



# THE FERTILITY DEPARTMENT

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THE FERTILITY CLINIC AND  
LABORATORY OF REPRODUCTIVE BIOLOGY



Rigshospitalet



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# PREFACE

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This booklet presents an overview of our activities at the Fertility Department in 2020. In Denmark 2020 one in ten children is conceived after fertility treatment and is like many parts of the world facing huge fertility challenges. The reasons behind this are numerous and include reproductive diseases in combination with societal, educational, cultural and behavioral factors and postponement of family formation.

The Fertility Department offers assisted reproduction to women and men with reproductive, genetic and infectious diseases. Further, we treat single women and women with a female partner and offers fertility preservation to patients at high risk of early loss of reproductive function. However, our activities go beyond this and covers also high level clinical, epidemiological and basic science, education, training, prevention, communication and collaboration with patients, colleagues, the general population,

media, politicians and others interested in human reproduction.

For parents, to have children is the most important thing to happen in their life. For patients suffering from infertility assisted reproduction is their chance of having a family. At the Fertility Department high standard fertility care goes hand in hand with empathy and understanding of the difficult situation that the infertile patients faces. Fortunately, we can assist most of our patients in fulfilling their wish for a child.

We would like to take this opportunity to acknowledge the professionalism and dedication from everyone working at the Fertility Department – the team effort is a huge part of what makes us unique. We would also like to thank our national and international collaborators and express our gratitude to everyone who have funded the research at the Fertility Department at Rigshospitalet.

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# OUR VISION

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The strategic goals of the Fertility Department can be divided into the three main areas, 1) world class fertility diagnostics and treatments covering all areas of reproductive medicine, 2) internationally high-class research and 3) education and initiatives targeting prevention of reproductive diseases.

The ambition of the Fertility Departments is to maintain a high degree of visibility and presence in both the international professional reproductive environments, the general public, and to strengthen national and international collaborations.

This is done by a) participating and distinguishing our self both at national and European levels on all our strategic goals, b) by participating in research and organizational work in national and international professional societies, c) by being politically recognized as experts in the field of reproduction and d) by publishing our research in international peer reviewed journals and in the lay press to disseminate knowledge on reproduction to as many people as possible.

The Fertility department is and must continue to be interdisciplinary and collaborative in every way and the clinic can only meet its professional, patient-centered and scientific goals if everyone is offering dedication, focus and professionalism. Hence the ambition of the fertility clinic is to ensure a workplace where staff attitudes is characterized by commitment, tolerance, inclusiveness and respect for each other's professionalism and for the patients. This ensures that we can continue to increase the quality of our treatments and patient satisfaction, as well as retain employees and recruit new competent staff.

The Fertility department is organized in two complementary sections – The Fertility Clinic with focus on diagnostics, treatments, clinical and epidemiological research and Laboratory of Reproductive Biology with a primary focus on basic research within reproductive biology. This organization supports our ambition of close integration of clinical activity and basic and clinical science.



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# TREATING PATIENTS

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# ASSISTED REPRODUCTIVE TECHNOLOGIES (ART)

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Fertility treatment is a major focus area at the Fertility Department. We are the largest public fertility provider in the Nordic countries and conduct around 2,500 treatments per year. Approximately 60 staff members - nurses, doctors, secretaries as well as technical and academic staff in the laboratory - assist our patients in establishing and supporting a pregnancy. On top of this the Fertility department have 10-15 externally founded PhD students and Postdocs conducting science.

To generate an increased number of oocytes for in vitro fertilization (IVF) women receive an individualized hormone treatment for ovarian stimulation. The recovered oocytes are fertilized in the laboratory using either IVF or intracytoplasmic sperm injection (ICSI) followed by embryo transfer on day 2 or day 5 (blastocyst culture).

Remaining embryos are cultured to day 5 or 6 and surplus blastocyst(s) are cryopreserved by vitrification. If a patient is at risk of ovarian hyperstimulation syndrome (OHSS), a “freeze all” approach is applied, in which all embryos are cryopreserved and used in a subsequent frozen embryo transfer (FET) cycle thereby avoiding severe OHSS. In frozen embryo transfer cycles vitrified blastocysts are thawed in the morning and transferred the same day.

The clinical part is organized in several teams with advanced expertise in a specific field including preimplantation genetic diagnostics, fertility preservation, egg donation, reproductive surgery, recurrent miscarriage and andrology. Our laboratory comprises highly experienced biologist and lab technicians specially trained in embryology both nationally and internationally. The expertise and skills of our staff is the backbone in our successful patient treatment and continued development to improve treatment for our patients.



# EGG DONATION

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Egg donation has been performed at the Fertility Department since 2007. In recent years legislation, practice and guidelines have changed resulting in an increasing number of treatments performed using donated eggs.

In egg donation, also called 'third party reproduction' healthy woman below 36 years of age undergo hormone treatment and oocyte pick-up, in order to donate eggs to a couple or a single woman without usable eggs. The main causes leading to the need for egg donation is idiopathic premature menopause, previous anti-cancer treatment or surgery involving the ovaries. Egg donation is the only possibility for these women to achieve pregnancy and motherhood.

Once the unfertilized eggs have been collected, they are fertilized with semen from the recipient's husband or donor semen, the latter also known as double donation. Five days after oocytes pick up from the donor the embryos are cryopreserved, and the recipient can start hormonal treatment to prepare her uterus for an embryo transfer.

Since the egg donors are from young and healthy women the delivery rate is high.

Egg donation is a story of success where women with a low ovarian reserve now has a high chance of motherhood. However, more complications are observed in egg donation pregnancies, hence antenatal care and delivery should take place in highly specialized units.



# FERTILITY PRESERVATION

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Girls and women treated with radio- and/or chemotherapy due to malignant or severe systemic disease might experience reduced fertility or shortened reproductive lifespan due to premature ovarian insufficiency (POI). Fertility preservation is therefore an important integral part of treating young cancer patients. Several methods for fertility preservation (FP) are available including freezing of mature oocytes or embryos as well as ovarian tissue cryopreservation. The oocytes, embryos or ovarian tissue harvested prior to the gonadotoxic treatment can offer a second chance of achieving pregnancy following radio- and/or chemotherapy. Recommendations of FP strategies are based on the type and treatment of malignancy, known predictors of POI, the woman's preference and time available for FP intervention.

In Denmark, fertility preservation has been offered to girls and women up to 41 years of age since 1999. Rigshospitalet is one of three national centers, where

cancer patients are counselled and treated prior to gonadotoxic treatment. Annually, we have about 60-70 young girls or women from the eastern part of Denmark referred to our clinic for counselling. Of these, about 1/3 opt for ovarian tissue cryopreservation, 1/3 have IVF with freezing of mature oocytes and/or embryos, and 1/3 do not wish or cannot be offered fertility preservation for different reasons. An increasing number of women are coming back to make use of their stored eggs and about 1/3 will succeed in having a child. For young cancer patients the opportunity of fertility preservation gives them hope for the cure of their cancer and for their future fertility prospective.

As the first clinic in Denmark, we offer evaluation of the ovarian function and fertility counselling after ended radio- or chemotherapy. This has shown to cover a large need for information on the future fertility chances in young female cancer survivors, in whom the risk of infertility is a great concern.



# REPRODUCTIVE SURGERY

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Since September 2019 the fertility clinic has performed reproductive surgery supplying fast track examination and treatment to our patients. Our vision is to build up a reproductive surgery team consisting of fertility experts performing the surgery in the perspective of subsequent fertility treatment to optimize reproductive outcomes.

Less complex procedures as office hysteroscopy are performed in our outpatient clinic reducing waiting time and costs. Until now we have performed more than 100 office hysteroscopies and 45 evaluations of the fallopian tubes using contrast and ultrasonography.

Office hysteroscopy is an examination of the uterine cavity. The examination is carried out with a hysteroscope which is a narrow telescope with a light, camera and a working channel. The working channel allows resection of pathology in the uterine cavity. In patients receiving fertility treatment lower pregnancy rates are observed in the presence of uterine cavity anomalies and pathology, such as fibroids and polyps. Correction of these conditions are associated with improved pregnancy rates. Laparoscopies with removal of blocked uterine tubes, ovarian cysts and large fibromas which are all fertility promoting operations are performed in the operation theatre in collaboration with the gynecologists and coordinated by a consultant with experience within both fertility and gynecology.



# RECURRENT PREGNANCY LOSS

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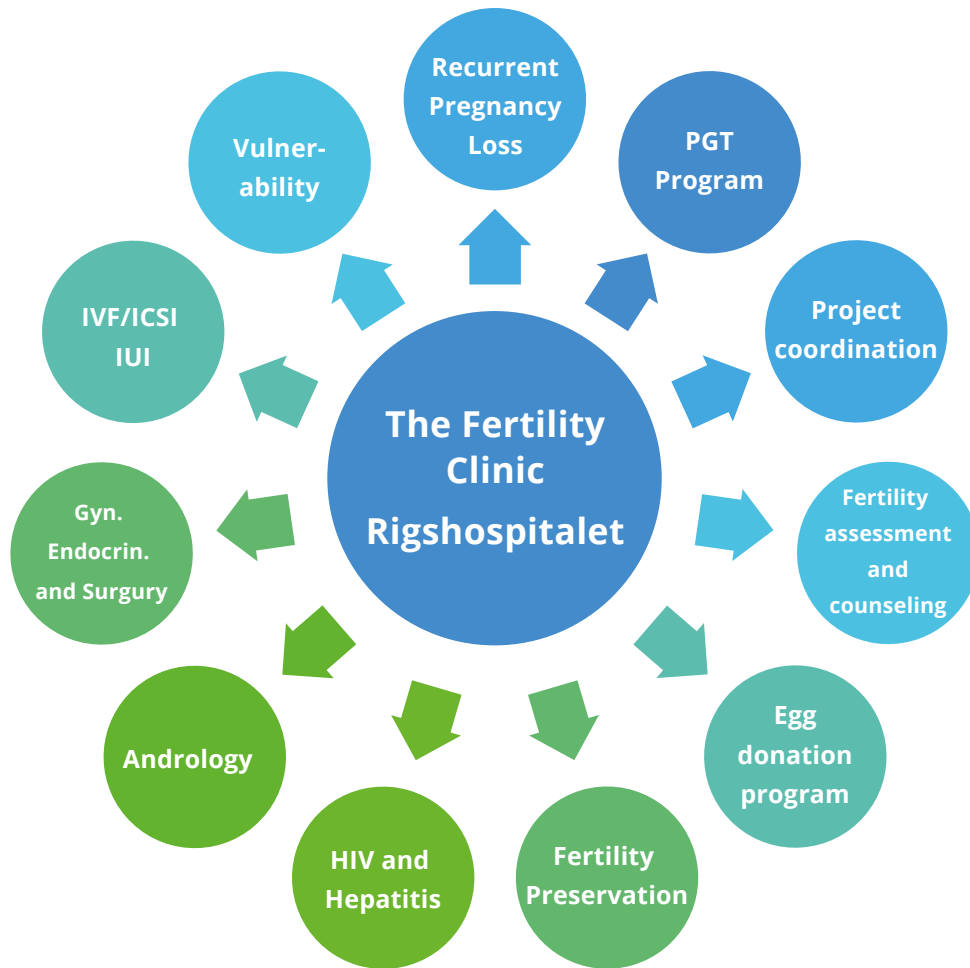
The fertility department has diagnosed and treated women with recurrent pregnancy loss for more than twenty years. In December 2019, the recurrent pregnancy loss team at the fertility Clinic became part of the Unit of Recurrent Pregnancy Loss in the Capital Region. This unit consists of two collaborating pregnancy loss clinics in the Capital Region - one located at the Fertility Department, Rigshospitalet and one located at the department of OBS/GYN at Amager-Hvidovre Hospital. The unit apply common standardized investigation programs and treatment protocols.

In Denmark, recurrent pregnancy loss is defined as three consecutive miscarriages before gestational week 22.

It is estimated that the condition affects 2-3% of all couples trying to conceive. The investigation program includes parental karyotyping, an examination of the uterine cavity and various blood tests in the female to evaluate thyroid status, immunological status and acquired and inherited thrombophilia.

Until now examination and treatment has primarily focused on the female part. However, there is increasing evidence that we also need to focus on sperm quality and male lifestyle habits as paternal factors are also involved in recurrent miscarriage.

Suffering from recurrent pregnancy loss is stressful and causes anxiety and depression in a significant number of patients hence research is highly prioritized in this special field of reproductive medicine.



# NURSING

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Nursing play an important role in the overall course of treatment performed in the fertility department. The nurses have many different tasks both instrumentally, teaching and guidance tasks as well as informing and counselling patients. Some tasks are performed in close collaboration with the doctors while others are performed solely by nurses, including careful instruction of the patients in the practical use of fertility medicine.

The fertility clinic is subdivided into several specialized teams consisting of staff from all relevant professions including the nurses.

Patients to be inseminated or allocated to the recurrent pregnancy loss unit are assisted by trained fertility nurses, who independently perform pregnancy scans, counseling and inform about further treatment plans.

In the egg donation team three nurses are responsible for managing the waiting list and for the daily telephone consultations with egg donors and recipients.

Both infertility and recurrent miscarriage are stressful conditions causing anxiety and depression in a significant number of patients. The nurses are passionate and dedicated to the psychosocial care and health in the infertile patients. This also includes discussion of ethical dilemmas with patients.

The department offers networking for single mothers managed by the nurses and a team provides special support to patients with psychosocial vulnerability.

Our nurses are professionally active both nationally and internationally and has been deeply involved in creating the ESHRE “Nurses and Midwives Certification” program. We have taken part in the ESHRE Steering Committee with tasks as chairman and invigilator at the exam held annually in connection with the ESHRE annual Meeting. Several nurses in our clinic have passed the ESHRE exam and we continuously encourage the nurses to engage in the nurse expert program and to take the exam.



# INTRAUTERINE INSEMINATION

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Intrauterine insemination (IUI) is one of the oldest and least invasive fertility treatments. The principle of intrauterine insemination is to support maturation of one or two eggs by mild ovarian stimulation, followed by insemination of prepared sperm into the uterus around the time of ovulation, thereby increasing the chances for obtaining a pregnancy.

Intrauterine insemination is used for couples with unexplained infertility, couples in which the male partner has mild decreased semen quality, in women with anovulation and in single women and women with a female partner.

Since the legislation in 2007 permitted fertility clinics to treat single women and women with female partners and this patient group has increased steadily in the insemination program, and 46 % of all IUI cycles are now performed using a sperm donor. In 2019 the clinic performed 568 intrauterine inseminations.

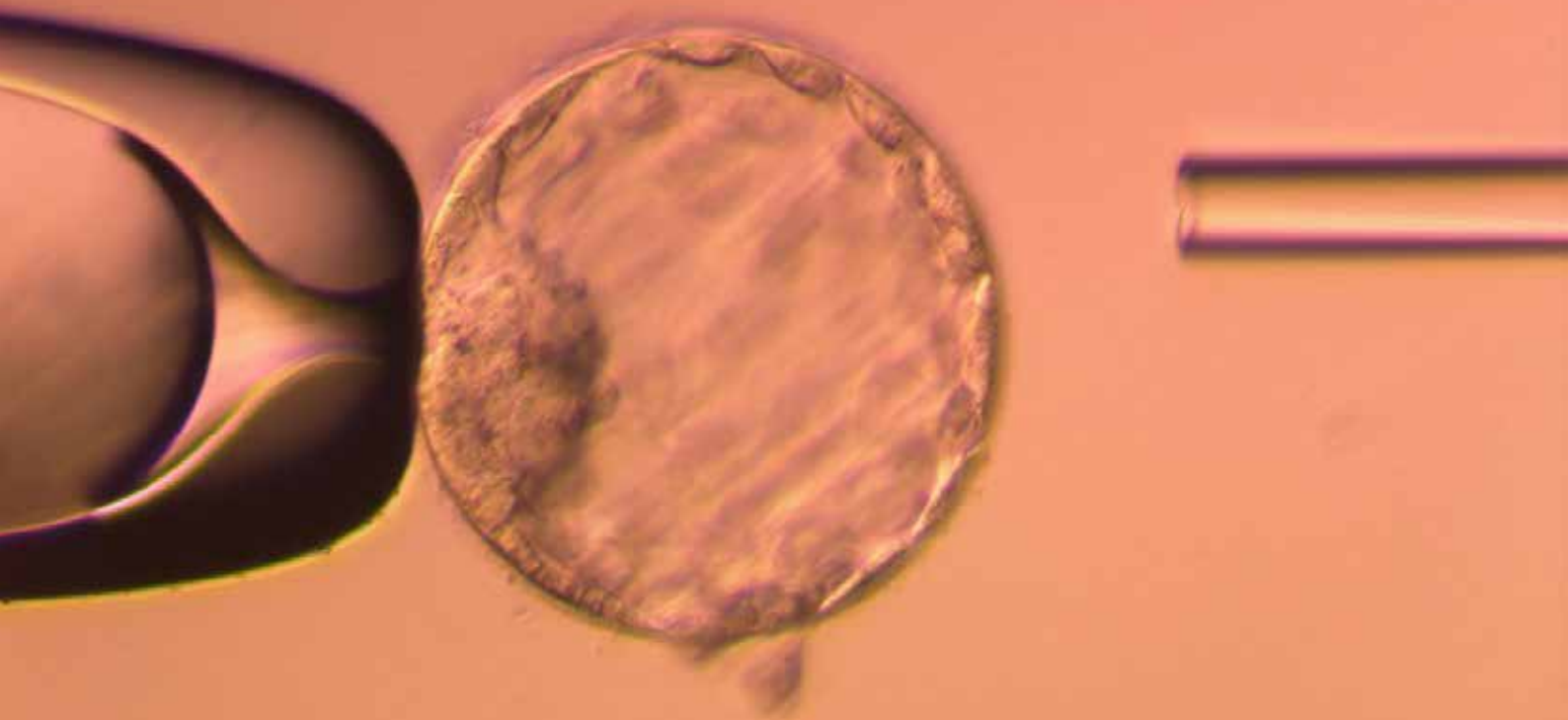
The intrauterine insemination program is managed by specially trained fertility nurses who survey and control the ovarian stimulation by ultrasound scans. A fertility doctor is consulted if necessary. The nurses also perform the procedure of insemination of prepared sperm into the uterus. The nurses are trained partly by bedside education and partly by more formal education at the department.



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HIGHLY SPECIALISED

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# PREIMPLANTATION GENETIC TESTING (PGT)

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Preimplantation genetic testing (PGT) is a highly specialized method to test embryos for a known genetic disease either a monogenetic disease or a structural chromosomal rearrangement.

In Denmark PGT is centralized to the Fertility Department at Rigshospitalet and the Fertility Clinic at Aalborg University Hospital and is performed in close collaboration with the Departments of Clinical Genetics at both sites.

At Rigshospitalet around 150 PGT oocyte retrievals are performed each year and the pregnancy rate is around 40% per embryo transfer.

## Benefits of PGT

- Genetic testing of embryos before implantation and establishment of pregnancy
- Selective transfer of embryos unaffected by the genetic disease in question
- Opportunity to avoid termination of an affected pregnancy diagnosed through traditional prenatal diagnosis
- A risk reduction regarding the known genetic disease from 25-50% to 1-5% per pregnancy.

- An opportunity to eliminate a known genetic disease in future generations

Embryos are cultivated 5-6 days in the laboratory until they reach the blastocyst stage. At this time a trophectoderm biopsy is retrieved by a highly specialized embryologist. Following biopsy retrieval, the blastocyst is frozen and kept in storage. The trophectoderm biopsy is examined at the genetic department and when the result of the genetic analysis is known, blastocysts without the genetic disorder can be thawed and placed in the uterus.

Expert skills are mandatory to perform the biopsy procedure and the genetic analyses. Furthermore, success depends on many other factors, including the woman's age, numbers of oocytes which can be retrieved and whether the couple have concomitant fertility problems.

Over the years, major improvements in the area of genetic "micro analysis" and assisted reproductive technologies have been achieved making PGT a well-established, accurate, and safe clinical treatment.



# CRYOPRESERVATION OF OVARIAN TISSUE

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Cryopreservation of ovarian tissue is the only fertility preserving option for prepubertal girls who do not produce mature oocytes and to young women who are facing urgent sterilizing cancer treatment. One ovary is removed by a laparoscopic operation and the outer cortex of the ovary containing 90% of the ovarian reserve is isolated, frozen and stored at  $-196^{\circ}\text{C}$ . Years later, after cure of the cancer, the patient can have the ovarian tissue re-transplanted and have ovarian function restored with the associated menstrual cycle and fertility.

In Denmark, cryopreservation of ovarian tissue is centralized to the Laboratory of Reproductive Biology, whereas patient consultations and removal/transplantation of ovarian tissue is performed by the fertility clinics and gynecological departments at the University Hospitals in Copenhagen, Aarhus, Odense. The centralization of the procedure has been internationally recognized as “the Danish Model” in which “the woman stays - the tissue moves” and has been applied

in other countries such as Germany and Norway. The advantage of a centralized program for ovarian tissue cryopreservation is that it keeps the expertise of both consulting doctors and technical performance concentrated and updated in a few centers, which secures a high-quality service and provides patients, who may be very ill or may not have the time to delay treatment, with an option to have fertility preservation without having to travel to distant institutions.

Cryopreservation of ovarian tissue has been offered clinically since 1999 and, to date, more than 1300 Danish girls and young women have had their ovarian tissue frozen. Of these, 117 women have returned and had their ovarian tissue re-transplanted and more than 25 children have been born. With our national fertility preservation program, we were one of the pioneering centers offering cryopreservation of ovarian tissue to patients, and we are still one of the world’s leading centers for the development of this technique.



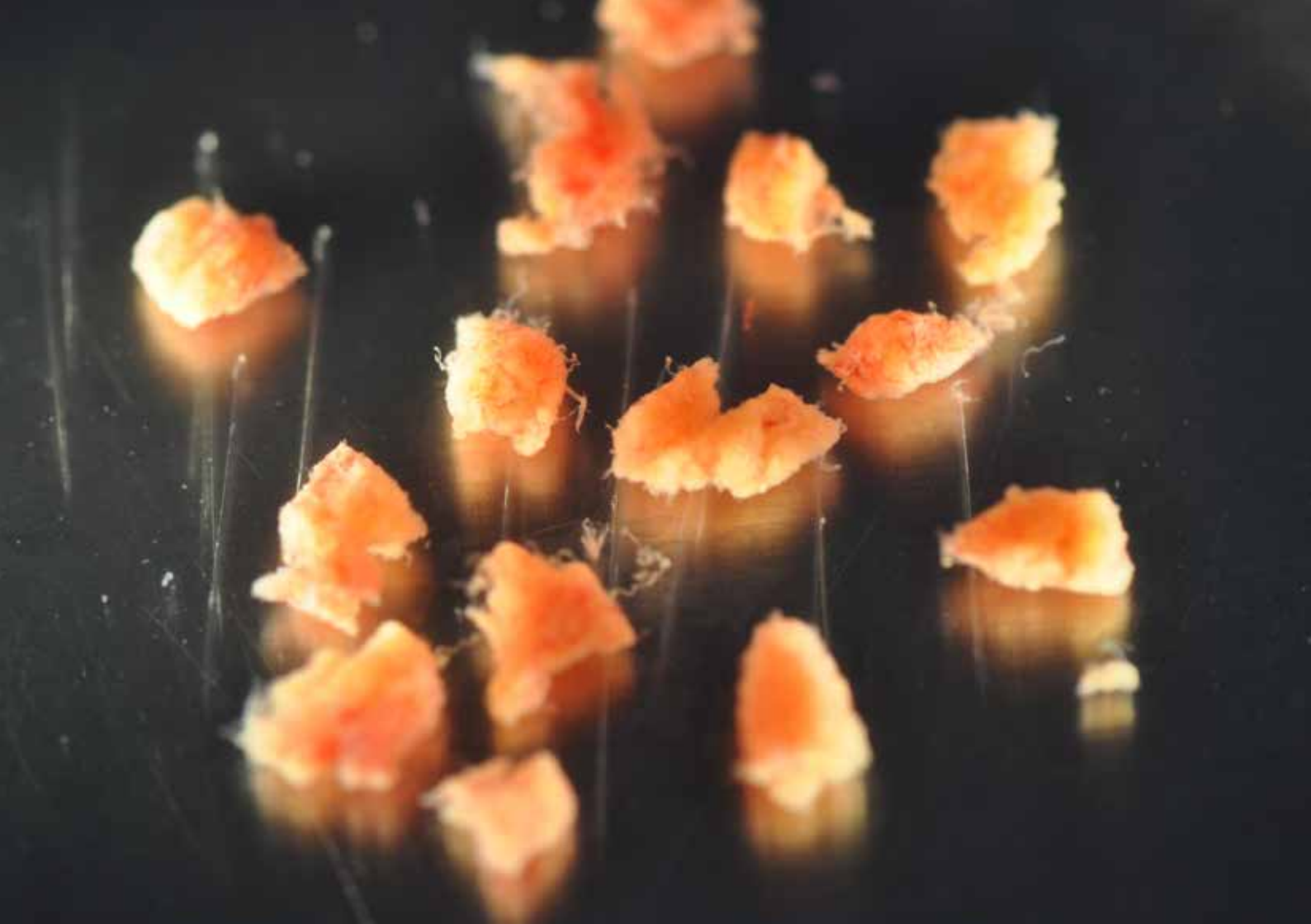
# WOMEN AND MEN POSITIVE FOR HIV- AND HEPATITIS B OR C

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The Fertility Department provide fertility treatment for women and men positive for HIV or Hepatitis B or C. According to the National Health Authority guidelines treatment of these women and men are centralized to two public clinics in Denmark.

Treatment of active and chronic viral infections has evolved significantly over the last decade, with decreased morbidity and mortality and increased life expectancy and quality of life. Fertility treatment of these patients must be done in close collaboration between specialists in infectious diseases and reproductive medicine. Fertility treatment of patients that

are HIV positive should only be performed when the patients received optimal anti-viral treatment documented by presence of a minimal virus load. Patients that are hepatitis B or C positive should also be fully investigated and if possible, receive medical treatment before initiating fertility treatment. Patients with HIV are recommended to try to obtain pregnancy without fertility treatment, however if they do not conceive within the first year, they can be referred to fertility treatment. The Fertility Clinic has a separate laboratory approved for handling sperm and eggs from these patients as required by the European Tissues and Cells directive.



# CRYOPRESERVATION OF TESTICULAR TISSUE

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Cryopreservation of testicular tissue is a relatively new clinical research program in Denmark, but worldwide more than one thousand young boys (aged 3 months to 18 years) have already undergone testicular tissue retrieval and storage for fertility preservation. In Denmark, cryopreservation of a small testicular tissue biopsy has been centralized to the Laboratory of Reproductive Biology and is now experimentally offered to:

- Prepubertal boys who are unable to produce a semen sample and at high risk of losing their fertility due to a disease in which the treatment is highly gonadotoxic (primarily cancer).
- Infant boys with cryptorchidism undergoing surgical positioning of the undescended testes to the scrotum during the first years of life.
- Men with non-obstructive azoospermia. These patients may have few testis tubes with active spermatogenesis, these will be stored for later culture and maturation and potential procreation.

Around 3% of all Danish boys' experience cryptorchidism and cryopreservation is offered to those, who are considered to have the highest risk of future infertility. For prepubertal boys, who are unable to produce a semen sample, there are no alternative fertility preserving strategies.

Today, a total of 79 boys and young men have had testis tissue cryopreserved at the Laboratory of Reproductive Biology. The indication for fertility preservation were cryptorchidism (n=52), Klinefelter syndrome (n=14), cancer (n=6), genetic variation and others (n=2). Currently there is no clinical proven fertility restoration option for these groups of patients. However, various approaches for the restoration of male fertility following oncological treatments or other fertility-compromising diseases are under investigation in our lab and other centers with promising results in the non-human primate model.



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RESEARCH, EDUCATION  
AND PREVENTION

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# FERTILITY RESTORATION CONSORTIUM

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The Laboratory of Reproductive Biology at Rigshospitalet is a central member of the Fertility Restoration Consortium (<http://fertility-restoration.dk/>), which is a collaboration between researchers within the field of reproduction, urology, tissue engineering, and stem cell science. The group has established a multi-disciplinary platform that aims to advance the understanding of human germline stem cells and develop new stem cell based therapeutic solution for treating infertility in both prepubertal and adult patients.

Goal:

- To understand the basics of germline cell development from fetal gonocytes to different types of

spermatogonia to develop therapeutic solutions for fertility preservation and restoration in the clinical settings.

The consortium includes well-established leading experts from basic and clinical science within reproduction; paediatrics, andrology, urology, and stem cell biology from centers at the University hospitals Rigshospitalet Herlev, and Odense, and Copenhagen University.

We are currently working on several projects involving germ cell in-vitro propagation and differentiation, testicular biology of fetal, infant to adult testes, fertility preservation and restoration techniques.



# REPROUNION CONSORTIUM

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The Fertility Department at Rigshospitalet was one of the founders of the Danish/Swedish Øresund-collaboration now named “ReproUnion” established in 2010.

ReproUnion has developed over the past 10 years and the experience from the initial phases of the collaboration has inspired the consortium to formulate and address five major reproductive challenges in research and communication. The five global challenges require inclusion of all perspectives and disciplines, from basic research, diagnostics to treatment. The Challenges require long-term cooperation with the world experts in order to fulfill the goals defined in the five challenges. Since the start in 2010 ReproUnion has received financial support from EU via the InterReg program, Capital Region in Denmark, Region Skåne and Ferring Pharmaceuticals. Over the years the collaboration has received funding of more than € 25 mill., educated more than 25 Ph.D. students and several post docs representing the future researchers in the field of reproduction and published more than 130 international peer-reviewed scientific papers. Further, ReproUnion have engaged in communication initiatives disseminating information and knowledge to the general public and politicians concerning our ability

to have children. Further we have been part of international fellowship financed by ReproUnion and ESHRE.

The Fertility Department are principal investigators of three of five ongoing challenges within ReproUnion; Challenge 2: Optimizing medically assisted reproductive treatment, Challenge 3: Securing female ovarian function and Challenge 5: Fertility awareness ([www.reprounion.eu](http://www.reprounion.eu)).

In 2013, our collaboration was awarded by the Capital Region of Denmark and the Region Skåne the “Oresund Award in Health” – given to promote groundbreaking collaborations in health research and clinical work. Further ReproUnion was a finalist in the EU RegioStars Awards 2018 and the Athena Award in 2019.

ReproUnion Biobank and Infertility Cohort (RUBIC) is a prospective cohort of 5000 infertile couples in Denmark and Sweden with collaboration of all public fertility clinics in the Capital Region and Department of Growth and Reproduction at Rigshospitalet and in Malmö ([www.rubic.nu](http://www.rubic.nu)). All data generated from the cohort are being collected prospectively over the next five years and biosamples are stored in the Copenhagen Hospital Biobank (RHB).



# FERTILITY ASSESSMENT AND COUNSELLING

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Individual Fertility Assessment and Counselling (FAC) is a concept initiated at the Fertility Department at Rigshospitalet in 2011. Originally the FAC clinic was funded by the Danish-Swedish EU/Interreg collaboration now named ReproUnion. FAC was from the beginning a success and the demand for this screening option from the citizens was great. Hence since 2019 fertility assessment and counselling has been a free screening option and the FAC clinic is now receiving permanent funding from the Capital Region. The concept is based on individual assessment of risk factors for low fertility for couples, and individual women and men. The FAC Clinic program is open to all individuals provided there is no previous known infertility issues.

The aim of the program is to empower individuals and couples, on how to fulfill their desires in terms of family formation based on individual examination and assessment.

For women the FAC offers an assessment of reproductive history and risk factors for infertility, a transvaginal sonography of the ovaries with measurement of antral follicle count as well as measurement of anti-Mullerian hormone (AMH) in the blood to estimate the ovarian reserve and thus assumed reproductive lifespan. Men are offered assessment of risk factors for infertility and a semen analysis.

Two-year follow-up studies of the FAC activity shows that future subfertility can be predicted to some extent, and 6-year follow-up studies show that women in general consider the consultation useful for their reproductive choices and fertility plan. Presently, we have 600 consultations annually and approximately 3,600 individuals have so far attended the FAC clinic. Three PhD projects have been defended based on data from the FAC clinic and sixteen scientific papers have been published. Hence the FAC clinic is also creating new knowledge in the field of fertility potential and awareness.



# FERTILITY AWARENESS AND REPRODUCTIVE SUSTAINABILITY

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The Fertility Department at Rigshospitalet have for several years played a central role in addressing prevention of reproductive diseases and their consequence on both a personal and societal level.

Fertility Awareness is about knowledge and awareness of our own and our partner's reproductive biology and the opportunities and limitations we are born with - and how our choices in life can affect our chances of having children. However, Fertility Awareness is also about knowledge and awareness of the societal and cultural framework of family formation and thus the conditions that can affect the opportunities for having children.

In collaboration with the organization Sex & Samfund, the Capital Region of Copenhagen, The Ministry of Health, The Ministry of Environment and the City of Copenhagen several initiatives have been launched. This includes revising sex education in elementary schools well as campaigns in the city of Copenhagen addressing the reproductive challenges in Denmark.

Based on the already existing Awareness initiatives and as part of ReproUnion, the Fertility Department at Rigshospitalet have over the past years worked to disseminate knowledge on our reproductive capabilities and provided new knowledge on the reasons why family formation is postponed in both Denmark and Sweden.



# CLINICAL RESEARCH IN THE FERTILITY CLINIC

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Since the opening of the fertility clinic in 1995 research has been one of the key priorities and we have aimed to increase the number of publications ever since and together with the Laboratory of Reproductive Biology we published more than 100 scientific publications in 2020. Our main research areas cover clinical research including international multicenter clinical trials and cohort studies of patients in fertility treatment, patients with recurrent miscarriage and fertility preservation programs. We have a strong collaboration with the other public fertility clinics in the Capital Region and the rest of the Denmark, allowing us to reach a patient volume sufficient to drive large randomized clinical trials to develop and evaluate new treatment strategies.

The Fertility Clinic play an important part in trials driven by the pharmaceutical industry facilitating the development of new medicine in the field of reproductive medicine. Together with researchers at

the Institute of Public Health at Copenhagen University we have gathered a large cohort of women and men who underwent fertility treatment including diagnoses on their morbidity, risk of cancer, reproductive health, family formation, psychosocial wellbeing and mortality for long term follow-up of fertility patients.

We have close collaborations with many departments at Rigshospitalet including; Departments of Obstetrics and Department of Gynaecology, Department of Growth and Reproduction, Cardiology Department, Neurobiological Research Unit and the Epilepsy clinic.

Two research programs in safety aspect of women and children conceived after ART are described separately the Committee of Nordic ART and Safety (CoNARTaS)([www.conartas.com](http://www.conartas.com)) and Health in Children born after ART (HiCART) ([www.hicart.dk](http://www.hicart.dk)).



# RESEARCH IN SAFETY OF MOTHERS AND CHILDREN CONCEIVED AFTER ART

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The Fertility Clinic at Rigshospitalet is one of the world's leading centers in clinical and epidemiological research concerning safety aspects of women in MAR treatment and their children. In Denmark approximately 10% of a birth cohort (6000-7000 children) are annually born after fertility treatment and 60% of those from medically assisted reproduction. The Committee of Nordic ART and Safety (CoNARTaS) was established 15 years ago and has ever since been responsible for a common database of children born after IVF and ICSI in the Nordic countries. The database is currently comprising information on short and long-term morbidity in 170.000 children conceived by ART born since 1982 and it also includes information on the background populations in Denmark, Sweden, Norway and Finland. The Fertility Clinic at Rigshospitalet is the primary responsible for the CoNARTaS data that are hosted

in Statistics Denmark. CoNARTaS is funded by the NORDFORSK foundation ([www.CoNARTaS.com](http://www.CoNARTaS.com)).

In 2018 we were awarded an initiator grant and in 2019 a distinguished clinical investigator Grant from the Novo Nordic Foundation which made it possible to initiate a large-scale research program on Health in Children born after ART ([www.HiCART.dk](http://www.HiCART.dk)) with physical examination including cardiac MR and DXA scans of 600 children aged 7-9 years to assess markers of compromised cardiovascular and metabolic health in children born after fresh and frozen embryo transfer. This work will be followed by a new study with cardiac examination of 15-17-year old IVF children, which will provide us information on a possible long-term risk of cardiovascular disease in children born after ART. With more than 9 million children born worldwide after ART knowledge on the short and long-term consequences is crucial.



# RESEARCH AT THE LABORATORY OF REPRODUCTIVE BIOLOGY

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The Laboratory of Reproductive Biology has been an international recognized center for research in reproductive biology and ovarian physiology during the last 60 years. We have been successful in developing and implementing a gonadal tissue cryopreservation program for both ovarian and testicular tissue. Through our cryopreservation of ovarian tissue program the unique access to donated human ovarian tissue is used to study human folliculogenesis during the natural cycle and compare follicular dynamics in ovarian pathologies like polycystic ovarian syndrome. Proteomic analysis, highly sensitive protein assays, and culturing of human ovarian follicles in 3D matrixes have provided us with tools for investigating folliculogenesis and oogenesis in vivo and under tightly controlled conditions in vitro providing unprecedented insight into the fundamental biology of follicle development and ovarian endocrinology.

In order to improve our clinical treatments, we aim not only to preserve fertility but also to restore fertility. We are approaching this from many angles;

- By optimizing follicle survival in transplanted ovarian tissue, which suffers from severe ischemic reperfusion damage after grafting.

- By understanding human folliculogenesis and endocrine function in order to develop better methods for in vitro maturation of oocytes, which could potentially increase the fertility potential in women undergoing fertility preservation.
- By deriving oocytes and granulosa cells from induced pluripotent stem cells to create hormone producing ovarian organoids for potential clinical use.

In addition, current research in male fertility restoration has focused on isolation and propagation of spermatogonial stem cells to restore male fertility. Bioengineering of an artificial ovary using 3D printing and cell-based hormone replacement therapy using steroidogenic cells in immune isolated constructs are also technologies which we are currently trying to develop for human follicles and ovarian cells.

Finally, more than 10-years of research has been focused on fetal development of human gonads including sex differentiation, and the environmental impact on fetal health providing critical evidence for the harmful effects of cigarette smoking and perfluorinated substances.



# CENTER FOR REPRODUCTIVE MEDICINE

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As a result of a united strategy work between politicians, administration and fertility experts from all public fertility clinics, the Capital Region of Copenhagen in 2019 decided on a new strategy for the fertility area. Part of this strategy was formulating a regional structure named “The Capital Region of Denmark’s Reproductive Medicine Center” including all public fertility clinics located in the Region.

The Capital Region of Copenhagen consists of 1.85 mill. inhabitants of which 685.000 is in the reproductive age. The Region has four fertility clinics with taken together delivers more than 4.500 fertility treatments per year.

The ambition behind a formalized structure for the fertility area, was to support increased collaboration between the clinics allowing for collaborative research initiatives, increased interaction concerning guidelines and to contribute to continued international recognition of Copenhagen as a significant fertility hub in the world.

Quality in treatment, research and education are all coherent elements needed if the vision of a world-class patient assessment and treatment is to be fulfilled. It is our ambition, as one of the fertility clinics in the Capital Region of Copenhagen to continue, and expanded collaboration on treatment, education, research and quality development in the field of fertility, in ways which can contribute to synergy in the field.



# EXTERNAL FUNDING 2015–2020

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In the period 2015-2020 the Fertility Department has received funding of 68 million DKK in total from the internal and external funding sources listed below.

Aase og Ejnar Danielsen	Fabrikant Einar Willumsens	Novo Nordisk Foundation
A.P. Møller Fonden	Mindelegat	Oda og Hans Svenningsens Fond
Boehringer Ingelheim	Ferring Pharmaceuticals	Repronion EU/Interreg, Region
Frimodts Fond	Gedeon Richter	Hovedstaden,
Bdr. Hartmanns Fond	Hørslev Fonden	Region Skåne
Børnecancerfonden	Knud og Edith Eriksens	Repronion Superproject
Capital Region Research	Mindefond	Rigshospitalets Research
Foundation	Kræftens Bekæmpelse	Foundation
Cook Medical	Lizzi og Mogens Staal Fond	Roche Diagnostics
Dagmar Marshalls Fond	Lundbeck foundation	Torben & Alice Frimodts Fond
DFF	Læge Sofus Carl Emil Friis og	Toyota Foundation
ELSASS Foundation	Hustru Olga Doris	Tømrermester J. Holm og hustru
Else og Mogens Wedell-	Friis' Legat	Elisa født Hansens Mindelegat
Wedellsborgs Fond	Merck	Vissingfonden
EUROVA	Nordforsk	

# PUBLICATIONS 2020

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## **COVID-19 and assisted reproductive technology services: repercussions for patients and proposal for individualized clinical management**

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**Antenatal magnesium sulphate for the prevention of cerebral palsy in infants born preterm: a double-blind, randomised, placebo-controlled, multi-centre trial**

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