I. Information vital to your decision to take part

Introduction

You are being invited to take part in a clinical study to evaluate an investigational medical intervention for the enhancement of your IVF cycle outcome.

The investigators hope that this intervention may offer advantages in the treatment of patients undergoing IVF. There is, however, no guarantee that you will benefit from taking part in this study.

Before you agree to take part in this study, we invite you to take note of its implications in terms of organization, 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 investigators or his/her representative. There are three 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 UZ Brussel Ethics committee.
- Your participation is voluntary and must remain free from any coercion. It requires the signature of a document expressing your consent. Even after having signed this document, you can stop taking part by informing the investigators. 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 investigators.
- 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 in connection with 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 investigators or a member of their 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 Appendix 2.

Objectives and description of the study protocol

We are inviting you to be a volunteer in the clinical trial Receptivity Enhancement by Follicular-phase Renewal after Endometrial Scratching (REFRESH Trial) that is to include around 360 patients.

The main objective of this trial is to assess the effect of endometrial repair following a biopsy of the endometrium during IVF on pregnancy rates. Furthermore, we would like to further assess these biopsies to determine if there are any specific characteristics of the endometrium which could help physicians predict IVF outcome prior to embryo transfer. The inclusion/exclusion criteria may found in Appendix 1.

This study is a randomized controlled trial. Accepting participants will be randomly allocated to one of two study groups: control group and intervention group. Women in control group will perform their regularly planned IVF with no changes in treatment while participants in the intervention group will additionally undergo an endometrial biopsy on the sixth to eighth day of ovarian stimulation. An endometrial biopsy is the collection of a small portion of cells from the internal uterine lining (the endometrium) using a sterile-packaged medical device (Pipelle de Cornier®, CCD International, Paris).

Besides the biopsy previously described for patients in the intervention group, all participants of this study will undergo an otherwise regular IVF cycle. The ovarian stimulation, ultrasound/hormonal monitoring, ovulation induction, oocyte retrieval, embryology procedure and choice of medications will be performed according to how they are normally executed in the CRG.

Treating physicians will decide on which ovarian stimulation should be used according to the patient’s profile and preference. Ovulation will be artificially triggered with either human menopausal hCG (Pregnyl®) or recombinant hCG (Ovitrelle®, Gonasi®) when more than two follicles of ≥17 mm are present. Oocyte retrieval will be performed ~36 h after triggering.

IVF or IVF–ICSI will be performed, using the specimen of sperm made available by the male progenitor on the day of oocyte retrieval. According to embryo quality, embryo transfer to the uterine cavity will be performed on either the third or fifth day of development under ultrasound guidance whenever possible. Following embryo transfer, luteal support will be provided with vaginally administered progesterone (Utrogestan®, Crinone®).

Course of the study

Participation in this study will not alter the general duration of your IVF cycle. We consider you as a participant in this study until your cycle is decided to withdraw from this study. As your cycle progresses, you will be monitored closely to assess ovarian response and the existence of any potential complications.
The duration of your participation varies according to your IVF outcome. If, after ~2 weeks following embryo transfer, your pregnancy test is negative, your participation will cease at that time. If, on the other hand, you become pregnant your participation will cease as soon as you deliver or if you suffer an abortion (which can both occur up to 41 weeks after embryo transfer).

NOTE: cycle cancellation is defined as any interruption of the IVF cycle that occurs before fresh embryo transfer. Cycle cancellation will occur (i) upon your request, (ii) if inadequate follicular development occurs and (iii) if no embryo is available for transfer.

Risks and discomforts

Women in the control group have no additional risks when participating in this study.

Women in the intervention group will undergo an endometrial biopsy during ovarian stimulation using a sterile-packaged medical device (Pipelle de Cornier®, CCD International, Paris, France) that complies with Directive 93/42/EEC. This device is routinely used in the CRG for endometrial sampling. The procedure is usually painless and otherwise inoffensive, requiring no pre- or post-medication. Slight uterine bleeding that subsides spontaneously is rare but can be seen after endometrial biopsy

Notification of new information

Occasionally, during a research project, new information on the treatment becomes available. If this occurs, you will be informed of any new information which may affect your decision to continue to participate in this study.

In this case, you will be asked to sign either an addendum to the consent form or a new informed consent form. If, in the light of the new information, you decide to stop taking part in the study, the investigators will see to it that you continue to receive the best possible treatment.

Benefits

If you agree to take part in this study, the use of induced endometrial injury/repair may or may not prove beneficial in treating your disease or relieving your symptoms.

To obtain a live-birth following IVF, an intricate series of steps have to successfully occur. Amongst these is implantation, when the embryo is embedded in the uterus lining. Although this process has been extensively studied, the mechanisms entailed remain largely a mystery.

In the absence of implantation, endometrial breakdown (menstruation) will ultimately occur. This ‘reset’ will prepare the endometrium for a new potential implantation. The similarity between this physiologic process and the mechanisms involved in the repair of endometrial injury raises the question if artificially induced endometrial injury and repair may have any effect on implantation.

The 14 out of 15 of the published studies on this topic have concluded that induced endometrial repair is associated with a doubling of pregnancy rates in both the ‘general IVF’ population and patients with a history of implantation failure. Nonetheless, these studies varied extremely in terms of methodology (namely, endometrial injury was performed either before or during ovarian stimulation) and require further confirmation in a randomised controlled trial similar to the one being proposed to you. The remaining trial found that endometrial injury performed after ovarian stimulation (on the day of oocyte retrieval, 2 days before embryo transfer) was detrimental for pregnancy rates. However, this will not be the case of this trial, as the biopsies are planned to occur during ovarian stimulation.

The information obtained thanks to this study may contribute to a better knowledge of the use of this medical intervention or to the development of a new medical device for the treatment of infertility in future patients.

In summary, your participation in this study will help us understand better if induced endometrial injury can counteract the negative effects of ovarian stimulation by ‘resetting’ the timing of the window of implantation. Furthermore, we will be able to study your uterine lining during ovarian stimulation and assess if any variations can potentially predict situations in which embryo transfer should be postponed due to hampered endometrial receptivity.

Withdrawal from the study

Your participation is voluntary and you are entitled to withdraw from the study for any reason, without having to justify your decision. Nevertheless, it may be useful for the investigators of the study to know if you are withdrawing because the constraints of the treatment are too great (too many uncomfortable side effects, for example).

It is also possible that the investigators withdraw you from the study because they consider it is better for your health or because they find out that you are not following the instructions given to participants.

Finally, the competent national or international authorities, the ethics committee that initially approved the study or the investigators may break off the study because the information gathered shows that the investigational treatment is not effective (does not deliver a sufficient level of improvement in the IVF cycle outcome), the investigational treatment causes more side effects or more serious side effects than anticipated, or for any other reason, such as, for example, the decision to stop research and development of the medical intervention.

Treatment after stopping the study

In all these situations of withdrawing from the study, but also when the scheduled participation period has ended, the investigators will assess your state of health and prescribe the best treatment available.

Samples of biological material collected during the study

1) Samples collected for the analyses described for the study in this document

   Since technical progress in this area is constant, if you agree, we would like to retain the surplus of your samples of biological material for 5 years for future studies in the context of the present clinical research, namely a better understanding of the endometrial receptivity and its potential treatment. Any research outside the context described in this document may only be conducted with the approval of an ethics committee.

If you take part in this clinical study, we ask you:

- To cooperate fully in the smooth running of this study.
- Not to conceal any information relating to your state of health, the medication you are taking or the symptoms you are experiencing.
You should also be aware that:
For your safety, it is advisable for your GP, if you have one, or other specialists in charge of your health to be informed of your participation in this study. We will ask you to confirm your agreement, but will respect your wish not to inform them where applicable.

Contact
If you need further information, but also if you have problems or concerns, you can contact the investigators Samuel dos Santos Ribeiro or Shari Mackens on the following telephone number (02/477.66.99)

If you have any questions relating to your rights as a participant in a clinical study, you can also contact the patient rights ombudsman of our institution. If necessary, they can put you in contact with the ethics committee.

II. Informed consent

Participant
I declare that I have been informed of the nature of the study, its purpose, its duration, any risks and benefits and what is expected of me. I have taken note of the information document and the appendices to this document.

I have had sufficient time to think about it and discuss it with a person of my choice, such as my GP or a member of my family.

I have had the opportunity to ask any questions that came to mind and have obtained a satisfactory response to my questions.

I understand that my participation in this study is voluntary and that I am free to end my participation in this study without this affecting my relationship with the therapeutic team in charge of my health.

I understand that data about me will be collected throughout my participation in this study and that the investigators of the study will guarantee the confidentiality of these data.

I agree to my personal data being processed as described in the section dealing with confidentiality guarantees (Appendix 2).

I agree to the study data collected for the purposes of this study being processed at a later date provided this processing is limited to the context of the present study for a better understanding of the disease and its treatment.

I agree to the investigators retaining samples of biological material collected during the study for 5 years for subsequent research purposes but limited to the context of the present study.

I agree/do not agree (please circle the appropriate option) to my GP or other specialists in charge of my health being informed of my participation in this clinical study.

I have received a copy of the information to the participant and the informed consent form.

Surname, first name, date and signature of the volunteer.

Witness/Interpreter
I was present during the entire process of informing the patient and I confirm that the information on the objectives and procedures of the study was adequately provided, that the participant apparently understood the study and that consent to participate in the study was freely given.

Surname, first name and qualification of the witness/interpreter:
Date and signature of the witness/interpreter.

Investigator
I, the undersigned, _________investigator/clinical study assistant, confirm that I have verbally provided the necessary information about the study and have given the participant a copy of the information document.

I confirm that no pressure was applied to persuade the patient to agree to take part in the study and that I am willing to answer any additional questions if required.

I confirm that I operate in accordance with the ethical principles set out in the latest version of the ‘Helsinki Declaration’, the ‘Good Clinical Practices’ and the Belgian Law of 7 May 2004 related to experiments on humans.

Surname, first name, date and signature of the investigator
Surname, first name, date and signature of the investigator’s representative

III. Supplementary information

I: Supplementary information on the organization of the study
Summarily, women undergoing ovarian stimulation for IVF will be included in either the control or intervention groups (Supplementary Fig. S1). Women in the intervention group will additionally undergo an endometrial biopsy during the early follicular phase, on the sixth to eighth day of stimulation.

The criteria for inclusion and exclusion for this trial are listed in Supplementary Table S1.

2: Supplementary information on the protection and the rights of the participant in a clinical study

Ethics Committee
This study has been reviewed by an independent Ethics Committee, namely the Ethics Committee of UZ Brussel, which has issued a favourable opinion. It is the task of the Ethics Committees to protect people who take part in a clinical trial. They make sure that your rights as a patient and as a participant in a clinical study are respected, that based on current knowledge, the balance between risks and benefits remains favourable to the participants, that the study is scientifically relevant and ethical. You should not under any circumstances take the favourable opinion of the Ethics Committee as an incentive to take part in this study.

Voluntary participation
Before signing, do not hesitate to ask any questions you feel are appropriate. Take the time to discuss matters with a trusted person if you so wish.
Your participation in the study is voluntary and must remain free of any coercion: this means that you have the right not to take part in the study or to withdraw without giving a reason, even if you previously agreed to take part. Your decision will not affect your relationship with the investigators or the quality of your future therapeutic care.

However, it is advisable for your safety to inform the investigators if you have decided to stop taking part in the study.

If you agree to take part, you will sign the informed consent form. The investigators will also sign this form to confirm that he/she has provided you with the necessary information about the study. You will receive a copy of the form.

Costs associated with your participation
All research expenses exclusively related to the research protocol in the intervention group (in other words, the endometrial biopsy device and endometrial biopsy analysis) are paid by the UZ Brussel.

If you decide to take part in this study, this will not therefore involve any extra costs for you or your insurer. You may only be charged for the costs corresponding to the standard medical care in your clinical situation.

Guarantee of confidentiality
Your participation in the study means that you agree to the investigator collecting data about you and using these data for research purposes and in connection with scientific and medical publications.

You are entitled to ask the investigator what data are being collected about you and what is their use in connection with the study. This data concerns your current clinical situation but also some of your background, the results of examinations carried out within the context of care of your health in accordance with the current standards and obviously the results of examinations required by the protocol.

You have the right to inspect these data and correct them if they are incorrect (These rights are guaranteed by the Law of 8 December 1992 on the protection of privacy in relation to the processing of personal data and by the Law of 22 August 2002 on patient rights).

The investigators have a duty of confidentiality vis-à-vis the data collected.

This means that they undertake not only never to reveal your name in the context of a publication or conference but also that they will encode

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**Supplementary Table S1** Study criteria.

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| • Women aged ≥18 and <40 years                                                    | • Other known reasons for impaired implantation                                     |
| • Fresh IVF/IVF–ICSI cycle                                                        | • Oocyte donation acceptors                                                        |
| • Antagonist down-regulation                                                       | • Frozen egg transfers                                                             |
| • Signed informed consent                                                          | • Embryos planned to undergo biopsy                                                |
| • Body mass index >35 or <18                                                       | • Women already recruited for another trial on medically assisted procreation during the same cycle |
| • Women who have previously enrolled in the trial                                 | • Those unable to comprehend the investigational nature of the proposed study      |

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**Supplementary Figure S1** Study design.
(your identity will be replaced by an ID code in the study) your data before sending them to the manager of the database of collected data.

The investigators and their team will therefore be the only ones to be able to establish a link between the data transmitted throughout the study and your medical records (For clinical trials, the law requires this link with your records to be retained for 20 years. In the case of an advanced therapy medicinal product using human biological material, this period will be a minimum of 30 years and a maximum of 50 years in accordance with the Belgian Law of 19 December 2008 on the use of human biological material and the applicable royal decrees.).

The personal data transmitted will not contain any combination of elements that might allow you to be identified (The database containing the results of the study will therefore not contain any combination of elements such as your initials, your gender and your full date of birth (dd/mm/yyyy)).

To verify the quality of the study, it is possible that your medical records will be examined by persons subject to professional secrecy and designated by the ethics committee or an independent audit body. In any event, this examination of your medical records may only take place under the responsibility of the investigators and under the supervision of one of the collaborators designated by him/her.

The (encoded) study data will be able to be sent to Belgian or other regulatory authorities, to the relevant ethics committees, to other Belgian doctors and/or to organizations working in collaboration with the investigators.

Your consent to take part in this study therefore also implies your consent to the use of your encoded medical data for the purposes described in this information form and to their transmission to the aforementioned people and authorities.

The investigators will use the data collected within the context of the study in which you are taking part, but would also like to be able to use them in connection with other research concerning the same disease as yours. Any use of your data outside the context described in this document is only possible with the approval of the ethics committee.

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.

Future of your sample(s) collected during the study
The sample encoding procedure is the same as that used for your medical data. Samples will therefore only include your study ID code.

The manager of these samples (the CRG) undertakes to use them within the context of clinical research and to destroy them at the end of the scheduled storage period.

The sample of biological material taken is deemed to be a ‘donation’ and you should be aware that, in principle, you will not receive any financial benefit (royalties) associated with the development of new therapies derived from the use of your donation of biological material and which may be of commercial value.

If you withdraw your consent to take part in the study, you may contact the investigators and have those of your samples that have not yet been used destroyed. The results obtained from your samples before you withdraw your consent remain the property of the study investigators.

Insurance
Any participation in a clinical study involves a risk, however small it is. Even if there is no fault, the CRG accepts responsibility for damage caused to the participant (or in the event of death, his/her dependants) and directly or indirectly linked to his/her participation in the study. The CRG has taken out insurance for this responsibility (In accordance with Article 29 of the Belgian Law related to experiments on humans (7 May 2004)).

In the event of disagreement either with the investigators or with the expert appointed by the insurance company and also whenever you feel it is appropriate, you or—in case of death—your dependants may bring proceedings against the insurer directly in Belgium.

The law provides that the insurer may be summoned to appear either before the judge of the location where the event giving rise to the damage occurred, or before the judge of your domicile, or before the judge of the insurer’s registered offices.