**Title of the study**: Effect of hyaluronan-enriched transfer medium on the cumulative ongoing pregnancy rate: a prospective randomized trial

**Researcher:** Prof. Dr. Sophie Debrock, Gynaecology and Obstetrics Department, UZ Gasthuisberg hospital

**Research Institute:** Leuvens Universitair Fertiliteitscentrum (LUFC – Leuven University Fertility Centre), UZ Gasthuisberg, Herestraat 49, 3000 Leuven

**Medical Ethics Committee:** Ethische Commissie Onderzoek (Ethical Research Commission) UZ/KU Leuven

**Local investigators**: Mrs Annemie Mengels, Dr. Arne Vanhie and Prof. Dr. Karen Peeraer, UZ Leuven

## I Information vital to your decision to take part

### Introduction

We invite you to take part in a clinical study to evaluate the effect of hyaluronan-enriched transfer medium on the cumulative ongoing pregnancy rate.

Before you agree to take part in this study, we invite you to take note of its implications in terms of organisation, possible risks and benefits, to allow you to make a decision with full awareness of the implications. This is known as giving "informed consent".

Please read these few pages of information carefully and ask any questions you want to the investigator or his/her representative. There are 3 parts to this document: the information essential to your decision, your written consent and supplementary information (appendices) detailing certain aspects of the basic information.

### If you take part in this clinical study, you should be aware that:

- This clinical study is being conducted after having been reviewed by the ethical committee research UZ/KU Leuven.
- Your participation is voluntary and must remain free from any coercion. It requires the signature of a document expressing your consent. Even after consenting, you can withdraw from the study at any time by informing to the investigator. Your decision, whether or not to participate, will not have any impact on the quality of care and on the relationship with your treating physician(s). Your decision not to take part or to stop taking part in the study will have no impact on the quality of your care or on your relationship with the investigator.
- The data collected on this occasion are confidential and your anonymity is guaranteed during publication of the results.
- Insurance has been taken out in case you should suffer any damage related to your participation in this clinical study.
- You will not incur any charges for the visits/consultations, examinations or treatments specific to this study.
- You may contact the investigator or a member of his/her team at any time should you need any additional information.

Further information about your "Rights as a participant in a clinical study" can be found in part III.

### Objectives and description of the study protocol:

The transfer of an embryo into the uterus is one of the most important steps in IVF treatment. The ability of the embryo - that was selected for transfer - to implant in the uterus is still limited. To increase the success rates of IVF treatment is attempted in different ways.

The medium in which the embryo is cultured is important. Several studies have studied the addition of certain substantia that could promote adhesion of the embryo to the uterus, such as hyaluronan or hyaluronic acid. Some studies showed a positive effect of hyaluronan on the implantation rate, whereas other studies did not observe any improvement. A meta-analysis of all data obtained from randomized controlled trials did show a trend towards an increased chance of implantation and live birth when hyaluronan-enriched medium was used. However, only few well-designed studies are performed. Therefore, it was stated that more well-performed studies with a good scientific design are needed to demonstrate that the use of hyaluronan effectively contributes to increase success rates of IVF

treatment. This is why we want to conduct a study in the laboratory of the LUFC in which the use of hyaluronan will be tested.

In the laboratory of the LUFC, the medium used for the transfer is the same medium in which the embryos are cultured, namely "conventional culture medium". The same company also provides a hyaluronan-enriched transfer medium that we want to use to study if it can offer an added value for our patients.

In this study we want to investigate whether the chance of a live birth can be increased by transferring the embryo using "hyaluronan-enriched transfer medium" compared to "conventional culture medium".

Therefore, patients are randomly divided into two groups (randomization) via a specially designed computer program. You have a 50% chance of ending up in group 1 and a 50% chance of ending up in group 2:

- Group 1: You will receive an embryo transfer in "normal culture medium" in which the embryos are cultured.

- Group 2: You will receive an embryo transfer in "hyaluronan-enriched transfer medium". For this, the embryo is incubated in hyaluronan-enriched transfer medium in a dish in the laboratory before transfer. The embryo is then taken into the catheter and transferred into the uterus.

We want to assess whether the use of hyaluronan-enriched transfer medium can increase the cumulative ongoing pregnancy rate. To achieve this, all transfers from two consecutive fresh cycles (second and third participation or third and fourth participation) will be included, both the transfers of the fresh and thawed embryos.

The treatment is an additional treatment for the embryo to be transferred, without risk to the patient or the embryo.

To participate in the study, following inclusion criteria must be fulfilled:

- The second and third or third and fourth participation in the IVF / ICSI treatment;
- No ongoing pregnancy (at 12 weeks of pregnancy) in previous transfers;
- Age of the woman at first entry into the study is less than 40 years
- BMI <32
- You can participate in this study once

If you meet the above inclusion criteria and wish to participate, you will be randomized to one of the two groups. There are no other changes in your fertility treatment.

The study is designed as a double-blind study: this means that you and your gynaecologist will not know in which group you will end up. Only the laboratory will be informed because they need to know whether the embryos should be placed in conventional culture medium or in hyaluronan-enriched transfer medium for the embryo transfer. When all results are obtained, we will break the code and it will be checked who belongs to which group and whether there is an improvement. It is important to keep blinding until after processing the results because the results may be biased if it is known who belongs to which group.

Participation in the study does not entail extra costs.

## Risks and discomforts

The proposed fertility treatment and monitoring are in accordance with good medical practice. Any health risks associated with your participation are no higher than the health risks associated with the treatment you would normally receive. The treatment with hyaluronan-enriched transfer medium is an extra treatment for the embryo to be transferred, without risks for the embryo or the woman.

Your participation in this study will not give you any personal benefits.

## Withdrawal of your consent

Your participation is voluntary and you are entitled to withdraw from the study for any reason, without having to justify your decision.

If you withdraw your consent any data accrued up to the time of your withdrawal will be retained to guarantee the validity of the study. After withdrawal of your consent, no new data will be sent to the research organisation.

## Contact

If you need further information, but also if you have problems or concerns, you can contact the investigator Sophie Debrock by email: sophie.debrock@uzleuven.be or a member of his/her research team Hanne Boonen, Annemie Mengels en Dr. Arne Vanhie by email: hanne.boonen@student.kuleuven.be; annemie.mengels@uzleuven.be; arne.vanhie@uzleuven.be; karen.peeraer@uzleuven.be

Should you have questions relating to your rights as a participant in the study you can contact your hospital Ombudsman on: 016 34 48 18 or via ombudsdienst@uzleuven.be. If necessary the Ombudsman can put you in touch with the Ethics Committee.

Title of the study: Effect of hyaluronan-enriched medium on the cumulative ongoing pregnancy rate: a prospective randomized trial

## II Informed consent

### Participant

I hereby confirm that I have been informed of the nature, objective, duration, possible benefits and risks associated with the study and I am aware of what is expected of me. I have read and understood the information document and its appendices.

I have had ample time to consider and talk to someone of my choice, like my general practitioner or a family member.

I have been able to raise any questions I had and received a clear response to them.

I understand that I am participating in this study voluntarily and that I am at liberty to terminate my participation in this study without it having an adverse effect on my relationship with the therapeutic team that cares for my health.

I understand that during my participation in the study data will be collated about me and that the physician/researcher and client guarantee the confidentiality of this data in accordance with relevant Belgian legislation. I understand that the performance of this study by UZ Leuven serves the general interest and that the processing of my personal data is necessary for the performance of this study.

I have received a copy of the information for participants and the informed consent.

Surname, first name, date and signature of the participant

### Researcher

The undersigned, Sophie Debrock - Researcher, or colleague and authorized research assistant Hanne Boonen, Annemie Mengels, Dr. Arne Vanhie and Prof. Dr. Karen Peeraer, declares to have provided the participant with any necessary oral information concerning this study and a copy of the information document.

I confirm that the participant has in no way been coerced into agreeing to participate in the study and I am prepared to answer any additional questions that may arise.

I confirm that I operate in accordance with the ethical principles stipulated in the latest version of the "Declaration of Helsinki", "Good Clinical Practice" and the Belgian Act of 7 May 2004 pertaining to experiments on humans.

Surname, first name, date and signature of the researcher's representative

Surname, first name, date and signature of the representative of the researcher

Surname, first name, date and signature of the researcher

Title of the study: Effect of hyaluronan-enriched medium on the cumulative ongoing pregnancy rate: a prospective randomized trial

## III Additional Information

### 1. Additional information concerning the organisation of the study

Participation in the study will not require you to invest extra time.

### 2. Additional information concerning the risks associated with participation in the study

Not applicable.

### 3. Additional information concerning the protection and rights of participants in a clinical study

***Ethics Committees***

This study has been assessed and sanctioned by an independent ethics committee (UZ/KU Leuven Ethical Research Committee). Ethics committees provide protection for participants in clinical studies. They verify that your rights as patient and participant in a study are upheld and whether the study is scientifically relevant and ethically justified. Ethics committees make recommendations in this respect in accordance with the Belgian Act of 7 May 2004.

However, you should not consider a positive recommendation from the Ethics Committees as an incentive to participate in this study.

***Voluntary participation***

Please do not hesitate to raise any questions you might consider useful before signing. Take the time to talk about it with a counsellor if you feel this is necessary.

You are entitled not to participate, or to terminate your participation, in this study without having to give a reason for doing so, even if you consented to participate earlier. Your decision will in no way affect your relationship with the physician and/or the continuation of your therapeutic treatment.

If you agree to participate in this study you will have to sign a consent form. The physician/researcher will also sign the form and thus confirm that they have provided you with any necessary information about the study. You will be provided with your copy of the form.

***Expenses associated with your participation***

You will not be remunerated for participating in this study. However, you will not incur any additional costs as a result of participating in this study.

***Guaranteed confidentiality***

By participating in this study you agree to the physician/researcher collating data about you and the client using them for research purposes and for scientific and medical publications.

The processing of your personal data is necessary to achieve the scientific research purposes as set out herein. The conduct of scientific research is one of the core missions of UZ Leuven as defined by law. As a university hospital, part of KU Leuven, UZ Leuven is indeed required to support research and education in the public interest. We would therefore like to inform you that the necessity of the processing for the conduct of scientific research as a task of public interest constitutes the lawful basis on which we process your information in the context of the study in which you are participating. UZ Leuven is also subject to specific legal requirements which require the processing of your personal in the context of safety reporting (such as for example the notification of adverse events to the regulatory authorities).

Your data will be processed in accordance with the European General Data Protection Regulation (GDPR). UZ Leuven shall act as data controller for your data.

You are entitled to ask the physician/researcher which data they have gathered about you and for what purpose it will be used as part of the study. This data relates to your current clinical status as well as your medical pre-history and the results of analyses carried out for your health treatment in accordance with current care standards. You are entitled to access this data and have corrections implemented should it be incorrect[1].

The physician/researcher must treat any collated data in the strictest confidence. This means that they agree never to reveal your name in a publication or at a conference and that your data will be coded (your identity will be replaced with an identification code for the purpose of the study) before it is transmitted to the databank (Leuven university Fertility centre, UZ Leuven).

Throughout the entire clinical study the physician/researcher and their team will be the only people who will be able to make a connection between the transmitted data and your medical dossier[2]. Transmitted personal data shall not contain any combination of elements that might identify you[3].

The research data manager appointed by the client will not be able to identify you on the basis of the transmitted data. This person will be responsible for collating the data gathered by all physicians/researchers who are participating in the study and for processing and protecting the data in accordance with Belgian legislation concerning the protection of privacy.

To check the quality of the study your medical dossier may be accessed by people bound by professional confidentiality such as representatives from ethics committees, the client who commissioned the study or external audit agencies. This will be governed by stringent conditions and conducted under the responsibility and supervision of the physician/researcher (or one of their research assistants).

The (coded) research data may be transmitted to Belgian or other regulatory authorities, the ethics committees and other physicians and/or institutions that are collaborating with the client.

Your agreement to participate in this study consequently also indicates that you agree to your coded medical data being used for purposes described in this information form and transferred to the aforementioned individuals and/or institutions.

The client agrees to use the collated data solely for the purpose of this study.

If you withdraw your consent to take part in the study, to guarantee the validity of the research, the data encoded up to the point at which you withdraw will be retained. No new data may be sent to the sponsor. If you have any questions relating to how your data are being processed, you may contact the investigator. The data protection officer in your hospital can be contacted as well: DPO - UZ Leuven, Herestraat 49, 3000 Leuven, e-mail dpo@uzleuven.be.

Finally, if you have a complaint concerning the processing of your data, you can contact the Belgian supervisory authority who ensures that privacy is respected when personal data are processed.

The Belgian supervisory authority is called:
Data Protection Authority (DPA)
Drukpersstraat 35,
1000 Brussels
Tel. +32 2 274 48 00
e-mail: contact@apd-gba.be
Website: https://www.dataprotectionauthority.be

1 These rights are defined by the EU Regulation 2016/679 (General Data Protection Regulation (GDPR)) and the Act of 22 August 2002 concerning patient rights.

[2] The Law stipulates that for clinical studies this link with your dossier must be retained for a period of 20 years.

3 The database containing the results of the study shall consequently not include any elements such as your initials, gender or full date of birth (dd/mm/yyyy).

***Insurance***

A potential risk here is, for example, a problem with the measures imposed to protect the confidentiality of your personal data. Even if not at fault, the client shall be responsible for any damage you, the participant, - or in the event of death your next of kin – may suffer, which is the direct or indirect result of participation in this study. The client has taken out insurance cover specifically for this purpose[4].

If the physician/researcher feels that there might be a potential link with the study (there shall be no link with the study in the event of damage as a result of the natural progression of your disease or known side effects of your standard treatment), they shall notify the client who commissioned the study, who will initiate the insurance notification procedure. If they consider it necessary, the insurers will appoint an expert to make a judgment on the link between your new health complaints and the study.

In the event of a dispute with the physician/researcher or the expert appointed by the insurers, and always if you consider this necessary, you or in the event of your death your next of kin will be able to summon the insurers directly in Belgium (Insurers: Amlin Europe via Vanbreda Risks & Benefits NV, contract number: 299.053.700; contact data: Vanbreda Risks & Benefits NV, Plantin en Moretuslei 297, 2140 Antwerp).

The Law stipulates that the summons of the insurers can be executed either before the judge in the location where the damaging events took place or before the judge in your location or before the judge in the location of the insurer's registered offices.

4 In accordance with article 29 of Belgian Law on experiments on humans (7 May 2004)