Information letter about participation in a health-science project

COPL – Copenhagen Pregnancy Loss cohort

MALE PARTICIPANTS

Project manager: Henriette Svarre Nielsen, Professor at the University of Copenhagen and consultant at the unit for recurrent pregnancy loss, Department of Obstetrics and Gynaecology, Hvidovre Hospital

Thank you for your interest in our research project. **In order to take part, your partner must be an inpatient who is being treated for pregnancy loss.**

We would like to ask you to participate in scientific research project. The project is headed by Henriette Svarre Nielsen, Professor at the University of Copenhagen and consultant at the unit for recurrent pregnancy loss, Department of Obstetrics and Gynaecology, Hvidovre Hospital.
The aim of the project is to research the causes of and risk factors behind pregnancy loss. Genetic analyses of pregnancy tissue and of the parents will be performed as part of the project. This means that we are researching the significance of genetic material on pregnancy loss.

Before you decide whether you want to take part in the project, you should fully understand what the project is about, what participation will entail and why we want to carry out the project. Therefore, please read the following information for participants carefully. You will also be briefed in person before making your decision. If you decide to participate in the project, we will ask you to sign a consent form. Remember that you are entitled to a period of reflection prior to signing the consent form.

Background and objective
Pregnancy loss occurs quite frequently. Almost one in four pregnancies end in a miscarriage. Pregnancy loss is often caused by problems with the foetus, but some women miscarry healthy foetuses. At the moment, we do not have effective methods to examine the miscarried foetus. Consequently, we know very little about risk factors, causes and, unfortunately, how to prevent and treat pregnancy loss. Today, we have advanced methods which could be used to determine whether the miscarried foetus was healthy. The objectives of this research project are:

1. To understand the mechanisms behind pregnancy loss (including distinguishing between healthy and unhealthy foetuses)
2. Targeted individual patient diagnostics
3. To identify new prevention and treatment methods

What are chromosomes and genes?
All cells in the body contain chromosomes. Chromosomes are small structures that contain our hereditary traits, known as genes. The information contained in genes determines our traits and

controls the development of our organs, e.g. the brain, heart and kidneys. Normal body cells contain 46 chromosomes grouped into 23 couples. In each couple, one chromosome is inherited from the mother, while the other is inherited from the father. The first 22 chromosome couples are identical for men and women. The 23rd couple is known as the sex chromosome. It is referred to as XX in women and XY in men. Chromosomes contain DNA. A gene is a piece of our DNA. There are approximately 20,000 genes in each cell. All genes have a specific function. However, we do not yet know the function of all genes. We carry our genes our entire life and the information contained in our genes is therefore different from other health information, which typically only provides a small snapshot of the whole picture. Gene mutations can be found in all humans. These mutations sometimes cause genetic disorders. Genetic disorders occur when one or more genes do not function correctly. This can be caused by defects in the gene or by changes to the information in a gene. Changes to a gene, known as a mutation, can form as new changes in a person or they can be inherited from one or both parents.

Why carry out comprehensive mapping of genetic material?
Previously, it was only possible to study one gene at a time. It could therefore take many years to identify the genetic cause of a congenital disorder. Comprehensive mapping of genetic material means that it is now possible to examine all 20,000 human genes at once. Among other things, this means that we can identify the causes of congenital disorders much faster than previously. Our research is likely to bring new knowledge to light that will enable more targeted treatment of patients and benefit public health. Genetic analyses lead to a large volume of surplus information, so-called genome data. The genome data will be stored with the project in accordance with the EU General Data Protection Regulation and the Danish Data Protection Act.

Who can participate?
We want to examine 6,000 couples seeking treatment at the gynaecological acute admissions department at Hvidovre Hospital or Odense University Hospital in connection with pregnancy loss before the 22nd week of pregnancy. Furthermore, we want to examine 2,000 couples (the control group) who undergo an induced abortion at Hvidovre Hospital.

Sampling
In connection with the clinical examination of your partner, we will ask for a urine sample (30ml) and blood sample (53 ml) from you. If you are not present during the acute situation, we will ask you to participate at another time, possibly in connection with your partner's check-up visit 6-8 weeks after the acute hospital visit. You will be asked to provide a sperm sample and a rectal swap. The quality of the sperm sample is better if you have not ejaculated for 2-3 days prior to providing the sample.

The sperm sample must maximum be less than 1½ hours old and must be kept at body temperature from the time it is deposited until it is handed over.

The sample can be delivered any weekday between 09:00-14:00.

Alternatively, it can be delivered in connection with the follow-up visit.

Your partner and you will be invited for a follow-up visit in 6-8 where we will perform ultrasound scans of your partner and ask both of you for a urine sample. We will contact you about the date and location of the check-up.

Electronic questionnaires
You will receive an electronic questionnaire two weeks after your visit to the hospital. It will contain questions about your medical and family history, physical, psychological and sexual health, and health behaviour. The questionnaire will take approximately one hour to complete. You will receive shorter follow-up questionnaires 6 and 12 months after the hospital visit.

Analyses
The rectal swab will be examined for the composition of microorganisms to find possible associations with pregnancy loss. Part of this analysis will take place at the laboratory MGI in Latvia. Your urine and blood sample will be analysed for the presence of a number of endocrine disruptors. Your blood samples will also be tested for metabolism disruptors and immune system disruptors. We will be researching the significance of sperm quality parameters for pregnancy loss. Part of the semen and urine test will take place in Professor Marcus Cooke's laboratory in the USA.

Genetic examination of discarded unfertilized and fertilized oocytes from fertility treatment
If you are treated on The Fertility Clinic at Hvidovre- or at Herlev Hospital, we will, at future oocyte pickup, collect unfertilized and fertilized eggs that do not develop correctly in the laboratory. These eggs cannot be used for the fertility treatment and are usually discarded. The unfertilized and fertilized eggs that do not develop correctly will be used for genetic analysis to investigate genetic causes of the defective development. This will not affect your fertility treatment in any way and the material will be destroyed after the genetic analysis.

Comprehensive mapping of your genetic material
Your blood sample will be used to complete a comprehensive genetic mapping of your genetic material to identify any possible genes that affected the pregnancy loss. Furthermore, the pregnancy tissue will be tested for changes in the genetic material (comprehensive genetic mapping) which may have contributed to the miscarriage. We will also test whether it is possible to analyse the foetus's genetic material via a blood sample from your partner.
This is a research project and not a patient study. In general, we do not expect you to directly benefit from participating, and you will therefore not be notified of any findings from the genome study. <u>However, you and your partner will be notified if an abnormal number of chromosomes is found in the pregnancy tissue.</u>
The comprehensive mapping may reveal unexpected information. You will be informed in the rare case that we discover a mutation in your genes that may lead to serious illness that can be prevented or treated. It may also be necessary to inform relatives if the information can prevent death or a serious deterioration of health. *It is important to think about this before you agree to participate in this project. In the consent form, you have the option to choose not to receive information on any genetic discoveries that may affect your health. Please note that we will not check for all pathogenic genes and will only contact you if we happen to discover a gene that may lead to serious illness.*

Side effects
The blood test might result in bruising and some temporary tenderness. There is no risk in connection the urine sample or semen sample.

Data processing
Biobank
The sample material (blood, urine, and semen sample) will not be anonymised or destroyed but will be stored in a research biobank until 2035. Once the sample material has been analysed for this project, the material and data (including genome data) will be transferred to a biobank with a view to future research at the Department of Obstetrics and Gynaecology at Hvidovre Hospital and stored until 31 December 2075. The Danish Data Protection Agency has authorised storage of this data. After 31 December 2075, the biomaterial will be destroyed, and the data will be anonymised and transferred to the Danish National Archives. The sample material will be examined in collaboration with a number of approved partners in Denmark, DeCODE in Iceland, MGI in Latvia and with Professor Marcus Cooke in the USA. The Data Protection Act and the Processing of Personal Data Act (applicable Danish legislation) will be complied with when sending samples to collaboration partners. The samples will only ever be identified by an ID number (pseudo-anonymised) and collaborators do not have any rights over data or biomaterial

Genome data
The comprehensive mapping of your genetic material will be carried out by the Icelandic company deCODE following approval from the Research Ethics Committee and after signing an approved data sharing agreement. Data will therefore not be made available for external companies but will only be used for the project. The data analysis will be carried out in a closed environment using pseudo-anonymised data. Researchers will not be able to identify individual project participants when working with the data.

With your consent, we will also:
- request permission to register the following information on you from the consultation and from your patient record in a research database: Information on any prior fertility treatment, blood pressure, waist measurement and BMI.

- request permission to collect information from different registries: i.e. information concerning psychological and physical diseases from medical records, health registries and databases, and information about your education, social status and income from Statistics Denmark.

Benefits of the project
This project has great value for any couple who experience pregnancy loss. By participating in the research project, you will be contributing to our understanding of the mechanisms behind pregnancy loss. The results of this project will increase our ability to provide a diagnostic evaluation and possibly even treatment, thereby helping others in the same situation.
By participating in this study, we will provide you with the answer of the fetal chromosome test. In case we find reasons to refer you for further investigation or treatments, we will inform you and refer you. You will not be remunerated for taking part in the project. No circumstances will prevent you from participating in the project or cause the project to be discontinued.

Participation is voluntary
Participation in the project is voluntary. You may withdraw your consent to participate at any time without giving a reason and have your genetic material destroyed. If you withdraw from the project, we will store and use the data we have already analyzed, but all further data generation will be stopped from the time you withdraw your consent. Wihtdrawing will have no consequences for your future treatment. You are always welcome to contact the project's contact people for additional information (see below).

Financial information
Professor Henriette Svarre Nielsen and Professor Eva Hoffmann from the University of Copenhagen are the initiators of the research project. The project is primarily funded by the Novo Nordisk Foundation (25 mio. DKK). The Independent Research Council Denmark supported the project with 2 mio DKK. The project previously received a grant from the BioInnovation Insitute under Novo Nordisk of 18 mio. DKK. Preparation of the project was funded by Rigshospitalet's research fund (combined position for the research project initiator, Henriette Svarre Nielsen) and the Ole Kirk's Fund (DKK 1,034,000). None of the researchers in the project are financially linked with the grant-makers or other stakeholders in the project. The researchers will apply for funding from a number of public and private foundations on an ongoing basis.

Approvals
The research project has been notified to and approved by the health research ethics committees for the Capital Region of Denmark in protocol ref. H-18024745 and approved by the *Videnscenter for Dataanmeldelser* (data registration center) for the Capital Region of Denmark (P-2020-1019).

Access to results of the project
Once the project has been completed, you will be able to find information about the results of the project at www.graviditetstab.dk. The project is completed once samples from the last participant have been collected and we have analysed the data. We hope that this information has provided you with sufficient insight into what participation in this project involves, and we hope we have given you the best grounds on which to base your decision.

Sincerely,

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We encourage you to read the National Committee on Health Research Ethics paper on the rights of test subjects found at www.nvk.dk