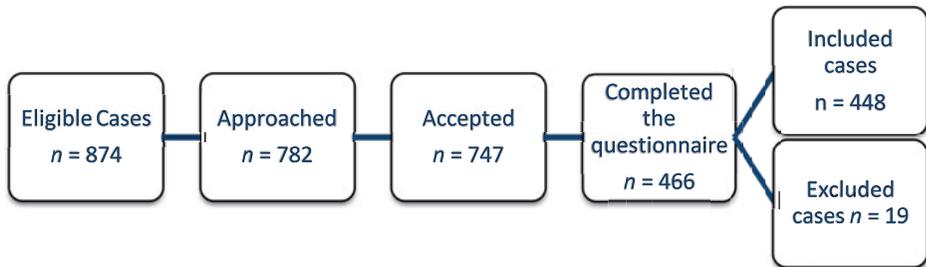


Figure 3: Flowchart of the study procedure.

Instruments

The questions covered two main areas, background characteristics and specific questions on the type of lifestyle factors in the baseline year, and number of lifestyle changes made while the women were trying to conceive. A pilot study with thirty women (unpublished data) was conducted, after which some items were adjusted. The final questionnaire consisted of seventy-one items.

The following factors were covered: age; partner's age; height and self-reported weight in the baseline year as well as one year earlier; marital status; duration of current relationship; country of birth; parents' country of birth; level of education; occupation and household income/month; understanding of the Swedish language; duration of infertility, immigrant background, medical and reproductive history, and methods for seeking information about infertility.

Questions regarding lifestyle changes covered: intake of folic acid and/or multivitamin supplements; daily tobacco use; weekly alcohol consumption; and daily coffee consumption; type of diet and weekly physical activity graded in number of hours. The participants were also asked to describe any changes to a healthier diet in free text. Access to sites for information seeking and type of professional counseling were also included. Questions covered the baseline year as well as the time from when they started to plan for pregnancy.

Data analysis

Differences in background characteristics between women with and without ***lifestyle changes*** during the time when they were trying to conceive were analyzed using the Mann–Whitney nonparametric *U* test for ordinal variables,

Student's *t* test for continuous variables, and Pearson's chi-square test for categorical variables. Logistic regression was used to analyze the **effect of background variables** (independent variables) on lifestyle changes (dependent variable). Results are reported as the odds ratio (OR) with a 95% confidence interval (CI). All variables that were statistically significantly ($p < 0.05$) associated with pregnancy planning were thereafter included in a multivariate regression analysis model.

Study III

This was a cross-sectional analysis of baseline measurements from two larger, longitudinal cohort studies (figure 4):

SWEPP study cohort

Among the pregnant women ($n = 3115$), 143 had conceived after infertility treatment and 2972 had conceived naturally.

Lifestyle study cohort

Data collection took place from May 2013 through September 2015 with a planned follow-up two years later. Of the 882 eligible women, 784 (94.5%) agreed to participate in the study and 485 of these (61.9%) completed the study. It should be noted though that, in the current study, the number of participants is higher than in study II as a result of ongoing recruitment of participants in the meantime.

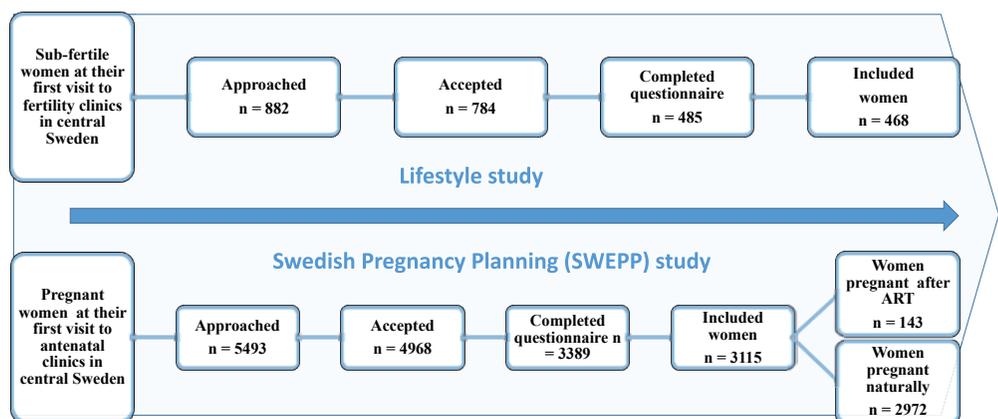


Figure 4: Flowchart of the study procedure

Instruments

The questionnaire in both study cohorts included validated instruments for psychological distress validated both for pregnant women and the general population. The Hospital Anxiety and Depression Scale (HADS) and Edinburgh Postnatal Depression Scale (EPDS) were used. The HADS score was categorized as normal (0- 7 points), possible case (8-10 points) and case (> 10) [149]. For the EPDS, a score of ≥ 12 points was considered indicative of depression symptoms for pregnant women, as formulated by the Swedish Council on Health Technology Assessment (SBU) [150].

Data analysis

Group differences (sub- fertile non-pregnant women, pregnant women who had conceived after ART, and naturally pregnant women) were initially evaluated. Differences were tested and P -values were generated based on the Chi2 test for categorical variables and one-way ANOVA or t-test for continuous variables. A cumulative variable reflecting lifestyle risk factors (i.e. daily tobacco smoking, weekly alcohol consumption, BMI > 25 kg/m², and < 2 h/week of regular physical exercise) was created. Thereafter, the variables were cross-tabulated based on the presence of anxiety (HADS-A: 0–7, 8– 10, or > 10) and depression (EPDS < 12 or 12) symptoms. Subsequently, **the prevalence ratios** (PRs) for anxiety (HADS-A ≥ 8) and depression (EPDS ≥ 12) symptoms in the study group (reference: naturally pregnant women) were estimated using Poisson regression analysis. Given the binomial distribution of the outcomes, the robust variance option has been used. **Covariates** were chosen based on existing literature and significance ($P < 0.10$) in bivariate analyses with the study group and the dependent variable. Results are presented as PR with 95% confidence intervals (CI).

Study IV

This is a cohort study based on two different prospective cohorts:

Lifestyle study (Hypothesis generation cohort):

Women from study II who underwent/completed their first IVF treatment ($n = 242$) were included. Participants were recruited from six public and two private fertility and reproductive health clinics. Follow-up data in the “Lifestyle study” regarding the reproductive outcomes were obtained from the medical records of women in January 2017. Women in the study cohort underwent ovarian stimulation with the use of a long GnRH agonist protocol in 31.0% of treatments and a GnRH antagonist protocol in almost 70.0%, with recombinant FSH in 78.5% of treatments and hMG in 21.5%. Embryologists have

determined the total number of oocytes retrieved per cycle and evaluated the maturity of the oocytes. Only metaphase II oocytes (MII) were considered mature. Normal fertilization, indicated by the presence of two clearly distinct pronuclei and the embryo quality was assessed on the day of transfer. The cleavage stage embryos were scored based on cell number and the degree of fragmentation, according to the grading system of Istanbul Consensus Workshop on Embryo Assessment [151].

UppStART study (Validation cohort):

The validation cohort was derived from the Uppsala-Stockholm Assisted Reproductive Techniques (UppStART) study [152]; i.e. a prospective cohort study of couples undergoing their first IVF treatment in the greater Stockholm region (Stockholm and Uppsala County) ($n = 432$). Recruitment took place from September 2011 to December 2013 and participants were followed up until December 2014 ($n = 432$). Participants were recruited from one public and two private fertility and reproductive health clinics in Stockholm and one private clinic in Uppsala County, which serves a large volume of patients from Stockholm. Signed consent forms were sent to the UppStART research nurse at Karolinska Institute (KI) who monitored recruitment and questionnaire responses. The IVF treatment protocols used in this study did not substantially differ from the one described above for the “Lifestyle study” participants.

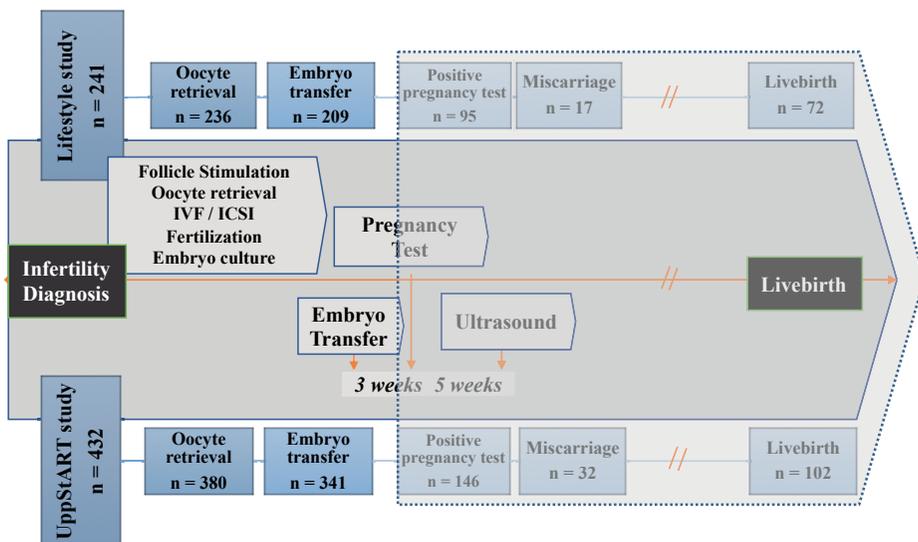


Figure 5: Flowchart of IVF cycles procedures included and their outcomes in the two study cohorts

Instruments and variables

In the validation cohort, the participants were asked to answer an extensive web-based questionnaire within a few days of their clinical visit and prior to starting their IVF treatment, which included questions on sociodemographic, anthropometric and lifestyle factors.

- **Predictor/exposure variables**

We considered the following exposure variables as possible risk factors: age, BMI, smoking currently and/or during the past year, alcohol consumption, daily caffeine consumption and physical activity score. In addition, the history of diagnosed depression (self-reported or via diagnosis registered in medical records) was also considered as one of the exposure variables.

- **Outcome variables**

The outcomes were: total number of oocytes aspirated; number of mature oocytes; number of embryos created; number of utilizable embryos (transferred fresh and frozen), as well as the proportion of mature oocytes, embryos created and utilizable embryos per aspirated oocytes.

- **Ovarian reserve**

Women in both study cohorts were tested for ovarian reserve using a combination of AFC and anti-Müllerian hormone (AMH) level at their first visit to the fertility clinic. Out of 242 women in the lifestyle study 98.35 % were tested for AFC and 82,24 % were tested for AMH. Out of 432 women in the Upstart study 68.06 % were tested for AFC and 79.87 % were tested for AMH.

Data analysis

Statistical analyses were performed using the Statistical Package for R3.4. A two-sided p value < 0.05 was considered significant.

To identify *differences between the two study cohorts*, the non-parametric Mann Whitney test was used for continuous variables, while for the comparison of categorical variables, the Chi square test was used. In the “Lifestyle study” cohort, a crude univariable quasi-poisson regression was performed evaluating the *association between each of the outcomes in the study cohort and each of the risk factors*. An adjusted multivariable analysis was then used, where all of the risk factors were included in a single model. Quasi-poisson regression was applied as the outcome variables were right-skewed. Variables that were significant at the $P < 0.05$ level in the “Lifestyle study” cohort in either the crude or adjusted analyses were used as potential *risk factors* for the respective outcomes. Furthermore, the “UppStART study” validation cohort was employed and a *new variable was created: "number of risk factors"*. If the potential risk factor showed an incidence rate ratio (IRR) less than one in the “Lifestyle study” cohort (i.e. is expected to reduce the number

of oocytes/embryos), then the variable "number of risk factors" was increased by one if the person had the potential risk factor. Likewise, if the potential risk factor showed an incidence rate ratio (IRR) greater than one in the "Lifestyle study" cohort (i.e. is expected to increase the number of oocytes/embryos), then the variable "number of risk factors" was increased by one if the person did not have the variable (because to have the variable would have a protective effect/increase the number of oocytes/embryos). If the risk factor was continuous, then it was dichotomized at the median.

For each outcome, we then ran four quasi-poisson regression statistical models: Model 1: No exposures; Model 2: Model 1 + number of risk factors as a categorical exposure; Model 3: Model 2 + Total AFC and Model 4: Model 3 + interaction between number of risk factors and Total AFC. Additionally, identification of the *effect modification of the number of risk factors by total AFC* was attempted using a likelihood ratio test comparing models 3 and 4.

Ethical considerations

Study I

The Regional Ethical Review Board in Uppsala, Sweden, approved the study (Reference number (2010/085)).

Study II, III

The Regional Ethical Review Board in Uppsala, Sweden, approved the study Reference number (2012/278) and (2010/085).

Study IV

The Regional Ethical Review Board in Uppsala approved the study (2012/278). The Regional Ethical Review Board in Stockholm approved of the UppStART study (2011/230-31/1, 2011/1427-32, 2012/131-32, 2012/792-32, 2013/1700-32).

The questionnaire included a few sensitive items for example questions regarding "Adverse Childhood Experiences". The patients were invited to contact healthcare staff who were well informed about the survey and could answer most of the patient's questions, which the patients had. In addition, antenatal care clinics and most fertility clinics in Sweden offer psychological counselor support when needed. Our assessment was that the scientific value and benefit out-weighed the discomfort of those surveyed. All participants were informed of their rights not to participate or to withdraw their consent to participate at any time without consequences.

Results

Study I

Level of pregnancy planning

Three out of four described their pregnancy as very or fairly planned (*Figure 6*). Five percent of the women had considered having the pregnancy terminated, but this proportion varied between the levels of pregnancy planning ($p < 0.001$). Less than 1% of women with very planned pregnancies had considered having a termination compared to 32% of women with very unplanned pregnancies. For all five levels of pregnancy planning, the median frequency of vaginal intercourse during the three months before pregnancy was twice a week. Over one fifth had used ovulation tests in connection with the current pregnancy, and 5% had received assisted reproduction. Use of ovulation tests and assisted reproduction were more common among women with the higher level of pregnancy planning ($p < 0.001$).

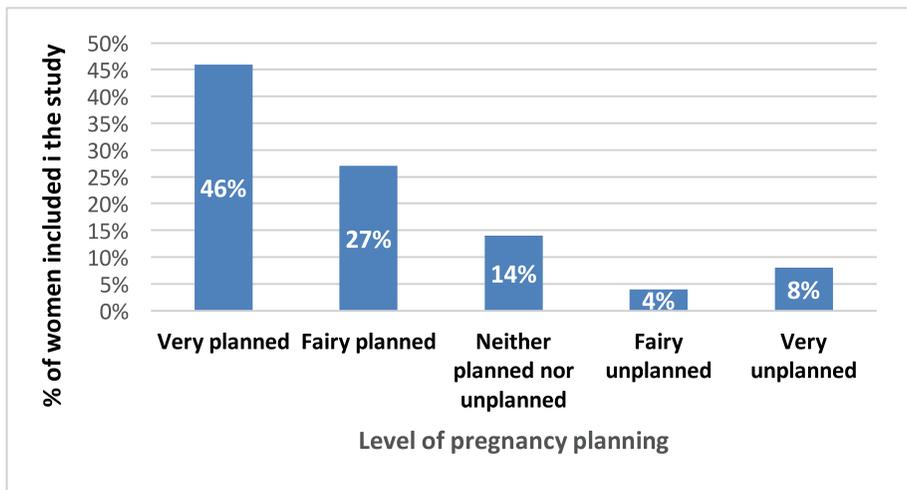


Figure 6: Proportion (%) of women according to level of pregnancy planning, n = 3389

Associations between pregnancy planning and background characteristics

The level of pregnancy planning was associated with the following background characteristics: woman's age; level of education; household income; occupation; country of birth; parent's country of birth; length of relationship; psychiatric diagnoses and the partner's age. The multivariate logistic regression model showed that women with planned pregnancies were 2.1 times more likely to have a high level of education (95% CI: 1.3-3.3), and 1.6 times more likely to be working (95% CI: 1.2-2.1) than women with unplanned pregnancies. Women with neither planned nor unplanned pregnancies were 1.5 times more likely to be working (95% CI: 1.1-2.1) than women with unplanned pregnancies but did not differ in any other background characteristic.

Health promoting behaviors in connection with the current pregnancy

One third of all women stated taking folic acid at least five times a week the month before pregnancy. During the three months before pregnancy, daily use of tobacco was reported by 17% and weekly alcohol consumption by 11%. There was a difference across the levels of pregnancy planning regarding folic acid ($p < 0.001$) and tobacco use ($p < 0.001$), but not alcohol consumption ($p = 0.100$).

More than three out of five women had sought information prior to the current pregnancy and almost half of all women had undertaken at least one health promoting action in preparation for pregnancy. Both information seeking and health promoting actions were more common among the higher levels of pregnancy planning ($p < 0.001$).

Study II

Lifestyle during the pregnancy planning period among sub-fertile women

The mean age of the women in the study was 30.2 years (range 19–42 years).

Almost half of the women (48.2%, $n = 216$) were taking folic acid supplements at their first visit to the clinics and 59.4% ($n = 266$) had started to take folic acid by the time they started to plan for pregnancy. Daily tobacco use was reported by 13% of the women ($n = 59$), and was more common among younger women (OR 0.93; 95% CI, 0.88–0.99), women of a lower level of education (OR 2.98; 95% CI 1.6–5.5), and women with lower household income (OR 0.98; 95% CI 0.96–0.99). Six out of ten women (61.6%) consumed 0–1 standard glasses of alcohol per week. Being older was the only significant

background characteristic among women who were consuming alcohol weekly ($p = 0.001$). The women were divided into three groups according to their BMI (in kg/m^2): underweight to normal with BMI < 24.9 in 60.9% ($n = 273$); overweight with BMI 25–29.9 in 23.9% ($n = 107$); and obese with BMI ≥ 30 in 12.5% ($n = 56$).

Lifestyle modifications during the pregnancy planning period and the association with background characteristics.

The results presented in this section of the thesis are those obtained after re-analysis of the data, excluding women who did not use tobacco or consume alcohol at baseline in the respective analyses. These are also reported communicated to the Editor of Uppsala Journal of Medical Sciences (updated tables in the Appendix).

Almost eight out of ten women in our study had one or more lifestyle risk factors, due to tobacco use, alcohol consumption, having BMI $\geq 25 \text{ kg}/\text{m}^2$ or not taking folic acid supplementation. Among the women who had ≥ 1 lifestyle risk behavior in our study ($n = 431$), 14% did not make any health-promoting lifestyle modifications during the time they were trying to conceive (Table 2- Appendix).

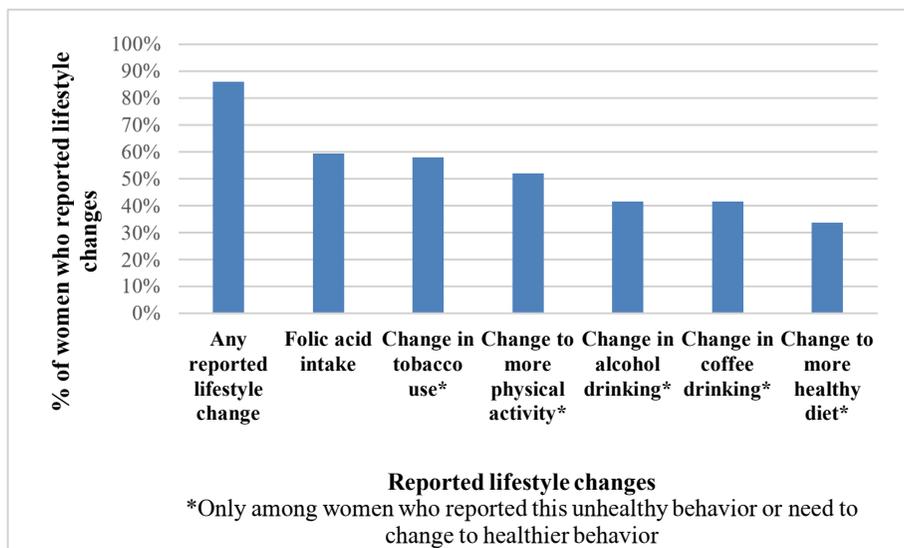


Figure 7: The proportion of reported lifestyle changes in the study

The univariate analyses showed a significant association between household income, level of education, duration of infertility, country of birth, parents' country of birth, BMI and the intensity level of information searching for taking folic acid supplements ($p < 0.05$). However, in the multivariate logistic

regression model only women with a higher education level and higher level of searching for information about fertility had increased the odds for folic acid supplementation (OR 1.8; 95% CI 1.1–2.9 and OR 2.1; 95% CI 1.2–3.8, respectively).

Overall, 42% (n = 188) of the sample reported tobacco use currently or during the last year. One third of those who used tobacco (cigarette smoking and snuff user) had stopped and one out of four reduced their consumption when they started trying to conceive. Those who changed their tobacco use habits were younger and were more likely not to be working. The only factor that remained robust in the multivariate logistic regression model for change in tobacco use was age (OR 0.930, 95% CI; 0.874- 0.991).

There were significant associations between the level of physical activity and changing to a healthier diet and BMI, with an overrepresentation among obese women (crude $p = 0.017$). The obese women exercised more and changed to healthy diets more frequently (adjusted $P = 0.08$, OR 2.037; 95% CI 0.898–4.621). However, they did not show a significant reduction in weight. Mean BMI change for the overweight women were 0.07 kg/m² (SD 3.1) and the mean BMI change for the obese women was – 0.36 kg/m² (SD 3.9), ($P = 0.439$). Duration of infertility, BMI and information seeking were associated with changes in physical activity among women with high BMI, with age and information seeking being independently associated in the multivariate analysis.

The information searching intensity and level of understanding of the Swedish language was associated with a decrease in alcohol consumption ($p = 0.04$ and $p = 0.09$ respectively).

Among women with risk lifestyle behaviors, younger age, longer duration of infertility, women with higher information searching intensity, and women who were born in Sweden took more health-promoting actions during the time they were trying to conceive ($p < 0.05$) (data not shown).

Study III

Demographic background data

Women becoming pregnant following ART were significantly older and more likely not have completed university level education compared to both sub-fertile non-pregnant women and naturally pregnant women. Sub-fertile non-pregnant women were also more likely to have a history of previous psychiatric diagnoses (including depression, bipolar disorder, or anxiety) than either women becoming pregnant following ART or naturally pregnant women. They also tended to report more than one lifestyle risk factor, such as tobacco smoking, weekly alcohol consumption and lack of regular exercise (< 2 h/week).

Prevalence and frequency of symptoms of anxiety and depression in all groups

Sub-fertile non-pregnant women reported a considerably increased prevalence of anxiety symptoms (HADS-A ≥ 8) in 57.6% of women, compared to 21.1% of women pregnant after ART and 18.8% of naturally pregnant women ($P < 0.001$).

Furthermore, 15.7% of sub-fertile women scored twelve points or higher on the EPDS, indicating the presence of depressive symptoms, compared to 8.5% and 10.3% of the pregnant women who conceived after ART and pregnant women who conceived naturally, respectively ($P = 0.001$). There were no differences in depression or anxiety symptom scores between the women pregnant after ART and women who conceived naturally (Fig 8).

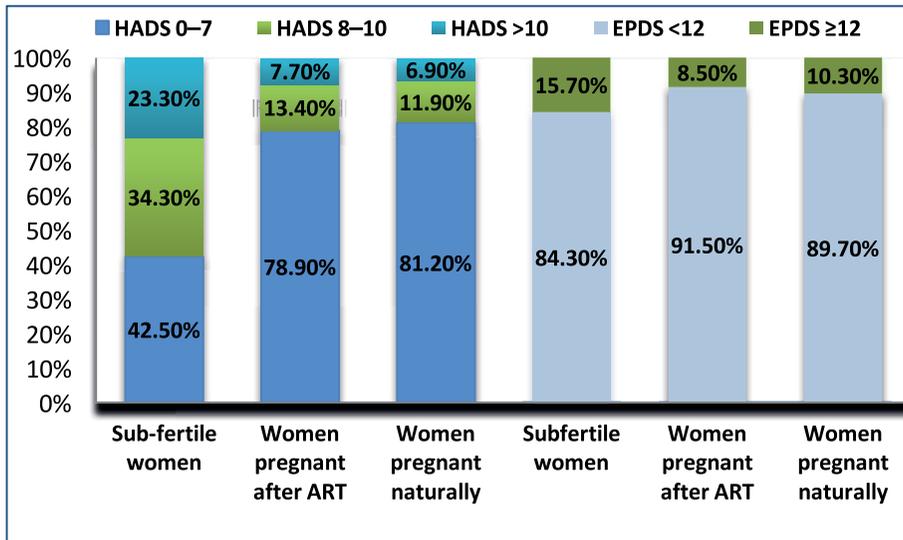


Figure 8: Distribution of sub-fertile non-pregnant women ($n = 468$), women pregnant after ART ($n = 143$) and women pregnant naturally ($n = 2972$) according to the Anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) and Edinburgh Depression Scale (EPDS) scores.

A multivariate regression model also showed a statistically significantly increased prevalence of anxiety (HADS-A ≥ 8 ; PR: 2.57; 95% CI, 2.27–2.90), but not of depression symptoms (EPDS scores ≥ 12 ; PR: 1.13; 95% CI: 0.90–1.41) among women in the sub-fertile non-pregnant group compared to naturally pregnant women. It is noteworthy, among women who became pregnant after ART, that no increased prevalence of either anxiety or depression symptoms was seen.

Sub-fertile non-pregnant women showed a three to four fold higher prevalence of self-reported history of psychiatric diagnoses, compared to those pregnant after ART and naturally pregnant women, respectively. Additionally, the multivariate regression analyses indicated that previous psychiatric history was associated with higher odds for current anxiety and depression symptoms (PR: 1.99; 95% CI: 1.75–2.26 and PR: 2.62; 95% CI: 2.16–3.18, respectively).

Importantly, the presence of at least one lifestyle risk behavior (daily tobacco smoking, weekly alcohol consumption, BMI >25 kg/m², or regular physical exercise < 2 h/week) was associated with symptoms of both anxiety (PR: 1.24; 95% CI: 1.09–1.40) and depression (PR: 1.25; 95% CI: 1.04–1.49).

We also used the variable “period trying to conceive” in another model instead of “study groups”; a duration of 1–2 years trying to conceive was associated with an increased prevalence of anxiety symptoms (PR: 2.00; 95% CI: 1.74–2.30), while a period of >2 years increased the prevalence by 2.2-fold (PR: 2.16; 95% CI: 1.80–2.58) compared to women who had conceived or were in the first year of attempting to conceive.

Study IV

Demographic background data

The median age of the population at the cycle start was lower in the “Lifestyle study” cohort 31.1 (IQR = 6.8) years compared to the “UppStART study” validation cohort 34.0 (6.0) years. However, there were more women with university education in the “UppStART study” validation cohort compared to the “Lifestyle study” cohort.

Association between lifestyle risk factors and number of aspirated oocytes and number of mature oocytes

Two significant risk factors were identified in the “Lifestyle study cohort”: smoking and BMI. Women with both risk factors had (on average) 25% less aspirated oocytes than women without risk factors (IRR of 0.75, 95% CI 0.61 - 0.94). Women with these risk factors had also an IRR of 0.78 (95% CI: 0.62 - 0.98) for the proportion of mature oocytes (in relation to the total number of aspirated oocytes), meaning that they would (on average) have 22% fewer mature oocytes than women with no risk factors.

Interaction with AFC

For the outcome of proportion of mature oocytes (in relation to the total number of aspirated oocytes), the number of risk factors was found to have a borderline significant interaction with AFC ($p = 0.099$): the larger the value of AFC, the less harmful the effect of the risk factors.

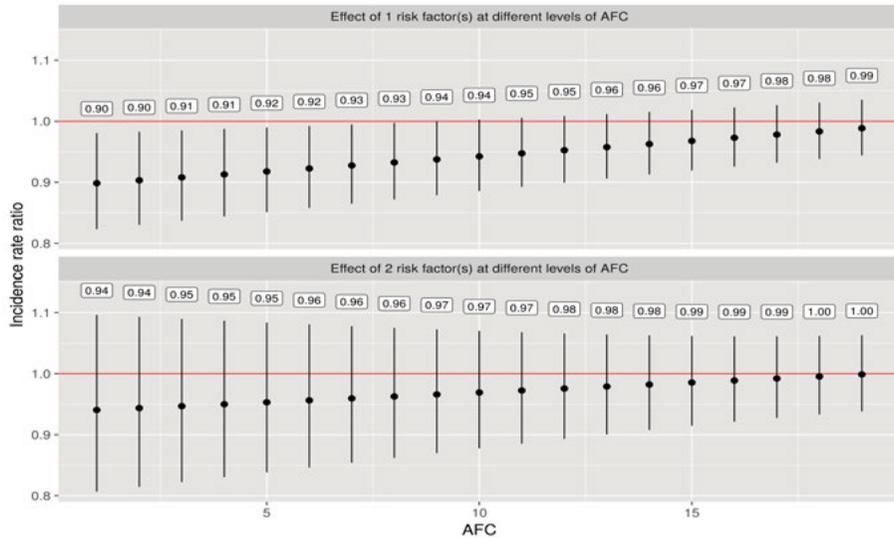


Figure 9: Interaction between number of lifestyle risk factors with Antral Follicle Count (AFC) in affecting proportion of mature oocytes (IRRs with related 95% confidence intervals displayed for different levels of AFC).

Discussion and conclusions

In order to be able to offer effective individual preconception counseling to women with or without fertility problems, it is necessary to have basic knowledge about what measures they themselves have taken to increase their chances of conception and having a healthy baby. The main finding in our project was that many women make unfavorable lifestyle choices in the period before conception. Our results indicate that the strategies for promoting lifestyle changes before conception should be mandatory in the initial stage of infertility treatment and should be individualized.

Level of pregnancy planning and association with background characteristics

Most of the pregnancies (74%) among women registered at Swedish antenatal clinics were planned. Women with planned pregnancies were more likely to have higher socioeconomic status and be living in a longer relationship than women with unplanned pregnancies. The high proportion of planned pregnancies is consistent with two previous studies from Sweden and Denmark, where 72–75% of the pregnancies were reported as being highly or quite planned [148,153]. The association between socio-economic status (SES) and pregnancy planning is also corresponds with previous studies [20,154].

The five-graded Likert scale (Swedish Pregnancy Planning Scale), to measure the level of pregnancy planning that was used in this study is time-efficient and shows acceptable reliability and construct validity, which makes it useful for measuring pregnancy planning [155]. Using a scale like this would enable further studies to explore health outcomes for the mother and the child according to pregnancy planning status. Women should be routinely asked about the level of pregnancy planning at registration at antenatal clinics to enable individualized counseling to women in need of extra support.

Lifestyle during the pregnancy planning period among pregnant women

The recommendations about preconception health promoting actions such as folic acid intake did not seem to be well-known among women wishing to become pregnant and did not cause a change in behavior. Only one third of the women reported taking folic acid supplementation as recommended, whereas almost one fifth of the women used tobacco daily and 10% consumed alcohol on a weekly basis. However, more than half engaged in pregnancy planning behavior such as seeking information or carrying out health promoting actions in preparation for pregnancy. Despite robust evidence for folic acid supplementation, studies continue to show that a majority of women fail to take supplements before conception. These results are in line with those of other European and US studies investigating the association between pregnancy planning and preconception lifestyle changes [20,21,148,154].

Lifestyle changes during the pregnancy planning period among sub-fertile women

Most women (86%) reported one or more actions to improve their health prior to pregnancy. The most common lifestyle change was folic acid intake (59.4%), while change to a healthier diet among women with BMI > 25 kg/m² was the least reported health promoting lifestyle change in our study (34%). Other studies from Europe and USA showed similar results [156]. Surprisingly, more than half of the women seeking help for infertility did not comply with preconception health and care recommendations and did not adjust their lifestyle accordingly for example the use of folic acid. A study from the United Kingdom showed that only 2.9% complied fully with the recommendations for alcohol and folic acid intake during the 3 months before becoming pregnant [157]. These findings are also in agreement with a review that concluded that patients do not appear to follow recommendations for lifestyle behavior modifications during fertility treatment [44,158]. It is interesting to note that being employed to at least 50% is associated with lower odds of changing tobacco use habits. One would expect working women to have more knowledge regarding preconception health and therefore be more likely to adopt a healthier lifestyle. However, one could speculate that women who were not fully working had somewhat more time to devote to a lifestyle change. Previous studies found conflicting results for the association between socioeconomic level and lifestyle changes [159]. Another interesting finding is the high proportion of women with overweight (23.9%) and obesity (12.5%), which is similar to the distribution of weight found among women in early pregnancy in antenatal care in Sweden [51]. Half of these women with

BMI > 25 kg/m² reported an increase in physical activity and one third changed to a healthier diet. Although weight loss for obese women was not significant, half of the obese women managed to reduce their BMI a little bit anyway. Gormack et al. (2015) found that 13% of women undergoing a fertility treatment reported achieving a lower BMI prior to the upcoming fertility treatment [160].

Prevalence and frequency of symptoms of anxiety and depression among sub-fertile women, women pregnant after infertility treatment, and naturally pregnant women

Women who conceived with ART were found to have lower rates of significant anxiety and depression symptoms compared to sub-fertile women seeking treatment. There was also no difference in depression and anxiety symptoms among pregnant women conceiving after ART and those who conceived naturally. The scientific discussion about the psychological aspects of pregnancies after in vitro fertilization (IVF) gives contradictory results [161,162]. Healthcare professionals treating women with fertility problems should be aware that this patient group may present high rates of significant depression and anxiety symptoms [163]. However, our results do not suggest that women who conceive with ART in Sweden are in specific need of prevention or intervention for depression or anxiety, compared to naturally pregnant women.

Correlates of symptoms of anxiety and depression

Another finding worth noting is that sub-fertile non-pregnant women had a three to four-fold prevalence of self-reported history of psychiatric diagnoses, compared to those pregnant after ART and naturally pregnant women, respectively. Our results are in line with the findings of Volgsten et al; thus suggesting that factors such as vulnerability or personality traits must be taken into account to identify patients at risk for depression before IVF [163,164]. Although it is hard to draw conclusions from this material alone, it seems plausible that psychological distress could affect subfertility as well as fertility treatment outcomes.

Notably, the presence of lifestyle risk factors, including lack of regular physical exercise, tobacco smoking, alcohol consumption, and overweight were independently associated with both depression and anxiety symptoms. This result is consistent with a previous Swedish study [165] which showed that the reporting of at least one lifestyle risk behavior, in the general population was associated with symptoms of both anxiety and depression.

Counseling concerning lifestyle risk behaviors could therefore be helpful, considering their high prevalence in the sub-fertile group.

Association between lifestyle risk factors and number of aspirated oocytes and number of mature oocytes in in vitro fertilization cycles

The primary aim of IVF treatment is to achieve live birth at term. However, as the number of oocytes retrieved is considered to be an important prognostic marker, IVF treatment protocols aim at optimizing this particular outcome first [166,167]. Although there are several studies addressing the impact of individual lifestyle risk behaviors on various IVF treatment outcomes, such as pregnancy rate or livebirth rate, only a few of them evaluate their cumulative effect, or the association between lifestyle behaviors and number and/or quality of aspirated oocytes [91,168]

The findings of study IV indicate that there is a cumulative effect of smoking and BMI on the number of aspirated and the proportion of mature oocytes in fresh IVF treatment-cycles. This is especially true for women with a low ovarian reserve. The effect of age and alcohol consumption on the number of aspirated oocytes was statistically significant in the “UppStART study” validation cohort, but not in the “Lifestyle study” cohort. This is probably because of the wider age range in “UppStART study” cohort in which the questionnaire included more detailed information regarding amount and type of alcohol.

Prior data have shown that both smoking and overweight individually or in combination unfavorably affect implantation, pregnancy, and live birth rates after IVF [90,169]. Our findings corroborate these results. It is also interesting to note the borderline significant interaction results with AFC, suggesting that at good levels of ovarian reserve, the impact of lifestyle is probably attenuated.

These results could contribute to individually tailored information to couples seeking treatment.

Methodological considerations

The questionnaires used in our studies were extensive. However, research in this field indicates that the questionnaire length is of secondary importance in comparison to motivating participants to partake in the first place and the comprehensiveness of the questions [170–172]. The questionnaires in our studies were generally carefully filled out, with relatively few missing fields. Of those who took the opportunity to leave a comment on the last page, many expressed

their gratitude for the opportunity to participate and suggested additional topics to be included in such a study. Several steps were taken to increase the return rate: usage of a carefully developed invitation letter, enclosing a stamped, self-addressed envelope, pre-coded questions and one reminder [170,173]. The response rate (62%) was satisfactory compared to other similar studies in Sweden [171].

The questionnaire was used to assess general background, information on dietary habits and use of dietary supplements, especially folic acid. This method was chosen since it gives relatively widespread information and it is easy to perform. Using a questionnaire has also been shown to be reliable in most cases in surveys of this type [174–176].

The sample of women with fertility problems was drawn from both public and private fertility clinics, which makes the sample representative regarding women undergoing fertility treatment in mid-Sweden and minimizes the risk for selection bias. Of the group of women in the “Lifestyle study” who had agreed to participate in the study but did not return the questionnaire, 14% were analyzed using information from patient records with regard to age, infertility duration, body mass index (BMI), tobacco use, and alcohol consumption. The results showed no significant difference between this group and the group of women who completed the study.

Assessing the level of pregnancy planning was a challenge in “SWEPP study”. There is a plethora of ways to measure and categorize pregnancy planning status which complicates comparisons of assessments of the incidence of unplanned pregnancies. Regardless of measure, one can question whether a retrospective measure of level of pregnancy planning is valid or distorted by recall bias. Furthermore, the retrospective measure for estimating the incidences of health-promoting actions and lifestyle changes were based on self-reported data from the questionnaire. Self-reported data could of course be either overestimated or underestimated [177].

The cross-sectional design has some limitations as well, primarily regarding the direction of causality. The design only allows for comparisons between individuals. However, the population-based design, large sample, and large number of individual focused variables are among the strengths of this material.

Lack of a control group of women planning natural conception could be a limitation in study III. Also, the use of EPDS for detection of depressive symptoms among sub-fertile non-pregnant women, a population where the test has not been validated, could raise concerns about potential misclassification. However, as EPDS has been validated even in community-based general population samples [178], we consider this possibility rather unlikely.

Study IV did not include the corresponding male variables on lifestyle, which is a limitation since fertilization rates are affected by semen quality, which is in turn strongly associated with lifestyle behaviors of the partner. Furthermore, the relatively small sample size, especially in the “Lifestyle

study”, might introduce some problems with statistical power. This might be reflected in the borderline statistical significance of some of the results, where, on the other hand, notable and stable trends are demonstrated. Despite these shortcomings, this study is one of the largest in the field evaluating lifestyle factors, their interaction and possible impact on assisted reproductive treatment outcomes and uses a larger, validation cohort from the same geographic area to confirm the study findings.

Implications at present and in the future

This is the first Swedish study focusing on lifestyle behaviors among women planning a pregnancy. The study focuses on an important reproductive period, the period before conception and early pregnancy. Our results show that ***there is a need for greater efforts from healthcare professionals to improve compliance*** with the recommendations for women planning a pregnancy. Women at a fertile age would benefit from ***preconception counseling*** to approve their chances to conceive as well as having a healthy newborn. All women of childbearing age would benefit from such counseling as well as support in improving their lifestyle. The changes, if needed, should preferably be taken even before ***the women start planning*** their pregnancy.

Despite an increasing body of evidence for the adverse effect of lifestyle risk factors on pregnancy outcomes, there is lack of ***evidence-based interventions*** for health promotion and disease prevention [179]. This might underlie the absence of ***guidelines*** and routine provision of preconception care and the mainly opportunistic approach employed today in all the participating European countries.

Lifestyle changes are a simple and cost-effective way to optimize fertility and reproductive outcomes. ***Screening for lifestyle*** factors and ***correcting*** those negatively affecting reproductive health could actually be mandatory in the ***initial stage of infertility treatment*** and preferably when women in general start planning to become pregnant.

In vitro fertilization is a resource-intensive treatment, often requiring a significant investment of time, money and emotional energy. Any lifestyles changes that could contribute to positive outcomes, would be significant. Future research is needed however, to further define the mechanism of the impact of lifestyle risk factors on IVF outcome.

A new paradigm of fertility care is suggested, in which ***assessment and interventions*** for lifestyle factors would have an important place in the reproductive care pathway, along with medical interventions, such as assisted conception techniques. This, in the long term, could lead to a substantial decline in the referrals for medical investigations and fertility treatments.

Clinic staff may have limited time with patients to provide them with written and verbal information on healthy lifestyle changes. The key messages may be diluted among the large amount of complex information that needs to be conveyed about the medications, tests and procedures involved in fertility

treatment. On the other hand, information could be provided through an interactive internet platform and fertility clinics may benefit from having a *designated staff member* to respond to patient queries and carry out discussions with them, offering motivation and support on an ongoing basis throughout their treatment.

The findings of these studies may assist care providers with individualized patient education and further help patients target their efforts towards meaningful lifestyle change.

Svensk sammanfattning (Swedish summary)

Bakgrund

Barnafödande är en central fråga både för individen och för samhället i stort. Moderns hälsa och livsstil innan, under och efter graviditeten påverkar det nyfödda barnets hälsa och överlevnad. Risken för fosterskador kan minskas om kvinnan avstår från alkohol och tobak samt har ett tillräckligt högt intag av folsyra redan från konceptionen. Svenska livsmedelsverket rekommenderar dagligt tillskott av folsyra en månad innan graviditet fram till och med 12:e graviditetsveckan. Studier har visat att bara var femte kvinna känner till denna rekommendation trots att den information som gått ut från alla ansvariga myndigheter.

Fertilitet är förmågan att få barn, medan fekunditet är kvinnans biologiska förmåga att bli gravid baserad på den månatliga sannolikheten för befruktning. Klinisk infertilitet definieras som oförmåga att bli gravid efter 12 månaders oskyddat samlag. Man har uppskattat att cirka 15 % av befolkningen i industriellt utvecklade länder är drabbade. Orsakerna till infertilitet omfattar diagnoser som, ägglossningsrubbingar, skador på äggledarna, endometriosis, kromosomavvikelser, manliga faktorer och oförklarlig barnlöshet. Det finns växande belegg för att livsstilsfaktorer kan påverka fortplantningsförmågan men effekterna av livsstil kan variera beroende på individuella orsaker och omständigheter. Ålder, övervikt och fetma samt tobaksbruk hos kvinnor minskar signifikant chansen till befruktning. Även stressnivå och psykisk hälsa före, under och efter graviditet kan ha samband med fertilitetspotential samt graviditets- och förlossningsutfall.

Behandlingen av infertilitet bestäms av bakomliggande faktorer. Assisterad reproduktiv teknik (ART) innefattar hormonstimulering, intrauterin insemination (IUI), in vitro fertilisation (IVF), intracytoplasmisk spermieinjektion (ICSI) och fryst embryoöverföring (FET). Behandlingarna kan vara påfrestande att genomgå och kan påverka patienten både kroppsligen och psykiskt samt innebär stora kostnader för patienten och samhället. Tidigare studier har undersökt effekten av individuella negativa livsstilsbeteenden som rökning, fetma, fysisk aktivitet mönster, näringsintag eller alkohol, som påverkar såväl naturliga graviditeter som graviditeter efter ART. Få studier har emellertid genomförts för att studera den ackumulativa effekten av flera negativa beteenden på graviditetsresultat efter fertilitetsbehandling.

Att kunna ge vetenskapligt underbyggd rådgivning till personer som söker läkarvård för ofrivillig barnlöshet och hjälpa dem aktivt att göra nödvändiga livsstilsförändringar är ett viktigt första steg för att förbättra deras chans till graviditet och få ett friskt barn. Projektets resultat kan användas för att utveckla evidensbaserad rådgivning om livsstilsfaktorer för par som planerar graviditet i allmänhet och för par som har fertilitetsproblem och söker hjälp för infertilitet.

Syfte

Det övergripande syftet med projektet var att undersöka i vilken utsträckning kvinnor följer rekommendationerna för en hälsosam livsstil under den tid de försöker bli gravida och under tidig graviditet samt effekterna av livsstilsfaktorer som kan innebära en risk för sämre behandlingsresultat vid assisterad befruktning. **Studie I:** Att undersöka om gravida kvinnor som planerar sina graviditeter och i vilken mån bakgrundsfaktorer som socioekonomisk status, utbildning samt kulturell bakgrund påverkar detta. **Studie II:** Att undersöka livsstilsvanor bland sub-fertila kvinnor som försöker bli gravida i förhållande till bakgrundsvariabler. **Studie III:** Att undersöka hur vanligt symptom på ångest och depression är bland sub-fertila kvinnor som söker för infertilitet och bedöma i vilken utsträckning de skiljer sig från kvinnor som är gravida efter fertilitetsbehandling och/eller kvinnor som är spontan gravida. **Studie IV:** Att kvantifiera den kumulativa effekten av livsstilsriskfaktorer på de reproduktiva resultaten efter en avslutad första färsk provrörscykel och testa en möjlig interaktion med antalet antralfolliklar.

Metod, datainsamling

SWEPP-studien (studie I, III): Gravida kvinnor (n= 5494) rekryterades av barnmorskorna vid registreringen på de deltagande mödrahälsovårdsmottagningarna (n=153) där de fick skriftlig och muntlig information. Svensktalande kvinnor erbjöds ett frågeformulär att fylla på kliniken eller hemma och då returnera enkäten per post i ett förbetalt kuvert. Gravida kvinnor (n = 4968) accepterade och i 4845 fall fick de en enkät på svenska och i 123 fall översatta enkäter till (arabiska eller engelska) eller blev föremål för en telefonintervju. Av gruppen gravida (n = 3115), hade 143 blivit gravida efter fertilitetsbehandling och 2972 kvinnor var spontangravida

Lifestyle-studien (studie II, III, IV): Barnmorskorna på fertilitetsmottagningarna (n=10) gav muntlig och skriftlig information om studien till kvinnor som uppfyllde inklusionskriterierna. Inklusionskriterier för denna studie var att kunna läsa och skriva svenska och att inte tidigare ha utretts för infertilitet. De

som samtyckte till att delta fick fylla i en enkät, antingen på kliniken eller hemma och i så fall returnera den per post i ett förfrankerat kuvert. Det undertecknade formuläret för samtycke, som åtföljde de ifyllda frågeformulären, arkiverades säkert och tryggt omedelbart efter mottagandet. De kliniker som ingick i studien var fertilitetskliniker i Västerås (n=2), Uppsala (n=2), Örebro (n=1), Gävle (n=1), Dalarna (n=3) och Eskilstuna (n=1). Av 782 tillfrågade kvinnor accepterade 747 att delta. 466 kvinnor genomförde studien (studie 2,3). Data från den gruppen följdes upp med hjälp av patientjournaler två år efter att patienterna fyllde i första enkäten (studie 4)

Enkäterna innehöll validerade instrument samt frågor om bakgrundsfaktorer, graviditetsplanering i samband med den aktuella graviditeten eller graviditetsförsök, fysisk och psykisk hälsa, sexuell och reproduktiv hälsa, livsstil och partner. En särskild fråga konstruerades för att mäta nivån av graviditetsplanering. Frågor om livsstilsförändringar omfattade: intag av folsyra- och/eller multivitamin tillskott; dagligt tobaksbruk; alkoholkonsumtion/vecka; daglig kaffe konsumtion; typ av diet och fysisk aktivitet/vecka graderad i antal timmar. För studie III används 2 instrument: Hospital Anxiety Scale (HADS) med cut-off (0-7 Normal, 8-10 Borderline och >10 sjuka fall), Edinburgh Depression Scale (EDS) med cut-off 0-12 Normal och >12 sjuka fall. Data samlades in med hjälp av journal- och registeruppgifter för att användas i syfte att följa upp kvinnorna för att studera effekter av livsstilsfaktorer på det reproduktiva utfallet vid assisterad befruktning.

Resultat

Studie I

Gravida gruppen: 68 % av de rekryterade kvinnorna slutförde enkäten. 73 % av kvinnorna skattade sin graviditet som väl eller ganska väl planerad, medan 13 % uppgav att graviditeten var ganska eller mycket oplanerad. Kvinnor med planerade graviditeter var i högre grad aktiva i arbetslivet (OR 1,6; 95% CI: 1,2 - 2,1) och hade högre utbildningsnivå, (OR 2,1; 95%, CI 1,3 - 3,3), högre inkomst (OR 1,1; 95% CI 1.1 - 1.2), och hade levt längre i sitt förhållande (OR 1,1; 95% CI 1.1 - 1.2) än kvinnor med oplanerade graviditeter. (se ovan studie 1)

Studie II

Infertila gruppen: 782 patienter blev tillfrågade och 747 accepterade att delta i studien. 466 (62%) svarade på enkäterna. Den genomsnittliga infertilitetsperioden var 1,9 år. Under den tiden hade 17,4% använt tobak, 13,4% druckit alkohol varje vecka, och 13,6% intagit mer än tre koppar kaffe per dag. Sex

av tio kvinnor tog folsyra när de började försöka bli gravida, men 11% slutade efter en viss tid. Folsyraintag var vanligare bland kvinnor med en högre utbildningsnivå ($p < 0,001$). Bland de deltagande kvinnorna i den infertila gruppen var 23,9% överviktiga och 12,5% obesa. De obesa kvinnorna ökade sina fysiska aktiviteter mer och ändrade oftare till sundare kostvanor än de överviktiga ($P = 0,08$, OR 2,037; 95% CI 0,898-4,621), men detta visade ingen statistisk signifikant ändring i BMI.

Studie III

Andelen infertila kvinnor som led av signifikanta ångestsymtom (HADS-A 8) var 57,6% jämfört med 21,1% av de kvinnor som blivit gravida efter ART och 18,8% av de naturligt gravida kvinnorna ($P < 0,001$). Signifikanta depressions-symptom (EPDS skala 12) förekom hos 15,7% av de infertila kvinnorna i jämfört med 8,5% bland de kvinnor som blivit gravida efter ART respektive 1,3% bland dem som var naturligt gravida ($P = 0,001$). Studien visade alltså inga skillnader i depression eller ångestsymtom mellan kvinnorna som blivit gravida efter ART och naturligt gravida kvinnor. Att ha en psykiatrisk diagnos i sjukdomshistorien och vara äldre än 29 år visade sig vara signifikanta riskfaktorer för både ångest och depressiva symtom. Förekomsten av minst ett ohälsosamt livsstilbeteende (daglig tobaksrökning, alkoholkonsumtion varje vecka, BMI ≥ 25 och mindre än 2 timmars fysisk träning/vecka var också associerade till symptom på ångest (OR: 1,36; 95% CI: 1,14–1,61) och depression (OR: 1,33; 95% CI: 1,06–1,68).

Studie IV

Materialet bestod av de sub-fertila patienterna från offentliga och privata fertilitetskliniker i mellersta Sverige som ingått i "Lifestyle-studien" ($n = 242$) som fick utgöra en "hypotesgenererande kohort" och 432 deltagare från den så kallade "UppStART-studien" som användes som en "valideringskohort". Från UppStART studien inkluderades kvinnor som startat sin första färska IVF cykeln inkluderades. Regressionsanalys användes för att identifiera riskfaktorer och deras betydande inverkan på behandlingsresultaten. Resultaten validerades sedan i valideringsstudien. En ytterligare analys utvärderade interaktionen mellan antal riskfaktorer och totalt antralfollikelantal (AFC) i valideringskohorten. Utfallsvariabler var antal aspirerade oocyter, antal mogna oocyter, totalt antal embryon, antal embryon som användes (återförd färsk och alla frysta) och andel mogna oocyter bland det totala antalet aspirerade oocyter. De livsstilsfaktorer som undersöktes var ålder, bodymassindex (BMI), rökning, alkoholkonsumtion, daglig koffeinförbrukning, fysisk aktivitet och depression i sjukhistorien. Resultaten från denna studie identifierade två signifikanta riskfaktorer i Lifestyle-studiekohorten: rökning och BMI. Kvinnor med båda riskfaktorerna hade en Incidens Rate Ratio (IRR) på 0,75 [(95% CI (0,61

- 0,94)] för antal aspirerade oocyter än kvinnor utan dessa riskfaktorer. Studien visade också att det finns en ”borderline signifikant” interaktion med AFC: ju större värdet av AFC är, desto mindre skadlig är effekten av riskfaktorerna på andelen mogna oocyter (i förhållande till antalet aspirerade oocyter).

Bedömning av projektets kliniska betydelse på kort och lång sikt

Detta är den första svenska studien med inriktning på livsstilsbeteenden bland kvinnor som planerar graviditet. Studien fokuserar på en viktig reproduktiv period, perioden före befruktning och den tidiga graviditeten. Livsstilsförändringar är ett enkelt och kostnadseffektivt sätt att förbättra fertiliteten och det reproduktiva resultatet. Screening för livsstilsriskfaktorer och korrigerande av dem som påverkar reproduktiv hälsa negativt kan vara ett viktigt första steg i processen vid en infertilitetsbehandling. Förändringarna bör helst vidtas under den period då kvinnor börjar planera sin graviditet. Alla kvinnor i fertil ålder skulle dra nytta av sådan rådgivning och dylikt stöd för att förbättra sin livsstil. In vitro fertilisering är en resurskrävande behandling, som ofta kräver en betydande investering av tid, pengar och emotionell energi. Eventuella livsstilsförändringar som kan bidra till positiva resultat av behandlingen skulle kunna ge betydande vinster. Denna studie föreslår ett nytt paradig för fertilitetsvård föreslås, där bedömning och åtgärder för förbättring av livsstilsfaktorer bör ha en lika självklar plats inom den reproduktionsmedicinska vården som medicinska ingrepp.

Resultaten av vår studie kan ligga till grund för vårdgivare att erbjuda bättre information och utbildning till patienterna och hjälpa patienterna att själva fokusera sina ansträngningar mot meningsfulla och vetenskapligt underbyggda livsstilsförändringar. De livsstilsförändringar som bidrar till en bättre reproduktiv förmåga.

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