Amsterdam UMC
University Medical Centers

EXPERTISE

CIRCLE OF LIFE

AMSTERDAM REPRODUCTION AND DEVELOPMENT

ANNUAL REPORT

2017

REPRODUCTION

DEVELOPMENT

RESEARCH

Contents

Amsterdam Reproduction & Development
is a research institute of Amsterdam UMC

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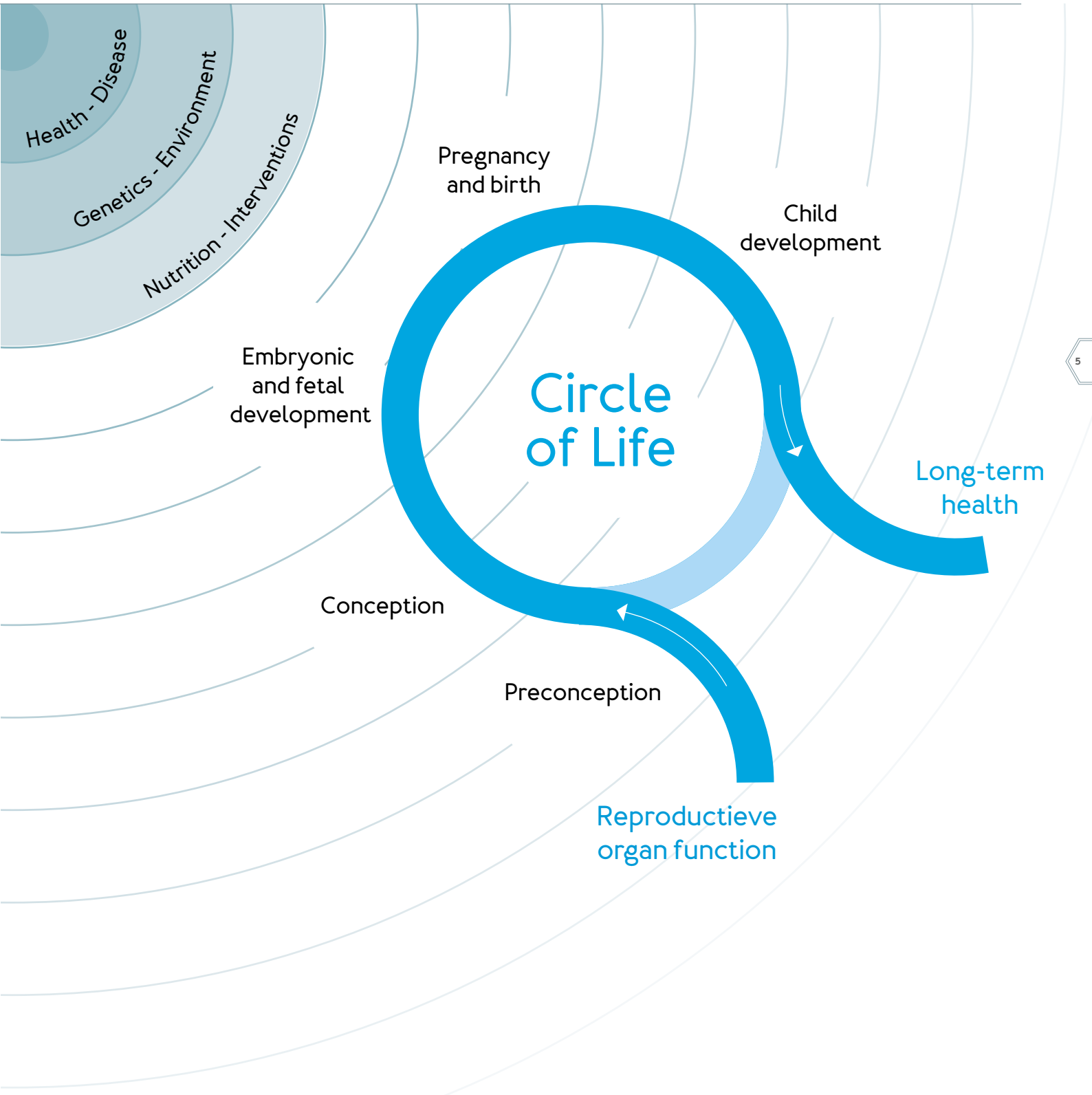
Met dank aan:
Tim de Hullu (interviews)
Luumen / Hanneke van der Meer (vormgeving)

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 foetal 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 child and future generations.

AR&D integrates various disciplinary approaches within the academic medical centers of 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, including environment, nutrition, disease and interventions on the developmental process from gamete to adult. In the institute, basic, translational and clinical research scientists work together to maximally improve health care for our future generations.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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 genetic mutations so we may prevent serious genetic diseases in their future children. 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 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 we develop 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 couple these fundamental studies to clinical trials. We use highly sensitive ultrasound measurements and genetic tests to examine the developing fetus. 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-centre clinical trials. With these trials we aim to establish the benefit of specific interventions in reproductive medicine, gynaecology, 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 shared decision making. Our trials are conducted in the context of a national networks of collaborating hospitals, gynaecologists and neonatologists, 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 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. We monitor development and follow individuals as they become the parents of the next generation and the circle of life begins again.

“Contributing to the improvement of reproductive and child health”

INTERVIEWS

CHRISTIANNE DE GROOT
EN SJOERD REPPING
Directors

MARIE VAN DIJK
Researcher reproductive biology laboratory

BIBIAN VAN DER VOORN
Researcher pediatric endocrinology

LIDEWIJ HENNEMAN AND MARTINA CORNEL
Researchers community genetics and public health genomics

A unique institute

Amsterdam focuses on reproduction and development with its very own institute. An exceptional centre in the Netherlands that ensures cross-pollination, top publications, talent development, and above all: relevant research in its field.

"In 2017 we continued to build on our research institute," says Christianne de Groot, who forms the managing board of Amsterdam Reproduction & Development (AR&D) together with Sjoerd Repping. "What's unique about it," she continues, "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. After a good start of our institute, we've already expanded our network. People know each other better, we have achieved a number of top publications, including papers in *Science* and the *New England Journal of Medicine* , and were able to award several attractive grants."

"Our subject is of great social importance," adds colleague Sjoerd Repping. "All hospitals investigate cancer, infections, and cardiovascular diseases, which are all very significant health problems. In general, the development of a child during its infancy, including the time before birth, is not a priority in most academic hospitals but that's exactly what we find very important here in Amsterdam. We know there are factors of influence early on in life or even before that, that can have a tremendous impact on a child's development. That's why it's so wonderful that we've been able to create an institute with which we also contribute to the current debates in society. How can you guide a pregnant woman through the different choices that exist with all of their advantages and disadvantages? And what are our thoughts on reproduction in general in the Netherlands? How far can you go with genetics? Should you offer a pre-conception test or not? These are all very relevant issues."

Sjoerd Repping

Christiane de Groot

Research into reproduction and development was already being conducted before this institute saw the light of day. What are the advantages of a dedicated institute? Christianne de Groot: “All people involved in this subject can now find each other more easily. Connections are tightened. People in the lab, people from clinical genetics and gynaecology, pediatricians, and all sub-specialties encounter each other much more often.” AR&D organizes symposia and awards grants to innovative research with a competition model. “We encourage young talent as well, for example by giving them a travel grant,” according to De Groot.

At the start of AR&D, a speed date meeting immediately led to cross-fertilization. “About a hundred researchers, many of whom did not know each other, were able to exchange their ideas in five minutes,” says Repping. “Great ideas for further research came about here. For example, a gynaecologist was dealing with a question that could be answered with the help of a model of an anatomist. As a specialist, you’re focused on your own subject. Tunnel vision is lurking. A fresh pair of eyes from someone from another discipline can help in such cases. And it’s important to be receptive. A biologist who is willing to come up with that clinical intervention and a doctor who is willing to understand how it works on a molecular level. That’s what an academic hospital stands for: innovating research and, as a consequence, improving the health of the population as a whole.”

The institute focuses on innovation and excellence in fundamental, translational, and clinical evaluation research, as well as research into nursing. Repping: “We want to understand why people are healthy or sick, but also translate this into the healthcare

system. So we can improve healthcare as much as possible with research." And with education. Developing a 3D atlas of a growing embryo is a great example here. De Groot: "In the atlas of formal doctoral student and now staff member Bernadette de Bakker, you can see the precise development of each organ of a fetus from day to day. Medics who work with ultrasound images are immensely helped by this. Using the atlas, they can better interpret how organs are developing. This allows them to easily judge whether something is going wrong in the development of an embryo when they're evaluating ultrasound scans." Repping: "Such 3D reconstructions are perfect for educational purposes of course. And this way our research strengthens what we're here for even more: providing care and educating new talent."

Much of the research by AR&D has a social impact and this will become increasingly important in our changing society. "Our research into psychosocial counseling of people who become pregnant with donor gametes showed that there is a great need for long-term support, both for parents, child, and donor," Repping illustrates. "The government picks it up and invests in a national information point for each of them. That's wonderful." AR&D first identifies changes and then conducts research matching those new findings, needs, and questions. "We are now investigating whether we can offer high-tech surrogacy to homosexual male couples," says Christianne de Groot. "This was not negotiable fifteen years ago. Now we state: the question has arisen, we will not answer it as physicians, but involve policymakers and instigate a public debate." Gender dysphoria, the deep sense of discomfort that people experience when birth gender and gender identity do not match, is another such example. Repping: "Interestingly, pediatrics is increasingly involved. This problem used to occur mostly at adult age, while the realization that one is in the wrong body occurs much earlier and is still more open for discussion then. Psychology plays an enormous role here. How do you deal with this situation as a person? And there is also a reproductive aspect. Suppose you are a woman and you want to become a man. Can you still have children and how do you do that? Do you keep the uterus or not, do you freeze your egg cells, and what are your options?"

"Reproduction and Development research is of great social importance"

This example confirms the importance of an institute that investigates the circle of life and involves all possible of disciplines. "We will facilitate more meetings in the coming years so that employees can find each other more and more easily and can truly experience this institute as a single entity," says De Groot. Repping: "We aim to present ourselves as an institute to the government, grant providers, and European partners as well. Sharing that we have a discipline-transcending platform here in Amsterdam, where we can study many social issues. With the ultimate goal of contributing to the improvement of reproductive and child health."


“There is nothing more beautiful than the analysis of a successful experiment”

“A single experiment is no experiment”

MARIE VAN DIJK, RESEARCHER REPRODUCTIVE BIOLOGY LABORATORY

Marie van Dijk contributes to research into the hormone ELABELA (ELA) which possibly protects women against preeclampsia. She is currently also studying a safer alternative to chorionic villus sampling. “There is nothing more beautiful than the analysis of a successful experiment.”

As a scientist, you need to have a lot of patience and resilience in the face of adversity. You have to accept that experiments fail, start over again, and repeat a successful experiment time and time again to be able to draw your conclusions with certainty. “A single experiment is not an experiment,” says researcher Marie van Dijk. But that does not mean that she doesn’t celebrate successes. “I can become very enthusiastic when things work out. Whenever that happens, I just have to share it with everyone in my research team.”

ELABELA AND PREECLAMPSIA

This was also the case with a finding first seen in mice that Van Dijk aimed to translate to humans. In the end, this key experiment became part of a Science publication in 2017. Together with technician Souad Boussata, Van Dijk studied photos of placenta cells (trophoblasts) both with and without the addition of the ELABELA (ELA) hormone. Van Dijk grew the trophoblasts in a gel layer of proteins. The pictures with the colored cells made it unmistakably clear: trophoblasts to which ELA had been added grew faster through the

Marie van Dijk

gel layer. “Yes, that was very nice to see,” says Van Dijk. Because, as she explained, these results are a strong indication that the hormone protects pregnant women against preeclampsia, generally known as toxemia of pregnancy. This disease occurs in five to eight percent of pregnant women, leading to high blood pressure and affecting organs. Van Dijk: “Trophoblasts penetrate the uterine wall and the blood vessels of the mother. This dilates the vessels and allows a lot of blood to flow through them. If this invasion does not go as it should and blood vessels are less wide, it can lead to preeclampsia.”

MEASURING ELA

Now one might think: give pregnant women extra ELA and you protect them from preeclampsia. “That would be a simplistic theory,” says Van Dijk. “But it’s not that simple. If you want to further investigate this in a clinical and translational manner, you must first be able to measure the amount of ELA in blood. Up until now, this has not been possible.” To find out why this is so difficult to measure, ELA is further examined, as well as its influence on trophoblasts. Van Dijk has already shown that several proteins are linked to the hormone and she is going to find out exactly which. She looks at the effect of inhibiting ELA on trophoblasts as well.

FULFILLMENT

In that way, more and more interesting, fundamental research questions are sparked. Often, the initiation of new research actually happens by chance. This was also the case for the research into ELA and its role in preeclampsia. Researcher Bruno Reversade, who is affiliated with the Institute of Medical Biology in Singapore and Amsterdam Reproduction & Development, found that mice that could no longer produce ELA showed symptoms of preeclampsia but mice that could produce the hormone did not. This finding then led to Van Dijk’s research into the role of this hormone in the human body.

In 2016, a research team was set up, led by Marie van Dijk. She achieves fulfillment from both fundamental research – which the ELA research is for the largest part at this point – and translational research: “I prefer to carry out fundamental research. Figure things out, think about experiments, come up with solutions. Considering: what happens if we add this and this? That’s an exciting and fun process. But we also constantly have to ask ourselves the question: what are we doing this for again? What is our goal? In translational research, these questions don’t pop up that often. You really have the feeling that you’re doing something useful for society.”

TRIC

Van Dijk may count herself lucky now, as she is currently heading an additional, purely translational study: she investigates an alternative to chorionic villus sampling (CVS), a test that comes with an increased risk of miscarriage. TRIC, which stands for t*rophoblast retrieval and isolation from the cervix*, is expected to be risk-free. Van Dijk: “You would expect that the amniotic sac is completely closed off, but it’s already been known since the seventies that you can get trophoblasts from the cervix with a Pap smear. The trick is then to separate the trophoblasts from the maternal cells in the smear. So that’s what we are going to do, by mixing the cells with magnetic particles. These contain an antibody that specifically recognizes the trophoblasts. And that is how we fish them out.”

OUT-OF-THE-BOX GRANT

The researchers can then carry out the same tests on the isolated cells as they would with CVS, to determine the genetic status of the fetus. For part of the research, Van Dijk received an Out-of-the-Box Grant from Amsterdam Reproduction & Development. She is very enthusiastic: “We haven’t applied this technique ourselves before, so that’s very fun and challenging. The first samples have already come in. If it turns out that this technique is an alternative to chorionic villus sampling, the clinical genetics department will most likely further investigate implementation. But it gives my team opportunities for follow-up research as well. In the future, we can create a separate bank with the cells we collect. Suppose a woman develops complications later on in her pregnancy, then we can examine the cells from her previous smear for abnormalities.”

PROOF

But there is more research on Van Dijk’s wish list. Take the Dutch famine research of her colleague Tessa Roseboom, which showed that people who had been in the belly of a mother living on a scanty diet of tulip bulbs during the hunger winter, had relatively more health and development problems later in life. “I would like to research that on a molecular biological level. That you can determine at birth: this child was apparently exposed to a suboptimal environment during the first trimester or later, we have to keep a close eye on this one. The current results of the hunger winter research mainly contain a lot of indirect evidence. I would like to support the conclusions with research into changes in protein levels and epigenetics. So that you can see that environmental factors during pregnancy affect the cells of an embryo or fetus. I am convinced that this is so, but I would like to prove that it really is,” Van Dijk concludes on her way to the next kick in her work. She is constantly searching for molecular biological evidence. “There is nothing more beautiful than the analysis of a successful experiment.”

“I am convinced that this is so, but I would like to prove that it really is”


“It’s magical how nature works: how a child born so small and vulnerable can survive”

“The magic of the stress hormone”

BIBIAN VAN DER VOORN, RESEARCHER PEDIATRIC ENDOCRINOLOGY

As a PhD student, Bibian van der Voorn studied stress hormones in extremely premature infants. She continues with hormone research. “The more I understood how a body works, the more magical it became.”

“I am a thinker, a puzzler. I found endocrinology the most interesting subject in Medicine. This area is enormously complex. It’s impressive how the body is always looking for balance and recovers itself but can also be completely out of balance. That hormones affect your entire body: from your crown to your little toe. The stress hormone for example. In order to understand the effect and function of this hormone, I always think of the following situation: imagine, you’re on the run from a lion in the savanna. What’s important then? That your muscles get blood flow, your brain is concentrated and focused. Your pupils become widened, your heart rate goes up, you have to fight for your life there. That’s what cortisol does for your body.”

“As a resident, I had the feeling that scientifically I still knew very little. I would be able to implement the protocols in the hospital but I found it difficult to translate the scientific literature into a patient’s individual case. Doctors in the hospital told me: you are a true researcher, see if you can learn more in that area. When I worked in pediatrics, and my interest

was raised by nutritional interventions and the human milk bank, this really sparked my research aspirations. A PhD position happened to be available and I could get started. “

“It became a beautiful course of studies. I had a nice research unit directly above the clinic together with fifteen to twenty other researchers in pediatrics. A luxury position. We’d quickly build bridges, brainstorm together, process the letdowns, and celebrate successes with each other. My supervisors gave me the opportunity to follow my instincts, really get that research mindset, and explore my possibilities freely. My goal was to deliver a thesis on relevant factors in the stress hormone development of the prematurely born. Factors like DNA variants, growth, stress in the womb or at the beginning of life, and the treatment of the child in the first few days after birth. We were able to cooperate with many ongoing studies.”

“I was grabbed by the hormonal system. It’s magical how nature works: how a child born so small and vulnerable can survive. So much of what needs to grow in the womb is still missing. With its immature brains and other organs, not only does the baby have to be in an incubator for the first weeks; it also has to deal with the stress it endures there. And yet its immature adrenal gland produces just enough stress hormones to survive. I think that’s impressive. I find it very fulfilling to do research on what we can learn from nature to support those processes.”

“To investigate the body’s strength, we looked at stress hormones in breast milk for example. It turned out that there’s a day and night rhythm in stress hormone concentrations in breast milk, which corresponds to the rhythm of the concentrations in the mother’s blood. The stress hormones may help vulnerable newborns to adapt to the conditions after birth. I am still involved in a follow-up study into the effect on the child’s neurological development and body composition. It’s based on the idea that the mother gives a signal, as it were, via her milk: your metabolism should adhere to this rhythm. It raises the question: if we give premature babies milk from the breast milk bank, can we give them the milk that fits best? But to answer that question

Bibian van der Voorn

and draw consequences from it, we must first better understand the rhythm of those stress hormone concentrations in breast milk by further investigation."

"My research was very exploratory, I looked at many factors. The most socially relevant finding, I think, is that physiological gender differences in the stress hormone balance already surface at early childhood. And not only in premature births. This touches on the discussion about women who would need a different approach than men when suffering from cardiovascular diseases. This could result in different treatments or choices made in a treatment strategy. Another thing that stood out in my research which is of great importance to society is the confirmation that a preterm birth can have subtle neurological consequences later in life. Anxious behavior, for example. Ideally, in their care for children, but also for adults, medics and care providers could ask about a possible premature birth and take this into account. This doesn't mean you'd instantly link someone to a psychologist for the rest of their lives, but you can give people extra tools, at school for instance. Ensure that people are familiar with the possible later symptoms if they were prematurely born. And that they know they can get help with that."

"There is still so much to investigate, so much to translate into clinical practice. That's why I think it's great that I can continue in an area that fits my thesis. In Rotterdam, as a post-doctoral researcher, I am going to work on the role of stress hormones in obesity in adults and children. I would not have been able to do that if I had not followed this PhD program and had I not been given this opportunity by Amsterdam Research & Development. I have also learned a lot about myself. Before I graduated, I thought: I want to become a better pediatrician by developing myself scientifically. Now I found that perhaps I am a better researcher than a pediatrician. A valuable discovery."

"There is still so much to investigate, so much to translate into clinical practice"


“Discussion is important. It stipulates the social relevance of our research”

“Feeding debate is a purpose of our work”

LIDEWIJ HENNEMAN AND MARTINA CORNEL, COMMUNITY GENETICS AND PUBLIC HEALTH GENOMICS

The research area of Lidewij Henneman and Martina Cornel, Community Genetics and Public Health Genomics, is constantly under discussion. It’s a field often associated with ethical and societal implications and policy choices. “In some way, feeding debate is a purpose of our work.”

The duo-interview is a reunion after a holiday for Martina Cornel. “How are things here?”, she asks. “Good, our research topics received a lot of attention again.” Both Henneman’s and Cornel’s expertise often show up in the media. Search online for “Martina Cornel” and you will surely find her opinion on the phenomenon *designer baby*, which is often envisioned when discussing gene editing for embryos. American researchers succeeded in removing a hereditary disease from an embryo’s DNA. “It is about time the Netherlands starts thinking about this issue,” said Cornel according to the newspapers. This time, the headlines were covering a DNA test for prospective parents. Six general practitioners in Groningen now offer intended parents the possibility to have themselves tested for seventy serious medical disorders that they might pass on to their future child. This news item brought attention to the Amsterdam based university medical centers as there has been a so-called preconception carrier screening offer in the capital since 2016. In the same way it’s happening now, this practice led to an immediate response from the public and policymakers. Positive notes but also critical

Martina Cornel

Lidewij Henneman

ones, claiming the medicalization of the birth of a child had gone too far.

"Discussion is important. It stipulates the social relevance of our research," says Henneman. "For many themes, I think it's even necessary to have a societal debate," emphasizes Cornel. "The new reproductive genetic technologies that are emerging for instance. It is very important to discuss this with each other. What do we expect from the different technologies? What are the ethical aspects of their implementation in practice? And what does this mean for patients and families, but also for other citizens?" Henneman: "We examine themes in which choices have to be made continuously at different levels. Like personal decisions of pregnant and expecting parents who want to take a certain test or not. Or health care professionals who provide information and counseling to these couples. But also politicians who have to decide what is and what isn't allowed in this country based on current legislation. It is our mission to inform people extensively and to feed the public debate. Therefore, besides doing research, we see that as an aim of our work in order to facilitate responsible implementation."

It is not uncommon for Cornel and Henneman to arrange the debate themselves. Cornel: "In research projects, we regularly organize meetings to bring different stakeholders together. Eventually, these assemblies really become part of the research." This was also the case for the study by PhD student Kim Holtkamp completed in 2017. Holtkamp did research into various preconception carrier tests in specific risk groups and explored the possibility to bring this type of screening to the general population. "Policymakers, patient organizations, and test providers all came together. Different perspectives at one table. That was exciting," says Cornel.

Holtkamp's study showed there is still a lack of knowledge and awareness. Both amongst healthcare professionals and citizens. Henneman: "People also find it difficult to interpret carrier test results. And ethical questions arise. At the same time, the target group reacts

positively. Although decisions are not easy, people who turn out to be a carrier couple often take measures. Opting for embryo selection for example." It is food for further research and debate.
This also applies to the NIPT (non-invasive prenatal test), in which the mother's blood is taken to test in the laboratory whether the unborn child may have Down's, Edward's or Patau's syndrome. NIPT is more sensitive and gives fewer false positives than the test that was previously offered, the combined test. Since April 2017, NIPT is offered as the first screening test for all pregnant women, without a prior test within a research setting (TRIDENT studies). Lidewij Henneman is a member of the core group of the national NIPT Consortium and project leader studying women's perspectives. "We're examining how we can best offer NIPT. We look at all the steps involved, from the counseling to pregnant women and the test in the laboratory to pregnancy outcomes. Afterward, we expect to give advice on further implementation."

"It is no longer just about technology"

An important question for media and public is: how often are these tests being used? Cornel: "Compared to 2016, we see an increase around 34%. But not every pregnant woman will do the test, and you have to take into account that in 2016 many women went abroad for testing, so uptake was probably already higher at that time." The researchers are also interested in the choices and considerations of pregnant women and their partners.

Cornel: “Pregnant women now have the choice to find out about other chromosomal aberrations than the three trisomies which are currently studied in the screening program. The great majority of women wishes to be informed about the so-called ‘incidental’ findings.” Henneman: “We’re learning from the study what people need. For example, in terms of information and support, in case the NIPT reveals other findings, including, although very rare, maternal cancer.” In 2020, when the study will be completed, it is up to the Minister of Health to determine what happens next. The findings and recommendations of the Consortium will play an important role in this decision. In the meantime, Amsterdam Reproduction & Development is taking on projects in line with new possibilities. For instance, with the technique CRISPR-Cas, which can potentially be used to edit the genome of early embryos. This could prevent a child from having a hereditary disease. This is not happening yet, for many technical reasons but also because the law does not allow it. PhD student Ivy van Dijke is looking into the dynamics between different reproductive technologies, including preconception carrier screening, embryo selection, non-invasive prenatal diagnosis, and germline genome editing. Henneman: “Van Dijke talks to parents, among other things. What do they think of these new techniques, would their availability influence their choices and if so, based on which arguments?”

“We’re learning from the study what people need”

Since her start in 2017, Ivy van Dijke has had many presentations. Cornel: “Everyone thinks that genetically changing embryos is super exciting.” The debate is broadening. “It is no longer just about technology. And this means you have to inform people even better.” For a layperson, the matter is complex. The term ‘designer baby’ is understandable but will also take on a life of its own. Henneman: “We nuance and clarify the discussion for that reason. You have to separate the advantages and disadvantages a bit.” Cornel: “And the opportunities and threats. With gene editing you could, for example, increase the immune response to protect the body against AIDS. So think of this hypothetical example: everyone resistant to HIV, that may sound good. But should we want that? If you change something within a small group of people at high risk of a serious disease, many people are in favor of that. But what if you change a gene for everyone for a disease that has an average risk? What happens if you make a mistake? And which consequences does this resistance have for your resilience to other diseases?” Henneman and Cornel did not openly have that discussion yet, but they certainly will. Cranking up and giving nuances to discussions in a technologically rapidly changing world. There is still a lot of work to be done for this duo.

Organization

AR&D RESEARCH BOARD

DIRECTORS

SJOERD REPPING
Center for Reproductive Medicine

CHRISTIANNE DE GROOT
Obstetrics and Gynaecology

RESEARCH BOARD MEMBERS

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ARNE POPMA
(FROM FEBRUARY 2018)
Child and Adolecence psychiatry

FORMER RESEARCH BOARD MEMBERS:
Pim Teunissen, Obstetrics and Gynaecology (until February 2017), Wouter Hehenkamp, Obstetrics and Gynaecology (Until July 2017).

AR&D OFFICE

CALLISTA MULDER

SANNEKE VAN VLIET

In 2017 the AR&D office was staffed by Sanneke van Vliet, Marga Schuit and Elsbeth Steenland (temporary).

Institute highlights

FROM SITE TO SYMPOSIUM

In 2017 the AR&D continued on building the institute structure by expanding the network and being more visible and incorporated in the organizational structures of the AMC and VUmc.

WEBSITE & NEWSLETTERS

The website and the newsletters were further developed. Six newsletters were published and videos we added to the website.

INFOGRAPHIC & VIDEOS

An animated infographic and videos covering the different aspects of the Circle of Life, showing images on (pre) conception, fetal/embryonic development, pregnancy and birth, and child development were developed. These videos are posted on the AR&D website and are available upon request for further promotional use.

www.amsterdamresearch.org/reproduction-and-development

SITE VISIT BY THE INTERNATIONAL EVALUATION COMMITTEE

On October 24rd 2017 AR&D welcomed the International Evaluation Committee (IEC) as part of the site visit to the AMC.

The delegation of the IEC visiting the AR&D presentations consisted of Lucilla Poston, chair, Janet Rich-Edwards and David Kerr.
The Research Board prepared a lively program with videos and research presentations. Sjoerd Repping and Christianne de Groot hosted the meeting.

Inge Mathijssen, Bernadette de Bakker, Martijn Oudijk and Martha Grootenhuis presented results of related research fields. Marsh Königs took care of the intermezzo with cognitive test. The presentation were introduced by an animated info graphic and videos showing the different aspects of the Circle of Life, showing images on (pre) conception, fetal/embryonic development, pregnancy and birth, and child development.

In the evaluation report, the committee was affirmative about the strong leadership, organization and commendable vision. They acknowledged the considerable progress that had been made in creating the new research institute. The IEC was positively impressed by the quality of the research and the proven translational and societal capacity. The committee made valuable suggestions on the future of the institute.

The International Evaluation Committee in action during the intermezzo

FLTR: Robbert Berkhout, Velja Mijatovic, Martijn Finken, Bernadette de Bakker and Christianne de Groot

SYMPOSIUM

The annual symposium took place on the 23 June 2017. With over 70 participants the symposium was well received. Goal of the symposium was to meet and to make crosslinks between the different disciplines.

AR&D RESEARCHERS GAVE AN INTERESTING INSIGHT IN THE FIELD OF REPRODUCTION & DEVELOPMENT.

SPEAKERS:

Bernadette de Bakker
Medical Biology
Title: 3D Atlas of Human Embryology

Robbert Berkhout
Center for Reproductive Medicine
Title: Implantation of the embryo: A matter of quality

Velja Mijatovic
Reproductive Medicine
Title: H2Olie & FOAM studie: Klinisch onderzoek in consortium verband

Ivy van Dijke
Clinical Genetics and Center for Reproductive Medicine
Title: The dynamics of reproductive genetic technologies

Martijn Finken
Pediatrics
Title: The HPA axis in development

The plenary presentations were followed by speeddating and the award of the AR&D post doc and travel grants.

AR&D GRANTS

PHD SCHOLARSHIPS

AR&D awarded in 2016 two PhD scholarships to projectteams of AMC-VUmc researchers who started a new collaboration. These PhD scholarships allow the project teams to have a PhD student working on the project for four years.

HELEEN SCHUSTER started working on the project *'The microbial signature of preterm birth'* awarded to Joris van der Post, Paul Savelkoul, Rebecca Painter, Marjolein Kok and Dries Budding.

IVY VAN DIJKE started on the project *'The widening scope of reproductive genetic technologies: responsible innovation and assisting individuals' decision-making'*:
awarded to Martina Coronel, Sjoerd Repping, Lidewij Henneman and Phillis Lakeman.

POSTDOC GRANTS

Two postdoc grants were awarded to Arend van Deutekom and Mandy Spaan. This allows them to work one year on a project to develop their own research line.

AREND VAN DEUTEKOM is working on the CHAMPION study, a study on children's Cardiovascular Health After Maternal Pre-pregnancy lifestyle InterventION (CHAMPION). By positively influencing the health of the mother, Van Deutekom aims to positively influence the health of the child.

MANDY SPAAN her goal is to investigate long-term health of children conceived using assisted reproductive technologies. Her main research question is whether these children are prone to a higher risk to obtain cancer. Both researchers collaborate on a national level but also internationally.

TRAVEL GRANTS

Five PhD candidates received travel grants of €1000 each to visit research institutes in Paris, Copenhagen, New York, Aberdeen and Brisbane.

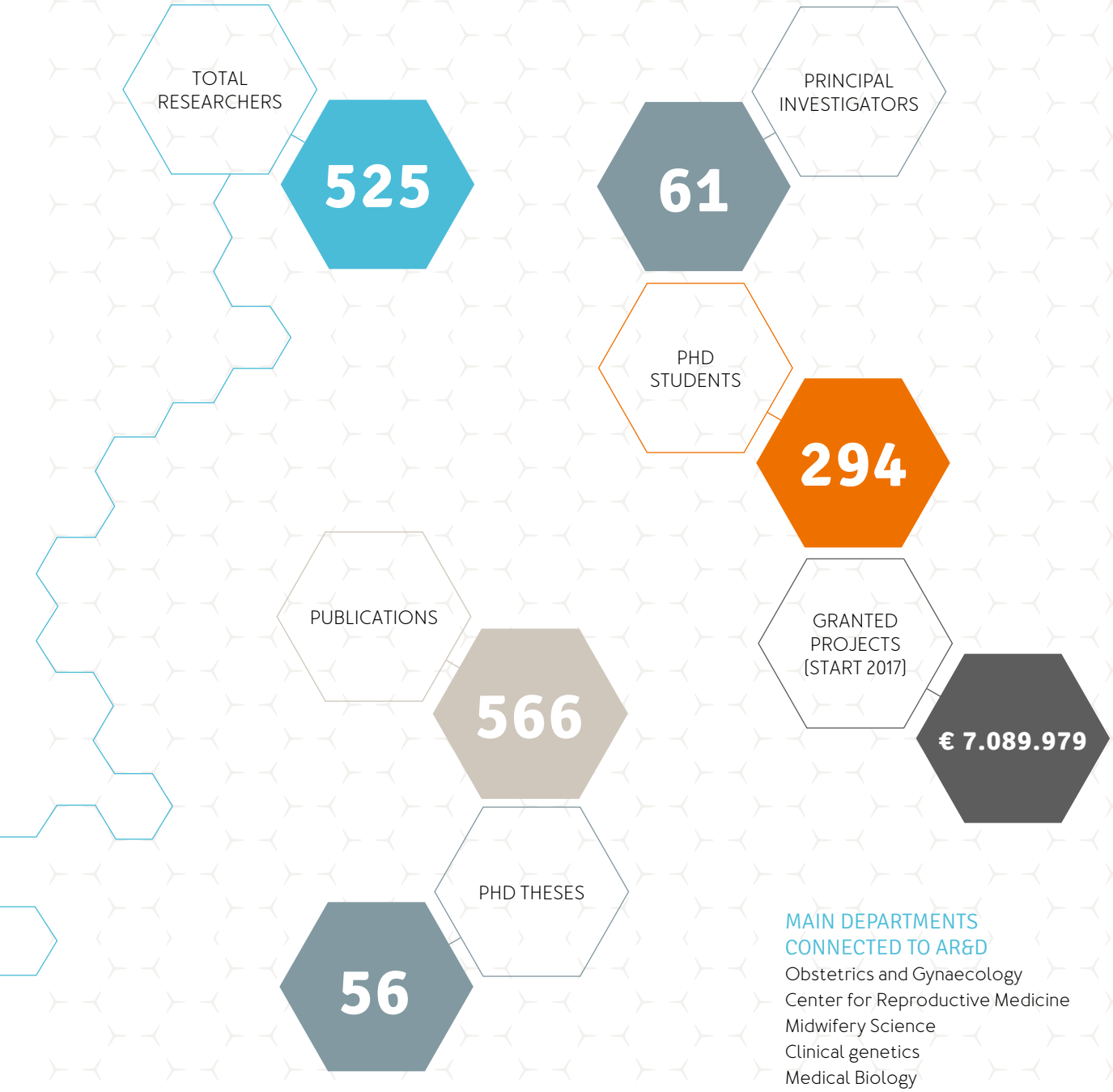
In the fall 2017 a call for the AR&D Out-of-the-Box grant opened. This call aimed to innovative ideas within the Reproduction & Development field. For 2018 AR&D is further developing their grants scheme.

Travel grant laureates: Nienke van Teijlingen, Judith Ensink, Rik van Eekelen and Robbert Berkhout (FLTR) Anouk Pels is not pictured.

Mandy Spaan

Research Highlights

AR&D IN NUMBERS



MAIN DEPARTMENTS CONNECTED TO AR&D

Obstetrics and Gynaecology
Center for Reproductive Medicine
Midwifery Science
Clinical genetics
Medical Biology
Public and Occupational Health
Social Medicine
Medical Psychology
Vascular Science
Child and Adolecence Psychiatry
Pediatrics
Pediatric surgery

PERSONAL HIGHLIGHTS

The personal research highlights of the research board members Jaap Oosterlaan, Tessa Roseboom, Marcel Mannens and Anton van Kaam.

FOLLOW ME PROGRAM

Jaap Oosterlaan is proud to be part of the AR&D community. Looking back on 2017, he can only describe it as "wonderful". In this wonderful year, the Women & Child Centres of AMC and VUmc have launched an ambitious follow-up program for all tertiary care patients: the Follow Me program. The program is embedded in AR&D and embodies the research institutes focus on research long term health. Two new outpatient follow-up programs have been introduced. One program focuses on paediatric patients who have undergone surgery for congenital malformations. The other program concentrates on the long terms sequels associated with intensive care treatments such as artificial ventilation and sedatives. Also, Jaap Oosterlaan and his team published two beautiful articles in high ranking journals in 2017 (Noordermeer et al. Biological Psychiatry 2017 and Königs et al. Hum. Brain Mapp. 2017)

WOMB PROJECT

When we asked Tessa Roseboom for the research highlight of 2017 she immediately chooses the finishing of the data collection of the WOMB project. This ambitious project aims to study the effect of lifestyle interventions in women on their health and that of their children. The data was collected in a mobile research unit "de Hart voor een Goede Start Bus" (Eng: Heart for a Good Start Bus), which travelled over 40.000 km to collect all the data. "Another beautiful research highlight is the publication of the very first RCT on the treatment of hyperemesis gravidarum (Red: an extreme form of "morning sickness" among pregnant women), a burdensome pregnancy complication that deserves more attention in the field." (Grooten et al. Am. J. Clin. Nutr. 2017)

A mother and daughter that participated in the WOMB study together with AR&D researchers Tessa van Elten en Stijn Mintjens posing in front of the Heart for a Good Start Bus.

OBTAINED GRANTS

EXPANDING COLLABORATIONS

Marcel Mannens points out the importance of collaboration that the AR&D research institutes facilitates. Not only collaborations within the AMC and VUmc, but also VU and UvA, enabled him to access data from large patient cohorts such as the ABCD cohort and the Dutch Hunger Winter Cohort, but also specific cohorts of for example Down syndrome children or children with foetal alcohol syndrome. Also in 2017, the research of Marcel Mannens group was recognized in international peer reviewed literature (Wakeling et al. Nature reviews Endocrinology 2017, Chatzispyrou et al. Human Molecular Genetics 2017) but also in national periodicals such as the "Tijdschrift voor kindermishandeling". He is proud on the accomplishments of his PhD students, one of them even won the student price for best presentation in two consecutive years at the Wellcome Genome Campus!

STOP-BPD STUDY

The research of Anton van Kaam has reached an important milestone in 2017 with the last inclusion that was needed for the STOP-BPD study. This multicentre study aims to study the effectiveness and safety of hydrocortisone treatment to prevent serious lung damage or even death in children after premature birth. Also, an important step in paediatric health was the publication of international criteria for Neonatal Acute Respiratory Distress Syndrome (De Luca et al. Lancet Respiratory Medicine. 2017). Another publication in Thorax on medical imaging of the chest using Electrical impedance tomography (EIT) is a highlight of 2017 (Frerichs et al. Thorax 2017).

In 2017 AR&D reserachers were very successful in obtaining grants. Here some highlights of the grants awarded to AR&D researchers.

ATOSIBAN VERSUS PLACEBO IN THE TREATMENT OF LATE THREATENED PRETERM LABOR

project leader Marjolein Kok
Granted by ZonMw € 1.432.139

CONTINUATION OF THE MULTIDISCPLINAIRY KNOWLEDGE INFRASTUCTURE GEBOORTEZORG

project leader Pim Teunissen
Granted by ZonMw € 175.175

TRIDENT-2: PILOT IMPLEMENTATION OF THE NON-INVASIVE PRENATAL TEST AS A FIRST SCREENING FOR FETAL TRISOMY 21,13 AND 18 DETECTION

project leader Lidewij Henneman
Granted by ZonMw € 351.795

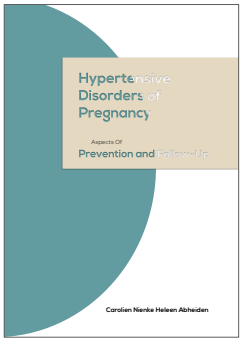
IMPROVING CHILDHOOD CANCER CARE WHEN PARENTS CANNOT BE THERE - REDUCING MEDICAL TRAUMATIC STRESS IN CHILDHOOD CANCER PATIENTS BY BONDING WITH A ROBOT COMPANION

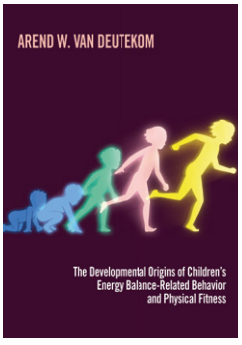
workpackage leader Martha Grootenhuis
Granted by NWO-STW € 195.092
(total sum € 543.000)

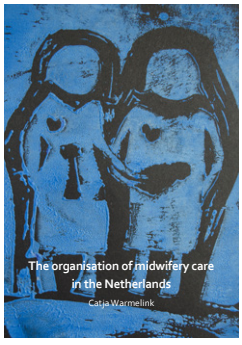
○ ○ ○ PHD THESES

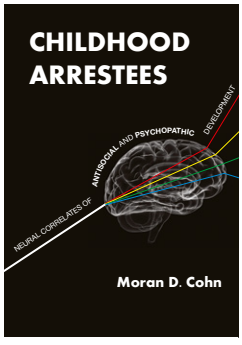
In 2017 56 researchers obtained their PhD in the area of

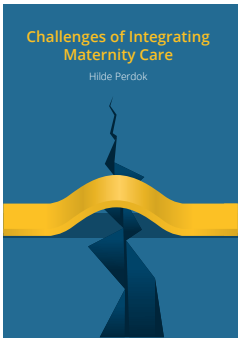
Reproduction & Development. Here below a cross section of the PhD theses.

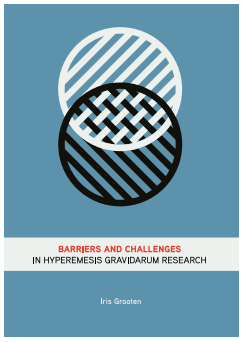


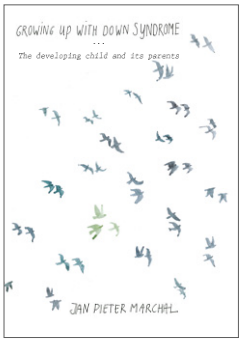


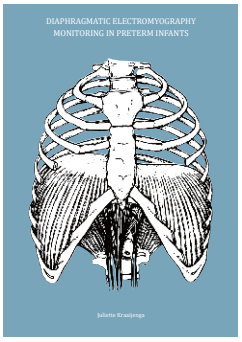


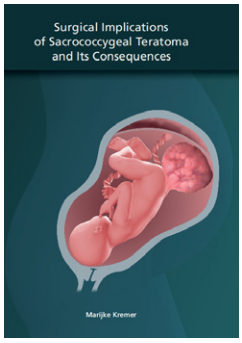


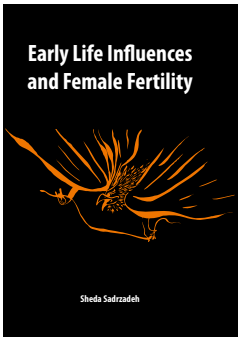


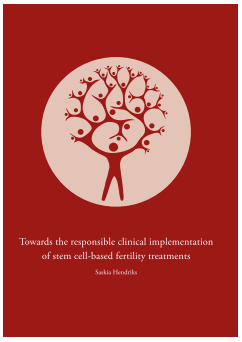


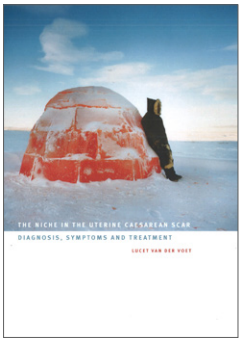


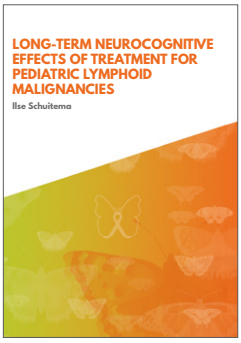












○○○ KEY PUBLICATIONS

2017 was a very productive year.

Here an overview of the key publications.

- WEISS *ET AL*
  Gonadotrophins versus clomifene citrate with or without intrauterine insemination in women with normogonadotropic anovulation and clomifene failure (M-OVIN): a randomised, two-by-two factorial trial.
  Lancet

- VLIEGENTHART *ET AL.*
  Ventilation in Preterm Infants and Lung Function at 8 Years.
  New England Journal of Medicine

- HO *ET AL*
  ELABELA deficiency promotes preeclampsia and cardiovascular malformations in mice.
  Science

- TEEPEN *ET AL*
  Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy.
  Journal of Clinical Oncology

- POGANITSCH-KORHONEN *ET AL*
  Decreased spermatogonial quantity in prepubertal boys with leukaemia treated with alkylating agents.
  Leukemia

- LAMBALK *ET AL*
  GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type.
  H*uman Reproduction Update*

- VAN DEN BERGH *ET AL*
  Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy.
  Neuroscience and Biobehavioral Reviews

- MILANI *ET AL*
  Bioimpedance and Fluid Status in Children and Adolescents Treated With Dialysis.
  American journal of Kidney Diseases

- WONG *ET AL*
  Fresh versus frozen embryo transfers in assisted reproduction.
  Cochrane database of systematic reviews

- JAN *ET AL*
  Unraveling transcriptome dynamics in human spermatogenesis.
  Development

- WOUDSTRA *ET AL*
  Origins and consequences of congenital heart defects affecting the right ventricle.
  Cardiovascular research

- DREYER *ET AL*
  Oil-based or water-based contrast for hysterosalpingography in infertile women.
  New England Journal of Medicine

- STOCKER *ET AL*
  Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns).
  The Lancet

- TIELBEEK *ET AL*
  Genome-Wide Association Studies of a Broad Spectrum of Antisocial Behavior.
  JAMA Psychiatry

- RUYS *ET AL*
  Birth weight and postnatal growth in preterm born children are associated with cortisol in early infancy, but not at age 8 years.
  Psychoneuroendocrinology

- CAANEN *ET AL*
  Effects of long-term exogenous testosterone administration on ovarian morphology, determined by transvaginal (3D) ultrasound in female-to-male transsexuals.
  Human Reproduction

- VAN OOSTWAARD *ET AL*
  Maternal and neonatal outcomes in women with severe early onset pre-eclampsia before 26 weeks of gestation, a case series.
  BJOG:An International Journal of Obstetrics and Gynaecology

- BOKSLAG *ET AL*
  Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life.
  American Journal of Obstetrics and Gynecology

“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.”

EXPERTISE

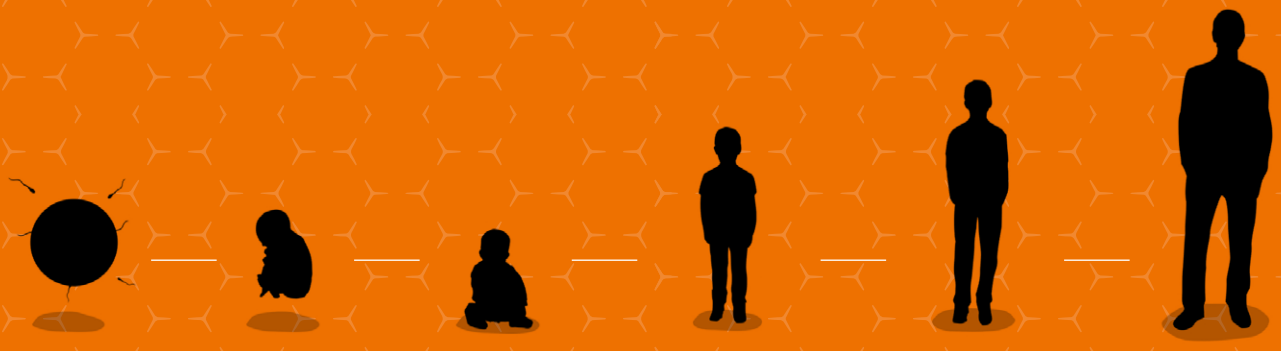
DISCIPLINES

INNOVATIVE RESEARCH

INCREASE IN SCIENTIFIC OUTPUT AND THE ACQUISITION OF NATIONAL AND INTERNATIONAL FUNDS FOR RESEARCH

AR&D WANTS TO BE AN INTERNATIONAL KNOWLEDGE HUB

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"