Dear Sir/Madam,

As patient of the Centre for Reproductive Medicine (CRG) of UZ Brussel you have called on our expertise in the treatment of fertility problems. We sincerely hope that we will be able to help you fulfil your wish to have a child.

Since its creation in 1983, our centre has been driven by two strong engines: clinical practice, which is all about the patient, and (scientific) laboratory work, which supports and strengthens clinical practice. Thanks to this powerful combination, the CRG - often together with the CMG, the Medical Genetics Department of UZ Brussel - has achieved several breakthroughs in the high-tech field of fertility medicine.

For medical progress, continuous scientific research is needed. However, such research is not possible without the contribution of patients who are prepared to donate supernumerary reproductive material (eggs, sperm, embryos).

The aim of this supplement is to give you all the necessary information based on which you can then decide to donate any material for scientific research.

We hope that this information will help you reach a positive decision regarding the donation of supernumerary gametes and/or embryos for scientific research.

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Responsible for the biobank and co-ordinator of the scientific research in the ART lab

I. Scientific research
These are the five domains.
Domain A – Laboratory techniques
Domain B – Embryonic development and implantation of the embryo in the uterus
Domain C – Genetic state of the embryo
Domain D – Embryonic stem cell research
Domain E – Genome modification

II. Training of laboratory staff
By ticking this option, you give us the opportunity to provide proper high-quality training to laboratory staff to perform difficult techniques, such as the micro-injection of eggs, embryo biopsy (the removal of a cell or a little material from embryos) and the freezing and thawing of gametes and embryos.
Domain A – Laboratory techniques
WHAT ARE YOUR RIGHTS AS A DONOR OF GAMETES AND/OR EMBRYOS?

> Donation of supernumerary gametes and/or embryos is voluntary. You are entitled to refuse to donate supernumerary gametes and/or embryos for scientific research. It will neither increase nor reduce your chances of success and your decision will have no effect on your subsequent treatment.

> Donating gametes and/or embryos does not result in any financial benefit, nor does it entail any additional cost.

> If you have consented to the use of your supernumerary gametes and/or embryos for scientific research or training purposes, you can still withdraw your consent before the research or training begins.

> If you are a couple, this withdrawal is valid if requested by either of you.

> You must inform us of your decision to withdraw your consent in a written, signed document.

> In accordance with the Belgian law of 8 December 1992 and the Belgian Law of 22 August 2002, we respect your personal privacy. You can be assured – this applies to both partners in the couple – that your name/names and other personal data will be kept strictly confidential. The research material is encoded to ensure your personal and clinical data are not disclosed to the researcher. In this way the research results cannot be linked to your file and your anonymity is guaranteed if we publish the results of a study.

> By consenting to the use of your supernumerary gametes and/or embryos for scientific research you are simultaneously consenting to the possible application for a patent for inventions that may result from the scientific research to which you have consented. You fully understand this and waive all claims to any compensation.

WHAT ARE THE REQUIREMENTS FOR SCIENTIFIC RESEARCH?

Most countries have strict laws on the use of human tissue and human embryos for scientific research. In Belgium this is governed by the law on research performed on embryos in vitro of 11 May 2003, published in the Official Gazette on 28 May 2003.

This law stipulates the following (research) actions are prohibited.

> The implantation of human embryos into animals or the creation of chimeras.

> The implantation in humans of any embryos that have been used in research, except where the research was carried out with a therapeutic intent for the embryo itself or in the case of an observation method that does not harm the integrity of the embryo.

> The use of embryos, gametes or embryonic stem cells for commercial purposes.

> Conducting research or developing treatments aimed at the selection or improvement of non-pathological genetic characteristics for the human race.

> Conducting research or treatments for the purpose of gender selection, except for the purpose of preventing gender related diseases.

> Cloning of human reproductive tissue.

> Conducting research on embryos after the first 14 days of development, not including the period when frozen.

In addition, scientific research must meet the following conditions.

> It has a therapeutic purpose or contributes to a better knowledge of (in)fertility, the transplantation of organs and tissues, the prevention or treatment of diseases.

> It is supported by the latest scientific findings and meets all methodological requirements of scientific research.

> It is conducted in or under the supervision of a certified laboratory associated with a university care programme for reproductive medicine or human genetics.

> It is conducted under appropriate technical and material conditions and under the supervision of qualified people.

These conditions are based on the guidelines for Good Clinical Practice of the ICH, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. These guidelines are included in the Declaration of Helsinki on the protection of individuals participating in clinical studies.

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2 Chimeras or hybrids are creatures made up of cells of different creatures.
INFORMATION ON THE USE OF SUPERNUMERARY GAMETES AND EMBRYOS FOR SCIENTIFIC RESEARCH AND TRAINING PURPOSES

SCIENTIFIC RESEARCH AT THE UZ BRUSSEL CRG

It goes without saying that scientific research at UZ Brussel meets all the requirements of the specified law and that all studies are carried out in accordance with the guidelines of the ICH/GCP (see above). Moreover, every research protocol for which human gametes or embryos can be used has received a favourable recommendation before the research begins from the two authorised committees in this area:
> the Medical Ethics Committee of UZ Brussel (LCE) and
> the Federal Commission for Medical and Scientific Research on Embryos in vitro (FCE).

In most cases the research that we describe here is conducted by scientific staff at the CRG laboratories. However, we also collaborate with other researchers.
> Genetic research mostly takes place in the laboratories of the Centre for Medical Genetics (CMG) of UZ Brussel, for example. Together, the CMG and CRG make up the PGT clinic, where we try – by testing the embryos genetically before they are transferred to the prospective mother's womb – to help couples with genetic problems to have a child free of the genetic defect.
> We also work with the Human Stem Cell laboratory (hESC lab) and with the REGE, REIM, FOBI and BITE research groups of the Vrije Universiteit Brussel (VUB).

WHICH GAMETES AND EMBRYOS?

Gametes and embryos that become available for scientific research may come from two sources.
> From a donor who donates (part of) the reproductive material he or she has donated as part of a donation programme for scientific research.
> From prospective parents who are undergoing fertility treatment with a view to fulfilling their desire to have a child. During the course of their treatment they may choose to donate supernumerary material for scientific research or training purposes.

The different types gametes and embryos that may be donated for scientific research are listed below. You will find the numbers set out in this list below at the end of the description of each type of research. You can then work out the types of tissue that are used in the various types of research.

1. Gametes

1a – Eggs that cannot be used for IVF or ICSI because they have failed to reach the appropriate stage of maturation.
1b – Eggs that cannot be fertilised during the treatment cycle and for which cryopreservation is not an option.
Eggs may be impossible to fertilise in the IVF laboratory, the partner’s ejaculate or testicular biopsy tissue has not yielded any sperm and when the use of donor sperm is not an option for the couple.
1c – Eggs made available by donors.
1d – Eggs which have been frozen in the context of ART treatment and are donated for scientific research after their predefined storage period.
1e – Sperm left over after IVF or ICSI.
1f – Testicular tissue.
1g – Sperm provided by donors.
1h – Sperm frozen in the context of ART treatment and donated for scientific research after the predetermined storage period.

If eggs are donated for research they can be used to create embryos using sperm from a consenting donor. This is only done if the aim of the research can only be achieved by creating embryos and subject to specific permission of the FCE.

2. Embryos

2a – Embryos originating from abnormally fertilised eggs. These therefore cannot be transferred to the uterus.
2b – Embryos of insufficient quality to be transferred to the uterus or cryopreserved.
2c – Embryos that have been genetically tested in the context of a PGT treatment of the prospective parents and have been found to have a genetic defect.
2d – Embryos frozen as part of ART treatment and then donated for scientific research after the predefined storage period.
2e – Fresh embryos of prospective parents who chose not to have their remaining embryos frozen.

Embryos are cultured in the laboratory no later than day 14 and are destroyed by the research technique.

3 IVF or in vitro fertilisation: the traditional method involves placing the eggs in a laboratory dish where they are brought into contact with a large (but selected) quantity of sperm. ‘In vitro’ literally means ‘in glass’
4 In ICSI or intracytoplasmic sperm injection, we inject a single sperm into each egg – once again this takes place in a dish in the laboratory.
5 In male infertility we sometimes try to collect sperm from a piece of tissue which we surgically remove from the testis or epididymis (a biopsy).
6 PGT or pre-implantation genetic testing means that we genetically examine embryos before they are eligible for transfer to the uterus.
WHAT SCIENTIFIC RESEARCH?
Below is a brief description of the scientific projects the CRG is involved in and in which we use human gametes and/or embryos.

Domain A – Laboratory techniques
Research material: 1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 2a, 2b, 2c, 2d, 2e
This domain is about the research in itself, but also includes the training of laboratory staff. The aim is to improve existing techniques in the fertility clinic and to develop and validate new procedures in the following sub-domains.
> Laboratory techniques to fertilise an egg outside the body (IVF and ICSI).
> Conditions under which embryos grow well outside the body.
> The best way to freeze and store embryos.
> The technique to remove a few cells from the embryo for genetic diagnosis (embryobiopsy).
> The refinement and fine-tuning of existing techniques to check DNA mutations, hereditary disorders and chromosomal abnormalities in embryos.

Domain B – Embryonic development and implantation of the embryo in the uterus
Embryonic development starts when the egg is fertilised by a sperm cell. A fertilised egg develops into a multicellular embryo, a morula and a blastocyst.
Research into embryonic development and implantation in vitro is aimed at understanding why embryos grow poorly or do not implant. Our aim is a better understanding of the function of the genes and proteins that play a crucial role in early embryonic development.
We hope this will lead to better diagnosis and treatment of couples with fertility problems.

Project 16 – Investigation of trophectoderm regulators playing a role in human embryo implantation
ADV080 – LCE (BUN 143201939165, permit 6/03/2019)
FCE (permit 29/04/2019, completion date 29/04/2024)
Research material: 1a, 1b, 1c, 1d, 1e, 1f, 1g, 2a, 2b, 2c, 2d, 2e
Project 16 focuses on the implantation of the embryo. In humans, the implantation mechanisms are not well known, which means that implantation failure is the main limiting factor in an IVF programme.
In this crucial stage in human reproduction – on day seven after ovulation – the embryo and the endometrium must interact perfectly. The process – for which both the embryo and the endometrium have to be optimally prepared – consists of three steps.
> Apposition, i.e. the initial loose attachment between the embryo and the endometrium.
> Adhesion, or the stronger attachment of the embryo to the endometrium.
> Invasion, when the embryo penetrates the endometrium.

To gain a better understanding of implantation, and implantation failure in particular, an in vitro model for implantation in humans has been set up. Human embryos are grown in the presence of human endometrial cell lines or biopsies.
Using molecular biological techniques and a microscope, we examine the role played by adhesion molecules, growth factors, hormones and the immune system during the three phases of implantation.
By fostering or preventing implantation in vitro, we hope to discern the factors that play a crucial role. In this way we hope to understand the causes of implantation failure and recurrent miscarriage.

Project 20 – Signalling pathways controlling trophectoderm lineage differentiation in early human embryos
AdV059 – LCE (BUN 143201526417, permit 9/12/2015)
FCE (permit 24/02/2016, completion date 24/02/2021)
Research material: 1a, 1b, 1c, 1d, 1g, 2a, 2b, 2c, 2d, 2e
Embryos can be created for this project.
Project 20 focuses on the early differentiation processes that take place in the embryo before, during and just after implantation.
The information on when and the mechanism by which the cells of the embryo will differentiate teaches us how the first differentiation – to placental tissue – and the second differentiation – to yolk sac – takes place in humans.
We also do research into the capacity of the cells to further develop into a complete embryo.
This research can help us understand why some embryos do not develop properly and do not lead to pregnancy.
Finally, we will grow stem cells from some embryos. These, in turn, will be used for stem cell biology research to find out more about the origin of embryonic stem cells in the embryo.
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Project 21 – Impact of maternal decidualisation on human blastocyst development
AdV066 – LCE (BUN 143201629028, permit 10/08/2016)
FCE (permit 19/09/2016, completion date 18/09/2021)
Research material: 2a, 2b, 2c, 2d, 2e
In project 21 we also try to broaden and deepen our knowledge about implantation in humans. More specifically, we research the communication between the embryo and the endometrium at the moment of implantation.
This communication is two-way and it is important to understand the role of both actors. Embryos are exposed to factors created by endometrial cells during different phases of the menstrual cycle and the effect on their development is examined. At the same time we also examine the factors that the embryos themselves create in response to the endometrium.

Domain C – Genetic state of the embryo
This domain studies techniques to examine the DNA of embryos before they are returned to the uterus.
The best-known application is pre-implantation genetic testing (PGT), in which we remove a few cells or a little tissue from the embryo for analysis in the lab.
There are two main reasons to genetically examine embryos.
> To prevent embryos with a genetic disorder from being transferred in a fertility treatment.
> To find out which genes play a role in embryonic development and implantation.

Project 22 – The search for the origin of chromosomal abnormalities in human preimplantation embryos
AdV069 – LCE (BUN 143201628722, permit 15/06/2016)
FCE (permit 24/10/2016, completion date 23/10/2021)
Research material: 1b, 1c, 1d, 1e, 1g, 1h, 2c, 2d, 2e
Embryos can be created for this project.

Through many years of research into embryos resulting from in vitro fertilisation, we know that many of them – up to half – have abnormal chromosomes. Most embryos with chromosome abnormalities fail to survive after being transferred to the uterus. Even after years of research we still don’t know the causes of these abnormalities. Project 22 tries to do something about this.

Thanks to the recent development of powerful new methods to look into our genome and because embryos remain in culture in the laboratory longer, we have discovered a number of things. We now know that on day five less embryos have chromosomal abnormalities than on day three. It is as if after day three embryos are able to correct the errors in their chromosomes.
We now also know that some embryos with normal chromosomes are unable to implant in the uterus, and some embryos with chromosomal abnormalities do result in a healthy pregnancy and baby. But we don’t know why this is. We expect the answers lie in the embryos’ genome.
The latest genetic technologies allow us to fully analyse the embryo’s genome, both in terms of the chromosomes and the proteins that are expressed. Moreover, strongly developed IT processes make it possible to integrate all these different elements – the chromosomes and proteins, epigenetics, the mitochondria, new mutations, etc. – and to obtain an overall picture of the embryo’s genome status.
In this project we want to study the interaction between the genome (chromosomes) and the transcriptome (proteins) in the embryos during the whole period preceding implantation, i.e. from the single-cell stage up to and including the stage of the blastocyst. In addition, from day four we want to study how abnormal cells are eliminated by the embryo.
Ultimately this will result in much higher prediction scores as to which embryos will develop into healthy babies, and which ones won’t.

Project 23 – The origin of mitochondrial DNA mosaicisms in human embryonic development
AdV076 – LCE (BUN 143201731657, permit 7/06/2017)
FCE (permit 26/02/2018, completion date 26/02/2023)
Research material: 2b, 2c, 2d, 2e

Mitochondria are the components in our cells responsible for the production of energy. They have their own DNA. Mutations in mitochondrial DNA can not only lead to hereditary disorders, but play an important role in our general state of health and ageing process.
Project 23 studies the possible differences in the mitochondrial DNA of each cell of the same embryo. The aim is to determine whether different cell lines develop during early development with different mutations in the mitochondrial DNA and when this happens.

7 By ‘epigenetic’ we mean genetic characteristics or disorders that may also be caused by external circumstances and not by genetic transmission alone.
INFORMATION ON THE USE OF SUPERNUMERARY GAMETES AND EMBRYOS FOR SCIENTIFIC RESEARCH AND TRAINING PURPOSES

Project 24 – The mitochondrial genome in the oocytes and granulosa cells of ART patients
LCE (BUN 143201939997, permit 24/04/2019, completion date 24/04/2023)
Research material: 1a, 1b
The aim of project 24 is to determine whether there are differences in the mutations in eggs of women who need fertility treatment for different reasons. Our hypothesis is that the eggs of women with an unknown reason for infertility carry more mutations than those of fertile women. To study this, we mapped the complete mitochondrial DNA of both the eggs and the granulosa cells surrounding the egg.

Domain D – Embryonic stem cell research
A human embryo of about five days old (the blastocyst) contains unique stem cells that, under certain conditions, can develop into any type of cell in the human body, such as nerve cells, muscle cells, blood cells, eggs and sperm.
This research wants to investigate whether these stem cells can be used in the future to replace damaged cells in diseases such as Parkinson’s, heart failure and diabetes.

Domain E – Genome modification
The aim of this research is to determine whether it is possible to modify the DNA of a human embryo safely and efficiently. This can be useful for two reasons.
> To avoid serious diseases by correcting the gene responsible for the disease.
> To conduct scientific research on genes that play a crucial role in early embryonic development. We do this by eliminating them and studying their effects on embryonic development.