BMJ Open  Food & Fertility Study: study protocol for a Danish multicentre prospective cohort study investigating the association between food intake and semen quality, pregnancy and birth outcomes in infertile women and men

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ABSTRACT

Introduction  Worldwide infertility is highly prevalent, and lifestyle factors, such as food intake, could have an essential role in the success of a fertility treatment. The literature is not consistent and adequate for recommendations to the increasing number of women and men of reproductive age who ask for lifestyle guidance. Therefore, the aims of the Food & Fertility Study will be to investigate the possible association between food intake and semen quality in men, and pregnancy and live birth rates in women undergoing intrauterine insemination or assisted reproductive technology treatment.

Methods and analysis  The Food & Fertility Study is a multicentre prospective cohort study which plans to enrol a total of 4000 women and men between 2022 and 2024. Data collection will take place in four fertility clinics through a web-based Food Frequency Questionnaire. Data on sperm quality and pregnancy and live birth rates will be obtained from medical records and national registers.

Ethics and dissemination  The study is registered with and approved by the Danish Data Protection Agency, the North Denmark Region (j.nr: 2019-055298), Further, a Statement of Work and a Master Collaboration Agreement have been submitted and approved by the regional legal departments (AGR-2019-731-9667). Dissemination of the results will be through national and international conferences, in scientific environments, in the form of publications to the broader public, and by peer-reviewed publications in international scientific journals.

Trial registration number  NCT05454046.

INTRODUCTION

Food and dietary supplements may have an impact on conception and live birth. Female intake of folic acid is associated with a lower frequency of anovulation and has been shown to yield a higher reproductive success during fertility treatment. Further, several studies have investigated the association between female vitamin D status and chance of a successful fertility treatment. Overall, women with low vitamin D status (25(OH)D <50nmol/L) have a decreased chance of achieving a pregnancy. In contrast, supplementation of antioxidants to women in fertility treatment does not seem to have an effect on conception or live birth. On the other hand, a meta-analysis showed that supplementation of antioxidants to the male partner in fertility treatment positively affected both the chance of pregnancy and of live birth. However, based on the results, it is difficult to recommend exactly which combination of antioxidants and the doses needed to achieve a potential, positive effect.

Modifiable lifestyle factors, like food intake, which could have an impact on reproductive health and the success of fertility treatment, are of major public health and clinical importance. Worldwide, infertility is an increasing problem, and the 12-month prevalence of infertility is 9%. Infertility is defined as a disease by the WHO, and more than 7 million children have been born after assisted reproductive technology treatment linking data from Food Frequency Questionnaires, medical records and national registries.

Assessment of nutrients and micronutrients based on validated algorithms.

Data collection from both infertile women and men.

Computerised, objective assessment of the sperm quality could have improved the homogeneity of this assessment.

The food intake is self-reported, and biomarkers of food intake are not available.
reproductive technology (ART) treatment. Despite the desire to become a parent, the total fertility rate is well below two in many Western countries and thus below the replacement level. There are many known causes of infertility, including ovulation failure, tubal factor, male factor, and ovarian or uterine factors, but in 20%–25% of couples seeking fertility treatment, the cause(s) remain unexplained. The high prevalence of worldwide infertility makes identification of modifiable predictors of a successful fertility treatment pertinent. The notion that fertility makes identification of modifiable predictors of a number of women and men with infertility. With an larger prospective cohort studies to guide the increasing it difficult to make recommendations.

In prospective cohort studies assessing dietary patterns, a healthy diet including seafood, poultry, whole grains, fruits and vegetables has been associated with higher pregnancy rates. Further, a recent systematic review and meta-analysis showed a positive association between a Mediterranean dietary pattern and live birth for women undergoing ART treatment. Also, association between dietary patterns and semen quality for men undergoing ART has been found. However, definitions of healthy and unhealthy diets differ between studies, which makes it difficult to make recommendations.

There is currently a knowledge gap and a need for larger prospective cohort studies to guide the increasing number of women and men with infertility. With an extended knowledge on the association between food intake and infertility, health professionals involved in fertility treatment could provide evidence-based recommendations to both women and men.

AIMS
The objectives of this study are among women and men undergoing ART treatment or intrauterine insemination (IUI) treatment to:
1. Describe their dietary composition.
2. Investigate the possible association between female diet and the probability of achieving a pregnancy and a live birth with the male partner.
3. Investigate the possible association between male diet and sperm quality.
4. Investigate the possible association between male diet and the probability of achieving a pregnancy and a live birth with the female partner.

METHODS
The Food & Fertility Study is planned and organised by the Department of Obstetrics and Gynaecology at Aalborg University Hospital in collaboration with the Department of Epidemiology Research at Statens Serum Institute, Copenhagen, Denmark. The recruitment of participants will be performed in collaboration with the fertility clinics at Herlev University Hospital and the regional hospitals in Horsens and Skive, Denmark, thus representing three of the five regions in Denmark. The study is planned to recruit participants from 1 August 2022 until 1 August 2024, and final data collection date for primary outcome will be 1 August 2025. Results from the study will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.

Design
The Food & Fertility Study is a multicentre cohort study with prospective data collection.

Study population
Women and men undergoing ART or IUI treatment at the fertility clinics at Aalborg University Hospital, Herlev University Hospital, and at the two regional hospitals in Horsens and Skive will be invited to participate in the study. Each study site has agreed to invite approximately 60% of eligible patients to participate. Inclusion criteria will be women and men undergoing in vitro fertilisation (IVF), intracytoplasmic sperm injection, frozen–thawed embryo transfer, pre-implantation genetic testing or IUI. Further, recipients of semen donation or oocyte donation can be included. Exclusion criteria will be treatments with double donation (donation of both semen and oocytes).

Exposure data
During enrolment into the study, the following exposure data will be measured: frequency and the amount of dietary components, intake of dietary supplements, coffee intake, alcohol intake, smoking habits, physical activity, height and weight. Information on alcohol intake will be obtained with questions on how often beer, cider, alcopops, wine and liquor are consumed on a 10-point frequency scale. Information on smoking habits will be obtained using questions regarding cigarettes, other types of tobacco (ie, pipe, cigars or heated tobacco), e-cigarettes and smokeless tobacco (ie, snuff or chewing tobacco) on a 6-point frequency scale. Information on physical activity will be obtained with questions regarding type of physical activity using 18 potential categories, how often on a 6-point frequency scale and for how long time per occasion recorded in minutes. Information on height and weight is self-reported and measured in kilograms and centimetres, respectively. The data collection will be carried out using a web-based Food Frequency Questionnaire (FFQ). The FFQ was developed from the validated Youth/Adolescent Questionnaire (YAQ) used in the American Growing Up Today Study. The YAQ was translated into Danish and modified to include typical Danish foods based on reports on National Danish Dietary Habits and Physical Activity. In the latest version, it consists of ~200 food items divided into overall food.
groups. Questions on food habits (frequency of breakfast, lunch and dinner intake and overall thoughts related to own food intake style, such as organic, sustainable or anti-inflammatory) are included. Use of dietary supplements is also included. This FFQ was applied in the 14-year-old follow-up in the Danish National Birth Cohort (DNBC).21 22 The FFQ will be sent to the participants’ personal digital post/e-box used by the Danish health system and other authorities to communicate with individuals based on the unique personal identification number (CPR) given to all residents in Denmark at birth or immigration. The FFQ will be accessed through a personal link, which leads the participant to the platform SurveyXact. The FFQ can be filled in by phone or computer and it will take around 30–40 min. Subsequently, intake of macronutrients and micronutrients will be calculated by the Department of Epidemiology Research at Statens Serum Institute based on algorithms used in previous validation studies within the DNBC.21 22

Outcome data
Pregnancy and live birth: information on all IVF and IUI treatment cycles in Denmark, including type of treatment and whether pregnancy was achieved will be recorded and reported on an ongoing basis by all public and private fertility clinics in Denmark to the national IVF register. Information on pregnancy and birth outcomes will be retrieved from the Danish Medical Birth Register, in which all births in Denmark are registered. Neonatal information on the child(ren) will be obtained from the Danish Medical Data Center (DMDC) used by all the fertility clinics in Denmark to the national IVF register.

Sperm quality: from the day the FFQ is answered, a semen sample delivered 3 months earlier or 3 months later at the laboratory at the respective fertility clinic will be included as an outcome measure. The semen sample will undergo an assessment under microscope. The semen quality will be assessed according to total volume (mL), degree of motility (1–5), total number of sperm cells/volume (million/mL), total number of motile sperm cells/volume (million/mL) and total number of progressive motile sperm cells (million) and total number of progressive motile sperm cells/volume (million/mL) will be assessed according to WHO guidelines. The information is registered and will be obtained from the DMDC. As a part of an annual in-house laboratory performance assessment, the participating clinics ensure consensus within the embryologist in the IVF laboratory regarding sperm assessment. In the multivariable analyses, there will be adjusted for clinic, as some variation on sperm assessment may exist between clinics.

Potential confounders/covariates
Potential confounders will be identified through the existing scientific literature and via directed acyclic graphs, and will include: age, smoking, caffeine intake, alcohol consumption, body mass index, physical activity, level of education, parity, indication for treatment and clinic, among others. This information will be obtained partly from the FFQs, DMDC and the National Patient Register.

Sample size calculation
Power calculations are based on the smallest difference expected to be observed, though actual difference might be bigger. The calculations are based on two-sample tests of proportions in an expected cohort of at least 1800 women and 1800 men and α=0.05. In Denmark, the chance of a live birth after IVF is 24% per cycle if the woman is <40 years. Assuming that different dietary factors occur with a frequency of 50%–80% in either the female or the male group, this study will have a power of 91%–92% to detect even a modest increase in chance of pregnancy of 25%, and a power of 94%–96% to detect a corresponding decline in chance of pregnancy of 25%. For sperm quality, even modest differences in concentration (at <0.5 million/mL) and proportion of motile sperm cells (±10%) will be detected with a power of 98%–100% with corresponding exposure frequencies at 50%–80%. The anticipated response rate is expected to be approximately 60%.

Pilot testing
Pilot testing of the FFQ was carried out among 11 project staff members in one of the fertility clinics. The pilot testing resulted in the period of evaluation being more clearly described and the description of the amount of bread eaten being modified. Further, the bar at the top of the FFQ showing the proportion of completed questions was subject to various considerations. To support the participants’ completion of the FFQ, we changed this feature, so it was as accurate as possible. Moreover, a few typing errors were corrected.

Data analysis plan
All analyses will be carried out in R (V.3.4.1, 2019), SAS V.9.3 or later, or STATA V.12 or later (StataCorp 194, Texas, USA). For continuous data, average values will be given as means (±SDs) or medians (range) depending on the distribution. Normally distributed data will be compared using a t-test and non-normally distributed data will be compared using Wilcoxon test and Mann-Whitney U test. Frequencies will be compared using the χ2 test. Relevant regression analyses will be used to adjust for potential confounders (for example, but not limited to parental age, smoking and body mass index, parity, education and clinic). If data are sufficiently robust, we plan to perform multiple imputation to handle missing data.
Patient and public involvement

As a health professional involved in fertility treatment, it is evident that many patients in fertility treatment seek information in relation to their lifestyle. This study was designed to answer the questions asked by the patients. Patients or the public were not directly involved in the specific design or conduct of the study. However, advice and special requests on areas of interest (i.e., dietary supplements or intake of enriched protein products, etc.) from patients will be considered when planning and designing specific analyses. Such advice will be collected through individual online interviews or focus groups with some of the enrolled patients and will help ensure that the results will be meaningful for the patients.

ETHICS AND DISSEMINATION

The FFQ measures food habits, diet intake, dietary supplement intake, coffee intake, alcohol intake, smoking habits and physical activity. The FFQ thus primarily contains questions that will also be asked in connection with usual consultations with a doctor and nurse, although to a more limited extent. Apart from the additional time spent, the participant will thus hardly experience the questions very differently than a standard consultation. There is no direct treatment-related benefit by participating in the study. Delivering a semen sample is risk free and generally effortless for the man. Sperm samples are routinely delivered as part of a fertility treatment, and the study therefore does not impose any further discomfort or risks on the participants. All eligible participants will be given oral and written information by the project staff at the fertility clinics. Further, participants must provide informed and written consent before enrolment.

The study has been registered and approved by the Danish Data Protection Agency, the North Denmark Region (j.nr: 2019-05-2988). Further, a Statement of Work, a Master Collaboration Agreement and data processor agreements have been negotiated and approved by the regional legal departments (AGR-2019-731-9667). According to Danish legislation, questionnaire-based surveys that do not include any deviations from the standard treatment do not need approval by the Scientific Ethics Committee. As delivering a semen sample when entering a fertility treatment is standard, an approval from the Scientific Ethics Committee is not necessary. All data will be stored at the research platform administered at the Danish Health Authority or Statistics Denmark to ensure adherence to General Data Protection Regulation rules and regulations. Subsequently, data from relevant national registers such as the Danish Medical Birth Register, the IVF Register and the National Patient Register may be added, using the CPR.

This new cohort is expected to generate knowledge about the possible impact of diet for female and male fertility. The results will be communicated on four levels: (1) directly through nurses and doctors by advising patients on fertility treatment; (2) the results of various studies using data from this cohort will be communicated to health authorities to enable development of new dietary guidelines for pregnancy planners; (3) the results will be shared with the international scientific community through peer-reviewed publications; (4) finally, the results will be presented at national and international congresses and meetings, both in scientific environments and also as a lecture to the broader public.

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Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Competing interests
None declared.

Patient consent for publication
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

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