Amsterdam UMC
University Medical Centers

EXPERTISE

CIRCLE OF LIFE

AMSTERDAM REPRODUCTION AND DEVELOPMENT

ANNUAL REPORT

2020

REPRODUCTION

DEVELOPMENT

RESEARCH

Contents

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

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A word from the directors

We are proud to present the 2020 Amsterdam Reproduction & Development (AR&D) annual report. There is no doubt that the COVID-19 pandemic made the year 2020 extremely challenging for everyone.

For researchers it was not easy to work from home or helping at our Amsterdam UMC intensive care/COVID units. COVID-19 also had great impact on the life cycle with e.g. a decrease in preterm birth, delay in women's treatment such as IVF and surgeries which created new research questions. We are full of pride of our researchers who continued to work in our multidisciplinary research teams on studies that have tremendous scientific and societal impact.

Our research institute AR&D focuses on innovation and excellence in the field of reproduction and development, and combines leading scientists of different disciplinary backgrounds, including clinicians, fundamental scientists, epidemiologists, psychologists, and social scientists. The stories of our researchers show some of the ground-breaking work being conducted across our institute, contributing to a better understanding of many aspects from preconception through pregnancy to child development and long-term health.

This year, one of our esteemed researchers, professor Hans van Goudoever, was nominated for the Amsterdam UMC Societal Impact Award. Media attention was given to several AR&D topics, including the COVID (breast) milk study and the pandemic impact on children and adolescents' mental health. Numerous grants were awarded, including an NWO Large Funding for Vincent Christoffels on "Pacing the heart". The scientific publication on the first year of the TRIDENT-2 study on the implementation of non-invasive prenatal testing was highlighted in the Top 10 of publications worldwide that had the most impact on the application of genetics in clinical care. Moreover, we want to underscore some of the AR&D COVID-19 research project in pediatrics, gynecology and mental health.

In 2020 our enthusiastic AR&D Retreat committee of young researchers organized a wonderful web-based series of lectures in three Episodes related to the Circle of life, with interactive workshops being offered to learn new skills. It was a great success!

With this report, we are delighted to show our successes of the past year, introduce several AR&D PhD candidates and their mentors who present and discuss their work, as well as three new inaugurated AR&D professors. We are honored to share our institute with you.

We look forward to combining strengths again in the year ahead!

Christianne de Groot & Lidewij Henneman
Directors Amsterdam Reproduction and Development

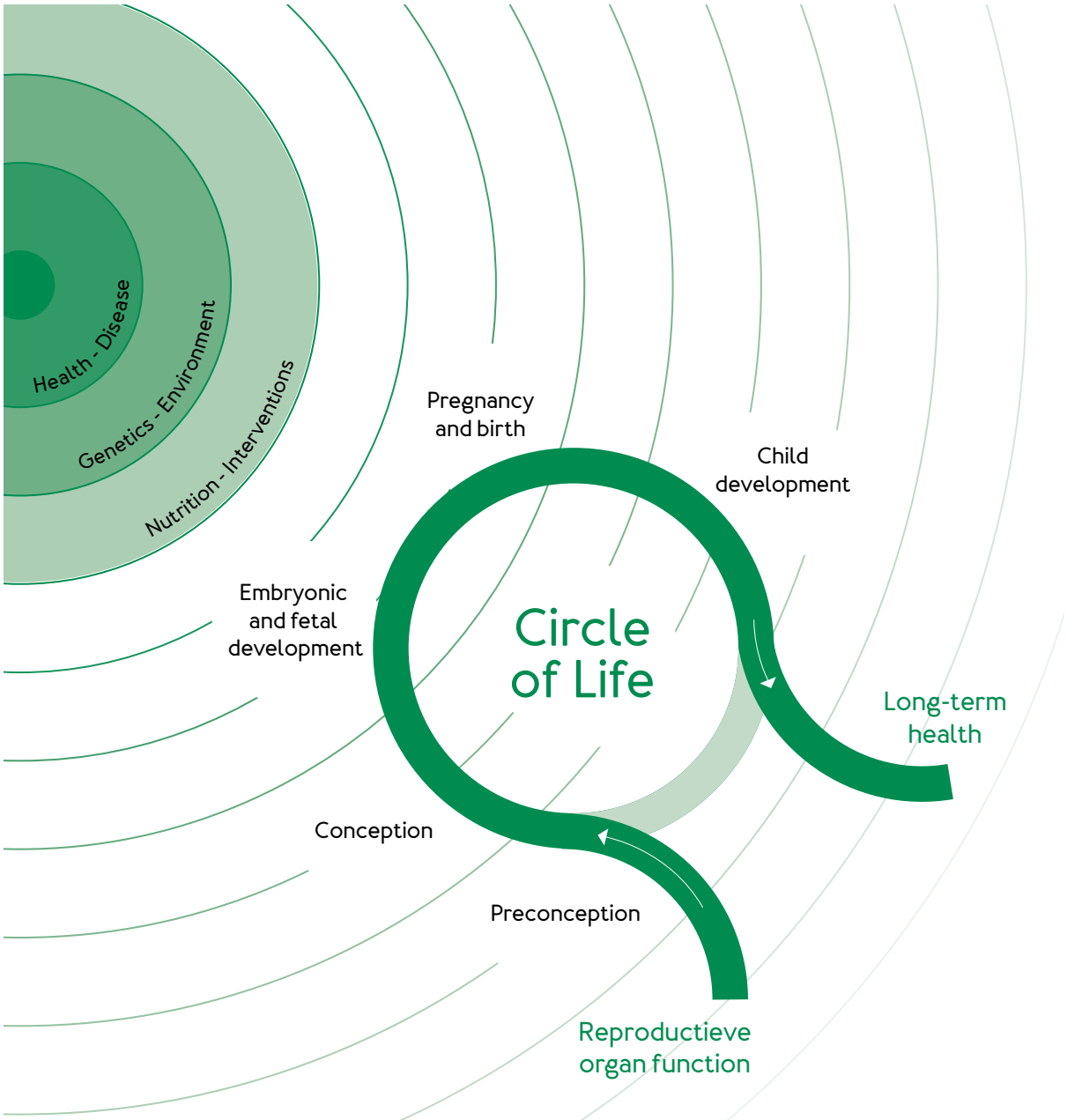
Starting the Circle of life

The Amsterdam Reproduction and Development (AR&D) research institute is unique in its goals and ambition. The institute covers themes that comprise the Circle of Life: from preconception through pregnancy and child development to long-term health. It encompasses research that focuses on long-term health effects on both mother and child, of disease and interventions during preconception, conception, embryonic and fetal development, pregnancy and birth, as well as child development and effects on reproductive organ function.

The ambition of AR&D is to enhance the field of reproduction and development nationwide and to sustainably improve health care for mother and children and as such for future generations. We strive for all people to have access to high quality sexual and reproductive health information, and to support the foundation that enables children to make the best start in life.

AR&D integrates various disciplinary approaches within the 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, psychosocial and clinical research scientists work together to maximally improve health care.

For more information and videos of AR&D, please visit www.amsterdamumc.org/ard.



Research Areas

FROM PRECONCEPTION TO CHILD DEVELOPMENT

PRECONCEPTION AND CONCEPTION

The desire to have children is a fundamental driving force for all species. We provide optimal care for people who have difficulty conceiving. Our prediction models provide accurate and reliable prognoses for medical help. Thus, we stand for optimal evidence-based shared decision-making. AR&D does not only offer novel medical treatments but we also evaluate whether they are truly of benefit for our patients. 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 embryo 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 late onset 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 and disease. By focusing on embryonic development, we provide the basis for understanding a huge variety of human disease and disease susceptibility. 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 mother and child. 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 the shared decision-making. Our trials are conducted in the context of national networks of collaborating hospitals, gynecologists, midwives, nurses, neonatologists, and health care provides 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 through their development after they have spent part of their early life in the 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.

AR&D COVID research

Human Milk from Previously COVID-19-Infected Mothers: The Effect of Pasteurization on Specific Antibodies and Neutralization Capacity.

Britt van Keulen, Michelle Romijn, Albert Bondt, Kelly A Dingess, Eva Kontopodi, Karlijn van der Straten, Maurits den Boer, Judith Burger, Meliawati Poniman, Berend Bosch, Philip Brouwer, Christianne de Groot, Max Hoek, Wentao Li, Dasja Pajkrt, Rogier Sanders, Anne Schoonderwoerd, Sem Tamara, Rian Timmermans, Gestur Vidarsson, Koert Stittelaar, Theo Rispens, Kasper Hettinga, Marit van Gils, Albert Heck, Hans van Goudoever

Dept. of Pediatrics, Amsterdam UMC, EMMA Children's Hospital & Others

Since the outbreak of COVID-19, many put their hopes in the rapid availability of effective immunizations. Human milk, containing antibodies against syndrome coronavirus 2 (SARS-CoV-2), may serve as means of protection through passive immunization. We aimed to determine the presence and pseudovirus neutralization capacity of SARS-CoV-2 specific IgA in human milk of mothers who recovered from COVID-19, and the effect of pasteurization on these antibodies. This prospective case control study included lactating mothers, recovered from (suspected) COVID-19 and healthy controls. Human milk and serum samples were collected. Human milk contained abundant SARS-CoV-2 antibodies in 83% of the proven cases and in 67% of the suspected cases. Unpasteurized milk with and without these antibodies was found to be capable of neutralizing a pseudovirus of SARS-CoV-2 in (97% and 85% of the samples respectively). After pasteurization, total IgA antibody levels were affected by HoP, while SARS-CoV-2 specific antibody levels were affected by HPP. Pseudovirus neutralizing capacity of the human milk samples was only retained with the HPP approach. No correlation was observed between milk antibody levels and neutralization capacity.

Human milk from recovered COVID-19-infected mothers contains SARS-CoV-2 specific antibodies which maintained neutralization capacity after HPP. All together this may represent a safe and effective immunization strategy after HPP.

Read the full article ›

Association between COVID-19 lockdown measures and the incidence of iatrogenic versus spontaneous very preterm births in singleton and multiple pregnancies in the Netherlands.

Job Klumper, Brenda Kazemier, Jasper Been, Kitty Bloemenkamp, Marjon de Boer, Jan Jaap Erwich, Wieteke Heidema, Frans Klumper, Sebastiaan Nij Bijvank, S. Guid Oei, Martijn Oudijk, Sam Schoenmakers, A.S. van Teeffelen, Christianne de Groot

Dept. of Obstetrics and Gynecology, Amsterdam UMC and Perinatal Centers

The COVID-19 pandemic led to regional or nationwide lockdowns as part of risk mitigation measurements in many countries worldwide. Recent studies suggested an unexpected and unprecedented decrease in preterm births during the initial COVID-19 lockdowns in the first half of 2020. Most studies failed to differentiate between spontaneous and iatrogenic onset of delivery and between singleton and multiple pregnancies. We therefore decided to collect data on the incidence of very and extremely preterm birth in the Netherlands during the first two months of the first national COVID-19 lockdown period. We collected data on preterm births <32 weeks of gestation from all 10 perinatal centers in the Netherlands during the first national lockdown from March 15 up to May 15, 2020. Incidences of spontaneous and iatrogenic preterm birth were calculated using an estimate of the total number of births in this period, derived from a national database (Praeventis). We compared the incidence of preterm births in 2020 with incidence in the corresponding period over 2015-2018 using data from the national perinatal registry (Perined).

The impact of the COVID-19 pandemic on infertility and endometriosis patients in the Netherlands: the use of telemedicine, quality of life and patient-centeredness.

Kimmy Rosielle, Jasmijn Bergwerff, Anneke Schreurs, J Knijnenburg, B de Bie, J Maas, A Nap, Madelon van Wely, Nils Lambalk, Mariette Goddijn, Ilse Custers, Laura van Loendersloot, Velja Mijatovic

Dept. of Obstetrics and Gynecology, Endometriosis Center, Amsterdam UMC & Others

The global outbreak of coronavirus disease 2019 (COVID-19) has led to a significant increase of pressure on health care systems all over the world. For infertility patients and endometriosis patients, this resulted in temporary cancellation of physical appointments, elective surgeries and assisted reproductive technologies during the COVID-19 pandemic.

Using online questionnaires, a cross-sectional cohort study was conducted amongst 555 infertility and endometriosis patients and 101 health care providers in the Netherlands, funded by ZonMw.

The results show that infertility patients, endometriosis patients and their health care providers rate the telephone and video appointments replacing the usual physical consultations as a good alternative during the pandemic. All participants agree that the telephone appointments are not a good replacement for future physical consultations after the pandemic.

Most patients with infertility reported an increase in stress levels due to the temporary shutdown of infertility treatments. This increase in stress was not seen as much in endometriosis patients. Using a questionnaire designed to score the fertility related quality of life, the infertility patients reported a lower quality of life than previously seen in the Netherlands. The endometriosis patients filled in a questionnaire on quality of care, and the results of this questionnaire show that these patients scored the quality of care the same as previously determined.

Read the full article ›

Stress, anxiety and depression in 1466 pregnant women during and before the COVID-19 pandemic: a Dutch cohort study

Sanne Zilver, Birit Broekman, Yvette Hendrix, Robert de Leeuw, Stijn Mentzel, Marielle van Pampus, Christianne de Groot

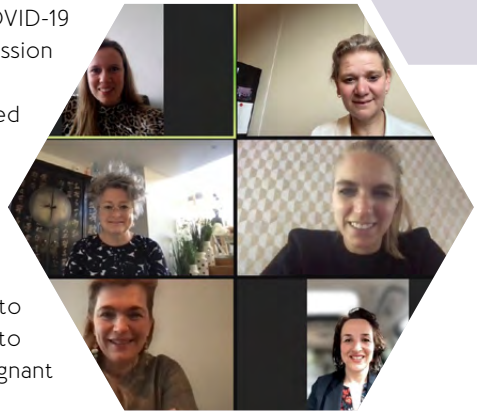
Dept. of Obstetrics and Gynecology, Amsterdam UMC and OLVG

The COVID-19 pandemic has negatively affected many people's mental health with increased symptoms of stress, anxiety and depression in the general population. Anxiety and depression can have negative effects on pregnant women and result in poor neonatal outcomes. Therefore, we analyzed stress, anxiety and depression in pregnant women during the COVID-19 pandemic compared to pregnant women before COVID-19.

Pregnant women were recruited through social media platforms in 2020. The Hospital Anxiety and Depression Scale (HADS) and the Perceived Stress Scale (PSS-10) were analyzed. 1102 pregnant women completed the questionnaires during COVID-19, and 364 pregnant women before COVID-19. We found no differences in clinically high levels of anxiety (HADS-A ≥ 8) and depression (HADS-D ≥ 8) in women during COVID-19 (19.5% and 13.2%, respectively) and women before COVID-19 (23.1% and 15.7%, respectively).

Women who related their stress to the COVID-19 pandemic reported significantly higher overall stress levels on the PSS-10 compared to women with stress unrelated to COVID-19 (mean, 15.62; standard deviation [SD], 6.44 vs. mean, 10.28; SD, 5.48; $p < 0.001$).

In contrast to previous studies, COVID-19 did not increase anxiety and depression levels in Dutch pregnant women. Women who related their perceived stress to the COVID-19 pandemic experienced higher stress levels than women who did not relate their stress to the COVID-19 pandemic, suggesting that interventions that specifically aim to reduce COVID-19 stress, may help to reduce overall stress levels in pregnant women during the pandemic.



Read the full article ›

COVID-19 work by the Cochrane Gynaecology and Fertility Satellite

Madelon van Wely, Elena Kostova

In March 2020, in a response to the emerging pandemic, drs Madelon van Wely and Elena Kostova from the Cochrane Gynaecology and Fertility satellite developed an online database containing data extracted from all published reports on pregnancy and neonatal outcomes in women with COVID-19. The database is updated weekly, presently kept up to date with help of Maxime Verschuuren and is freely available. The COVID-19 dedicated page was visited 27,000 in 2020 and remains among the top 5 ranked pages on the topic on Google.

The database is used for the largest living systematic review on COVID-19 in pregnancy, a collaboration with the University of Birmingham and World Health Organization (WHO). The first version was published in the BMJ in September 2020 and included 77 studies. The update from March 2021 included 192 studies. Results showed that pregnant and recently pregnant women were more likely to need intensive care treatment for COVID-19 compared to non-pregnant women. There was extensive news media coverage, and the story was featured on popular outlets such as CNN Health, Medscape, and EurekAlert.

Read the full article ›

The impact of lockdown during the COVID-19 pandemic on mental and social health of children and adolescents

Michiel Luijten, Maud van Muilekom, Lorynn Teela, Tinca Polderman, Caroline Terwee, Josjan Zijlmans, Leonie Klaufus, Arne Popma, Kim Oostrom, Hedy van Oers, Lotte Haverman

Child and Adolescent Psychiatry & Psychosocial Care, Emma Children's Hospital, Amsterdam UMC & Others

During the COVID-19 pandemic in the Netherlands, governmental regulations resulted in a lockdown for adults as well as children/adolescents. Schools were closed and contact with other people was limited.

In this cross-sectional, population-based study, we aimed to investigate the mental/social health of children/adolescents during COVID-19 lockdown. Two representative samples of Dutch children/adolescents (8–18 years) before COVID-19 (2018, N = 2401) and during lockdown (April 2020, N = 844) were compared on the PROMIS domains: global health, peer relationships, anxiety, depressive symptoms, anger, sleep-related impairment. Participants reported worse PROMIS T-scores on all domains during COVID-19 lockdown compared to before (absolute mean difference range 2.1–7.1 (95% CI 1.3–7.9). During lockdown, more children reported severe Anxiety (RR = 1.95 (1.55–2.46) and Sleep-Related Impairment (RR = 1.89 (1.29–2.78) and fewer children reported poor Global Health (RR = 0.36 (0.20–0.65)). Associated factors with worse mental/social health were single-parent family, ≥ three children in the family, negative change in work situation of parents due to COVID-19 regulations, and a relative/friend infected with COVID-19. A large majority (> 90%) reported a negative impact of the COVID-19 regulations on daily life.

This study showed that governmental regulations regarding lockdown pose a serious mental/social health threat on children/adolescents that should be brought to the forefront of political decision-making and mental healthcare policy, intervention, and prevention.

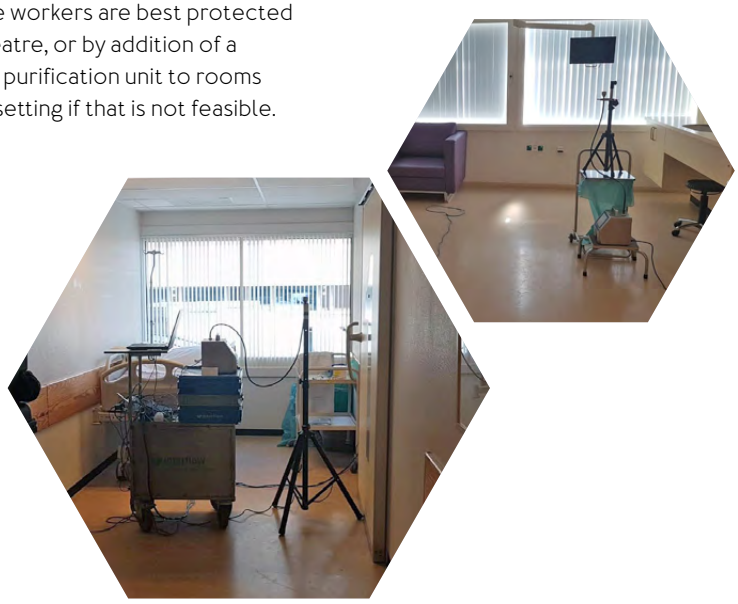
Read the full article >

Simulation of measures to contain aerosol spread

Nicolaas Sperna Weiland, Roberto Traversari, Jante Sinnige, Frank van Someren Gréve, Anne Timmermans, Ingrid Spijkerman, Wessel Ganzevoort, Markus Hollmann

In the early months of the COVID-19 pandemic the health care system struggled with the implementation of measures to restrict SARS-CoV-2 virus spread. Worrying reports from Italy indicated that personnel involved in airway management procedures were prone for severe disease. The general advice was to perform airway management procedures in isolation rooms with negative pressure and high ventilation settings. In our hospital, although in operation theaters ventilation settings are ideal, most theaters have a positive pressure setting because they are not designed for airborne isolation, but to protect the surgical field from contamination. A discussion rose what the relative contribution was of ventilation and pressure settings in aerosol spread.

To inform our protocols, we designed and executed in collaboration (Anesthesiology, Medical Microbiology, Gynecology/ Obstetrics Amsterdam UMC; and TNO Delft) a simulated aerosol-generating procedure on six single-patient hospital rooms with different combination settings of air exchange rate and pressure differences between the room and adjacent hallways. We found that high ventilation settings contributed more to aerosol wash-out than the pressure settings. Thus, healthcare workers are best protected in operation theatre, or by addition of a recirculating air purification unit to rooms outside of that setting if that is not feasible.



RESEARCH AT AR&D

JENNY VAN DONGEN, VERONIKA ODINTSOVA AND DORRET BOOMSMA
Twins, omics, development

MADDY SMIES, STEFANIE DAMHUIS AND WESSEL GANZEVOORT
Fetal Doppler ultrasound in suspected placental insufficiency

KAVISH KOHABIR, ROB WOLTHUIS AND ERIK SISTERMANS
Towards CRISPR-Based Diagnostics

IRENE LOK AND ANTON VAN KAAM
Bronchopulmonary dysplasia i n preterm infants

MARISSA HARMSEN, LYNDA JUFFERMANS AND JUDITH HUIRNE
Diagnosis and treatment of adenomyosis

JENNY VAN DONGEN, VERONIKA ODINTSOVA AND DORRET BOOMSMA

Twins, omics, development

Within the AR&D research institute, the research led by professor Dorret Boomsma focusses on twin studies and genetics. We study variation in human behavior, development and health by applying the classical twin design as a 'tool' to assess genetic variance. We also investigate the etiology of twinning itself and consider whether being a twin influences development and disease risk.

Dorret Boomsma

Veronika Odintsova

Jenny van Dongen

TWINS AND GENETICS

When we say twins as a 'tool' we refer to the classical twin study, which compares the similarity of monozygotic (MZ) and dizygotic (DZ) twins to estimate the contribution of the genome to variation among humans for any trait or disease we can reliably measure. This insight led Boomsma in the 1980's to establish the Netherlands Twin Register (NTR) at the Vrije Universiteit Amsterdam. The NTR initially recruited (young) adult twins and their family members. Soon afterwards, newborn twins and triplets who are registered by their parents were also included and recruitment is ongoing. Large-scale studies in genetic epidemiology have established the importance of genetic variation in growth and development, cognition and psychopathology, lifestyle, health and disease. One of our ongoing lines of research focuses on unraveling genomics and epigenomics variation associated with human MZ and DZ twinning. For this focus, Boomsma, van Dongen, Mbarek and colleagues established the twinning genetics consortium (twinningconsortium.org).

NTR BIOBANK AND BIOBANK PROJECTS

Biological sample collection has been part of many NTR projects, with the first samples collected in the 1980's for cardiovascular and linkage studies. Between 2004 and 2010 a large enterprise with home visits to ~10.000 participants laid the foundation for the NTR Biobank and more recently, the NTR-Action Biobank in children was established. DNA isolation from blood or buccal cells and multiple biomarkers, epigenetic and expression profiles and metabolite assessment in blood and urine, led to insights into the role of the DNA sequence in epigenetic regulation, RNA expression and other OMICS processes.

Veronika Odintsova works on her second PhD with Boomsma and van Dongen as two of her supervisors. Her research includes the (epi) genetics of early life traits, e.g. Apgar scores, handedness and (pediatric) aggression. She implemented new machine learning tools to optimize literature selection for systematic reviews, that were developed by the group of Rens van de Schoot (Utrecht University), and

was the first to apply the tools to a literature review of aggression. The Automated Systematic Review Software (ASR) detected relevant articles based on title and abstract analysis via machine learning algorithms (active learning) and allowed to analyze much broader lists of literature than can be done with "manual" selection. The review on the genetics of aggression was published in Psychiatric Genetics (2019) after screening over 14,000 records that mentioned human aggression and genes. It reported 35 relevant papers on genome-wide association studies of aggression. A next step is to apply AI to biomarkers detection for the complex traits and diseases.

Our review on aggression indicated that its genetic basis largely remains to be uncovered. With increases in sample size, we expect aggression to behave like any other complex human trait for which association studies have been successful. We collaborate with (inter)national colleagues in the Action consortium (www.action-euproject.eu) to identify genetic variants for childhood aggression and associated traits, combining samples from childhood cohorts, for phenotypes from other domains associated with aggression, and developing new approaches for analysing heterogeneous, family and longitudinal data.

Collaborations also were initiated for epigenetics studies of aggression and ADHD. Epigenetic studies do not focus on the DNA code, but on mechanisms that regulate the expression of genes, e.g. DNA methylation. DNA methylation mediates effects of genetic variants in regulatory regions on gene expression and is modifiable by early life social environment, as demonstrated by animal studies, and by chemical exposures including (prenatal) exposure to cigarette smoke. Epigenome-wide association studies (EWAS) test for hundreds of thousands of locations in the genome (usually at cytosines in cytosine–guanine (CpG) dinucleotides), if the proportion of methylated alleles differs between cases and controls, or is associated with a continuous trait that varies from e.g. low to high.

To identify genes that are differentially methylated in people with aggressive behavior or ADHD symptoms, Jenny van Dongen led a consortium of 21 cohorts from Action and other research groups worldwide to analyze DNA methylation profiles from > 15,000 children and adults with data on aggressive behavior and nearly 5,000 adult participants with phenotyping for ADHD. The ADHD study came out in Biological Psychiatry (2019) and the one on aggressive behavior was published in Molecular Psychiatry (2021), representing the largest EWAS of a behavioral phenotype to date.

"Boomsma, van Dongen, Mbarek and colleagues established the twinning genetics consortium"

For aggression, 48 locations were identified with associated DNA methylation levels. The genes are involved in a variety of functions, including the immune and central nervous system, and their methylation levels have been linked to chemical exposures, smoking, cognition, metabolic traits, and genetic variation. Van Dongen explains "The genetic code is fixed, but epigenetic mechanisms are dynamic and epigenetic studies improve our understanding of behavioral problems that originate from an interplay between environmental and genetic influences".
Our results provide a starting point for applications of methylation profiles as peripheral biomarkers and studies examining causal pathways of multiple exposures with aggression and related traits. The EWAS study found six aggression-associated loci where methylation in blood correlated with DNA methylation in the brain. We know that effects of genetic variants on nearby DNA methylation (cis mQTLs) correlate strongly between blood and brain cells, suggesting that we can use DNA methylation blood to study the downstream epigenetic effects of genetic variants that contribute to variation in behavior. Interestingly, DNA methylation signatures of chemical exposures and maternal rearing also show a certain (but less understood) degree of conservation across tissues.
The smaller ADHD study identified differentially methylated regions in two cohorts, including the major histocompatibility complex, where methylation levels correlated with expression levels of the C4A and C4B genes, previously implicated in schizophrenia. However, none of the loci were robustly associated across cohorts, warranting larger studies. These are to be initiated in the nearby future. In 2020, an international group from the fields of ADHD epigenetics, including Boomsma and van Dongen, founded a new consortium to study epigenetics in ADHD, embedded in the Psychiatrics Genomics Consortium (PCGC).
Odintsova also searched for epigenetic signatures of early life exposures and traits. Epigenetic alterations might be associated with events in prenatal life and early postnatal nutritional differences. In a study on breastfeeding, she found the epigenetic signatures of being breastfed in buccal cells in a younger group of children, but not in an older group of 10-12 years. The breastfeeding-associated epigenetic signatures showed larger correlations in MZ twins compared to DZ twins suggesting that these signatures are also subject to heritable influences.
There is a growing interest to improve the prediction of early life traits with multiple

"The genetic code is fixed, but epigenetic mechanisms are dynamic"

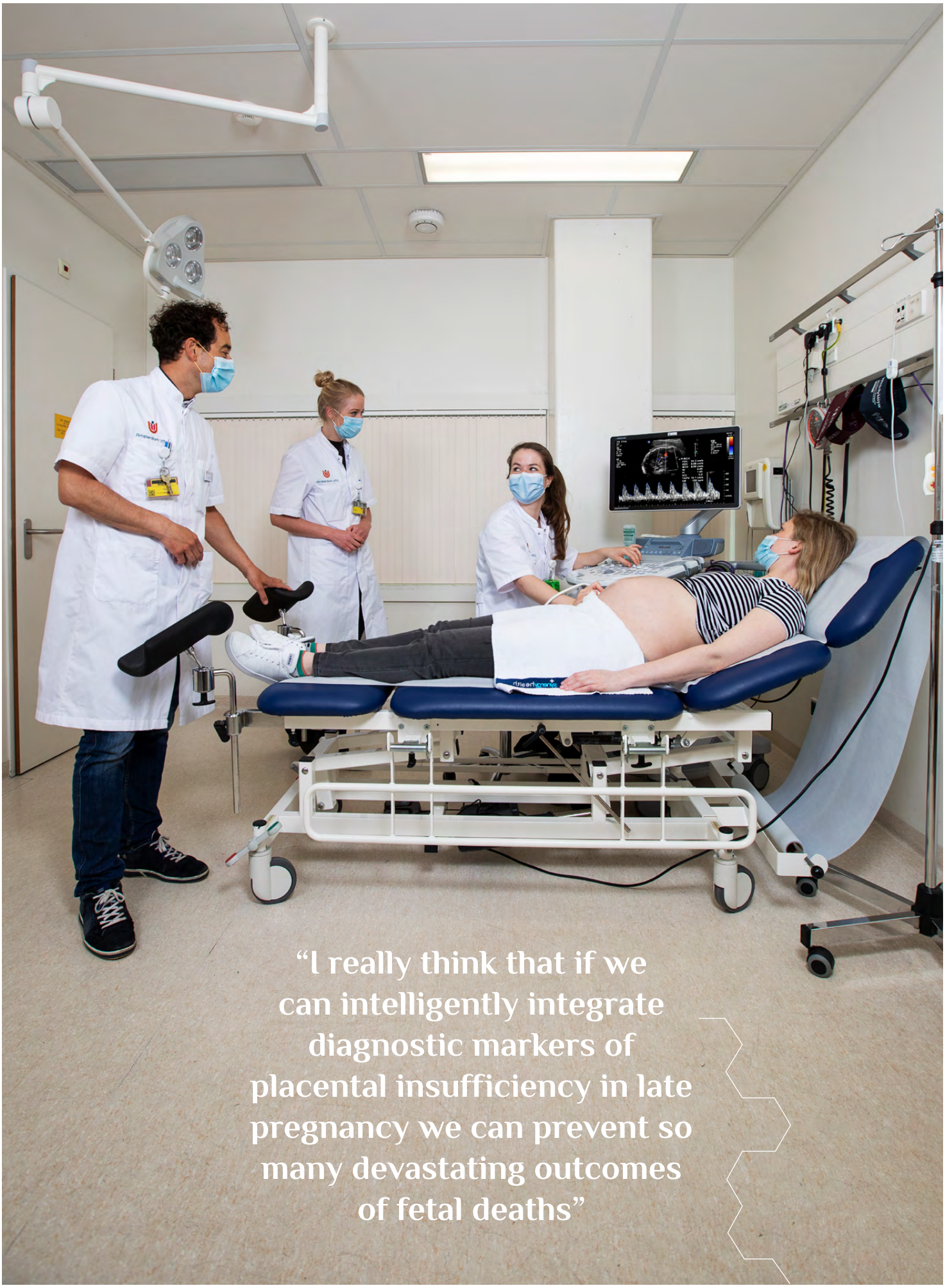
omics data. Combining polygenic and epigenetic scores, we showed epigenetic scores outperformed polygenic scores, based on currently available GWASs, for prediction of maternal smoking and body mass index in adults. This provides new insights into the predictive performance of polygenic and epigenetic scores for different traits, across different tissues and ages.

TWINS, TWINNING AND EPIGENETICS

As a design to study the heritability of human traits, twin studies have made tremendous contributions to science. To many scientists and the general public, it is therefore a surprise that the fundamental question as to why and how often identical (monozygotic) twins arise has remained a mystery. An important reason for this - intriguing in itself - is that monozygotic twinning, unlike most human traits, does not segregate in families and appears to occur at random, making it hard to study monozygotic twinning in animal models.

Jenny van Dongen recently published a manuscript with entirely new findings from epigenetic data, reporting the exciting discovery of a molecular signature for MZ twinning in NTR with replication from multiple international twin cohorts. She reports that this epigenetic signature is highly replicable and that it persists, through many rounds of mitosis, to adult somatic tissues. There are multiple implications from this finding: for a number of congenital disorders a higher rate of MZ twins among affected individuals is seen, notably Beckwith Wiedemann Syndrome and neural tube defects. It has even been hypothesized that some affected singletons with such disorders began life as part of a pair of MZ twins in the womb, without the mother's knowledge (vanishing twin syndrome). Van Dongen is highly motivated to investigate the possible links between MZ twinning and congenital disorders, and the molecular signature they have discovered in MZ twins opens up new avenues for this. In collaborations with AR&D, they hope to extend these studies on samples from healthy twins to samples from cases with congenital disorders and to obtain funding to extend this work in somatic tissues from twins to cell types that can bring us closer to the early window in development when MZ twins arise, such as induced pluripotent stem cells.

Meanwhile, we also continue working on the inheritance and gene finding for DZ twinning, where more results obtain with increases in sample size. A polygenic risk score based on the latest discovery does significantly predict the trait 'being a mother of DZ twins' and next we aim to look at its characteristics in mothers who had twins after IVF.



“I really think that if we can intelligently integrate diagnostic markers of placental insufficiency in late pregnancy we can prevent so many devastating outcomes of fetal deaths”

MADDY SMIES, STEFANIE DAMHUIS AND WESSEL GANZEVOORT

Clinical evaluation studies of the use of fetal Doppler ultrasound

in suspected placental insufficiency in (near) term pregnancies

At AR&D, large research trials focus on placental insufficiency in pregnancy in relation to adverse perinatal outcome.

Wessel Ganzevoort

Maddy Smies

Placental insufficiency in late term pregnancies is one of the major contributors to adverse perinatal outcomes due to the risks of fetal hypoxia, including fetal death. Prevention of fetal death due to this cause can be the main route to decrease perinatal deaths worldwide. The major challenge in these gestational ages is the diagnosis: how to determine which fetuses are at risk and benefit from expedited delivery. The best-known parameter that indicates placental insufficiency is poor fetal growth leading to a small for gestational age fetus. However, assessment of fetal growth and defining (ab)normality is complex and unreliable due to the imprecise measurement tools. Besides, being small for gestational age does not necessarily reflect pathology and an appropriate size is not a guarantee that placental function is sufficient. At these gestational ages the breathing function of the maternal-fetal exchange in the placenta is so delicate that a fetus will not withstand this challenge for a long enough period of time for this to become apparent in lagging fetal growth. One of the first alarming symptoms of imminent fetal hypoxia is reduced fetal movements. Alternative tools to detect an impaired placental function, added to the assessment of fetal size, are eagerly wanted. The main candidate is Doppler ultrasound of fetal vessels. They can indicate redistribution of blood flow in the fetal circulation, in which blood flow is selectively redirected to the most important organs including the brain. This phenomenon has been dubbed the “brain-sparing effect” and can be expressed in an abnormal ratio between the pulsatility index of the umbilical artery and the middle cerebral artery, the so called cerebroplacental ratio (CPR). The measurement of CPR and its use in decision-making has been adopted universally. However, the underlying evidence which fetuses benefit (with imminent risk of hypoxia) or harm (small fetuses with normal placental function) from expedited delivery is lacking. In a collaboration between Amsterdam UMC and UMC Groningen two ZonMw-funded evaluation studies are deployed, within a broader research line on placental insufficiency. The DRIGITAT study focuses on small for gestational age fetuses as expression of impaired placental function whereas the CEPRA study looks into reduced fetal movements as the first manifestation.

OVERVIEW OF CPR TRIALS

The DRIGITAT study (PhD candidate Maddy Smies) is

“The challenge in clinical practice is to prevent unnecessary interventions in the healthy (small) fetuses and to pick up the fetuses at risk”

an ongoing multicenter RCT nested in a prospective cohort study. In the cohort, small for gestational age fetuses between 32 and 37 weeks are monitored until delivery with follow-up until 2 years of age. If an abnormal CPR is diagnosed, there is a randomized comparison of expedited delivery between 34 and 37 weeks versus watchful waiting until 38 weeks.

The CEPRA study (PhD candidate Stefanie Damhuis) recently started recruiting patients in a multicenter cluster randomized trial of women presenting with reduced fetal movements between 37 and 41 weeks. Centers are randomized for concealed or open measurement of CPR. If an abnormal CPR is diagnosed in an open center, the management protocol warrants expedited birth. In all other cases, management is ‘as usual’.

It is likely that the results of DRIGITAT and CEPRA may not completely answer all questions. However, it will surely be a platform of rich individual patient data in which diagnostic strategies can be further refined. In both studies a significant amount of other potential diagnostic variables, including serum biomarkers (proteins in maternal blood that reflect placental function), are collected. It is likely that we will provide evidence how to best integrate all the available monitoring variables and other prognosticators in the risk models. Our project group is fully committed to improve the field on this subject, because any small progress will decrease the number of unnecessary interventions in many healthy small fetuses and decrease the risks of perinatal death in the few who need the intervention.

Stephanie Damhuis

“We have been aiming to use this impressive gene editing tool in translating basic research to clinical applications”

KAVISH KOHABIR AND ROB WOLTHUIS, ERIK SISTERMANS

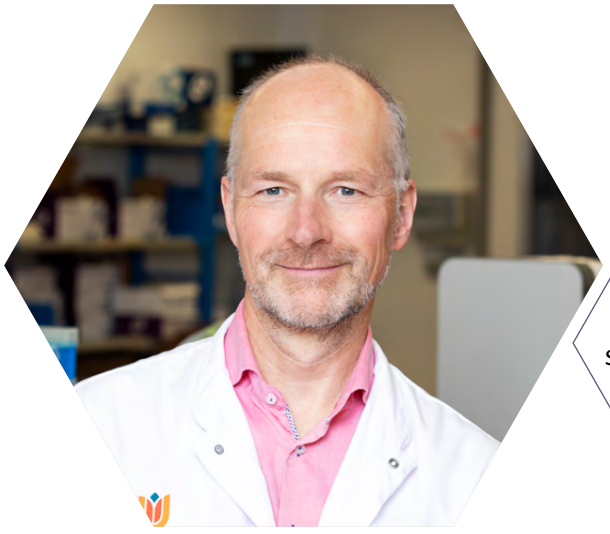
Towards CRISPR-based diagnostics: a “cutting” edge technology

CRISPR-technology takes a leap towards its applications in clinical genetics and is now also used in AR&D research. Principal investigators Rob Wolthuis (Clinical Genetics, section of Oncogenetics) and Erik Sistermans (Clinical Genetics, section of Genome Diagnostics) join forces and explore with their PhD candidate Kavish Kohabir CRISPR’s possibilities for noninvasive medical diagnostics and screening, including Non Invasive Prenatal Testing (NIPT).

REPROGRAMMABLE SCISSORS

Originally evolved to function as a bacterial cognate immune system, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and the affiliated nucleases have come a long way to now function as molecular biology tools and beyond. The discovery that CRISPR-associated (Cas) proteins can be directed at specific DNA sites of interest by means of reprogrammable guide RNAs marked a new era in nuclease biology, distinguished by experimental flexibility, reduced costs and shorter experimental pipelines. As of 2020, these major improvements have led to the recognition of CRISPR-Cas as a Nobel prize-awarded technology (Nobel prize for Chemistry 2020 for Emmanuelle Charpentier and Jennifer A. Doudna).

Ever since its first demonstration as a reprogrammable molecular scissor to cut DNA, a plethora of more natural Cas-protein variants continue to be discovered, revealing an astonishing diversity in terms of structures and catalytic capability. Additionally, Cas-proteins are commonly engineered and given novel features of interest. This led to an explosive growth in molecular biology tools based on CRISPR-technology. The pace at which diversification and standardization take place allows for a continuously increasing integration into modern-day research and biotech industries.



Erik Sistermans

FROM SCISSORS TO SHREDDERS

Genome editing in cell-lines, performing high-throughput knock-out screens and testing for drug candidates are among the few of many CRISPR-embedded experiments routinely done at the Wolthuis lab (section of Oncogenetics) at the Cancer Center Amsterdam. Most of these experiments are typically done with the originally discovered CRISPR-nuclease Cas9, or derivatives thereof. Typically, Cas9 is supplied with a guide RNA that contains information on which target DNA Cas9 should cut. Cas12, a more recently discovered Cas protein shows somewhat different behavior than the regular 'scissor-like' Cas9. Upon cutting the target DNA, Cas12 induces a 'shredder-like' behavior, cutting other nearby DNA indiscriminately. Similarly, Cas13 shreds ambient RNA upon recognition of the target RNA sequence.
These inherently different CRISPR-systems allow for novel applications in which CRISPR is used to detect the presence of specific nucleic acid sequences and subsequently shred a reporter nucleic acid coupled to a read-out. The Covid-19 pandemic prompted rapid development of CRISPR-based SARS-CoV-2 detection as a response to shortage of remote, or Point-of-Care (POC), diagnostic tests. Insights in the remarkable sensitivity and specificity at which CRISPR detects nucleic acid targets drives exploration of CRISPR-diagnostics to other areas as well.

COLLABORATION FOR CRISPR AND NIPT

Erik Sistermans (head of Genome Diagnostics location VUmc and project leader of the TRIDENT studies that realized the implementation of Non Invasive Prenatal Testing (NIPT) in the Netherlands) monitors a broad range of clinically relevant genetic diagnostic screens. Amsterdam UMC is one of the three laboratories in the Netherlands that performs NIPT, a prenatal screening that can accurately detect trisomy 13, 18 and

Kavish Kohabir

Rob Wolthuis

21 based on sequencing fetal cell-free DNA present in the mother's bloodstream. There is much interest into further technological development of NIPT, as the demand increases. As a revolutionary technique itself, CRISPR may play a role in this, and in liquid biopsy diagnostics and screening in general. Hence, the section of Genome Diagnostics initiated a collaboration with the section of Oncogenetics, which was one of the first labs at Amsterdam UMC to start using CRISPR technology and co-hosts the Amsterdam UMC CRISPR expertise center. As of September 2020, Kavish Kohabir was hired as the first PhD candidate to work on this joint venture. Rob Wolthuis: "Ever since we started to use CRISPR in 2014, we have been aiming to use this impressive gene editing tool in translating basic research to clinical applications. What's new is that CRISPR also appears to work as an extremely sensitive "one-test-tube" detection kit for specific DNA sequences. This exciting development allowed us to team up with Erik to explore CRISPR applications in new forms of genome diagnostics. We were lucky to attract Kavish's attention with our project, as he already was quite familiar with CRISPR's unique DNA detection powers thanks to his TU Delft graduation project."

AGAROSE GELS AND DNA FRAGMENTOMICS

Kavish: "The first paces in this line of research are challenging, as we try to build an experimental pipeline from scratch. Apart from the many variables to be taken into account, the more recent Cas protein derivatives have simply not been fully characterized yet. Currently I am optimizing experimental conditions and running many agarose gels to detect Cas activity, before moving on to detecting cell-free DNA. At the same time, I submerge myself into literature on cell-free DNA fragments to understand the type of target I will direct my molecular scissors and shredders to. It turns out there are consistent size, epigenetic and sequence patterns in cell-free DNA fragments that may be useful for distinguishing between the tissues of origin. This emerging field of cell-free DNA fragmentomics is still young, but points towards approaches to enrich for targets of interest, while providing more insight on the underlying biology of DNA fragmentation. This literature study even led to a review paper which recently has been submitted."

Erik Sistermans: "It took a lot of work from many people in the Dutch NIPT consortium to implement NIPT as a first tier test in prenatal screening, including work from our AR&D PhD student Karuna van der Meij. Since the start in 2017 the screening has been very successful, and it's now time to see how we can further improve prenatal screening. This can be done by either developing cheaper alternatives for the current methods, or by improving the resolution of the test to detect smaller anomalies as well. CRISPR is able to do both, which is why we were lucky to have Rob's group in our department to join forces at AR&D."

“A common issue in clinical practice is the difficulty differentiating adenomyosis from other uterine conditions”

MARISSA HARMSEN, LYNDA JUFFERMANS AND JUDITH HUIRNE

Towards advanced diagnosis and treatment of adenomyosis

At AR&D extensive research is done by professor Judith Huirne and her team on the diagnosis and treatment of adenomyosis, a uterine disorder.

Judith Huirne

Lynda Juffermans

Marissa Harmsen

ADENOMYOSIS

Although adenomyosis is fairly unknown among both patients and physicians, it is a uterine disorder that affects approximately 20-30% of women. Common symptoms of abnormal uterine bleeding, pain, and subfertility that have a considerable impact on the quality of life, are often caused by adenomyosis. Current treatment strategies are based on hormonal treatment, while many patients experience non-acceptable side-effects and end up requiring a hysterectomy. Professor Judith Huirne has a special interest in diagnosing and treating uterine disorders and a few years ago the center for uterine disorders was founded in the Amsterdam UMC, a tertiary referral center for complex uterine disorders. Recently our team received grants to develop and study advancements in diagnosing and treatments for adenomyosis.

The diagnosis of adenomyosis was traditionally made by histological examination. However, many women that suffer complaints might not want a hysterectomy. In these women, the diagnosis is made using ultrasound or MR imaging. Our team participated in the so called the MUSA (Morphological Uterus Sonographic Assessment) group. An international collaboration of experts in gynecological ultrasound that aims to enhance understanding and to reach a

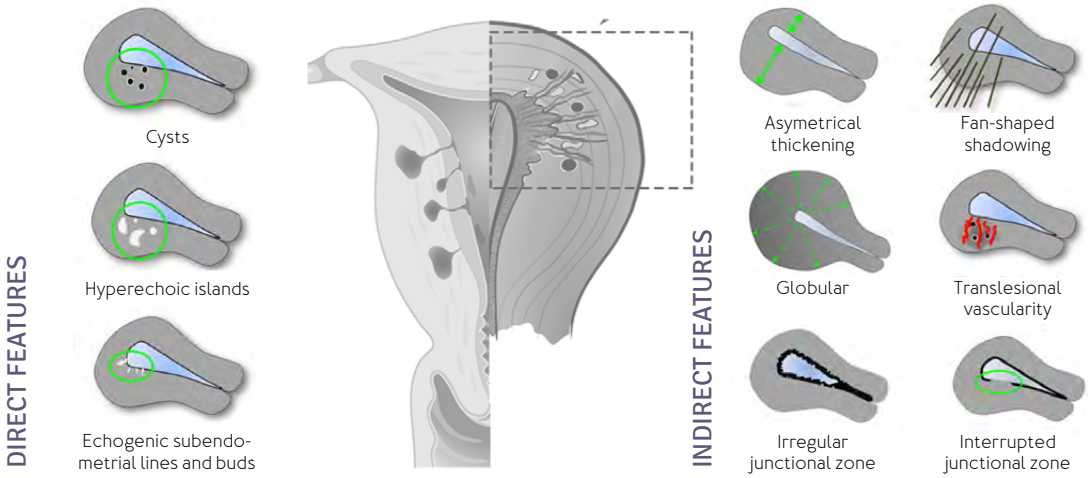


Figure 1: Ultrasound featrues of adenomyosis

uniform terminology describing adenomyosis, among other uterine disorders. In the past year, Marissa and Judith coordinated a modified Delphi study with experts from the MUSA group which has resulted in improved definitions of ultrasound features of adenomyosis and a classification into direct and indirect features (Figure 1). This project is important because uniform terminology is required before studies can be performed on the association between the ultrasound findings and clinical symptoms. A further step to achieve this, is a next study that will explore how we can define the severity of adenomyosis. Again, the team will seek collaboration with international experts to reach a consensus on not only diagnosing adenomyosis, but also grading the severity of the condition. This project will be coordinated by our new PhD student Lisa van Trommelen.

A common issue in clinical practice is the difficulty differentiating adenomyosis from other uterine conditions, such as uterine fibroids and sarcomas. An MRI scan can be performed, but it might remain difficult to give a definite diagnosis. A novel and very innovative method to enhance the differentiation between this disorders is contrast enhanced ultrasound (CEUS). This method is already used by radiologist to diagnose liver and renal masses, but the diagnostic potential for gynecological disorders has only been studied in small pilot studies up to now. While CEUS is a technically advanced technique and is capable to visualize the microvasculature and quantify measurements, the great advantage is that it can be applied in an outpatient setting. This diagnostic potential has been recognized by NWO (Nederlandse Organisatie voor Wetenschappelijk Onderzoek) who granted Judith and Lynda a large research grant to further develop this technique.

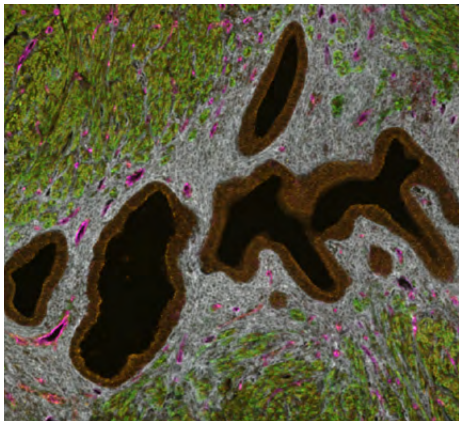


Figure 2: Adenomyosis glands (orange) and stroma (grey) in the myometrium (green) surrounded by a great amount of micro blood

Once the diagnosis of adenomyosis is made, there are little treatment options that a gynecologist can offer a patient. When women do not tolerate the side effects of hormonal treatment, the only option is to remove the uterus (hysterectomy). Both strategies are not an option in women with adenomyosis who try to become pregnant or who are faced with fertility problems. To offer an alternative, our team is searching for non-hormonal treatment targets to relieve symptoms of adenomyosis. A possible target could be the evidence of increased angiogenesis, the formation of new blood vessels, that they found in the literature and in immune-histochemical staining of hysterectomy specimens of adenomyosis patients. Through a novel technique that allows the staining of multiple antibodies in one sample, we identified increased angiogenesis in adenomyosis tissue under supervision of Katja Jordonova (Figure 2). After this finding we initiated a project together with Arjan Griffioen from the Angiogenesis laboratory in the Cancer Center, with funding of an AR&D grant (2019), to test two strategies to inhibit angiogenesis in a recent developed mouse model for adenomyosis (Figure 3). Inhibiting angiogenesis is expected to be a non-hormonal therapeutic treatment strategy to treat adenomyosis in women who want to preserve their fertility.

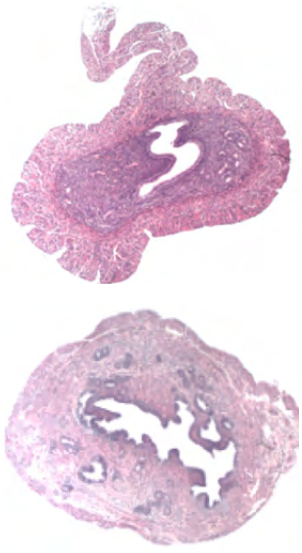
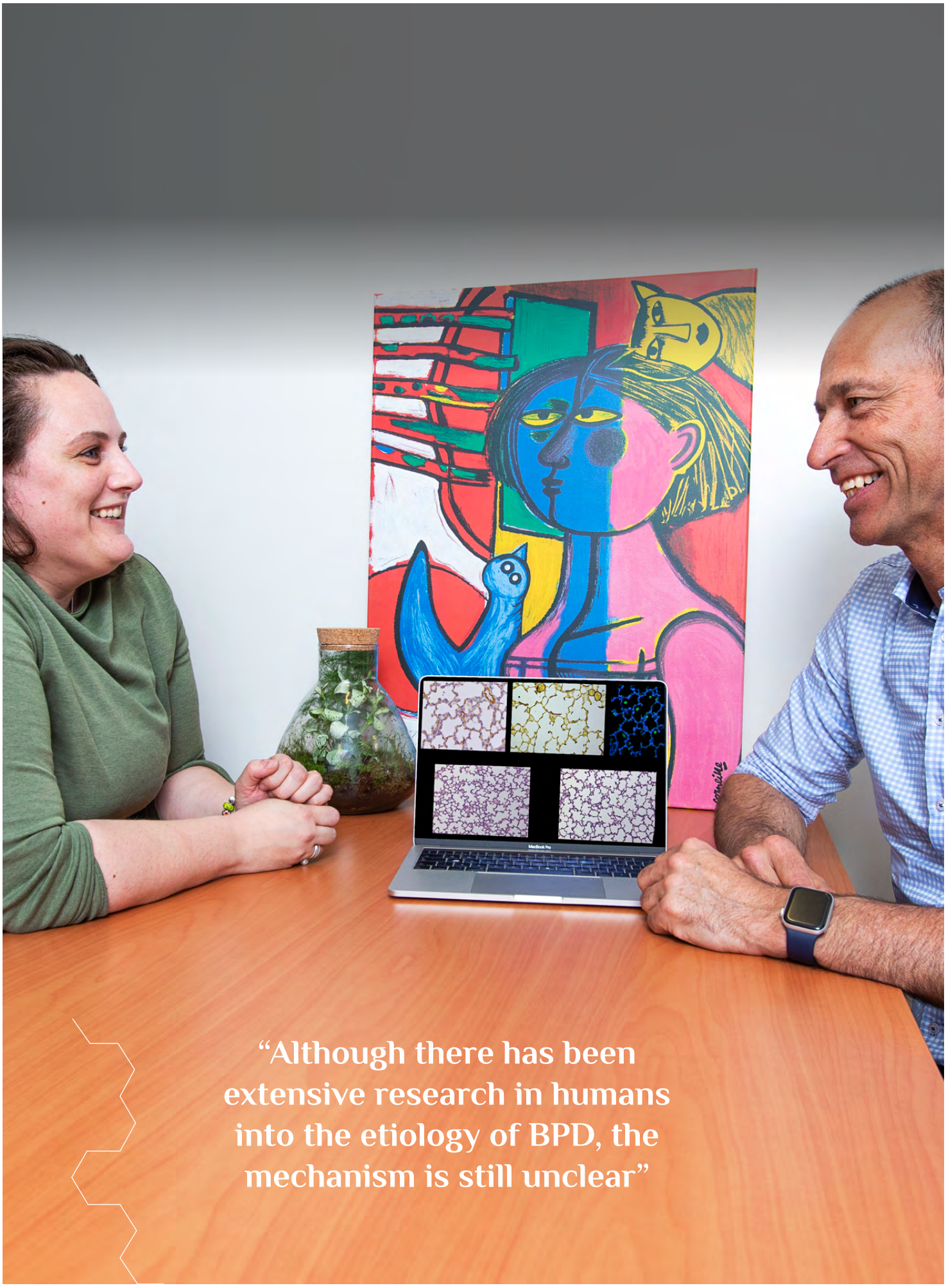


Figure 3: Mouse uterus without adenomyiosis (above) en with adenomyosis (below)



"Although there has been extensive research in humans into the etiology of BPD, the mechanism is still unclear"

IRENE LOK AND ANTON VAN KAAM

Understanding the pathophysiology and optimizing the treatment

of bronchopulmonary dysplasia in preterm infants

Professor Anton van Kaam is the head of the department for Neonatal Intensive Care at Emma Children's Hospital, Amsterdam UMC and leads the Neonatal pulmonology group. His group focusses on neonatal lung physiology, control of breathing, lung injury, neonatal respiratory support, and bronchopulmonary dysplasia (BPD).

BRONCHOPULMONARY DYSPLASIA

Perinatal and neonatal care has improved considerably over the last decades and as a result mortality and most morbidities after preterm birth have shown a significant improvement. However, this is not the case for bronchopulmonary dysplasia (BPD), the most common complication of preterm birth. BPD, is a chronic pulmonary condition that is histologically characterized by a delay in lung development due to an imbalance of injury and repair. Infants with BPD require prolonged respiratory support and experience respiratory complaints such as wheezing/shortness of breath and respiratory tract infections during the first years of life. Lung function testing shows reduced lung capacity reaching into adolescence and there are concerns that BPD patients may have an increased risk of developing Chronic Obstructive Pulmonary Disease (COPD) at older ages. In addition to pulmonary sequelae, BPD patients also have an increased risk of neurodevelopmental impairment at long-term follow-up.

> "Several animal models have been used to study BPD development"

Effective and safe interventions to reduce the risk of BPD are therefore urgently needed. However, up to now most interventions studied in randomized controlled trials have shown disappointing results. A recent example is the STOP-BPD trial which was a multicenter study initiated in the neonatal intensive care of the Emma Children's hospital in Amsterdam. This study could not confirm a beneficial effect of systemic hydrocortisone on the incidence of BPD, as previously described in other (observational) studies.

One of the reasons for these disappointing results from clinical trials is probably a lack of understanding on how BPD develops in preterm infants. Although there has been extensive research in humans into the etiology of BPD, the mechanism is still unclear. There is evidence that the disease is multifactorial with prematurity, pre- and postnatal inflammation, oxygen exposure and mechanical ventilation as the most important risk factors. These insults on an underdeveloped lung with reduced antioxidant capacity, can cause significant injury to the lung tissue. To gain a better understanding of the underlying mechanisms and to explore possible treatment and preventive strategies, several animal models have been used to study BPD development. Animal studies allow for strictly controlled conditions when testing a possible mechanism in the development of BPD or the effect of an intervention on a wide variety of outcome parameters, including histology. However, the downside is that most of these animal studies are based on exaggerated single hits, for example treating rats with a high dose of oxygen for several weeks or high tidal volume ventilation, to induce lung damage. This is not in line with clinical practice where preterm infants are never exposed to just one single hit but instead face several hits that may cause lung injury and subsequent BPD. Furthermore, most of these hits are limited in size due to a more gentle application of respiratory support. This difference in complexity between animal studies and actual clinical practice may be one of the reasons why interventions tested effective in animals do not work in real life.

PHD PROJECTS

To address this discrepancy between the current animal studies and clinical practice, PhD candidate Irene Lok, pediatrician-neonatologist Minke van Tuijl and Anton van Kaam developed a novel multi-hit animal model in collaboration with professor Martin Post of the department for Translational Medicine at The hospital for Sick Children (SickKids) in Toronto, Canada.

By taking the multifactorial etiology into account, the group tried to combine four known risk factors for BPD; prenatal inflammation (chorioamnionitis), hyperoxia, postnatal inflammation (sepsis) and mechanical ventilation. All individual hits have been shown to induce a BPD-like lung disease in rodents but the combination of all four has never been studied.

Irene Lok

Anton
van Kaam

With a focus on lung development, injury and repair the lab of Prof. Post has decades of experience in working with rodent models for neonatal lung diseases. As every individual hit gives the risk of mortality or rejection by the mother, the accumulated knowledge of the lab proofed to be essential to establish the model. The aim is to unravel which (combination of) hit(s) leads to the most BPD-like disease, either on a histological or biochemical level. As one of the goals was to create the possibility to investigate prolonged effects on lung development, rat pups needed to be in- and extubated and ventilated with low to modest tidal volumes, thereby mimicking standard of care in the NICU, but also allowing the rat pups to be reintroduced into the litter after ventilation. For this project, a Ter Meulen beurs from the KNAW was awarded and a grant from Stichting Steun Emma.

Preliminary results show that the hits postnatal inflammation and ventilation are the main risks factors in the development of a BPD-like histological phenotype. This knowledge was used for the next step of this PhD project: to investigate the impact of dexamethasone on lung development in pups subjected to these hits. Up to now, dexamethasone has only been studied in rodents exposed to high concentrations of oxygen without ventilation. Furthermore, most studies only reported short-term outcomes. In this study we will assess the short- and long-term effects of dexamethasone after exposure to postnatal inflammation and mechanical ventilation.

In addition to dexamethasone we will also examine the effect of active alveolar-like macrophages, which were recently discovered in the lab of Prof. Post to treat airway disease, on ventilation induced lung injury given their ability to promote repair in the developing neonatal lung.

Currently, the last samples of these additional experiments are being processed after which we will analyze all outcome parameters and publish the results.
The results of this PhD project will enhance our knowledge on mechanisms involved in the development of BPD and will provide the opportunity to test the efficacy and safety of existing and new interventions to reduce the rate of BPD. By using a more realistic model of lung injury we can hopefully increase the success rate of these interventions in clinical trials.

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AR&D events 2020

AR&D SYMPOSIUM: DIANA BIANCHI

Thursday January 9th

The University of Amsterdam (UvA) has awarded American neonatologist and medical geneticist **Prof. dr. Diana Bianchi** with an honorary doctorate in January 2020. This honorary doctorate has been awarded to Bianchi for her crucial contributions to research into the health of mother and child before, as well as during pregnancy, and especially because of her contribution to the development of the NIPT (non-invasive prenatal test).
Diana Bianchi is director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development in Bethesda, Maryland. In honor of the honorary doctorate of Diana Bianchi our AR&D institute organized a symposium on January 9, 2020.

During this symposium Bianchi gave a lecture on *'The Impact of Prenatal Genomics on Fetal Screening, Innovative Therapies and Maternal Health'* followed by senior researcher Erik Sistermans on *'NIPT in the Netherlands, what we learned from Diana Bianchi'* (see interview with dr. Sistermans on page 24). The symposium ended with Phillis Lakeman, clinical geneticist, who gave a talk on the evaluation of preconception carrier screening for recessive disorders at AMC, offering the listeners food for thought on how to move on from there.

More information on the honorary doctorate can be found here.

AR&D MINI SYMPOSIUM GRANT AWARD CEREMONY

Friday September 11th

On September 11, 2020 the first AR&D online event took place. Due to Corona the symposium had to be held online instead of in the home venue of AR&D Het Volkshotel in Amsterdam. During the webinar two invited speakers gave lectures and a festive award ceremony closed this well attended event.
The first speaker was dr. Norah van Mello who gave a lecture about Gynaecological and obstetric aspects of trans men. She introduced the audience to the patient group and the challenges the Center of expertise on gender dysphoria of Amsterdam UMC faces when treating people with gender dysphoria who have a child wish.
The next speaker was Prof. dr. Martine de Vries of the Department of Medical Ethics & Health Law Leiden University Medical Center who took the audience on a journey into the ethics of infertility treatments.
After some questions of the audience it was time for the grant ceremony in which the awardees pitched the study they received funding for. Previous years the awardees were given a big grant cheque to celebrate their prize. The organizing committee had even taken care of that by home-delivering this cheque to each winner. This made the festive ceremony even better.
Even though everything was hosted online the first webinar was both educational as well as a festive ceremony, followed by almost 70 web-participants!

AR&D RETREAT 2020

Thursday October 29th – Episode 1

On Thursday October 29th the first episode the AR&D Retreat 'the series' was held with **Katia Bilardo** as speaker. Katia Bilardo is a well-known specialist in the field of obstetric ultrasound and perinatology and the former president of the International Society of Ultrasound Obstetrics and Gynaecology (ISUOG). In her talk she took us on a trip down memory lane by telling us about the history of screening for congenital anomalies. She told us about the special position that first trimester ultrasound screening holds in the Netherlands, how the combined test was substituted by the NIPT, the (protection by law against) risk of screening for incurable conditions, and how omitting the first trimester ultrasound lead to an increasing number of late pregnancy terminations.
In the afternoon there were 3 workshops: Personal leadership, Mindfulness and LinkedIn for researchers.
The afternoon ended with a digital pub quiz by Peer Jochems. Questions ranged from flags, to music, to movies. Almost everyone recognized the theme songs from Harry Potter and Frozen, however, some things were a little less known such as the birthday paradox (google it!). In the end, Ruud, Zeliha and Claire and Liz emerged victoriously, congratulations! With their victory came and end to the first digital ARD retreat.

Thursday December 10th – Episode 2

At the second Episode of the Retreat we welcomed **dr. Hilgo Bruining** as our key-note speaker. Hilgo Bruining is a child & adolescent psychiatrist, and as a researcher he focuses on diagnosis and treatment of sensory processing abnormalities in neurodevelopmental disorders. During his talk about 'Personalising treatments for neurodevelopmental disorders', he took us through the essential aspects of individualised medicine in autism spectrum disorders and gave us insight in the development of N-of-1 trials towards personalised treatments.

In the afternoon there were 3 workshops: Infographics, Scientific Storytelling and LinkedIn for researchers.

Thursday January 28th (2021) – Episode 3

The third and final episode of the AR&D digital retreat was kicked off by keynote speaker dr. ir. Beatrijs van der Hout, medical engineer and midwife. She gave an update about perinatal life support (PLS) for extremely preterm infants; more commonly known as the artificial womb project. She spoke about the general principles of perinatal life support, design principles and aspects to take into account such as the stimuli needed, chamber-in-chamber design, clinical transfer procedures and PLS research and technology. Finally, she revealed what we can expect from the perinatal life support consortium in the future: a liquid based prototype, preterm manikins, manikin based simulation, mathematical modelling and a vaginal transfer procedure.

In the afternoon there were 3 workshops: Infographics, Scientific Storytelling and Personal Leadership.

AR&D grants 2020

OPEN RESEARCH GRANTS, AND PRINTING COSTS OF THESES

In 2020 AR&D awarded two kinds of grants: The Open Research Grant 1 ,2 and 3 for all research in the field of Reproduction and Development. And the printing costs of thesis, a financial compensation for the expenses of bringing AR&D theses to print.

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

Marsh Königs
PErsonalized PRognosis for Children with Traumatic Brain Injury: the PEPR Study

My name is Marsh Königs, I am neuroscientist and assistant professor at the Emma Neuroscience Group of the Emma Children's hospital. We investigate the impact of disease and treatment on the structure and function of de developing brain in the context of daily life functioning. I live in Utrecht, with Mariëlle and our son Sacha. In (normal) daily life, I like to play soccer at SV Kampong in Utrecht and to have a drink with friends afterwards. Also like to cook, curry is my favorite dish! Cece Kooper (PhD candidate) coordinates the PErsonalized PRognosis (PEPR) Study. This study aims to develop more personalized prognosis for neurocognitive, behavioral and academic outcome of children with traumatic brain injury by the use of a broad and multimodal predictor set in combination with machine learning. Thanks to AR&D's grant, we are able to investigate the additive value of advanced neuroimaging with MRI. We have now set up the sequences and analyses to determine brain volumes, white matter integrity, structural connectivity, functional connectivity and the presence of brain metabolites. We hope that this detailed information on brain integrity can improve clinical outcome prediction for children with traumatic brain injury and will lead to readily usable prognostic models for clinicians.

Miriam Zagers
The in vivo environment of human preimplantation embryos: analysis of human uterine temperature and pH and uterine fluid composition

Miriam Zagers always had a sincere interest in the human body and a strong will to understand the beginning of life, early embryo development and the development of diseases. From March 2016 until March 2018, she acquired specific experience in Artificial Reproductive Technologies (ART) and embryology when working as in vitro fertilization (IVF) technician at the Center of Reproductive Medicine at the Academic Medical Center in Amsterdam (currently Amsterdam UMC, location AMC). After these two years of extensive practical IVF laboratory training Miriam resumed her academic training by starting a PhD program at the same department. While pursuing her doctorate, she is ambitious to make a difference in optimizing in vitro culture of human pre-implantation embryos.
The aim of this study is to measure the human uterine temperature and pH and to analyze the composition of aspirated uterine fluid of 20 normal fertile women of a Dutch population. This is a much needed confirmation of the hypotheses derived from the earlier measurements. It will for the first time demonstrate whether there is a difference in uterine conditions between women with different (genetic and nutritional) backgrounds. The results of this study will be used to optimize the culture systems currently used for human embryo culture.

IN BETWEEN GRANT (TYPE 2):

€ 50.000

Yousif Dawood

The human fetal microbiome: fact or fiction?

My name is Yousif Dawood, I am currently working as a MD at the Obstetrics and Gynecology department in the Flevoziekenhuis in Almere and doing my PhD at the Amsterdam UMC, location AMC. I am really proud and honored to receive the in between grant for the project "Fetal microbiome: fact or fiction?". For me, as a young scientist, it feels as a reward for the hard work we have put in this project as a team.
My deepest gratitude goes to Prof. E. Pajkrt and dr. B.S. de Bakker for their essential input. The aim of the project is to investigate whether there is a fetal microbiome, and if there is, from what gestational age it starts to develop. This will help us understand when and how the human host-microbial symbiosis is established. This will provide the scientific and clinical community new insights for further research on the role of the fetal microbiome. Thanks to this grant we are able analyze fetal tissue retrieved from the Dutch Fetal Biobank on the presence of a microbiome. Unfortunately we had some delay due to COVID, however the tissue is being analyzed and the first results are to be expected real soon.

Myrthe Smits

Senescence as a driving force in ovarian ageing and female fertility decline.

My name is Myrthe Smits, I'm a twenty eight years old researcher at the Center for Reproductive Medicine at Amsterdam UMC. In 2017, I started my PhD at the Amsterdam UMC with the aim to unravel the mechanisms behind the lower chances of pregnancy in women after the age of 35 years by studying ovarian aging. So far, we found that, contrary to popular believe, oxidative phosphorylation and ROS-induced damage are present within primordial follicles. Therefore, together with the Laboratory of Genetic and Metabolic diseases, we hypothesized that this induces senescence in oocytes and neighboring cells, which could impair fertility. I was extremely excited to learn that AR&D funded our proposal to study this hypothesis, as I do think we are on the verge of better understanding the age related fertility decline. It also allows me personally to extent my research work, and with that it will provide a solid basis for future research grants that I am planning for.

Marieke Buijtendijk

THE BIGGER PICTURE GRANT (TYPE 3): €100.000

Marieke Buijtendijk
3D foetal heart models to improve prenatal detection of congenital heart disease

My name is Marieke Buijtendijk, a second-year PhD candidate at the department of medical biology. My research focuses on novel 3D imaging technology for fetal anatomy assessment. I studied medicine at the University of Amsterdam, where I developed a great interest in the etiology, diagnosis and management of birth defects. During my senior elective at the pediatric intensive care unit and pediatric cardiology department of the Starship Hospital in Auckland, New Zealand, I developed a special interest in congenital heart defects. The grant we received supports a project in which we will establish an open-access online learning aid for the performance and interpretation of fetal echocardiography. This tool specifically aims to develop the skill to mentally build a 3D model of the fetal heart based on the serial 2D cross sections that are obtained during a prenatal ultrasound scan. To achieve this, we will develop 3D reconstructions of the heart of healthy fetuses and fetuses with congenital heart defects based on clinical fetal echocardiography datasets. These reconstructions will form the basis for the development of this interactive online learning tool. I feel strongly about the need for investing in training and education to optimize prenatal diagnosis and care for congenital heart disease. The excitement I felt when reading the letter with the committee's decision to award the grant is hard to describe, and lasted for several days. In two years' time, we aim to have the learning tool available online so keep an eye out on our work!

THE AR&D PRINTING COSTS OF THESIS

Matty Karsten
Women's Lifestyle and Sexual Function: the effect of a preconception intervention in women with obesity

This dissertation describes the effects of a lifestyle intervention in women with overweight and unmet wish to conceive. The lifestyle intervention caused women to improve their lifestyle and to lose weight and did also result to a better sexual function five years after participation in the program. The research in this thesis shows that physical, psychological and social factors in the field of lifestyle, overweight and sexual function are interrelated.

Joana Diogo Portela
Spermatogonial stem cell-based models for male fertility preservation

Cryopreservation of a testicular biopsy is offered as a fertility preservation strategy for prepubertal cancer patients. It is hoped that spermatogonial cells within the stored tissues can be used to generate sperm for assisted reproductive techniques. However, there are no current methods that allow restoring the fertility of a childhood cancer survivor. This thesis aimed to analyze an in vitro spermatogonia-based fertility restoration method and challenges that need to be overcome.

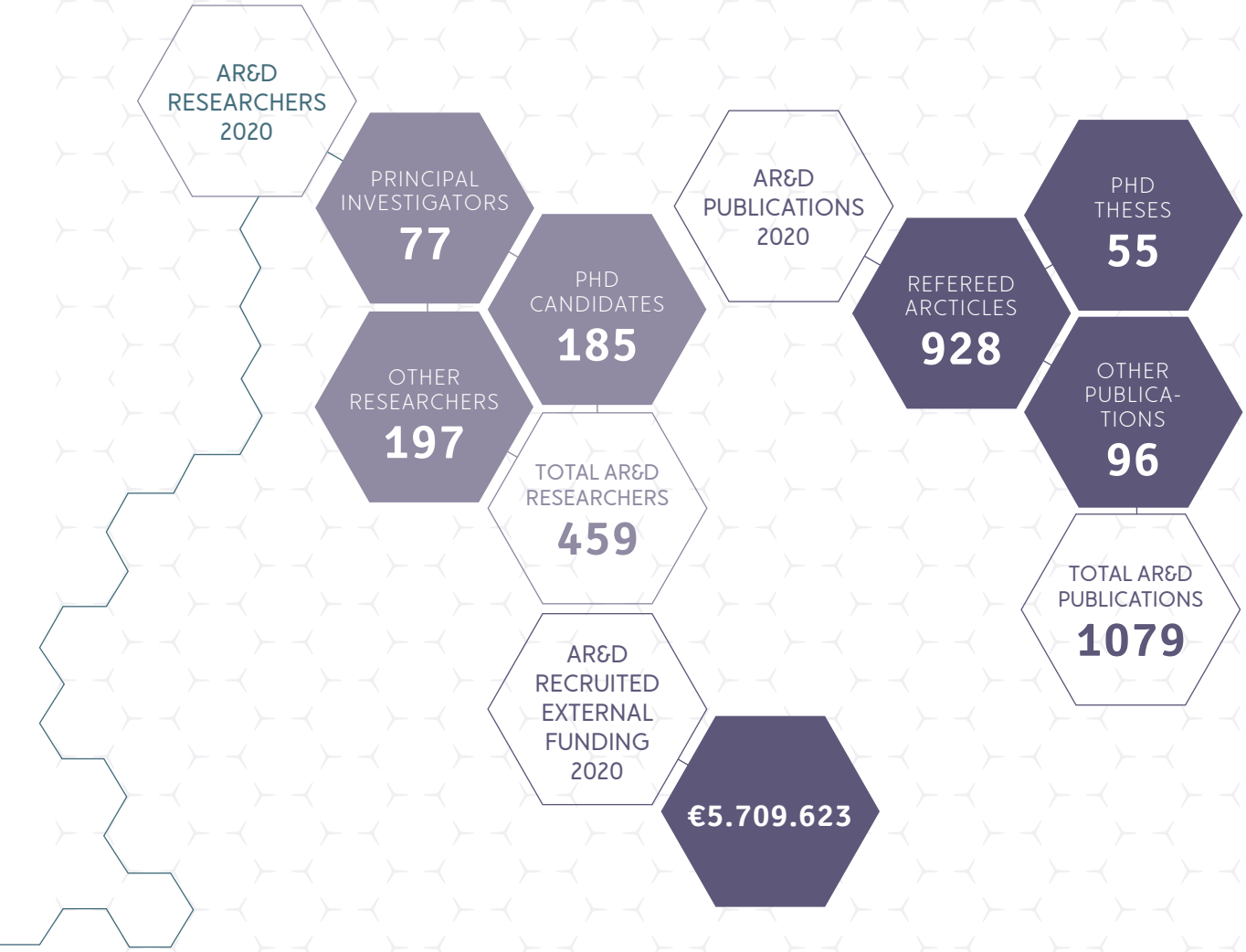
Henrike Peters
Intrauterine mix-up: chimerism and endocrinology

In this thesis was hypothesized that uterine development with MRKH syndrome is inhibited by AMH exposure in utero, for which a male co-twin is the identified source. This is a well-known phenomenon in cattle called freemartinism (with resulting twin chimerism).

Most of the results are not in support of our hypothesis. Twin chimerism does exist in humans, however rare. The high prevalence of microchimerism in a general population highlight a need for further studies.

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 April 30th, 2021. 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.

PUBLICATIONS

The reported data include all published research output as registered in the Research Information Systems Pure VUmc and Pure AMC on April 30th, 2021. 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.

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 2020, 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.

NWO GROOT
€1.600.000
Pacing the heart; studying the underlying principles of biological pacemakers.
Vincent Christoffels, Dept. of Anatomy, Embryology and Physiology

AMSTERDAM UMC INNOVATION FUND
€195.000
Augmented Reality for teaching, diagnostics and counseling for cleft lip/palate.
Corstiaan Breugem, Dept. of Plastic, Reconstructive and Hand Surgery

DEKKER CLINICAL SCIENTIST GRANT
€240.000
Targets for treatment and prevention of autoimmune cardiovascular disease
Thijs van Mens, Dept. of Vascular Medicine

TKI-PPP GRANT
€381.741
Cocoon: Combining cord-free uterine elektrohysterography and standard clinical measurements for refining the detection of premature birth.
Anna Rietveld, Dept. of Obstetrics and Gynecology

ZONMW ETHIEK EN GEZONDHEID
€100.000
Preconception carrier screening in the Netherlands.
Lidewij Henneman, Dept. of Human Genetics

HEVAS
€20.000
Pregnancy and vascular malformations.
Naomi van Hout, Dept. of Plastic, Reconstructive and Hand Surgery

ZONMW COVID-19
€19.800
Impact and consequences of the restrictive measures following the COVID-19 outbreak for fertility patients and patients with endometriosis.
Laura van Loendersloot, Dept. of Obstetrics and Gynecology

PRIZE FOR THE YOUNG RESEARCHER (NVK)
Parents' possible role at the NICU.
Nicole van Veenendaal, Dept. of Paediatrics

AMC PHD SCHOLARSHIP
€216.000
Hyperoxia in Critically-ill Children.
Thijs Lilien, Dept. of Cardiology

KEY PUBLICATIONS

2020 was a very productive year. Here is a selection of peer-reviewed publications that were highlights for our researchers.

Tumors widely express hundreds of embryonic germline genes.
Bruggeman et al.
Cancers 2020;12:3812.

The stepwise development of an interactive web-based sex education programme for subfertile couples: the Pleasure & Pregnancy programme.
Dreischor et al.
Hum Reprod 2020;35:1839-1854.

Who ever heard of 16p11. 2 deletion syndrome? Parents' perspectives on a susceptibility copy number variation syndrome.
Kleinendorst et al.
Eur J Hum Genet 2020;28:1196-1204.

The bivariate NRIP1/ZEB2 RNA marker permits non-invasive presymptomatic screening of pre-eclampsia.
Manders et al.
Scientific Reports 2020;10(1):21857.

Application of PECARN rules would significantly decrease CT rates in a Dutch cohort of children with minor traumatic head injuries.
Niele et al.
Eur J Pediatrics 2020;179:1597-1602.

Incidence of symptomatic submucous cleft palate in the Netherlands: A retrospective cohort study over a period of 22 years.
Smit et al.
Cleft Palate Craniofac J 2020;58:1121-1127

Psychological functioning in transgender adolescents before and after gender-affirmative care compared with cisgender general population peers.
van der Miesen et al.
J Adolesc Health 2020;66;699-704.

Diaphragmatic electromyography in preterm infants: The influence of electrode positioning.
van Leuteren et al.
Pediatr Pulmonol. 2020;55:354-359.

Thyroid function in neonates conceived after hysterosalpingography with iodinated contrast.
van Welie N et al.
Human Reproduction 2020;35:1159-1167.

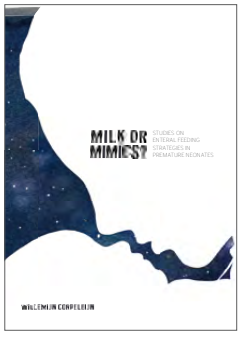
Effects of tocolysis with nifedipine or atosiban on child outcome: follow-up of the APOSTEL III trial.
van Winden et al.
BJOG 2020;127:1129-1137.

PHD THESES

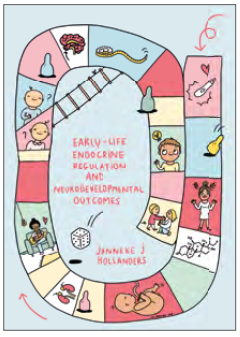
In 2020, 52 researchers obtained their PhD in the area of Reproduction & Development.

Here below a cross section of the PhD theses.

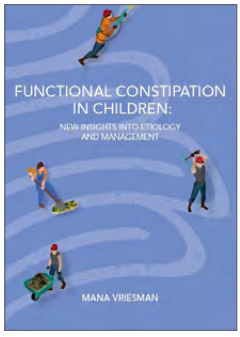
Smart Moves! Physical activity and cognitive performance of young adolescents
Vera van den Berg



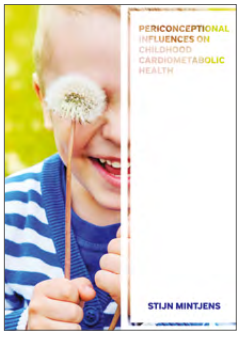
Milk or Mimics? Studies on enteral feeding strategies in premature neonates
Willemijn Corpelleijn



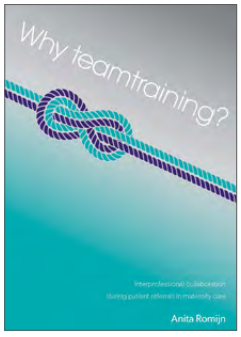
Early-life endocrine regulation and neurodevelopmental outcomes
Jonneke Hollanders



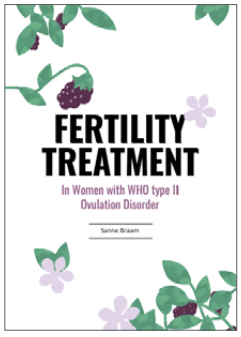
Functional constipation in children: new insights into etiology and management
Mana Vriesman



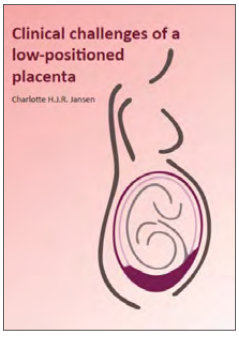
Periconceptional influences on childhood cardiometabolic health
Stijn Mintjes



Why teamtraining
Anita Romijn



Fertility treatment in women with WHO type II ovulation disorder
Sanne Braam



Clinical challenges of a low-positioned placenta
Charlotte Jansen

SOCIETAL IMPACT

In 2020, AR&D researchers have been contributing to the Societal Impact of research. A selection of societal impact events is presented.

AR&D INTERVIEWS

If your semen does not succeed: "It sometimes seems that as a man, you play a supporting role"
Ans van Pelt explains for Eva Jinek

Sexuality across generations
Ellen Laan and daughter in Volkskrant newspaper

Pregnancy and delivery during COVID-19
Martijn Oudijk explains at "De Balie"

COVID-19 infection of the baby via the placenta
Liesbeth van Leeuwen in LINDA magazine.

Medical research is constrained by bureaucracy.

Christianne de Groot was interviewed on NPO Radio 1, EenVandaag.

GUIDELINES

Federation Medical Specialists guideline: Preconception carrier testing for high-risk groups
Philis Lakeman, Silvana van Koningsbruggen and others

Most impact on care paper
The scientific publication on the first year of the TRIDENT-2 study on the implementation of non-invasive prenatal testing (NIPT) in the Netherlands (Van der Meij et al.) was selected by the Genomic Medicine Working Group of the National Human Genome Research Institute (NHGRI) in the Top 10 publications worldwide that had the most impact on the application of genetics in clinical care in 2019-2020.

BOOKS

'Ministries for the new age'
Tessa Roseboom contributed to the book. Chapter on five measures that will benefit the health and life of all generations.

AR&D TV APPEARANCES

A lot of children that are obese cannot help it

Jeugdjournaal,
Lotte Kleinendorst.

COVID MILK study

Britt van Keulen and Hans van Goudoever at Eva Jinek TV Show.

The impact of cleft lip and palate on quality of life
Tijd voor MAX,
Corstiaan Breugem.

Newly appointed professors

In 2020, three professors were appointed at the Amsterdam UMC in the field of AR&D.

PROF. DR. LIDEWIJ HENNEMAN

Lidewij Henneman is professor of Patient Perspectives on Genetic Testing at the Department of Human Genetics, Amsterdam UMC, location VUmc. She is co-director of AR&D and board member of the Dutch NIPT Consortium. Her research focuses on how the applications of new genetic technologies before, during and after pregnancy impact individuals and society.

Patient perspectives & agenda setting

Together with her team, Dr. Henneman investigates the perspectives and decisions of (potential) users to help align responsible implementation of applications with the needs of the community, employing both qualitative and quantitative research methodologies. Active areas of interest are preconception carrier screening for recessive disorders, prenatal screening using the non-invasive prenatal test (NIPT) (TRIDENT studies), the expansion of newborn bloodspot screening, and the use of next generation DNA sequencing for prenatal and postnatal diagnosis of children with a congenital condition. To set policy agendas and fill the gaps in patient care and support, the research is done in close collaboration with the patient organization Dutch Genetic Alliance (VSOP), relevant healthcare professionals, key (inter)national organizations, and other stakeholders in the field.

Teaching and mentoring

Lidewij Henneman earned her doctorate at Vrije Universiteit Amsterdam in 2002. Her PhD thesis was focused on the feasibility and desirability of preconception cystic fibrosis carrier screening, for which she received the Dutch Public Health Award. Dr. Henneman has been a senior researcher at the Department of Human Genetics since 2012 and was appointed VU professor in October 2020. She enjoys teaching and has mentored the successful completion of 13 doctoral dissertations.

PROF. DR. CORINE VERHOEVEN

Since January 1st 2020, Corine is appointed as Professor in Midwifery at the University of Nottingham, UK. Corine is a midwife and clinical epidemiologist. She is working as an assistant professor at the department of Midwifery Science, AR&D, APH research institute, Amsterdam UMC location VUmc. And next to this, she is a practicing midwife in Maxima Medical Centre in Veldhoven.

Evaluation of maternity and midwifery care

At the department of Midwifery Science at VUmc she is leading the research on evaluation of maternity and midwifery care. Her research is focused on several themes related to physiological pregnancy and childbirth and client involvement. Her main research topics are optimal management of term labor and women's experiences with their care. Five years ago she set up the Childbirth Network, an academic network of client representatives, midwifery practices, research and education, that aims to stimulate cooperation between pregnant women, maternity care providers, lecturers and researchers. The Childbirth Network offers reliable information for both women and maternity care professionals. Research within the Childbirth Network focuses on the content and quality of maternity care. The results contribute to improving care and education.

“Five years ago Corine Verhoeven set up the Childbirth Network”

International networking
At the Division of Midwifery, part of the School of Health Sciences, University of Nottingham, she brings in her quantitative research skills and supervises PhD students. She has the ambition to achieve an international network between both midwifery departments, to exchange knowledge and to provide PhD students with an opportunity to collaborate internationally and learn from each other. In her opinion, working internationally is truly of added value to the work of midwifery researchers.

PROF. DR. CORSTIAAN BREUGEM

On 12 May 2020 Corstiaan Breugem was appointed professor of plastic surgery. He focuses mainly on children with cleft lip/palate, with the Robin sequence (micrognathia and obstructive respiratory problems) and children with microtia.

Health evaluation and innovation
“How can we improve surgical outcomes?” Is the question that occupies Breugem every day. A better understanding of embryology and development plays an important role in this. Breugem is involved in care evaluation and innovation. Children with cleft lip and palate often have feeding problems and later speech problems. “I see opportunities in “imaging”. By developing better preoperative imaging techniques, we can for example see muscles in the palate and maybe improve our surgical outcomes”. At a time when Value Based Health Care and “patient related outcome measures” are important, Breugem wants to help determine better outcome measures in order to compare and improve the quality of operations and care.

Global Health
He believes it is his job as a professor to inspire and teach others. In addition, Breugem has a passion to improve healthcare in “Low Income Countries”. Surgeons used to operate for two weeks and then left. His dream is to form local teams in these countries around cleft lip and palate care, whereby knowledge exchange and support from the Netherlands can be deployed. The first steps towards this have already been taken. In any case, further international cooperation is one of Breugem’s spearheads; more data can be collected and knowledge can be exchanged by working together more. This applies to Low Income countries but also to Europe. Breugem is currently vice president of the European Cleft and Craniofacial Association and president of the Dutch Cleft Palate Association.

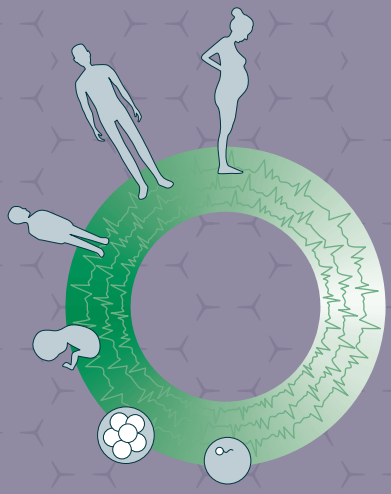
Corstiaan Breugem

Lidewij Henneman

Corine Verhoeven

“The ambition of AR&D is to enhance the field of reproduction and development nationwide, and to sustainably improve health care for mother and child and future generations”

Amsterdam UMC
University Medical Centers



"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"