

IMPROVING HEALTH

CIRCLE OF LIFE

# AMSTERDAM REPRODUCTION AND DEVELOPMENT

ANNUAL REPORT

2021

REPRODUCTION

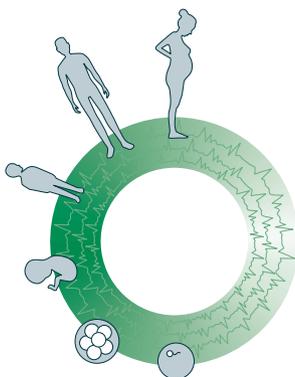
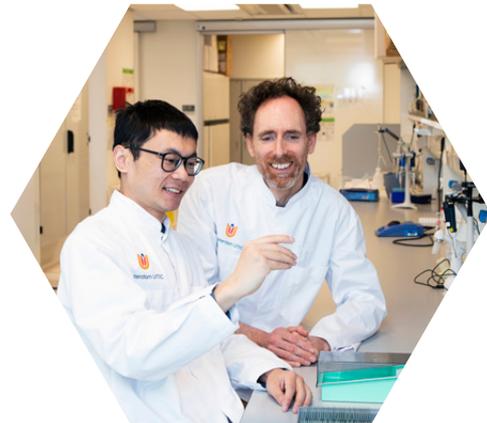
SOCIETAL IMPACT

DEVELOPMENT

RESEARCH

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**Amsterdam Reproduction & Development**  
is a research institute of Amsterdam UMC.

**E-mail:** [ARandD@amsterdamumc.nl](mailto:ARandD@amsterdamumc.nl)

**Website:** [www.amsterdamumc.org/ard](http://www.amsterdamumc.org/ard)

**Photography:** Martijn Gijsbertsen: [www.martijngijsbertsen.nl](http://www.martijngijsbertsen.nl)

**Graphic design and layout:** Hanneke Overhorst: [www.luumen.nl](http://www.luumen.nl)

**Coordination:**

Linda van den Noord: secretary

Tamar Kruit: policy officer

Eva Dirx-Beuling: policy officer

Lidewij Henneman: director

Tessa Roseboom: director



# A word from the directors



We proudly present the 2021 Amsterdam Reproduction & Development (AR&D) annual report. The report provides an impression of the research within our institute, the highlights and milestones reached in 2021. In the 5th year of our existence, we have refined our mission and vision, broadened our research board, initiated new research, gained new insights and continued to make societal impact while the world continued to be challenged by the COVID-19 pandemic.

Our research institute hosts a wealth of talented and highly motivated scientists from various disciplines who work together to gain knowledge about human reproduction and development through innovative and excellent academic research. With the ultimate aim to contribute to health and health care from the very beginning. The stories of our researchers show some of the groundbreaking work conducted within our institute, contributing to a better understanding of many aspects from preconception through pregnancy to child development and long-term health.

In 2021, COVID-19 continued to impact the world, as well as research and our researchers. Across the circle of life, we have investigated prevention, treatment and impact of COVID-19. For example, in our research and outreach in relation to vaccination against COVID-19 during pregnancy, our COVID-19 breastmilk studies, the call to action to prevent long-term damage of COVID-19 to unborn and young children, as well as the research and advocacy from our professor of Child and Adolescent Psychiatry Arne Popma, who actively worked towards limiting the damaging effect of the lockdowns on the mental health of children.

Aside from the COVID-19 work, there were significant highlights in 2021, including grants for new research around unplanned pregnancies, a discovery on the epigenetic origin of monozygotic twinning published in Nature Communications, the first in history image of a 6-week old human embryo. Significant input into the coalition agreement written by the government to include reimbursement of the NIPT, a pledge to alter the law around research on human embryos and a big investment in the first 1000 days of life and mental health of youth, thanks to research and advocacy from AR&D researchers. We celebrated the lifetime achievement award and royal decoration that was given to our Professor of Sexology Ellen Laan, who sadly passed away in January of 2021. We are saddened by her loss and immensely grateful for the contribution that she has made to science and society, and her

tremendous dedication to making the world a better and safer place for all, fighting for sexual rights and freedom.

Our AR&D Retreat committee of young researchers organized a successful retreat and gatherings, both online and offline, in order to continue building our network and inspire each other in a continued challenging time.

At the end of 2021, Christianne de Groot stepped down as director of our institute to take up her new role as chair of the Women & Children division, taking over from Hans van Goudoever who was appointed as vice-dean and member of the Board of Directors of Amsterdam UMC. We are grateful for the dedication and leadership of Christianne de Groot and thank her for her work for AR&D. We are happy that while both Christianne and Hans have taken up responsible roles in Amsterdam UMC management, they will continue to be active members of AR&D. Continuing to build evidence to build healthy generations from the very beginning.

With this report, we are delighted to share some of our highlights, introduce several AR&D lines of research across the circle of life and our newly appointed professors. Enjoy the reading!

**Lidewij Henneman & Tessa Roseboom**  
*Directors Amsterdam Reproduction and Development*



# Starting the Circle of life



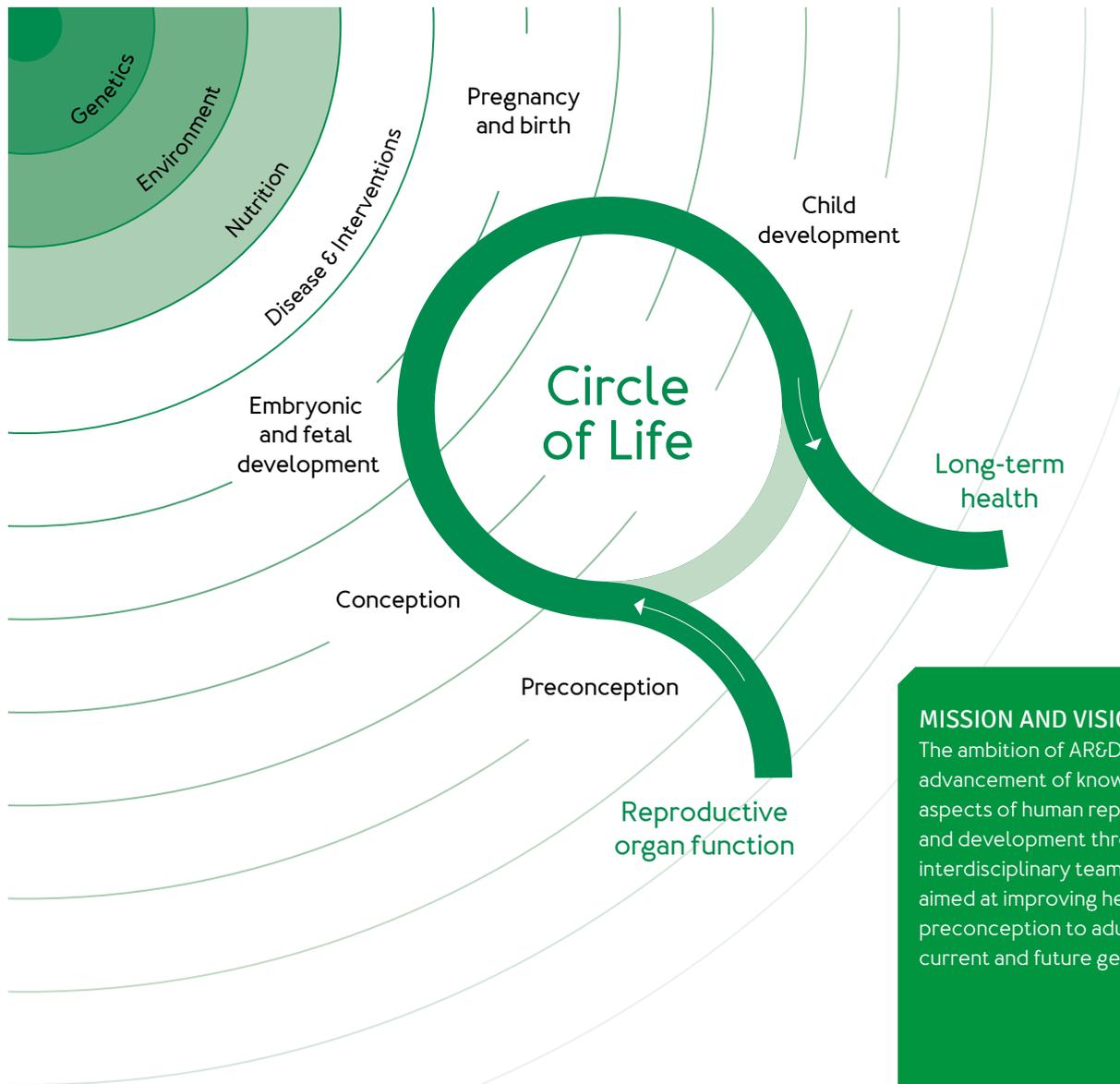
The Amsterdam Reproduction and Development (AR&D) research institute is unique in its goals and ambition, and Amsterdam UMC is the only academic medical center in the Netherlands with a research institute focusing on reproduction and development. AR&D is one of the eight research institutes of Amsterdam UMC, and as such related to both the University of Amsterdam (UvA) as well as the Vrije Universiteit Amsterdam (VU). AR&D encompasses research themes that cover the Circle of Life: from before conception through pregnancy and child development to lifelong health. Our research focuses on all aspects of the process of human reproduction and development, spanning from preconception, conception, embryonic and fetal development, pregnancy and birth, to child development and reproductive organ function.

We are inspired by a future of continuous and sustainable improvement in health for all. We aspire a role at the forefront

of fundamental, translational, and clinical science and public health research in human reproduction and development, creating a knowledge hub to guide science that serves the wider society.

AR&D integrates various disciplinary approaches within Amsterdam UMC and their affiliated centers and has connections with virtually all other Amsterdam UMC research institutes. AR&D researchers study the effects of genetics, environment, nutrition, disease and interventions on the developmental process from gamete to adult. In the institute, basic, translational, epidemiological, psychosocial and clinical research scientists work together to increase the knowledge and use of that knowledge to improve health and health care.

For more information please visit the website of AR&D: [www.amsterdamumc.org/jard](http://www.amsterdamumc.org/jard).



## MISSION AND VISION

The ambition of AR&D is the advancement of knowledge in all aspects of human reproduction and development through interdisciplinary team science aimed at improving health from preconception to adulthood of current and future generations.

# Research Areas

○○○ FROM PRECONCEPTION TO CHILD DEVELOPMENT



## PRECONCEPTION AND CONCEPTION

The desire to reproduce and raise children is a fundamental driving force for all species. We provide optimal care for people who wish to conceive, now or in the future. We develop prediction models to provide accurate and reliable prognoses and strive to provide optimal evidence-based shared decision-making. AR&D does not only offer novel medical fertility treatments but we also evaluate whether they are truly of benefit for our patients and their children. We investigate how to best counsel couples who are confronted with a high risk of serious genetic diseases in their future children, and to provide them with options for autonomous reproductive choice. We evaluate how medical professionals and other stakeholders view novel genetic and reproductive techniques and how innovative techniques should be ethically weighed and implemented. Within AR&D, we also study the process of spermatogenesis and oogenesis and the earliest stages of embryonic development from fertilization to implantation and translate this knowledge to new therapies.



## EMBRYONIC AND FETAL DEVELOPMENT

Humans all originate from a single cell, the fertilized oocyte, and developing through a fascinating highly orchestrated process to become the individuals that we currently are. AR&D studies how these processes are regulated, how perturbations can lead to congenital abnormalities or diseases and how genetic and environmental factors affect development. We use experimental model systems to study and simulate human development and use our unique twin register to disentangle environmental and genetic contributions to health, behavior and disease. By focusing on embryonic development, we provide the basis for understanding human development and health as well as disease susceptibility. We have mapped human embryo development in the 3D embryo atlas, and are extending our mapping effort towards fetal development for which we have set up the fetal biobank. We link these fundamental studies to clinical trials. We use highly sensitive ultrasound measurements and genetic tests to examine the developing fetus, and evaluate innovative implemented techniques. These are used for developing new tests to improve our clinical capacities.



## PREGNANCY AND BIRTH

AR&D constantly strives to provide the best possible care for prospective parents and their children. Therefore, we routinely perform multi-center clinical trials. With these trials, we aim to establish the benefit of specific interventions in reproductive medicine, gynecology, obstetrics and neonatology. Results of these trials are integrated into clinical protocols so that we can provide the best possible treatment for our patients and to allow for truly informed decision-making. In addition, we are developing tailored made tools for this shared decision-making. Our trials are conducted in the context of national networks of collaborating hospitals, gynecologists, midwives, nurses, neonatologists, and health care providers coordinated from Amsterdam. These professionals focus on optimally treating pregnancy complications and preventing premature delivery, as well as optimizing care for prematurely born infants. We study the requirements for responsible implementation of advancements in prenatal screening. We also investigate effects of environmental exposures during pregnancy on women's and offspring's health. This in order to learn more about how to give each child the best possible start in life.



## CHILD DEVELOPMENT

Healthy child development is essential for later health and wellbeing. AR&D follows children from the earliest phases through their development into childhood and young adulthood. We have a follow-up program for children who spent part of their early life in hospital, for instance because they were born prematurely. We monitor their behavior, growth and development to better understand the long-term consequences of our treatments and to inform our patients more accurately. We develop online tools that help patients and their parents keep track of various aspects of child development. This covers the full range of psychosocial, mental as well as physical and behavioral aspects of life. We follow up children whose mothers participated in intervention trials. This provides insight into the underlying mechanisms of diseases before they become clinically overt. With the advancement of sequencing technologies, we strive to optimize the genetic diagnosis in children with developmental disorders. We monitor development and follow individuals as they become the parents of the next generation and the circle of life begins again.



**“Improving  
health across  
the lifecycle”**

YOUSIF DAWOOD AND  
BERNADETTE DE BAKKER  
*The potential of micro-CT imaging*

QIJING LEI AND  
GEERT HAMER  
*Growing sperm in vitro:  
myth or reality?*

# RESEARCH AT AR&D

MICHELLE ROMIJN,  
WES ONLAND AND  
MARTIJN FINKEN  
*Research at the crossroad  
of Neonatology and  
Pediatric Endocrinology:  
Endocrine profiling  
of vulnerable infants  
to improve long-term  
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BAHAREH GOODARZI, JOLANDA  
LIEBREGTS AND ANK DE JONGE  
*Maternity care*

DOORTJE RADEMAKER  
AND REBECCA PAINTER  
*Beyond the scope of obstetrics  
alone – gestational diabetes*



“Imaging the  
earliest stages  
of new human  
life developing”

The fetus on this photo is a 3D print of a donated fetus.

# The potential of micro-CT imaging



For the first time in history researchers have been able to make an image of a human embryo of six weeks pregnancy (3 mm) in the intimacy of the placenta and membranes. AR&D researchers Yousif Dawood and Bernadette de Bakker published this micro-CT scan in the [journal Radiology](#), where it was selected as best Radiology image of 2021.



Yousif  
Dawood



Bernadette  
de Bakker

## HUMAN EMBRYO IMAGE

The image of a human embryo of six weeks pregnancy in the intimacy of the placenta and membranes published by Yousif Dawood and Bernadette de Bakker received the Radiology best image award for showcasing a cutting-edge imaging technology that could capture the fascinating beauty of early human development and emphasized the potential role of imaging in many areas of clinical and bench research.

*Figure 1* shows an image of an ectopic pregnancy that was implanted in the left fallopian tube. After laparoscopic tubectomy, the tube containing the embryo was donated to the Dutch Fetal Biobank. After submersion of the complete fallopian tube in a staining solution, it was imaged using microfocus computed tomography [micro-CT] at a resolution of 3  $\mu\text{m}$ . Micro-CT is a 3D imaging technique utilizing X-rays to see inside an object, slice by slice. Micro-CT is similar to clinical CT imaging but on a much smaller scale with greatly increased resolution. To achieve this improvement in the used micro-CT system has a fixed X-ray source with the sample mounted on a rotating platform

and an adjustable detector. This allows for the adjustment of the “radiation source-to-sample” and “sample-to-detector” distance, giving improved resolution. As embryos and fetuses do not have sufficiently dense tissue, contrast needs to be enhanced to allow visualization. After staining the fetal tissue using modified Lugol’s solution, the fetal soft tissue can be imaged at high resolution imaging of soft tissue. *Figure 1* shows a human embryo of 3 mm in length in which, among the forming internal organs, the otic vesicles, brain vesicles and heart tube including its lumen can easily be distinguished. Comparison to the 3D embryo atlas showed full resemblance with a stage 12 embryo, corresponding with 28 developmental days [6 pregnancy weeks].

Up until now, highly detailed images of human embryos could only be obtained by removing the embryo from its surrounding tissues, followed by a more or less destructive imaging technique [e.g. histological sectioning]. Contrast-enhanced micro-CT imaging now enables researchers to capture detailed images of an embryo within its natural environment, being surrounded by

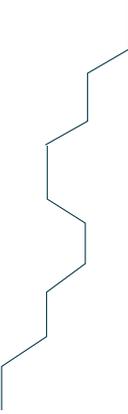
its fetal membranes, the forming placenta (referred to as trophoblast at this stage), and within a highly vascularized uterine tube.

The ectopic pregnancy in *Figure 1* is the first of a series of 25 specimen ranging in age from five to eight weeks pregnancy that will be imaged using contrast-enhanced micro-CT. Apart from the high-detailed 3D images of the developing human, this study will also provide us with detailed images of the yolk sac, early placenta and membranes. As placentation is getting increased attention by clinicians and scientists, because placental disorders can lead to potentially serious complications such as placental insufficiency and preeclampsia, this imaging technique provides us a unique possibility to study early placentation.

As an additional bonus, the surrounding mother's blood vessels and the embryonic vessels [e.g. the pharyngeal arch arteries and the dorsal aorta] are highlighted because blood has a high binding affinity for iodine from the Lugol's staining solution, both the mothers and the embryonic vessels [e.g. the pharyngeal arch arteries and the dorsal aorta] are highlighted.



*Figure 1: first ever image of a 6-week human embryo.*  
Source: [Radiology](#)



# “Contrast-enhanced micro-CT imaging now enables researchers to capture detailed images of an embryo within its natural environment”

## DUTCH FETAL BIOBANK

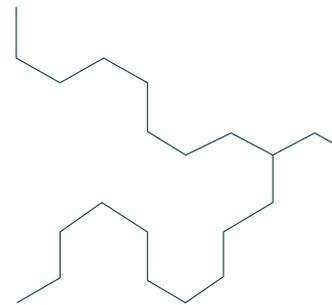
Most of the embryonic and fetal research conducted by researchers De Bakker, Dawood and team is on material collected via the Dutch Fetal Biobank (DFB). This biobank was founded in 2017 at Amsterdam UMC and it represents a continuously growing infrastructure for centralised collection, storage and management of fetal material. The biobank team formed by PhD and Master students and coordinated by Yousif Dawood, is 24/7 on call to pick up any fetus in the greater Amsterdam region and Rotterdam within 2-6 hours after birth. The biobank was initially established through a collaborative effort between the departments of Obstetrics and Gynecology, Pediatrics, and Medical Biology and is led by De Bakker and Maurice van den Hoff.

Several tissue banks have been created across the world to enable researchers to gain access to human embryonic and fetal samples. These are normally organised around defined scientific projects and the samples are usually not available to the wider scientific community. However, there are exceptions, such as the Dutch Fetal Biobank,

that provides material globally. The DFB now encompasses over 250 embryonic and fetal specimens (ranging from 5 to 24 weeks of pregnancy) of medical terminations, preterm labour and ectopic pregnancies. Unlike most fetal tissue banks, that receive their material from pregnancy termination using vacuum aspiration or surgical abortion, which destroys the tissue, the specimen collected in the DFB are most often intact. As a result, complete and accurate dissection based on anatomical landmarks can be performed.

## STATE-OF-THE-ART IMAGING TECHNIQUES

Since 2017, De Bakker and Dawood have been working on imaging first and second trimester human embryos and fetuses collected through the DFB. After publication of the 3D embryo atlas (until 10 weeks of pregnancy) the goal was to extend this atlas into the second trimester until 24 weeks of pregnancy – the 3D fetal atlas. However, histological sectioning, which was used for the embryology atlas, would be technically very challenging. Although not impossible, it is a very costly and extremely time-consuming



method considering the increasing size of the fetus. Therefore, De Bakker, Dawood and team have been studying alternatives to histological sectioning, such as 3D imaging of the intact fetus have been explored and tested. Novel (contrast-enhanced) micro-CT and High Field (HF; 3.0 Tesla [T] and higher) MRI (HF-MRI) techniques now enable histology-like resolution, that overcome the disadvantages of the abovementioned imaging techniques and allow Yousif Dawood to complete the 3D fetal atlas in due time.

Through this initiative, high quality and unique material of a broad range of human embryonic and fetal organs is available to the international research community. When sufficient funding is in place, the services of the biobank can be offered to all other Dutch hospitals. With the Dutch Fetal Biobank, De Bakker and Van den Hoff hope to provide an opportunity to progress knowledge in the field of human development.

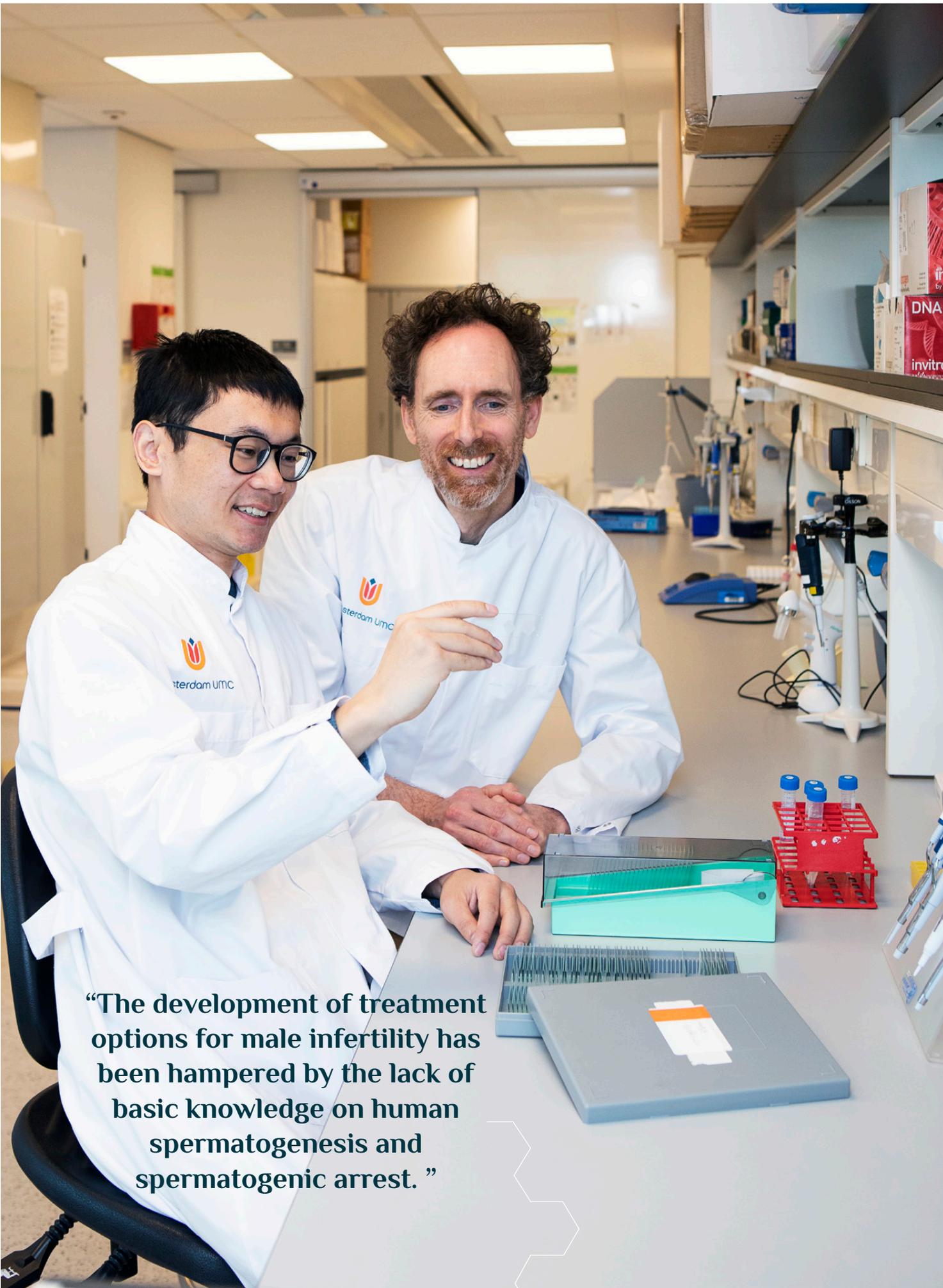
### CLINICAL POTENTIAL OF MICRO-CT IMAGING

Over the past years, De Bakker, Van den Hoff, Dawood and team have gained elaborate experience in the techniques involved in

micro-CT imaging. These techniques include fixation and staining protocols, scanning parameters and post-processing of the images. The team is internationally renowned because of the recipe they discovered for staining tissues without shrinkage artefacts. They currently perform their scans in a scanning facility in the University of Leuven, Belgium.

As micro-CT imaging holds large potential for many other clinical purposes mainly in the field of pathology (e.g. scanning resected tumors to study micro metastases), anatomy, development and forensics. Based on this enormous potential, De Bakker predicts that within 10 years all Dutch hospitals will have a micro-CT scanner.

De Bakker and Dawood their ultimate goal is to set up the Dutch Fetal Imaging Center, an expertise center for embryology, fetal development and birth defects. This center could serve as an European reference center for (forensic) postmortem high resolution imaging of human embryos and fetuses, as a noninvasive alternative for classic invasive autopsy. ●



**“The development of treatment options for male infertility has been hampered by the lack of basic knowledge on human spermatogenesis and spermatogenic arrest.”**

# Growing sperm in vitro: myth or reality?



Within the AR&D research institute, Qijing Lei and Geert Hamer of the Reproductive Biology Laboratory have developed an in vitro culture system for mouse sperm development.

### SPERM DEVELOPMENT

Lei and Hamer have developed an in vitro culture system for mouse sperm development. Although it is successful, several mechanisms involved in genome stability maintenance were identified to malfunction in vitro, including meiotic checkpoints that normally prevent generation of aneuploid sperm. These safety issues should be thoroughly investigated before the translation to clinical use of human in vitro generated gametes can be made.

## “An in vitro model for human spermatogenesis will thus accelerate both fundamental and translational research on male fertility”

Of the couples seeking medical aid to fulfill their child wish an estimated 50% are diagnosed with male factor fertility problems. Although assisted reproductive technologies can help in some of these cases, at least testicular sperm development (spermatogenesis) is required. For couples in which spermatogenesis is not complete (spermatogenic maturation arrest) or absent (Sertoli cell only syndrome), no treatment options are currently available. Moreover, spermatogenesis can be affected by many gonadotoxic cancer treatments that potentially eliminate the spermatogenic stem cells, the so called spermatogonial stem cells (SSCs), and thus lead to permanent male infertility. This is especially problematic for prepubertal boys from whom no sperm can be frozen prior to the treatment.

### FUTURE CLINICAL APPLICATIONS

Spermatogenesis is initiated at puberty and relies on functional SSCs, which are located at the basement membrane of the seminiferous tubules within the testes. The SSCs will either self-renew to maintain stem cell numbers or differentiate to undergo meiosis to form

haploid spermatids that will ultimately give rise to spermatozoa. Spermatogenesis is tightly regulated by interactions with testicular somatic cells, including Sertoli cells, peritubular cells and Leydig cells. With the aim of potential future clinical applications, such as male fertility preservation or treatment, many laboratories worldwide have attempted to generate functional sperm in vitro. However, the complex physiology of the testis that is needed to support spermatogenesis has so far not been successfully mimicked in vitro. Several studies, starting with mouse embryonic or induced pluripotent stem cells, were able to recapitulate most key events of spermatogenesis. However, these studies still required addition of gonadal tissue to the culture system to maintain function of the testicular somatic cells. Moreover, the safety, efficiency and functionality of the in vitro derived mouse gametes has not been sufficiently studied. Especially meiosis, the cell division in which DNA replication is followed by two successive rounds of chromosome segregation to give rise to genetically diverse haploid gametes, seems to be particularly challenging to replicate in vitro. Meiotic problems, for instance impaired pairing and recombination of the homologous chromosomes during the meiotic prophase, are considered as the main factors causing chromosome nondisjunction and, subsequently, sperm cells with a wrong number of chromosomes (aneuploidy). Aneuploidy in human gametes can ultimately cause genomic instability, infertility, recurrent pregnancy loss and developmental defects such as Klinefelter's and Down syndrome in offspring.

Because many patients with impaired spermatogenesis still have their own SSCs, Qijing Lei, under supervision of Geert Hamer of the Reproductive Biology Laboratory from Amsterdam UMC, location AMC, developed a culture system using mouse SSCs growing on a Sertoli cell line to support spermatogenesis in vitro. This culture system very accurately induced SSC differentiation, supported completion of meiosis and, occasionally, formation of round spermatids (immature sperm).

Meiosis is notoriously error-prone. Therefore, in vivo, several checkpoint mechanisms are present to closely monitor meiotic progression. During the



Qijing  
Lei



Geert  
Hamer

meiotic prophase, meiotic homologous chromosome pairing and recombination are strictly monitored. Any problem with one of these meiotic processes activates a specific meiotic prophase checkpoint, leading to elimination of the effected meiotic cells. During the two meiotic metaphases, a specialized spindle assembly checkpoint acts to prevent incorrect chromosome segregation and subsequent aneuploidy in sperm cells. Despite the importance of these meiotic checkpoints for the formation of safe and functional sperm, we found that they failed to eliminate aberrant meiotic cells in vitro. We therefore argue that investigation of meiotic checkpoint functionality should be part of the development of future in vitro male fertility preservation or treatment strategies.

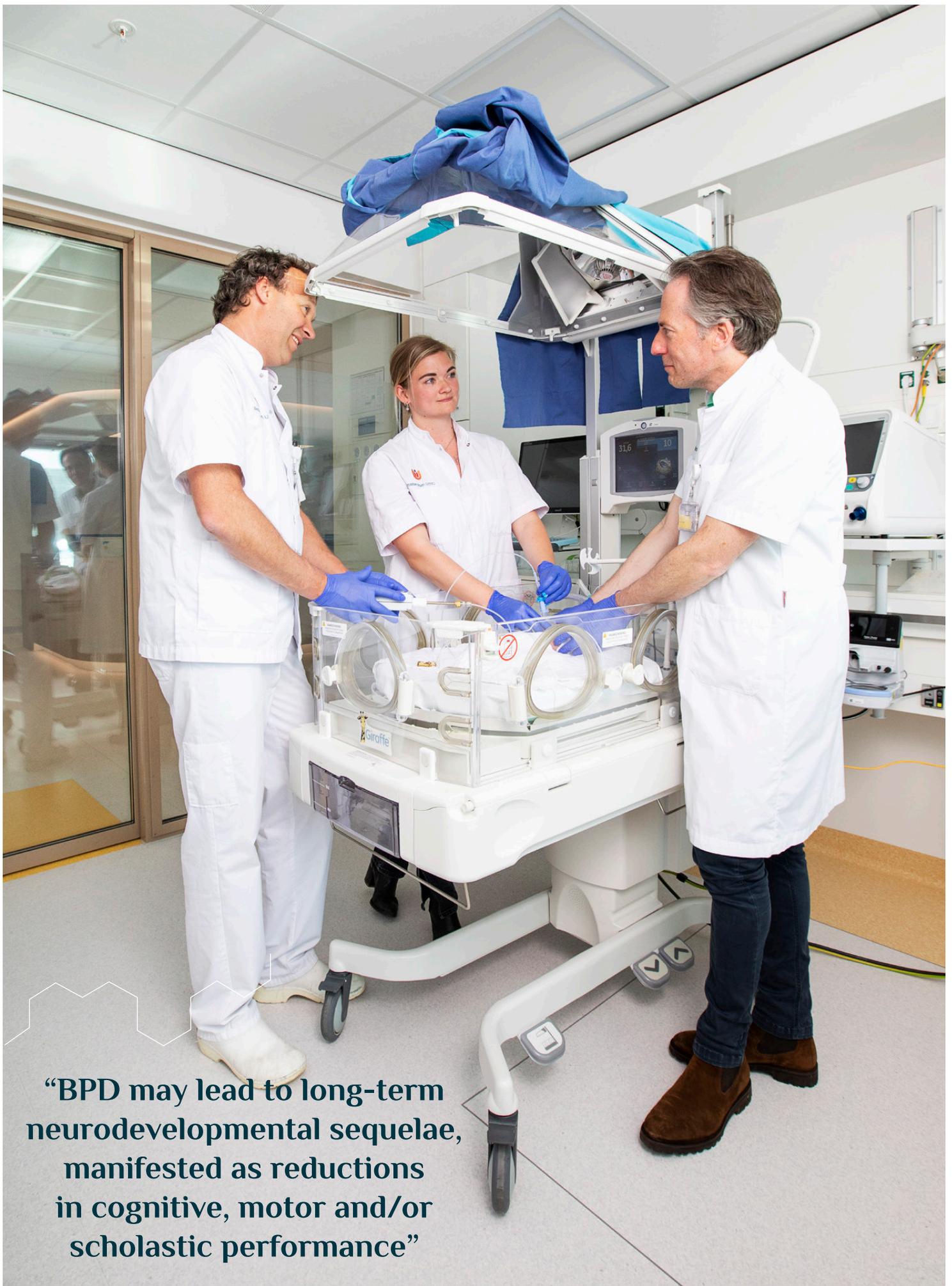
### PHD PROJECTS

As part of the NWO program Pluripotent Stem cells for Inherited Diseases and Embryonic Research (PSIDER), the Reproductive Biology Laboratory has recently received funding for two PhD research projects that will

continue this project using human induced pluripotent stem cells (hiPSCs). Under supervision of Geert Hamer and Ans van Pelt, one PhD student will use hiPSCs to generate human male gametes in vitro. The second PhD student will use hiPSCs to generate the gonadal somatic cells that are essential to support spermatogenesis in vitro. The entire project will be co-supervised by Callista Mulder, senior post-doc at the Reproductive Biology Laboratory. Also at Amsterdam UMC, Corrette Ploem will investigate the legal aspects of in vitro generated reproductive cells. The project is part of a large national consortium with additional expertise in e.g., hiPSCs (LUMC), female gametes (Erasmus MC), ethics (Maastricht University) and societal impact (Rathenau Institute).

The development of an in vitro culture system for human gametes will benefit greatly from the pioneering work of Qijing Lei, which has been described in his thesis “Spermatogenesis in vitro: myth or reality?”. Specific emphasis will be put on proper functioning of meiotic checkpoints. These

checkpoints frequently cause human male infertility by arresting spermatogenesis at the level of meiosis. However, at the same time, they are of extreme importance to prevent generation of aneuploid human sperm. The development of treatment options for male infertility has been hampered by the lack of basic knowledge on human spermatogenesis and spermatogenic arrest. Most of our current knowledge is based on mouse research while human and mouse spermatogenesis differ fundamentally in their physiological and molecular regulation. An in vitro model for human spermatogenesis will thus accelerate both fundamental and translational research on male fertility. ●



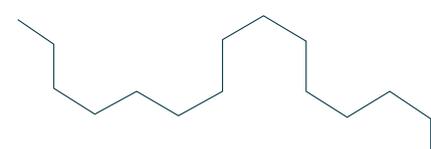
**“BPD may lead to long-term neurodevelopmental sequelae, manifested as reductions in cognitive, motor and/or scholastic performance”**

# Research at the crossroad of Neonatology and Pediatric Endocrinology:

Endocrine profiling of vulnerable infants  
to improve long-term outcome



Despite advances in the management of very preterm (<30 weeks of gestation) infants, a considerable proportion of them remain at high risk of morbidity. One of the major challenges is bronchopulmonary dysplasia [BPD].



### BRONCHOPULMONARY DYSPLASIA

Bronchopulmonary dysplasia (BPD) results from injury superimposed on immature lungs. Among the clinical features of BPD are prolonged respiratory support, respiratory symptoms like wheezing and shortness of breath, and risk of hospitalization during respiratory tract infections. These features tend to improve with age. Lung function tests of adolescents previously diagnosed with BPD show a reduced lung capacity and evidence of obstructive airway disease. In addition to pulmonary symptomatology, BPD may lead to long-term neurodevelopmental sequelae, manifested as reductions in cognitive, motor and/or scholastic performance. In very preterm infants, of all perinatal factors BPD was estimated to explain 65% of the variance in intelligence quotient.

### CLINICAL PREDICTION MODELS

The pathophysiology of BPD is complex, and is thought to involve a combination of immaturity, ventilation-induced trauma, toxicity due to supplemental oxygen, and (pre- and postnatal) inflammation. Due to their anti-inflammatory effects, systemic corticosteroids have proven to be effective for the prevention of BPD, but their use is complicated by concerns about brain damage. Studies have shown that infants at high risk of BPD may benefit from corticosteroids, whereas in infants at low risk of BPD the adverse effects of this treatment probably outweigh the beneficial effects, illustrating the need for a highly accurate prediction model for BPD. However, current clinical prediction models for BPD lack accuracy, as was recently confirmed by a systemic review from a multinational team, led by our group. An accurate prediction model for BPD is urgently needed, so that infants at risk of BPD can be timely treated with prophylactic corticosteroids, and infants not at risk of BPD are withheld from this treatment, assuring optimal neurodevelopment.

### CORTISOL

A factor in the road to BPD that has not been studied in detail is the preterm adrenal

**“An accurate prediction model for BPD is urgently needed, so that infants at risk of BPD can be timely treated with prophylactic corticosteroids, and infants not at risk of BPD are withheld from this treatment, assuring optimal neurodevelopment”**

cortex. The adrenal-cortex hormone cortisol is key for the dampening of inflammation. However, very preterm infants in their first weeks of life often fail to mount a sufficient cortisol response for the degree of inflammation, leading to a pro-inflammatory state. Studies investigating associations between cortisol concentrations and development of BPD have shown conflicting results, probably due to the complex regulation of the preterm hypothalamus-pituitary-adrenal (HPA) axis. Multiple levels along the HPA axis may be compromised in preterm infants. In any pregnancy, the placental barrier enzyme  $11\beta$ -hydroxysteroid dehydrogenase type 2 protects the fetus from overexposure to maternal cortisol, by converting it to its inactive form cortisone. Near parturition, the activity of this enzyme decreases, resulting in an increased transplacental supply of maternal cortisol. Furthermore, later in gestation the placenta secretes increasing amounts of corticotropin-releasing hormone (CRH), which stimulates the fetal adrenal to secrete cortisol in a self-perpetuating positive feedback loop. Both these mechanisms suppress fetal hypothalamic CRH, which may continue for weeks after birth. In sick very preterm infants, who have high cortisol demands, this may manifest as adrenocortical insufficiency.



Wes  
Onland

Michelle  
Romijn

Martijn  
Finken

### ADRENAL-CORTEX ENZYMES

Another mechanism contributing to cortisol depletion after very preterm birth is immaturity of adrenal-cortex enzymes, notably a decreased expression and activity of 11 $\beta$ -hydroxylase, which is necessary for the conversion of 11-deoxycortisol to cortisol. Due to the accumulation of the cortisol precursors 11-deoxycortisol and 17-hydroxyprogesterone the binding of cortisol to the glucocorticoid receptor is hindered. In other words, a given concentration of cortisol is less effective in tissues in the presence of high levels of cortisol precursors. In addition, the effectivity of cortisol in tissues may depend on genetic factors involved in glucocorticoid signaling and lung development.

### INTERDISCIPLINARY COLLABORATION

As part of Michelle Romijn's PhD trajectory, with a team of pediatric endocrinologists, neonatologists and pediatric neuroscientists, the team is currently developing a

prediction model for BPD, based on a set of pro-inflammatory and anti-inflammatory markers. The tested model includes serial assessment of: [1] adrenocortical output as assessed from cortisol, 11-deoxycortisol and 17-hydroxyprogesterone (in blood); [2] single-nucleotide polymorphisms in corticosteroid-responsive genes expressed during lung development (in cord blood or placenta), and [3] pulmonary inflammation as assessed by volatile organic compounds (in exhaled breath) and interleukins (in blood). Consistent with the hypothesis, in the feasibility part of the project (of N =70) the researchers found that those very preterm infants who developed BPD had higher concentrations of 11-deoxycortisol and 17-hydroxyprogesterone, in spite of a similar cortisol concentration, at various points during the first week of life.

In a larger multicenter cohort the team is currently validating the performance of the above methodology for the prediction of BPD. Next, they will test neurodevelopment

at follow-up. This will not only be ascertained by regular tests, i.e., the Bayley Scales of Infant Development [at the corrected age of 2 years], but also by eye tracking [at the corrected age of 1 year], which is able to isolate fundamental cognitive processes with strong predictive value for later neurodevelopmental outcome. The proposed strategy may have the potential to specifically target the prescription of corticosteroids in order to improve outcome after very preterm birth. As such, this project is a striking example of the need for interdisciplinary collaboration to solve clinical dilemmas. ●



# Beyond the scope of obstetrics alone – gestational diabetes



Gestational diabetes mellitus (GDM) is the most common metabolic disorder in pregnancy and complicates around 3-5% of pregnancies in the Netherlands.



Doortje  
Rademaker



Rebecca  
Painter

## GESTATIONAL DIABETES MELLITUS

Gestational diabetes mellitus (GDM) is defined as hyperglycemia first diagnosed in pregnancy. GDM carries substantial risks for mother and baby, both in the short as well as in the and long-term. Short-term consequences for the baby include large-for-gestational-age, shoulder dystocia, and neonatal hypoglycemia. For the mother, preeclampsia and caesarean section are amongst the short-term risks. Long-term consequences include increased type 2 diabetes mellitus (T2DM) and cardiovascular disease in later life, both among mothers affected by GDM as well as their children. Treatment of GDM consists of a combination of dietary advice and glucose monitoring, supplemented with antihyperglycemic agents in the minority of cases unable to achieve euglycemia with dietary measures alone.

Historically, and in analogy to T2DM, GDM was diagnosed by using a two-point oral glucose tolerance test (OGTT). Blood draws were performed after an overnight fast and 2-hours after a 75 gram oral glucose load (a 250 ml drink). The OGTT thresholds for diagnosis of T2DM were based on the increased risk of cardiovascular disease and diabetic complications, but had been poorly studied in relation to pregnancy outcomes. This changed in 2008, when the large international HAPO (Hyperglycemia and Adverse Pregnancy Outcomes)

study provided evidence for the link between increased glycemia in pregnancy and increased adverse pregnancy outcomes, hoping to define a clear cut-off at which level of glycemia the disease entity GDM should be diagnosed. The HAPO study had used a three-point OGTT, adding a third blood draw after 1-hour after 75 gram oral glucose load. However, the graded linear increase in adverse perinatal outcomes with increasing fasting, 1-hour and 2-hour glucose values upon OGTT did not delineate clearly where normoglycemia ended and hyperglycemia in pregnancy began. Nonetheless, new WHO diagnostic guidelines for GDM were established in 2013 using an arbitrary threshold based on the HAPO study's results. There has been considerable international uptake of the new GDM definition. As a result of the stricter guidelines, upon full implementation in the Netherlands, a surge in incidence of GDM from 3-5% to 10-12% was to be anticipated. To the present day, it remains unclear to which extent the additional and newly diagnosed 7-9% cases of mild GDM are likely to benefit from GDM treatment, initially developed for those with much higher levels of hyperglycemia in pregnancy.

## WHEN TO DIAGNOSE GESTATIONAL DIABETES?

### TANGO-DM TRIAL

*At present, there is no randomized trial evidence that GDM treatment according to these*

new thresholds leads to improved perinatal outcomes for additionally diagnosed GDM cases. The TANGO-DM is an ongoing multicenter randomized controlled trial, in which women who have undergone an OGTT yielding mild hyperglycemia in pregnancy are eligible for participation. Mild hyperglycemia is defined as (a) glucose concentration(s) on OGTT discordant between the old and new WHO diagnostic criteria for GDM. Three features mark out the unique qualities of the trial. First: the trial design uses a discordancy design, which means only those for whom there is treatment equipoise are offered participation. Randomization is to either treatment for GDM or normal obstetric care. Second, this trial is currently taking place in hospitals as well as community midwifery practices, a setting unique to the Netherlands. Participants are therefore offered the full spectrum of antenatal care, including home delivery, when this is deemed appropriate. Third, the trial was funded by 'Leading the Change' as well as ZonMw, and both in its project team as well as its funders - involving the federation of medical specialists, representatives of health care insurance companies as well as 'Het Kennisinstituut' - is an example of how collaboration between multiple stakeholders can result in high quality research.

After its completion, the TANGO-DM trial will be able to guide policy in the Netherlands regarding cost effectiveness of GDM diagnostic criteria. Moreover, the trial's findings will help systematically interrogate the question of overdiagnosis of GDM, using a 9-point checklist which evaluates trigger for change, test quality and the balance of benefits and risks of altering the diagnosis. Remaining questions, not addressed in the TANGO-DM trial, are which women (all women, or only those with a risk factor for GDM) qualify for screening for GDM. Finally, TANGO-DM will provide the opportunity to investigate whether the identification of (mild) GDM can lead to improvements of the long-term metabolic risks in mothers and their offspring.

### OPTIMAL TREATMENT OF GESTATIONAL DIABETES

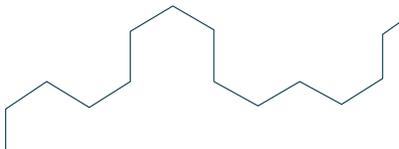
When euglycemia is not reached with diet alone, antihyperglycemic agents are started. Subcutaneous insulin injections have traditionally been used as first-choice treatment for GDM in the Netherlands

and are still advocated in many guidelines. Alternatively oral glucose lowering drugs have been proposed, most commonly metformin. Both insulin and oral agents have advantages and disadvantages. Insulin is safe and effective; however, it is considered burdensome by pregnant women, requires intensive glucose monitoring and can result in episodes of maternal hypoglycaemia. Oral agents are less costly, less burdensome, hypoglycemic events do not occur and these agents are associated with higher patient satisfaction, but may be less potent than insulin.

#### SUGAR-DIP TRIAL

*In the SUGAR-DIP trial, a separate multicenter randomized controlled trial, the aim is to assess non-inferiority of oral GDM treatment with metformin (plus glibenclamide if required), compared with insulin. The study team expects that a large proportion of patients will achieve glycemic control with metformin only. By adding glibenclamide in combined treatment with metformin, the researchers expect to achieve glycemic control, as well as perinatal outcomes, similar to those achieved by insulin, while maintaining the benefits and ease of a less burdensome treatment with oral medication. This trial has required collaboration of different medical and paramedical specialists: obstetricians, endocrinologists and diabetes nurse-educators.*

After its completion, the SUGAR-DIP trial will be able to guide policy in the Netherlands regarding cost effectiveness and patient preferences of GDM treatment, as well as investigating the role of medication in offspring long-term cardiometabolic outcomes. Separate from the SUGAR-DIP trial, the possible effects of oral agents including metformin in pregnancy on the offspring's health are being studied in a systematic reviews and meta-analyses of human and also, separately, of animal studies. ●



**“TANGO-DM will provide the opportunity to investigate whether the identification of (mild) GDM can lead to improvements of the long-term metabolic risks in mothers and their offspring”**

**“A good collaboration between all professionals involved in maternity care is essential to achieve optimal maternal and perinatal outcomes”**



# Maternity care



Within the department of Midwifery Science, the organisation of maternity care is one of its main areas of research. The focus used to be on the echelon of care and place of birth. More recently the organisation of integrated maternity care is an important topic of study.



## “An important aspect of integrated maternity care is risk selection to identify the level of care women and neonates need”

### HOME BIRTH AND MORE

When people think of maternity care in the Netherlands, they think of home births. From all high income countries, the Netherlands has the highest percentage of women who give birth at home. Most women start their antenatal care in primary midwife-led care. If they develop risk factors or complications, they are referred to secondary obstetrician-led care where they receive care from midwives, nurses and (trainee) obstetricians. Women who are still in primary care at the onset of labour can choose to give birth at home, in a birth centre or in a hospital assisted by their primary care midwife. Because of its unique features, the Netherlands provides an ideal setting to study the quality of midwife-led care. The findings are important for the Netherlands and for other countries in which midwives have an autonomous position and where home birth is increasingly offered as a birth option.

A good collaboration between all professionals involved in maternity care is essential to achieve optimal maternal and perinatal outcomes. Our earlier research showed that among low risk women these

outcomes are equally good for those who start labour in midwife-led care compared to obstetrician-led care and among planned home versus planned hospital births. Women have fewer medical interventions if they start labour in midwife-led care and if they start labour at home.

However, several women are referred from midwife-led to obstetrician-led care during pregnancy and labour for example if they develop hypertension, if they want medical pain relief or if labour progress is slow. In that case, they have to get used to a new set of health professionals that they usually have not met before. Research has shown that receiving midwife-led continuity of care from one or a small team of midwives throughout pregnancy, labour and the postpartum period is associated with better outcomes, fewer medical interventions, increased satisfaction among women and lower costs.

### INTEGRATED CARE

To provide more continuity and improve collaboration, maternity care collaborations (MCCs) move towards integrated maternity care. They do that in many different

ways. Innovations include changes in the organisation of care, payment systems, the involvement of women in developing maternity care policies and closer collaborations between professionals in medical and social care and public health. Little research has been conducted into the effects of these innovations. Recently, we started the Variations in the Organisation of Integrated CarE (VOICE) study funded by ZonMw in which we work closely together with the National Institute for Public Health and the Environment (RIVM) and many other researchers, client organisations and care professionals. Jolanda Liebrechts has started recently as the VOICE PhD candidate. In this study, the team will examine which elements of integrated maternity care are associated with optimal maternal and perinatal outcomes, good experiences of women and professionals and limited costs. First, a scoping review will be conducted into these elements of integrated maternity care. Defining the search strategy will be challenging because integrated care means different things in different countries. For example, the researchers took part in a study for the US National Academies of Sciences,

Bahareh  
Goodarzi



Ank  
de Jonge



Jolanda  
Liebrechts



Engineering, and Medicine (NASEM) in which maternity care systems were described of four countries with better outcomes and lower costs than the United States to identify opportunities to improve the US system. Based on the findings, the contemporary maternity care systems in the four countries, including the Netherlands, were already considered to be 'integrated across birth settings'. The scoping review therefore needs to be focused on elements of organisation of care in addition to integrated care.

### RISK SELECTION

An important aspect of integrated maternity care is risk selection to identify the level of care women and neonates need. In every country in which midwives work autonomously, there are indication lists for situations in which a consult or transfer of care to obstetrician- or pediatrician-led care is recommended. In the move towards integrated maternity care, professionals look for ways to improve this risk selection process. However, this process is hindered by disagreement about the definition and effects of risk selection and how best to organise it. To enhance the understanding of risk selection, PhD candidate Bahareh Goodarzi conducted five studies, analysing the concept, the history, the organisation, and the practice of risk selection in maternity

care in the Netherlands. In her scoping review she found that risk selection has three main dimensions: 1) it is an organisational measure to optimally align women's and children's needs and resources, 2) it is a practice to detect and assess risk and to make decisions about the delivery of care, and 3) it is a tool to ensure safe care. Risk selection is focused on how care providers can prevent underuse of care. Less attention is paid to avoiding overuse of care and to adjusting care to women's needs.

In Bahareh's study on organisation of care, she identified three methods of risk selection (MRS) in the Netherlands. [[Models of Risk Selection in Maternal and Newborn Care: Exploring the Organization of Tasks and Responsibilities of Primary Care Midwives and Obstetricians in Risk Selection across The Netherlands - PMC \(nih.gov\)](#)] In 42 of the MCCs, midwives and obstetricians work according to the usual MRS, where primary care midwives assess risk at the booking appointment and, when necessary, initiate a consult or transfer of care without consulting an obstetrician first. In 16 MCCs, primary care midwives assess risk at the booking appointment and make the decision to consult or transfer care in collaboration with obstetricians. In the third model (11 MCCs) the organization of tasks and responsibilities

regarding risk assessment is varied or unclear. No significant difference was found between MRS and professionals' level of satisfaction. This study will be used in the VOICE study.

Bahareh used data from the national perinatal registry [Perined] to study the perinatal mortality rate among different subgroups of women and found that this rate differed when taking multiple maternal characteristics into account. The highest probability of perinatal mortality was found among non-Dutch, low-SES women, nulliparous women aged  $\geq 40$  years and women aged up to 29 years with  $\geq 3$  previous births. The findings indicate that making a decision about induction of labour to prevent fetal and neonatal mortality based on a single determinant may lead to the overuse or underuse of this intervention.

#### CONTINUITY OF CARE BY MIDWIVES

Another important aspect of integrated care is continuity of care. In the COntinuity of Midwifery Care (COMIC) study, a realist evaluation into successful and unsuccessful continuity of care interventions will be conducted. This will result in building blocks that can be used by midwifery practices and MCCs that want to enhance continuity of care. The first part of this study is funded by the Dutch Organisation of Midwives (KNOV). By conducting a series of challenging studies

with an enthusiastic research team, we contribute to evidence that is needed to improve the maternity care system in the Netherlands and other countries. ●

**“By conducting a series of studies we contribute to evidence that is needed to improve the maternity care system in the Netherlands and worldwide”**



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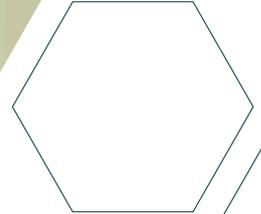
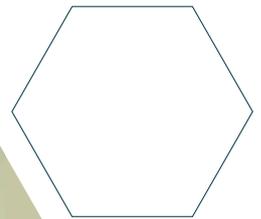
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# AR&D events 2021

○○○

## AR&D ANNUAL SYMPOSIUM

May 19th, 2021

On May 19, the annual AR&D Symposium 2021 was organized. The theme of this year's [online] symposium was 'COVID-19: virology, vaccines and the clinical experiences in children and adults'.

The symposium's hosts and AR&D board members Prof. Dr. Jaap Oosterlaan and Prof. Dr. Anton van Kaam introduced the first keynote speaker, Prof. Dr. Cécile van Els (UMC Utrecht and National Institute for Public Health and the Environment (RIVM)), who spoke about the COVID-19 vaccinations. She gave insights into the different vaccines and the fast development and implementation. Further, she discussed some first data, current challenges and what to expect in the near future.

The afternoon continued with the grant award ceremony and pitches from AR&D grant winners. After the pitches, Prof. Dr. Taco Kuijpers gave an insight in the Multi-Inflammatory syndrome in Children (MIS-C), and talked about how there is overlap in features between MIS-C patients and KD (Kawasaki Disease) or KDSS (Kawasaki Disease Shock Syndrome) cases. The final speaker was Prof. Dr. Janneke Horn, Neurologist-Intensivist at the Intensive Care Unit (ICU) of Amsterdam UMC. She took the audience back to winter 2020 and all the creative measures which were taken to prepare the hospital and staff for all the extra admissions. At the time of the presentation, 12,000 patients had been admitted to the ICU and many lessons have been learned, such as the benefits of high flow nasal oxygen therapy or immune suppressive medication.



## AR&D 5TH YEAR ANNIVERSARY EVENT

September 24th, 2021

In 2021, the AR&D research institute was celebrating its fifth year anniversary, in honour of which the anniversary event was organized on September, 24th. This hybrid event was held in AMC and was also available via livestream. We looked back on what we have achieved together in the last five years and had some inspiring guests who gave us a glimpse of the future.

The first speaker was Prof. Lucilla Poston, head of School of Life Course Sciences and affiliated to St Thomas' Hospital, London. Prof. Poston was virtually present from London and told us about challenges in randomised controlled trials in pregnancy and the need for more basic science. She gave her thoughts on future research perspectives by going back to the drawing board and focus on translational and fundamental research before starting new randomised controlled trials. After her talk, Prof. Sjoerd Repping, one of the founding fathers of the AR&D research institute and currently working at the National Healthcare Institute (ZIN), told us all about the creation of the research institute and looked forward to the strategic vision for 2021 to 2025. His plea was to increase the quality of our research even more and become visible as an





European top research institute by focusing on research teams and not only on individuals.

The event ended with two great AR&D researchers who were awarded with an AR&D grant in the past five years. Dr. Mariëlle Alders, from the department of Human Genetics, presented her work on epigenatures as a diagnostic tool for developmental disorders. With the AR&D grant she and her research group were able to expand EpiSign, a epigenetic test, that is currently able to detect 62 different syndromes. Then, Dr. Callista Mulder from the Reproductive Biology Laboratory, presented her research on in vitro spermatogenesis. Despite human in vitro spermatogenesis is not yet possible at the moment, the AR&D grant gave new opportunities to investigate this problem.

### AR&D RETREAT 2021-(RE)CONNECTED November 4th, 2021

On November 4th, the third edition of the AR&D Retreat took place at Kleurstoff in Amsterdam. Around 70 PhD students, post-docs and PI's (re)connected with the experts and fellow researchers after a full year of working from home.

After a short introduction of the program by the AR&D board directors, Christianne de Groot and Lidewij Henneman, the day started with a motivational talk by Joyce Browne., Assistant Professor, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht. She presented challenges

in her personal research career and inspired us to think about integration of global health, health equity and sustainable development in our own research projects surrounding the theme 'Let's make things better together (and enjoy the process)'. The program continued with presentations from AR&D PhD students and PI's who received an AR&D grant in previous years representing all four phases of AR&D. The first phase is Preconception & Conception in which Geert Hamer presented his research on reproductive cells and development of cancer. The phase Embryonic & Fetal Development was presented by Marieke Buijtendijk and Bernadette de Bakker, who told about their project on imaging human development. For the next phase, Pregnancy & Birth, Sanne Zilver spoke about the design of the project on COVID-19 vaccination in pregnant women. The last phase, Child Development, was completed by Cece Kooper and Marsh Königs who presented about Personalizing prognosis for Children with Traumatic Brain Injury. After lunch, a key-note lecture was given by Prof. Dr. Ivana Išgum, Department of Biomedical Engineering and Physics, Amsterdam UMC and her PhD student Louis van Harten. Van Harten took us into the world of artificial intelligence (AI), machine

learning and deep learning for imaging analysis and Išgum told us about the use of AI for Neonatal Brain Analysis.

To (re)connect with our fellow AR&D researchers a lively speed-date session was organized. Questions like 'what is your most research finding?' and 'if you were on X-factor, what talent would you show?' were discussed in small groups. Hopefully, new connections have been made. The program ended with an interactive panel discussion with Prof. Dr. Nils Lambalk as moderator. He discussed together with a panel including AR&D researchers Arjan Griffioen, Madelon van Wely, Karuna van der Meij and the audience on the topic of what makes a scientific paper of good quality. ●

# AR&D grants 2021

○○○ OPEN RESEARCH GRANTS, AND PRINTING COSTS OF THESE

As part of the AR&D mission and vision to contribute to the advancement of knowledge about all aspects of human reproduction and development, we provide research grants, travel grants and funding for publication of PhD theses. The studies that were funded in 2021 are diverse and multidisciplinary and show the breadth and width of AR&D research.



## START SMALL, THINK BIG GRANT (TYPE 1): € 25.000

### Kelly Dingess

*Immunity against SARS-Coronavirus 2 in breast milk: Deep Immunoglobulin clonal profiling by mass spectrometry of the COVID-19 MILK – Extended and POWER MILK Studies.*

My name is Kelly Dingess, and I work as a Senior Scientist in the Human Milk Research and Analytical Sciences team. The prospect of becoming a mother interestingly ties into my own research where I have worked to help innovate research in neonatal health and development. Specifically I have sought to do this through the study and analysis of human milk.

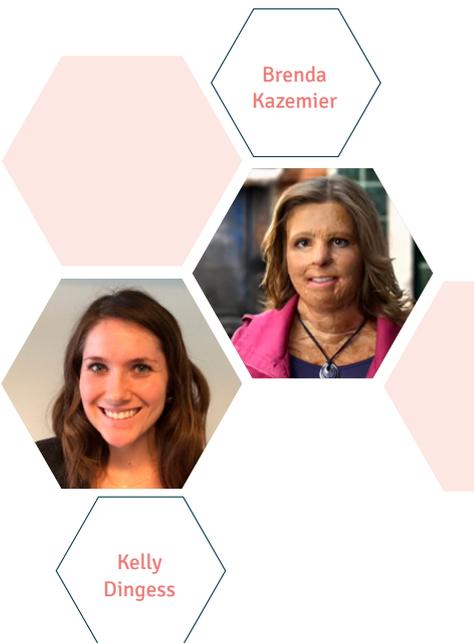
The aim of the research project for the 2021 AR&D grant was to elucidate the longitudinal human milk and serum immunoglobulin A1 (IgA1) antibodies from SARS-CoV-2 infected and vaccinated women to determine antibody longevity and evolution after infection or vaccination. When I realized that this would become a reality I had a mix of emotions, happy and excited being the most prevalent. This was an important grant for me because it meant that I could not only continue the work that I was dedicated and passionate about but also that I would have the funding needed for my Postdoc. Because of this grant I was able to finalize the work I started as a PhD, gain grant writing and Postdoc experience.

### Brenda Kazemier

*Lockdown for COVID-19 and prevalence of infections in pregnancy in the Amsterdam UMC.*

My name is Brenda Kazemier, I am a resident obstetrics and gynecology and researcher at the Department of Obstetrics and Gynecology in Amsterdam UMC. Since the outbreak of COVID-19, mitigation measures and hygiene advises were implemented to prevent spread of infection. Relatively soon reports of a marked drop in preterm births during the lockdown were published. Since previous research showed an association between infections and preterm birth, our team therefore wondered whether infections in pregnancy have been affected by lockdown measures as well.

The aim of our study was therefore to investigate to what extent the incidence of infections in pregnancy was altered during the period of lockdown for COVID-19. Me and my team were so grateful to receive the grant and be able to unravel this mystery a little further. Thanks to this grant, PhD student Dominique Werter was able to completely dive into the subject and establish a great collaboration with the Department of Microbiology of Amsterdam UMC. Together with the Amsterdam UMC Research Data Platform and researchers from both original location AMC and VUMC,



we were able to construct a solid database containing pseudomized laboratory results from pregnant women and interpret the results correctly. We have obtained the first exiting results on seroconversion of CMV virus during and before the lockdown, carriage of group B streptococcus and the number of women with a positive urine culture.

### Mauritia Marijnen

*Linking national registries PALGA and Perined to understand the effect of specific placental lesions on key obstetric outcomes.*

My name is Mauritia Marijnen and I am working as a medical doctor and PhD student at the Department of Obstetrics and Gynecology of Amsterdam UMC, location AMC. My PhD consists of research projects related to fetal growth restriction and placental insufficiency.

In 2021, I received the Start small, Think Big grant for our research project 'Linking national registries PALGA and Perined to understand the effect of specific placental lesions on key obstetric outcomes'. When I found out I was selected for the grant, I felt super excited and grateful to have the opportunity to set up this important research project. I am also thankful to my supervisors Wessel Ganzevoort and Sanne Gordijn for their supervision and support.

Thanks to this grant we are able to set up a nationwide cohort study about the relation between placental lesions and the development of pregnancy complications. The national birth registry of the Netherlands (Perined) will be linked to the Dutch pathology database (PALGA). By using a predefined search strategy we search through more than 230,000 records for specific placental lesions. Specific lesions and their relation to perinatal outcomes, such as fetal growth restriction and fetal demise, are analyzed. This unique dataset enables us to better understand pregnancy complications and improve care for future pregnancies.

### Eva van der Meij

*Developing multidisciplinary convalescence recommendations for recovery after childbirth; a modified Delphi study.*

My name is Eva van der Meij, and I work as a gynecologist in training and senior researcher at Amsterdam UMC. After receiving my PhD in 2019, it was clear that I wanted to continue doing research which should focus on preventive medicines and eHealth.

This was based on my experiences in this field during my PhD period (During my PhD period I developed an eHealth intervention which focused on improving recovery after surgery), but also on my experiences as a resident in gynecology where I am faced several times a day with recovery problems of women after childbirth.

Women are discharged soon after delivery and do not get instructions about the recovery process. As a consequence, recovery takes much longer than expected, with a negative impact on general health and society. To address this problem, last year I received an AR&D grant (which was quite an honor!) to develop multidisciplinary convalescence recommendations in relation to the recovery period after childbirth. We have performed a Delphi study among a multidisciplinary panel of fifteen experts consisting of gynecologists, midwives, general practitioners and maternity nurses, and have developed detailed convalescence recommendations for graded resumption of 25 activities after a vaginal delivery and caesarian section, tailored to the patient. We are writing a scientific article about the study and the results and we are incorporating the recommendations in a national guideline and an eHealth intervention called 'ikHerstel'. By doing this, a large group of women can benefit from the recommendations during their recovery after childbirth. Many thanks to AR&D for making this possible!



Mauritia  
Marijnen



Eva  
van der Meij



Liesbeth  
van Leeuwen



Velja  
Mijatovic

## IN BETWEEN GRANT (TYPE 2):

€50.000

### Liesbeth van Leeuwen

*PREGCOVAC-19: The efficacy, optimum timing and safety of COVID-19 vaccination in pregnant women.*

My name is Liesbeth van Leeuwen and I am a maternal fetal medicine specialist. The aim of my research project was evaluation of IgG antibody response and virus neutralization in pregnant women after one and two COVID-19 vaccinations with mRNA vaccines, evaluation of the optimal timing of vaccination in relation to maternal antibody response and trans placental IgG antibody transfer, and evaluation of the frequency of side effects and obstetric outcomes after COVID-19 vaccination.

I received the grant in the spring of 2021 and I was thrilled as it was the first time I got a grant and I was really eager to be able to do COVID-19 research. We have executed the PREGCOVAC-19 trial, included almost 200 patients and are now doing the final analyses of the results. Hopefully this will also lead to spin off for more research.

### Velja Mijatovic

*Evaluating the long-term neurocognitive effects of preconceptional exposure to iodinated contrast on the offspring (Neuro-H2Oil Study).*

My name is Velja Mijatovic. I am a gynecologist working at the Department of Reproductive Medicine at Amsterdam UMC. As a principal investigator at AR&D and as a professor in obstetrics and gynecology with special focus on endometriosis, I am responsible for research on tubal (dys)function and endometriosis. In the spring of 2021 we were awarded an AR&D grant to conduct a follow-up study in the children of mothers who participated in a nationwide multi-

centre clinical trial of a fertility diagnostic that is frequently used in the Netherlands and around the world. When women have trouble conceiving, a gynecologist might conduct a hysterosalpingography (HSG) to visualise any blockages of the Fallopian tubes using iodinated contrast. We are investigating if the use of iodinated contrast in this procedure has any consequences for the brain development of the offspring, now age 6-9 years, conceived less than 6 months after the HSG procedure. Our team consists of gynecologists, pediatricians, neuroscientists, and epidemiologists. Our research group was very glad that our research proposal was awarded with the AR&D grant. We immediately started to work on the research protocol in order to submit it as soon as possible to the ethical board.

So far, the parents of nearly seventy children have agreed to participate in the Neuro-H2Oil study, and we have tested more than forty children at Amsterdam UMC, partnering clinics in which the original H2Oil trial took place, or through home visits throughout the Netherlands. Through this research we hope to verify the safety of this frequently used medical intervention and inform future parents better on the long-term impacts of the procedure. Two master students in clinical psychology and one MD/PhD student will use these data to investigate whether children whose mothers received an HSG just before conception differ in neurocognition, intelligence, school outcomes, or behaviour at home or in the class room from children that were conceived naturally without any medical intervention.



Wendy Dankers

### Wendy Dankers

*Designing an in vitro placenta model to study maternal-fetal tolerance in SLE patients.*

My name is Wendy Dankers and I am a postdoc working in the Department of Rheumatology and Clinical Immunology and the Department of Experimental Immunology at Amsterdam UMC.

Last year I came back to the Netherlands after having spent 3,5 years in Australia for my first postdoc, studying the molecular mechanisms of a potential glucocorticoid alternative in the autoimmune disease systemic lupus erythematosus (SLE).

Next to my studies in autoimmunity I have always been very interested in the role of the immune system during pregnancy. These two things come together in the new research program that I am now building at Amsterdam UMC together with Marjon de Boer, Irene Bultink and Lisa van Baarsen. Our goal is to understand the biological processes behind the high risk of pregnancy complications for women with SLE, and the AR&D grant was the fantastic first step towards starting this program!

With this grant we are able to build and validate an innovative 3D model to study the maternal-fetal interface in vitro, obtain new insights about the elusive processes that drive maternal-fetal tolerance and how this fails in women with SLE.

### Renee Burger

*Obstetric conditions and cardiovascular health across ethnic groups in the Netherlands.*

My name is Renée Burger. I am a PhD student at Amsterdam UMC, Department of Obstetrics and Gynecology, working under supervision of Wessel Ganzevoort (Amsterdam UMC) and Sanne Gordijn (UMC Groningen). At the same time, I work as MD in the Department of Obstetrics and Gynecology. The focus of my PhD is on long-term consequences of pregnancy complications on maternal and offspring health.

I was very honored to be awarded an AR&D internal grant in 2021 for our research project on obstetric conditions and cardiovascular health across ethnic groups in the Netherlands. The aim of this study is to examine the relationship between cardiovascular risk factors before and after pregnancy and major obstetric complications across ethnic groups, in order to guide future management and identify possibilities for preventive measures in women of non-western descent.

The grant enabled us to start this interesting project. We are working on the association of hypertensive disorders of pregnancy, gestational diabetes, preterm birth and fetal growth restriction with cardiovascular risk in the years after pregnancy across ethnic groups. We collaborate closely with colleagues from the Amsterdam Public Health research institute, and I am very grateful specifically to Irene van Valkengoed for her expertise and guidance. Furthermore, we managed to secure additional funding from ZonMw, that enables me to continue and fully execute the next stages of the project.



Renee Burger



Mandy Spaan



Wes Onland

**Mandy Spaan**

*School performance of children conceived by assisted reproductive technology.*

My name is Mandy Spaan, and I work as a postdoctoral researcher at the Department of Epidemiology and Data Science at Amsterdam UMC. In 2017, I received my first AR&D grant. With this grant, I expanded our nationwide cohort of children born to subfertile couples that were treated with assisted reproductive technology (ART) in 1983-2000, with children born to subfertile couples treated in 2001-2010. Within this expanded cohort study we investigated the long-term risk of childhood cancer in ART-children.

The overall purpose of the nationwide ART-offspring cohort study is to achieve knowledge about the influence of the ART procedure on developmental trajectories of children. As academic performance is an early indicator of later wellbeing, and associated with better overall health in adult life, we applied for a second AR&D grant aiming to study school performance among ART-children. To achieve this, the cohort is linked with data from Statistics Netherlands enabling to collect exam scores from primary and secondary school, and highest achieved educational level. Results are expected in the summer of 2022.

I am very grateful to AR&D for granting two of my projects. Besides the scientific evidence, the AR&D grants also resulted in a very important collaboration between Amsterdam UMC (Prof. Roseboom, Prof. Goddijn, Em. Prof. Lambalk) and the Netherlands Cancer Institute (Prof. van Leeuwen). Furthermore, the grants give me the opportunity to build our cohort to a nationwide source for studying several health outcomes among ART-children, which

will contribute to a complete picture of the long-term health of ART-children.

**Wes Onland**

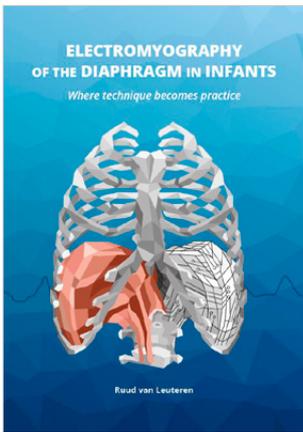
*The effect of Systemic Hydrocortisone on the Preterm Brain assessed by neuroimaging in the SToPBPD (Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants) study.*

My name is Wes Onland, neonatologist at the IC department of Neonatology of the Emma Children's Hospital Amsterdam UMC since 2008.

In our department we treat the most vulnerable patients of the hospital. The most common complication of preterm birth remains bronchopulmonary dysplasia (BPD, a chronic lung disease with life lasting consequences. With all Dutch and Belgium departments, we have performed a placebo controlled randomized controlled trial investigating if hydrocortisone reduces the BPD incidence in high risk preterm infants without adverse neurodevelopmental outcomes.

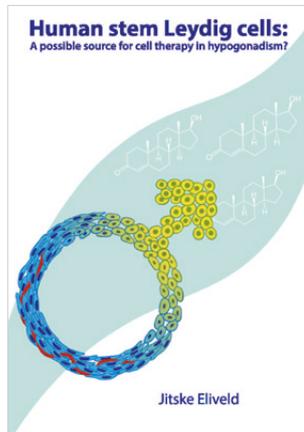
Thanks to the AR&D's grant, we will be able to in great detail investigate the effect of this anti-inflammatory medication on brain development using advanced MRI neuroimaging. We have now set up the sequences and analyses to determine cerebral white matter integrity using diffusion tensor imaging (DTI) and fractional anisotropy (FA), cortical, deep gray matter, cerebellar abnormalities, and brain volumes. This study will determine if hydrocortisone is safe to use on the young brains of preterm infants. ●

○○○ A SELECTION OF THE PHD THESES FROM AR&D THAT RECEIVED FINANCIAL SUPPORT FOR PRINTING



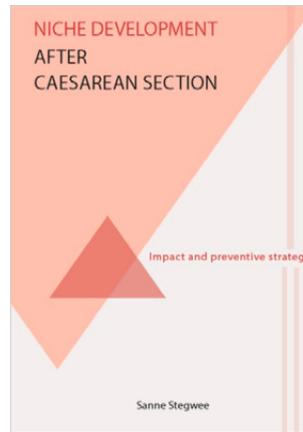
**Electromyography of the diaphragm in infants. Where technique becomes practice**  
Ruud van Leuteren

Electromyography of the diaphragm in infants. Where technique becomes practice  
Transcutaneous electromyography of the diaphragm (dEMG) was investigated as a non-invasive measurement technique to monitor respiration, quantify respiratory effort at the start of life and assess the possibilities of dEMG as a clinical tool in the neonatal intensive care unit. The studies show that signal acquisition and analysis require standardization. The clinical studies support future use of dEMG in the delivery room and show that dEMG can provide clinically useful information to improve the titration of respiratory support in the future.



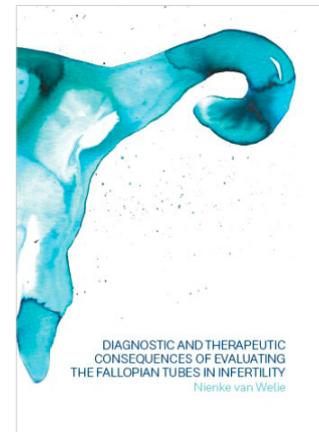
**Human stem Leydig cells: a possible source for cell therapy in hypogonadism?**  
Jitse Eliveld

Hypogonadism, a clinical condition due to low testosterone levels, might occur after testicular sperm extraction. We aimed at clarifying this risk by performing a systemic literature review and a cohort study. A potential future therapy for hypogonadism might be cell therapy to restore testosterone levels. As a first prerequisite step we investigated the expression of multiple proteins in human testicular cells, and their potential as markers for the isolation of human stem Leydig cells.



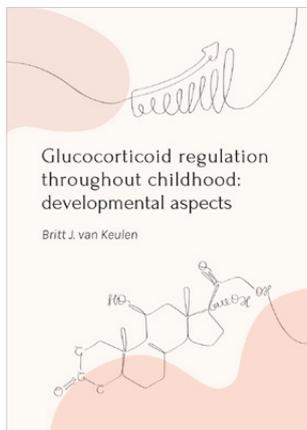
**Niche development after caesarean section – impact and preventive strategies**  
Sanne Stegwee

The development and internal validation of a prediction model for the development of a niche. We describe univariate analysis of these factors on the outcome 'niche' (indentation  $\geq 2$  mm). The strongest predictors were gestational age, twin pregnancy, double-layer closure, less surgical experience, smoking (risk factors) and multiparity and vicryl suture material (protective factors). It remains very difficult to predict who will develop a niche and who will not and we have probably not taken into account all possible predictors.



**Diagnostic and therapeutic consequences of evaluating the fallopian tubes in infertility**  
Nienke van Welie

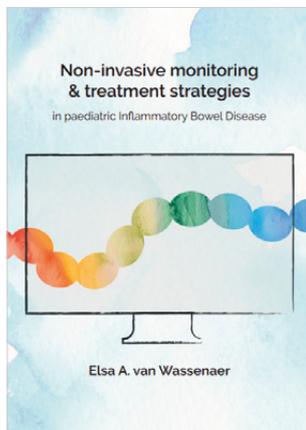
Tubal flushing with the use of an oil-based contrast increases the short-term [6 months] pregnancy chance and subsequent live birth chance compared to the use of a water-based contrast in couples infertility. Also on the long-term (up to 5 years), an hysterosalpingography (HSG) with oil-based contrast results in a higher pregnancy and subsequent live birth chance, chance of a naturally conceived pregnancy and a shorter time to pregnancy. Furthermore, this thesis showed that HyFoSy can replace HSG as first choice diagnostic tubal patency test during fertility work-up.



**Glucocorticoid regulation throughout childhood: developmental aspects**

Britt van Keulen

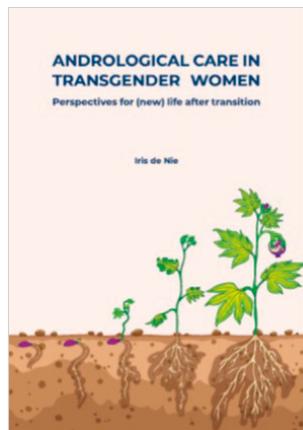
We have tried to study the variability in the production and metabolism of the stress hormone cortisol. We found that the environment plays an important role in the production of the stress hormone, and that these environmental influences are dynamic over time. These insights offer opportunities for future research to optimize long-term health. Moreover, sex differences in cortisol metabolism emerge during pubertal development. This may have consequences for cortisol replacement therapy.



**Non-invasive monitoring & treatment strategies in paediatric Inflammatory Bowel Disease**

Elsa van Wassemaer

Inflammatory Bowel Disease (IBD) is a debilitating chronic relapsing and remitting condition. This thesis focused on non-invasive monitoring strategies for IBD in children, with a focus on the use of intestinal ultrasound (IUS). We analysed the patient perspectives on IUS and assessed diagnostic accuracy of IUS. Furthermore, we assessed whether a physician can be trained to perform a point-of-care IUS with equal accuracy as a pediatric radiologist and lastly, we demonstrated the clinical added value of IUS as point-of-care monitoring tool.



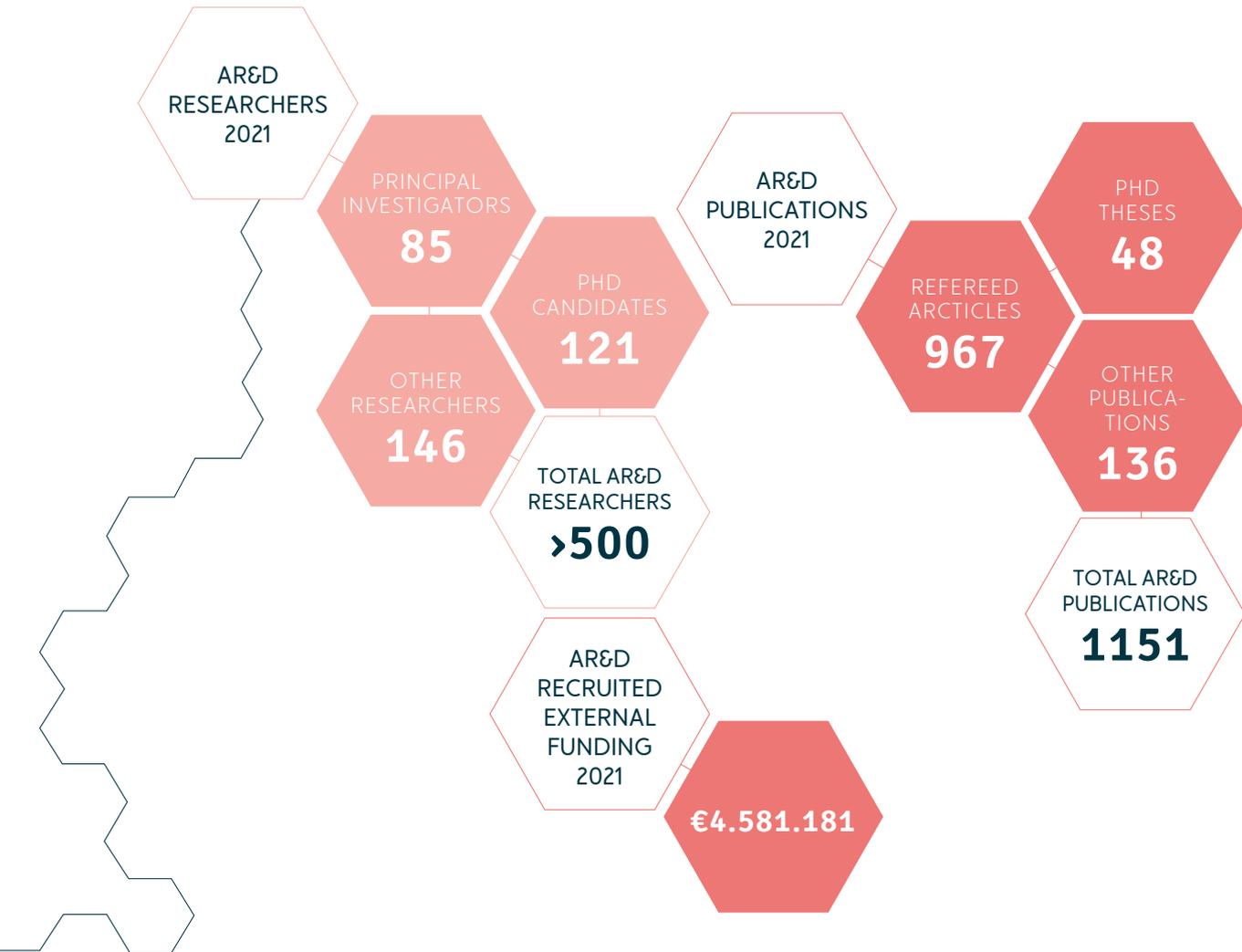
**Andrological care in transgender women - Perspectives for (new) life after transition**

Iris de Nie

This thesis focusses on Andrological care in transgender women. We explored topics such as a desire to have children, the importance of having genetically related offspring, semen quality and the influence of lifestyle, and possibilities for fertility preservation in transgender women. Furthermore we assessed to influence of gender affirming hormone treatment on testicular and prostate cancer and observed no increased risk in transgender women. Taken all our results into account, the perspectives for (new) life after transition seem positive.

# Numbers and highlights

○○○ AR&D IN NUMBERS



## DISCLAIMER RESEARCH INFORMATION RESEARCHERS

Information about the number of researchers affiliated with AR&D was collected using the Research Information Systems Pure VUMC and Pure AMC on May 18th, 2022. Registration of research institute affiliation was done by the researchers themselves, by personnel from the Medical Library AMC, by secretary of corresponding AMC/VUMC department or by the policy officers of the AR&D research institute. Due to incomplete linkage to Pure (VU/UvA/VUmc/AMC) the actual numbers affiliated to AR&D is higher.

## PUBLICATIONS

The reported data include all published research output as registered in the Research Information Systems Pure VUMC and Pure AMC on May 18th,

2022. Publications are ascribed to AR&D based on the affiliations of the authors and the content of the publication. A publication can be ascribed to one or more research institutes depending on the affiliations of the authors. Publications registered in the VUMC and AMC Pure instances have been combined and deduplicated. PhD-theses are ascribed to AR&D based on the affiliations of the (co-)supervisors. A thesis can be ascribed to one or more research institutes depending on the affiliations of the (co-)supervisors. Due to incomplete linkage to Pure (VU/UvA/VUmc/AMC) the actual numbers affiliated to AR&D is higher.

## RECRUITED FUNDING

Information about funded research projects has been provided by the separate project administrations from location AMC and location VUMC.

## EXTERNAL GRANTS AND PRIZES

In 2021, AR&D researchers were very active in obtaining grants and prizes. Below some of the external grants and prizes awarded to AR&D researchers are highlighted.



### ZONMW GRANT

€3.483.750

Onderzoek naar stamcellen om jonge kankerpatiënten weer vruchtbaar te maken

*Geert Hamer, Reproductive Biology Laboratory, Ans van Pelt, Obstetrics and Gynecology, and Corrette Ploem, Health law, and others*

### KNAW PILOTFUNDING

€10.000

Wetenschapscommunicatie door Wetenschappers; Gewaardeerd!

*Tessa Roseboom, Obstetrics and Gynecology and Clinical Epidemiology, Biostatistics and Bioinformatics*

### GRANTS: E-TOP

€300.000

Aanvullende digitale ondersteuning voor ouders zeer prematuur geboren kinderen

*Martine Jeukens-Visser, Rehabilitation*

### ZONMW OFF ROAD GRANT

€100.000

The biological clock in sperm formation

*Callista Mulder, Obstetrics and Gynecology*

### ZONMW GRANT

€423.414

When pink clouds are absent: Effects of unwanted pregnancy on psychosocial health of women, men, and their children, and the protective role of partner involvement

*Jenneke van Ditzhuijzen, Obstetrics and Gynecology*

## ○○○ KEY PUBLICATIONS

2021 was a very productive year. Here is a selection of peer-reviewed publications that were highlights for our researchers.



Diagnostic accuracy of ultrasound screening for fetal structural abnormalities during the first and second trimester of pregnancy in low-risk and unselected populations  
*Buijendijk et al.*

Cochrane Database of Systematic Reviews Protocol – Diagnostic.  
21 July 2021. ePub ahead of print.

Intrapartum interventions and outcomes for women and children following induction of labour at term in uncomplicated pregnancies: a 16-year population-based linked data study  
*Dahlen et al.*

BMJ Open 2021;11:e047040.

Mortality trends over five decades in adult transgender people receiving hormone treatment: a report from the Amsterdam cohort of gender dysphoria  
*De Blok et al.*

Lancet Diabetes Endocrinol 2021;9:663-670.

Early Postnatal Cardiac Stress Does Not Influence Ventricular Cardiomyocyte Cell-Cycle Withdrawal  
*Günthel et al.*

J Cardiovasc Dev Dis 2021;8:38.

Effect of Systemic Hydrocortisone Initiated 7 to 14 Days After Birth in Ventilated Preterm Infants on Mortality and Neurodevelopment at 2 Years' Corrected Age: Follow-up of a Randomized Clinical Trial  
*Halbmeijer et al.*

JAMA 2021;326:355-357.

The Imperative of Responsible Innovation in Reproductive Medicine  
*Mastenbroek et al.*

N Engl J Med 2021;385:2096-2100.

Circular RNA Sequencing of Maternal Platelets: A Novel Tool for the Identification of Pregnancy-Specific Biomarkers  
*Oudejans et al.*

Clin Chem. 2021;67:508-517.

Couples' experiences with expanded carrier screening: evaluation of a university hospital screening offer  
*Van Dijke et al.*

Eur J Hum Genet 2021 ;29:1252-1258.

Identical twins carry a persistent epigenetic signature of early genome programming  
*Van Dongen et al.*

Nat Commun 2021;12:5618.

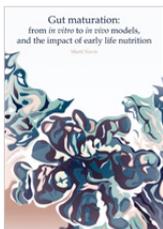
Cost-Effectiveness of perioperative Vaginally Administered estrogen in postmenopausal women undergoing prolapse surgery (EVA trial): study protocol for a multicenter double-blind randomized placebo-controlled trial  
*Vodegel et al.*

BMC Womens Health 2021;21:439.

○○○ PHD THESES

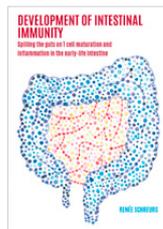
In 2021, 48 researchers obtained their PhD in the area of reproduction and development.

Below a cross section of the PhD theses.



Thesis defence:  
15th January 2021

Gut maturation: From in vitro to in vivo models, and the impact of early life nutrition  
Marit Navis



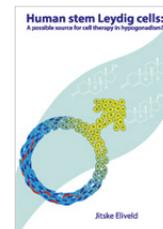
Thesis defence:  
26th March 2021

Development of intestinal immunity: Spilling the guts on T cell maturation and inflammation in the early-life intestine  
Renee Schreurs



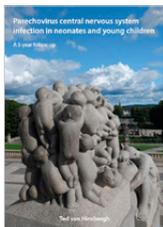
Thesis defence:  
7th April 2021

Functional analysis of genetic variants: contribution to the diagnosis of inherited metabolic diseases  
Ana Pop



Thesis defence:  
19th May 2021

Human stem Leydig cells: a possible source for cell therapy in hypogonadism?  
Jitske Eliveld



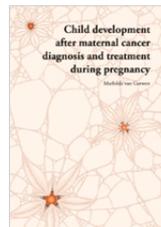
Thesis defence:  
16th June 2021

Parechovirus central nervous system infection in neonates and young children A 5-year follow-up  
Ted van Hinsbergh



Thesis defence:  
2nd July 2021

Genetic Obesity: Disorders and Diagnostics  
Lotte Kleinendorst



Thesis defence: 24th  
September 2021

Child development after maternal cancer diagnosis and treatment during pregnancy  
Mathilde van Gerwen



Thesis defence:  
29th October 2021

MY DAILY MOVES Determinants and measurement of movement behaviours from the child-perspective  
Lisan Hidding



Thesis defence: 24th  
November 2021

Parents of children with cancer: sleep, distress and quality of life  
Niki Rensen



Thesis defence: 10th  
December 2021

Mucopolysaccharidosis type III: beyond the biomedical issues  
Thirsa Conijn

## ○○○ SOCIETAL IMPACT

In 2021, AR&D researchers have been contributing to the Societal Impact of research. A selection of societal impact events is presented.



### VGZ Zinnige Zorg Award voor IkHerstel-app

Judith Huirne, Han Anema  
and Jeroen de Wilde



### ZonMw Parel voor samenwerking rond kind en wetenschappelijk onderzoek

Irma Hein, Hans van Goudoever, Ronella Grootens and Mira Staphorst

### Te vroeg geboren? Dan nog even groeien in de kunstbaarmoeder

Sebastiaan Mastenbroek  
in newspaper NRC

### Meedoen aan hersenonderzoek in de Emma Breinbus

Marsh Königs, Jaap Oosterlaan and Hilgo Bruining on Amsterdam UMC website

### Centrum voor kindergynaecologie: 'Ook problemen bij kinderen'

Emmy van de Boogaart for RTL News



### Twee baby's gevonden op straat: de vondelingenkamer als laatste redmiddel

Christianne de Groot in newspaper NRC

### Een gerichtere aanpak bij autisme

Hilgo Bruining on Twitter @Nieuwsuur

### Menstruatie meisjes

### Op spreekuur bij de gynaecoloog #2

Anne Timmermans in Podcast  
'Menstruatiemeisjes'

### Epigenetica laat ons trauma's door kindermishandeling beter begrijpen

Marcel Mannens in Augeo Magazine

### The first one thousand days and prenatal screening (no out of pocket costs NIPT) in Coalition Agreement Dutch government based on research results from AR&D

AR&D research in Coalition Agreement  
Dutch Government

## ○○○ AR&D COVID-19 RESEARCH

Also in 2021, AR&D researchers did research on COVID-19-related topics.

Below some of the publications are highlighted.



### Is schoolsluiting de schade aan kinderen waard

*Arne Popma in newspaper NRC*

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### Zwanger in coronatijd: wat zijn de risico's?

*Liesbeth van Leeuwen in Medisch Contact*

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### COVID-19 and child and adolescent psychiatry: an unexpected blessing for part of our population?

*Bruining et al.*

Eur Child Adolesc Psychiatry. 2021;30(7):1139-1140.

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### Comparison of SARS-CoV-2-Specific Antibodies in Human Milk after mRNA-Based COVID-19 Vaccination and Infection

*Juncker et al.*

Vaccines [Basel]. 2021;9(12):1475.

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### Saliva SARS-CoV-2 Antibody Prevalence in Children

*Keuning et al.*

Microbiol Spectr. 2021;9(2):e0073121.

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### Unheard, unseen and unprotected: DOHaD council's call for action to protect the younger generation from the long-term effects of COVID-19

*Roseboom et al.*

J Dev Orig Health Dis. 2021;12(1):3-5.

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### Experiences of Dutch maternity care professionals during the first wave of COVID-19 in a community based maternity care system

*Van Manen et al.*

PLoS One. 2021;16(6):e0252735.

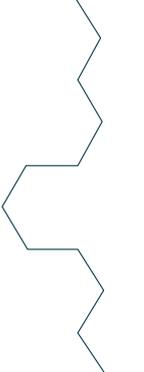
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○○○ IN MEMORY OF ELLEN LAAN



It is with intense sadness and great respect that we bid farewell to Prof. Ellen Laan. Ellen was an important scientist and advocate in the field of sexology, both in the Netherlands and globally. She made important contributions to science and society for sexual health and wellbeing and as a colleague, fellow scientist, teacher and health care professional she will be forever missed. With her work, she entered the broad field of sexology by combining high-quality scientific research with education and patient care. Ellen Laan was given several prestigious awards:

Royal decoration the Order of the Lion of the Netherlands, Societal Impact Award Amsterdam UMC and The ESSM Lifetime Achievement Award.



# Newly appointed professors



In 2021, five professors were appointed at the Amsterdam UMC in the field of AR&D.

## PROF. FRANS PLÖTZ

Frans Plötz is an endowed Professor of Pediatric Health Care Evaluation at the Emma Children's Hospital, Department of Pediatrics, Amsterdam. The chair was established on behalf of the Tergooi Foundation. He was appointed on January 1st 2021. He also works as a pediatrician at Tergooi MC.

### Research

His research focuses on pediatric health care evaluation in general pediatrics. This involves systematically examining how the care provided can be improved. He was one of the initiators, and currently co-chair, of the in 2018 established Pediatric Research Evaluation Network (PREN) Amsterdam. PREN aims to develop a structural basis for conducting health care evaluation research within general pediatrics. This is achieved through solid cooperation and the establishment of a good infrastructure between Emma Children's Hospital-Amsterdam UMC and all hospitals in the Amsterdam region. Each hospital has a representative within PREN. Our vision is that every child should receive the best

**“Our vision is that every child should receive the best substantiated care at any time and place”**

substantiated care at any time and place.

We want to create a culture of learning and change based on scientific knowledge from health care evaluation research. Our mission is to ensure that health care evaluation is part of general pediatric patient care in all hospitals that are part of PREN Amsterdam. In addition, we will use education and training to actively disseminate health care evaluation among medical students, interns, physician assistants and pediatricians, as well as among other hospital employees.

# “Making things better: doing research to improve the health of future generations”

## PROF. ANNET BOSCH

Since January 5th 2021, Annet Bosch is appointed as professor of Pediatrics, Metabolic Diseases. She is a pediatrician for Metabolic Diseases and head of the Department of Pediatric Metabolic Diseases of Amsterdam UMC, location AMC. Besides her work in Amsterdam UMC, Annet Bosch is a member of the Board of the Dutch Medicines Evaluation Board (CBG-MEB).

### Research

Her clinical and translational research focusses on Classical Galactosemia, Phenylketonuria and Riboflavin Transporter Deficiency. Amsterdam UMC, location AMC is a national Center of Expertise for all three inborn errors of metabolism. She is the Amsterdam UMC representative for the European Reference network for Hereditary Metabolic Disorders [MetabERN]. Annet enjoys a large international network, through among others the Galactosemia Network [Gal-Net] of which she is a board member, and through

the European Phenylketonuria Guidelines group. She is involved in the organization of Newborn Screening for inborn errors of metabolism in the Netherlands, as a member of the ‘Adviescommissie Neonatale Screening voor Metabole Ziekten’ (ANS-MZ) and the ‘Programmacommissie Neonatale Hielprik Screening’ [PNHS]. In close cooperation with the laboratory for Newborn Screening located in Amsterdam UMC, location AMC, she performs research aimed at the evaluation and optimization of the Dutch Newborn Screening program.



Frans  
Plötz



Annet  
Bosch



### **PROF. MARTIJN OUDIJK**

On 1 July 2021 Martijn Oudijk was appointed Professor of Obstetrics with special focus on Prevention and Treatment of Preterm Birth at the Vrije Universiteit and Amsterdam UMC. He is the chairman of the division of Fetal-Maternal Medicine and chairman of the Scientific Committee of the division of Fetal-Maternal Medicine within the Dutch Society of Obstetrics and Gynecology (NVOG).

#### **Research**

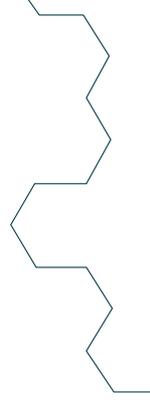
In collaboration with NVOG, the Dutch Organisation of Midwives (KNOV), the Dutch Association for Pediatrics (NVK) and patient organizations, Oudijk strives to reduce preterm birth rates in the Netherlands through introduction of new guidelines on Prevention of Preterm Birth, focused on implementing effective interventions. He frequently organizes conferences and symposia on prevention of preterm birth, in order to inform other health care professionals within the obstetric field, to make sure every pregnant woman gets the same level of care. Together with the preterm birth research

team at Amsterdam UMC and the NVOG research consortium, he initiates and performs large (inter-)national RCT's, evaluating new and existing treatments for prevention of preterm birth. In addition, he is set to optimize treatment for women in preterm labour, evaluating current treatments in multicenter RCT's.

Together with his colleagues, Oudijk is responsible for the Preterm Birth Prevention Clinic at Amsterdam UMC, a national top referral center, where state of the art care is provided to women with a high risk on preterm birth. His ultimate goal is to reduce preterm birth rates drastically, in order to improve outcomes for children and reduce the huge impact of preterm birth on families and society.

### **PROF. DASJA PAJKRT**

Dasja Pajkrt is Professor of Viral Pediatric Infectious Diseases since October 5th 2021. She works at Amsterdam UMC, at the Department of Pediatrics. After finishing her PhD in 1996, Dasja obtained her post-graduate degree in pediatrics to further subspecialize



## “New professors from the fields of metabolism, obstetrics, pediatrics and psychiatry will contribute to interdisciplinary science to improve the health of future generations.”

to become a pediatric infectious disease specialist-immunologist at Amsterdam UMC in 2005. In 2010 Dasja obtained her Master degree in Business Administration (MBA) at the Rotterdam School of Management. For the H2020 networks, Dasja developed a pre-Master of Business Administration (pre-MBA) and since 2017 she coordinates the ‘Honours Programma Wicked Challenges in Health’ in collaboration with the Institute for Interdisciplinary Studies, University of Amsterdam (IIS) and Amsterdam UMC. Since March 2022, she is a member of the Senate, an advisory committee on research and education of the Executive Board of the University of Amsterdam.

### Research

Since 2015 she is Principal Investigator Pediatric Infectious Diseases & Immunology. She is co-heading OrganoVIR (Organoid for Virus research) Labs at Amsterdam UMC. She is founder of the Amsterdam Organoid Center, coordinator of two international H2020 networks: OrganoVIR and GUTVIBRATIONS (Gut Virus Brain Axis Technology in Organoid Science) and one national TPI-PPP Allowance project: Focus-on-Virus (Picornavirus and HIV infection using a complex gut-brain model). She is a member of the Dutch network Transition animal-free innovations (TPI).

Her expertise is on pediatric viral infections, most specifically on picornavirus, cytomegalovirus and HIV infections. Her research group participates in multiple research projects on clinical disease, viral

pathogeneses, host-pathogen interactions and outcomes of pediatric viral infections.

### PROF. HILGO BRUINING

Hilgo Bruining was appointed professor of Neurobiological Developmental Disorders since October 5th, 2021. Bruining was trained as a pediatrician and a child and adolescent psychiatrist and works as a child and adolescent psychiatrist at the Department of Child and Adolescent Psychiatry & Psychosocial Care of Amsterdam UMC/Emma Children’s Hospital. He is the founder and PI of the N=You neurodevelopmental precision center at the Emma Children’s Hospital in Amsterdam UMC partnering with Level.

### Research

The multi-transdisciplinary team of N=You focusses on the development and implementation of personalized mechanism-based treatments for neurodevelopmental disorders. The cornerstone of their approach is to match each individual child to the most optimal available n-of-1 therapy design by the integration of genetic, cellular (iPSC), neurophysiological (EEG) and cognitive diagnostic information. ●



**“The ambition  
of AR&D is the  
advancement of  
knowledge in all  
aspects of human  
reproduction  
and development  
through  
interdisciplinary  
team science  
aimed at improving  
health from  
preconception  
to adulthood of  
current and future  
generations”**







**“Unique about the research institute Amsterdam Reproduction & Development is that we pay attention to reproduction and development in its totality: the stage before pregnancy, conception, pregnancy, childbirth, the child as it’s growing up, and the resulting health of the adult stages of life”**