Feasts, famines and pregnancy

Inaugural lecture in acceptance of the Chair in Obstetrics

With a focus on

Maternal Health, Nutrition and Pregnancy

Faculty of Medicine

On Friday December 2nd 2022,

by

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Rector, dear audience

In early 1979, I came to Holland from Australia. I was almost 5. From then on, we were to be known as 'the Dutch Painters'. We were up there with Rembrandt and van Gogh. Which is why I will be treating you to some other Dutch Painters to keep you going during this lecture: here is Vincent van Gogh's Starry Night. Reminiscent of Aboriginal dot painting, yet so distinctly European, it fills me with that feeling of wonder and curiosity.

The Dutch Painters arrived in Holland amidst one of the most severe winters in Dutch history. There were blizzards, ice, and 'ijzel'- a phenomenon my Australian parents didn't even know a word for in English. This must have made a lasting impression on me, and perhaps sparked my interest in severe winters. More about that later.

Despite being a Dutch Painter, I did **not** pursue a career in the Arts. In the course of my medical studies, two things stood out that shaped my later career as a doctor:

First, my time in Darwin, in 1998, in Australia's 'Top End'. In my master thesis, which I wrote with Wendy Hoy, professor in Nephrology, I concluded that the number of nephrons (these are the filter units in the kidney) needed to last you a lifetime, were laid down before birth. And that Aboriginal Australians started life with fewer nephrons than white people in the 'Top End'. Starting life with fewer nephrons meant the score tables were stacked against them from birth: Aboriginal Australians end up 4 times more likely to die of end stage renal failure.

Second, my time in Turiani Mission Hospital in Tanzania as a medical student, supervised by Barend Gerretsen. In 2001, as it is today, malaria, AIDS, TB and malnutrition were the major causes of death. I had little to offer for many of my patients. There were no anti-retrovirals, we had no solution for the extreme poverty that caused the malnutrition. I also had no strategy to address the Mission hospital's religiously motived opposition to condoms, which seemed to be fanning the flames of the HIV epidemic. Here I learned to practice with no more than my eyes, ears, hands and gut feeling.

These 2 encounters taught me:

- Firstly: That good health takes far more than good hospitals.
- Secondly: That 'There is no such thing as a free lunch'. Which means that everything comes at a price. In the context of my work this means that what happens around you as a developing fetus or child **will** shape you, for better or for worse.
- And finally, that Medicine is after all an Art. An essential realization when 'Medicine the Science' does not always have an answer (yet).

Today, the world is tackling a number of major crises, which are closely intertwined: *Climate, nutrient deficiency and Obesity*.

The drivers that have led to the Climate crisis, with crop failures, floods, human conflict and therefore undernutrition in its wake, have important links to the way we view food quality and production. We have come to prefer animal protein-based, calorically dense, ultra-processed food. Exactly these products have the largest footprint, and are associated with a myriad of adverse health outcomes including obesity. Food production accounts for almost a quarter of global emissions.

Limiting red meat and processed food consumption has the ability to address the obesity pandemic, slow climate change and address undernutrition. What's not to like? But it will require us to re-examine our views on the role food plays in our society and how it gets to our plates.

This may strike you as an unusual opening for an inaugural lecture by an obstetrician (and I will leave climate here), but bear with me: the roots of obesity may lie in maternal nutrition, both OVER and UNDERnutrition, as I will discuss later.

Let me start with feasts. Here you see Pieter Aertsen's 'The fat kitchen' (~1565). The table is creaking under the weight of the feast of plenty with which it is laden. The picture is also laden with critical symbolism of such excess. Aertsen, Amsterdam born himself, painted this while in Antwerpen (Belgium), where his Dutch frugality was probably poorly understood.

And here's the beautiful "Milk maid" (1660): the most nutritionally excessive picture I could find by a Dutch painter, Johannes Vermeer, who never left Holland. 'Splashing out on milk and bread' conformed to the Dutch idea of a feast.

How different is today. In the Netherlands, *half of all adults are overweight or obese*. Despite the 2018 Dutch 'Prevention Treaty',[1] the unbridled growth of us all continues.

Future parents, the teenagers of today, are entering their reproductive life span heavier and unfitter with each passing year. Despite our status in the world as a nation of tall, lean people- perhaps owing to generations of steady protein availability (milk), and safe exercise (cycling)- an estimated 13% of women are entering pregnancy with obesity. Compared to the statistics of the UK, Australia, and the USA [2] (25%) we are lean, but the trend is upwards and burdens both health care systems, as well as affected individuals.

Pregnancy with obesity adds to the chance of mother and baby not coming through pregnancy well: Complications include hypertensive disorders, preterm birth and large babies.

Obesity clusters with other risk factors for complications in pregnancy, for example poverty or low educational attainment. Healthy food choices are more difficult to make for those with housing insecurity, mental health issues, financial problems, or domestic violence. Obesity and social disparity unfortunately act in synergy when it comes to unhealthy pregnancy outcomes.

Yet, the legacy of obesity in pregnancy is not limited to outcomes around the time of birth, and is *certainly not only due to confounding by maternal socio economic* disadvantage. In animal models, regardless of species, maternal obesity leads to a broad range of poor outcomes. In our systematic review, in >21,000 animals in 5 species, we found detrimental effects on adult body weight, blood pressure, glucose, insulin and lipids. The size of effects translates to an increase of *one standard deviation in adult BMI*: around 3-4 kg/m^2. Far from trivial. For someone of my proportions, it would mean a shift from healthy to overweight **just** based on having a mother with obesity in pregnancy (don't worry mum-this is just for

[1] https://www.rijksoverheid.nl/onderwerpen/gezondheid-en-preventie/nationaal-preventieakkoord
[2] https://www.cdc.gov/nchs/products/databriefs/db392.htm

the sake of illustration). So: Having a mother with obesity has clinically relevant effects on children's health in later life, regardless of genetic make-up or what is on the table as children grow up.

Let's take a look at the considerable body of *research to tackle to pregnancy problems stemming from obesity.* Large trials in Australia and the UK assessed the effectiveness of lifestyle interventions in pregnancies with obesity. These interventions had all the right ingredients to find out which of a variety of lifestyle strategies could benefit these pregnancies. The interventions studied:

- Specific diets, like low glycemic index diet,
- Increasing step count,
- Were delivered in group sessions or individual sessions, and were
- Co-developed with patients.

And yet, these interventions essentially had no impact on poor perinatal outcomes in expecting mothers with obesity. Moreover, they are not attractive to participating women: eg LIMIT study could only convince 60% of those they approached to participate, and, of those who decided to join the trial, 20% stopped after the first session.

And yet, these interventions should not be shelved based on their lack of effects on perinatal outcomes.

Four questions need answering to understand their true value:

First: Did we start too late or stop too soon? Are preconception interventions the way forward?

Apparently not, or at least not in the way we have been trying so far: Trials on preconception lifestyle improvements targeting those with obesity have largely yielded a null result: no improvements in any of the outcomes, neither those fertility-related, nor those related to perinatal outcomes. Perhaps the limited scope of action is exactly why: None have straddled the entire period from before, throughout and post pregnancy. We should consider more joined-up approaches when planning future interventions.

Second: Why only target obesity in pregnancy? If tomorrow, we would implement healthy diet and exercise in early pregnancy for ALL pregnancies, solid evidence suggests we would see 57% fewer preterm births, 21% reduction in gestational diabetes and 32% fewer NICU admissions. Moreover, every dollar invested in these interventions would yield 4.75 dollars return. What's not to like? We need to be implementing this as soon as we can!

Third: Was our perspective too near sighted? When Tessa Roseboom in collaboration with a multi-university team, including myself, gained funding for the follow-up study of mothers and children who had participated in the LIFESTYLE trial, I was curious. Could an intervention before pregnancy, that had not affected birth outcomes, still have benefit on children's health at school entry age?
What did we find? There were some indications of durable improvements in lifestyle after the preconception intervention, but the overarching conclusion in the 6 PhD theses was, that this preconception lifestyle intervention did not affect long term health in mothers or in their children.
That was, **until** we found sustained improvement on children's cardiac structure and function at school age. Echoed by similar findings in the UK's lifestyle intervention in pregnancy study (UPBEAT) show the importance of the **long term perspective in the value of what we do around the time of pregnancy**.

And finally: Were we barking up the wrong tree? Despite all our clinical efforts, I have come to the realisation that to achieve big change, we need to change tacks. We are never going to be able to tackle the perinatal effects of the global obesity pandemic from behind hospital walls. Interventions targeting a single person during a number of months while she is trying to conceive or while she is pregnant, disregards the fact that the obesity epidemic's drivers are powerful and multisystem. We are going to need to reach out and join forces with the world outside.

I am therefore overjoyed that earlier this year two opportunities came my way that are going to help bridge this gap. First, I became the lead and gained funding for the prolongation of the Regional Network for Maternity Care North West Netherlands, and became a board member of the National Consortium of Regional Childbirth Networks

(NRCG). These organisations aim to connect medical and social domains in the interest of mothers' and babies' health.

The second was that I became a member of the Amsterdam Coalition "Kansrijke Start". The City of Amsterdam has committed to partnering with many of those involved in the care for families and children in a drive to improve the first 1000 days of life for all children in Amsterdam.

Let me present to you what these organisations might do to stop obesity in pregnancy in its tracks: What if the City of Amsterdam expanded free bicycle access to low-income families, encouraging exercise among these groups of the population? Or decided to ban fast food chains from the City? What if the NRCG can achieve a national policy of unlimited free availability of healthy mother walking and cooking groups, maybe even provide 'Healthy Food boxes' by medical prescription? Or the federal government would decide to introduce a 'sugar tax'?

How would we know whether these measures were affecting actual health outcomes, and not just lifestyle or risk factors for later obesity? We might be able to do just that by making use of pregnancy outcomes- at present this is an underutilised source of assessing effects of policy changes. But we do need to have fast access to data, and we need to know more than just whether the baby was born at term, and survived. We need to have high-quality in-depth data, including BMI at pregnancy entry. Let's think Blue Sky here. I will summarize:

So what, dear audience, needs to happen?

- **First: A concerted national strategy that targets obesity, and at the same time benefits sustainability (which considers how food is grown and energy is used in transport and preparation) and equitable access to healthy food.** *Okay, that may be a little ambitious and I won't hold my breath. I will keep pushing nutrition within sustainability goals within Amsterdam UMC, in collaboration our Green Teams, and within medical curricula. Amsterdam UMC has an opportunity to take the national lead here.*

- **Second: Utilise the amazing resource that pregnancy offers: we need to harness pre-pregnancy BMI, perinatal outcomes and patient reported measures as a 'barometer' to know whether policy strategies are reaching their target.** *This is what we are working towards in the Stadscoalitie Kansrijke Start Amsterdam.*

- **Third: Improve the quality of data we collect on pregnancy: broaden the dataset, improve the turnaround time of data availability.** *This is what many stakeholder groups, including my own Obstetrics College and NRCG, are pushing for.*

- **Fourth: Implement lifestyle programmes for all pregnancies as soon as we can.**

- Where is the **Art of Medicine** in all of this? It is with the realisation that it is unhelpful to label obesity in pregnancy as a predicament for which those affected need to be held individually accountable. The fact that we do exactly that, has to change. **Yes**, obesity is accompanied by risks of a poor outcome. But no: it is not self-chosen and it is not easy to treat, and drivers are societal rather than individual.

I have just painted a picture of the societal perspective we may need to adopt to tackle obesity in pregnancy. There are, however, specific issues we need to address from within hospital walls*. It is time to talk about carbohydrates.*

Here is the iconic Dutch carb painting by Vincent van Gogh, 'De Aardappeleters'.

Mirroring the global rise in obesity, gestational diabetes (GDM), or high blood sugar first detected in pregnancy, affects ever increasing numbers. Global estimates have over 16% diagnosed with GDM, with some local estimates as high as 30%. GDM is linked to large babies, obstructed labour, preeclampsia, low blood sugars in newborns.

When I started my career in obstetrics in 2001, we did not screen for GDM. There was no national guidance. The WHO had only just carefully issued a definition in 1999, based on the WHO definition for impaired glucose tolerance at the time. It saw little uptake here. There

was doubt about whether GDM should be viewed as a clinical entity of any concern. A degree of increased insulin resistance coupled to the presence of the placenta is, after all, a hallmark of healthy pregnancy: necessary to maintain sufficient glucose (which is able to cross the placenta freely) to fuel the baby's energy requirements.

From 2005 on, that all changed: Caroline Crowther (Adelaide Australia) published the first trial in GDM screening and treatment and found that treatment helped avoid large babies and shoulder dystocia (which is where the baby's shoulder gets stuck behind the mother's pubic bone during delivery).

The size of the effects was large: two thirds of adverse outcomes were avoided by treatment. And there was a price. Induction of labour increased by 10%, and there was a 10% rise in babies needing neonatal care. Since then, we have seen a number of landmark trials shape the way we see GDM in the present day. HAPO, a large international observational study published in 2008, found that, what it had hoped to establish did not exist: *there was no 'safe threshold' for hyperglycemia in pregnancy*. The higher mum's blood sugars are, the higher her chance of a GDM-related adverse outcome. The HAPO researchers, based on their findings, redefined GDM. They broadened the definition considerably, adding a large group of pregnancies previously viewed as healthy.

All over the world, the health care system creaked in response: where we had gone from 'not a disease' we had come to 'disease affecting up to 30% of all pregnancies and needing intensive multidisciplinary care' in the space of under 20 years. Conservative estimates had implementation of these new thresholds in the Netherlands driving the incidence of GDM up from 5% (n= 8500/year) up to 10% (17000/year). At an additional annual cost of €60M. These investments might be offset by gains in neonatal health, and reductions in maternal complications, but the fact was no one had demonstrated whether providing the intensive GDM treatment- daily self-monitoring of blood sugars, dietary restrictions, medication if necessary- would lead to improvements in the exceedingly mild, newly added GDM diagnoses.

In 2016, just three years after the WHO had endorsed the new broad definition of GDM, the Netherlands had the unique opportunity of postponing their implementation pending the evidence for efficacy. Together with others including Bas van Rijn, Arie Franx, Hans de Vries, Patrick Bossuyt and Ben Willem Mol, I gained funding from Leading the Change for the TANGO-DM randomized controlled trial, which has now recruited almost as many patients as Crowther's landmark study did in 2005. There are still a large number of participants needed to complete this important trial, which is making steady but slow progress as hospitals buckle under pandemics and budget cuts. So, if you are or could be a recruiting centre for TANGO-DM: I need you!

This is an important issue. GDM is not the only recently expanded disease definition in my field. The definition for preeclampsia was amended by the ISSHP a few years ago, based on associations with outcome, but not based on the fact that diagnosis aids improvement of outcomes. The same has happened outside obstetrics with hypertension and type 2 diabetes. In collaboration with my former promotor Patrick Bossuyt and Paul Glasziou (of Bond University, Surfer's Paradise, Australia), Doortje Rademaker has set out to systematically test the benefits, harms, and costs of the introduction of broadened disease criteria. 'Harms' we may not consider as doctors are evident from a qualitative work, where women describe after diagnosis being in constant anxiety about what they ate, and finding the focus on blood sugars, many appointments and daily monitoring robbing them of the joy of pregnancy. Harms also include medical interventions, like induction of labour at early gestational age, if these do not clearly benefit outcome.

An issue that could vastly improve the (cost) effectiveness of GDM diagnoses, is that fact that GDM is strongly linked to future Type 2 diabetes in mothers, and to obesity and diabetes among their children. The more severe the GDM, the larger these risks appear to be. Does it help to identify women at risk of type 2 diabetes? Does it motivate them to change their lifestyle? Does this help the prevention of vascular sequaelae? We do not know the answers to these questions. Equally unknown is whether treatment can curb the future risks for children born after GDM. Can the fact that GDM treatment reduces the chance of macrosomia and fetal hyperinsulinemia also aid improved cardiometabolic risk of the offspring?

This concept- how interventions in pregnancy impact life-long health- is certainly not new. But obstetricians are trained to act fast on emergent situations with immediate danger, and are used to seeing immediate bang for buck. I am glad to say that the efforts of many, including Amsterdam UMC colleagues Janneke van t Hooft, Martijn Oudijk and Eva Pajkrt in overcoming the near sightedness that trial funders often demand of us, may hold the key to knowing how to best manage high risk pregnancies.

Taking a step back to view their actions from a perspective of long-term health requires patience. But this perspective lends great gravity to the things we do during pregnancy, making us custodians of the health of mother and of baby across the life span. And this perspective can be a key motivator to change policy, because of the immense value of life-long health. I feel absolutely compelled to use the TANGO DM follow up to find out in the near future what GDM treatment means for future health.

I am therefore proud to be part of the **only** University Medical Centre to have its own **Research Institute** '**Amsterdam Reproduction and Development'**, headed by directors Lidewij Henneman and Tessa Roseboom, which recognizes and fosters research on what happens around you as a developing fetus or child that **will** shape you, for better or for worse. No such thing as a free lunch as I said before.

In summary, audience, what needs to happen?

- **First: Only focus on blood sugars in pregnancy if we are able to use them to improve outcomes or quality of life.** *A series of national and international trials I am now conducting with many others, including a series of meta-analyses, will distil when the effort and costs of intensified glucose control are worthwhile.*

- **Second: Quantify the impact of diagnosis and treatment of GDM on outcomes after pregnancy on both the mother and her child.**

- **Third: Double check we are doing more good than harm when we broaden diagnoses.**

Some more statistics on severe winters, as I had promised. In 1978 on this day, just before I arrived in Amsterdam as a young child, it was just above zero, clear weather with a cold easterly wind, maybe a little like this Winter Landscape by Andreas Schelfhout.

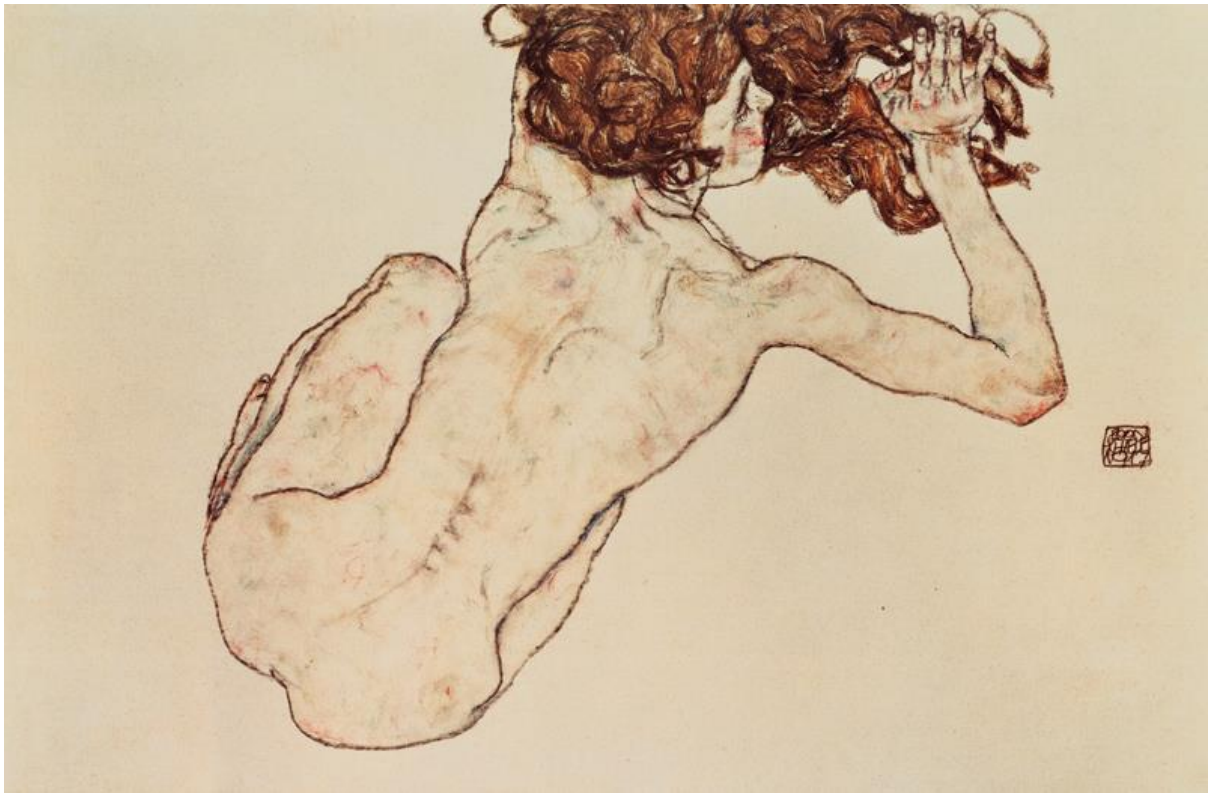
Wind back the clock a little further to the 2nd of December 1944. Average temperature 3.3 degrees, a cloudy wet windy day with southwesterly winds, maybe more like this Breitner of the Rokin in Amsterdam.

On that day in 1944, the food ration stamps afforded the people of Amsterdam 729 calories per day. For you reference, we like to have 2000-2500 calories a day- or maybe a little more this time of year. Amsterdam, like all western cities in the Netherlands at the time, was at it's bleakest in recent history: the Dutch Famine was upon us. Availability of food plummeted following a series of events following the grinding halt of the Allies' attempts to liberate northern Holland.

The Dutch Famine hit a previously well-nourished population. It hit all members of society, without regard of social class. Due to its sharply demarcated start and finish upon liberation of the western Netherlands (May 5th 1945), and the meticulous ration record keeping, we were able to study the effects of this humanitarian disaster on the health of a cohort of men

and women born at the Wilhelmina Gasthuis during and just after the war. The Dutch Famine Birth Cohort is a landmark study, that established that circumstances during pregnancy have lifelong effects.

Thanks to Tessa Roseboom, David Barker, Clive Osmond, Otto Bleker, Anita Ravelli, Susanne de Rooij and a long line of researchers since, in the past 25 years we have learned that maternal undernutrition in pregnancy has large and lasting effects on a broad swathe of outcomes, cardiometabolic, ageing, cancer and even longevity. Importantly, timing was of the essence: effects were largest in number and size among those exposed to maternal famine in **early pregnancy**. Across the world today, communities, policy makers and health care workers are collaborating to use this knowledge to make a change for future generations. I feel particularly fortunate and proud to have started my career in science in this outstanding part of the warm DOHaD family, many of whom are here today.



My only non Dutch painter today, Schiele- an Austrian (I have a soft spot for Austrians).

Maternal undernutrition is unfortunately not something we had left behind us in the Dutch Famine. It exists today all over the world. And it has persisted in a particular group of pregnancies in the high income countries.

Hyperemesis gravidarum or HG, is extreme nausea and vomiting in pregnancy. HG is not morning sickness. Where normal pregnancy sickness affects 80% of pregnancies, HG is something completely different. It affects just a few percent of pregnancies and leads to caloric deficits very similar to those in the Dutch famine; 400-800 calories a day are no exception. And it happens at exactly the time in pregnancy that Dutch Famine research had marked out as of particular importance for the developing baby.

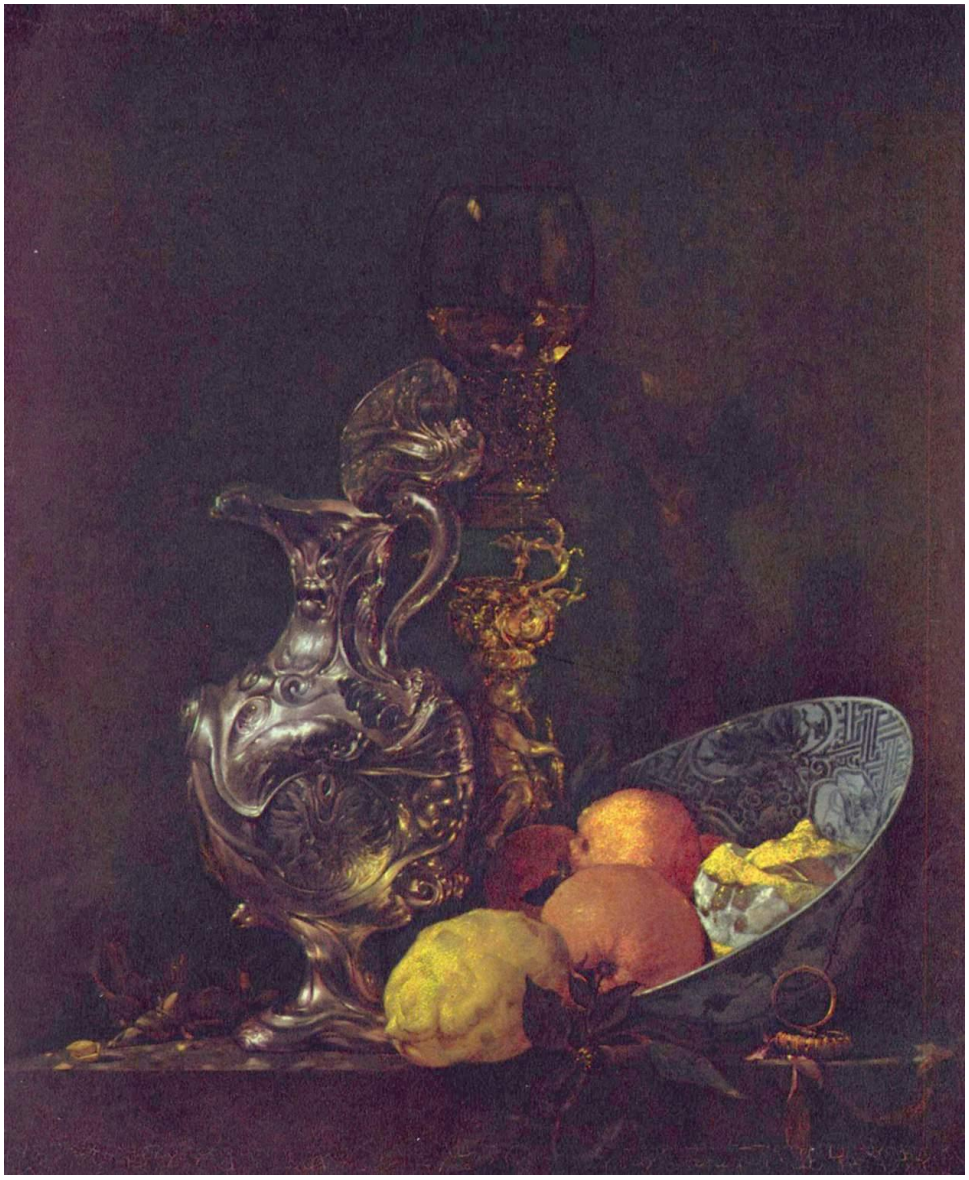
HG leaves women incapacitated for months, sometimes throughout their entire pregnancy. It remains the most common reason for admission in the first half of pregnancy.

Unbelievably, we are still only just starting to learn what causes it and how it should be managed.

When I came across this picture, painted by Gerard Dou, in Vienna last year, it struck me that we hadn't come very far since this charlatan 'doctor' looked at the colour of urine to determine what was ailing his patient in 1653.

To this day, ketonuria is used to diagnose HG, and to decide whether a patient qualifies for rehydration. No other gastrointestinal illness, from chemotherapy induced nausea and vomiting to acute gastroenteritis, is diagnosed by this means. Ketones are produced when the body is out of carbohydrates and starts burning fat. They are not a marker of dehydration, as many so often have mistakenly thought. Together with Marieke Niemeijer, Marjette Koot and Iris Grooten we investigated whether there was any clinical utility in using ketonuria in the context of HG. We found no association with markers of disease severity in our own data, nor on meta-analysis with other studies. *So, we can safely ditch the ketones*

It turned out that research on HG was scarce. We were sweeping what there was together to find out what the effects of HG might be on offspring health. The variety of definitions for HG in the available studies meant it was near impossible to compare them to each other. **Apples and oranges,** like in this painting by Willem Kalf**.**



The second issue we ran into is that the same scarce research reported on vastly different outcomes, all measured with different scales and methods. This meant that what precious research on HG we had, was rendered useless in meta analyses. **More apples and oranges.**

Enter the International Collaboration on HG (ICHG) network, which had been gathering strength since our first meeting in Bergen, Norway in 2015. As a community, we published the first internationally recognized definition for HG, which (not after Kate Middleton, but after the location of our second ICHG meeting) is called the Windsor definition. With the support of the same ICHG network, Iris Grooten, Larissa Jansen and Lois vd Minnen have gone on to develop and publish an internationally recognized set of minimum requirements

of outcomes that all trials should measure in future, and guidance on how these outcomes should be measured.

The third issue was that a large proportion of existing HG research appeared to address futile questions using opportunistic methods. Studies that don't contribute to meaningful improvements in care for HG patients. It was my utter privilege to supervise the chair of the UK Charity for HG, Caitlin Dean, as she put together *top 10 of most urgent knowledge gaps in HG research* in the course of her PhD. Before I go on to discuss the top 10, let me pause to say how meaningful my collaboration is with patients in making research much, much better. I can highly recommend to anyone in the audience who is planning clinical research to ask a patient member to join your team. Why? It will make it easier to recruit, it will make it more likely you have complete data. It will make your study more relevant for what matters to the people affected. And I can vouch for the fact that you will have a lot of fun on the way.

Back to the top 10: The number 1 question on this list is: **Find a cure!** A question that seemed an impossibility 10 years ago, but now seems within realistic grasp. Marlena Fezjo's lab in the US will help us find an answer to with her ground-breaking work on GDF-15: this is a hormone that fits the bill in explaining what causes HG.

- It is highly expressed in the trophoblast.
- It has receptors in the part of the brain that makes you sick.
- If you have a mutation in either the gene that codes for the hormone, or for its receptor, your chance of having HG is vastly increased.
- The higher the levels measured in pregnancy, the sicker women feel.

But there is still a lot of work to be done before we can find a way of offering women with HG a GDF 15 blocker and know the ICHG community is ready to take this idea forward.
I hold great hope.

Hope, because, HG's effects **outlast early pregnancy**, even if the vomiting abates. Babies are more likely to be small for dates and come preterm after HG. Addressing maternal nutrition and weight loss in the treatment of HG has long been ignored. In the MOTHER trial, Iris Grooten found that early tube feeding could not improve outcomes for women with HG or

their babies. So, for now, medication to enable women to hold down foods and fluids is the mainstay of HG treatment.

But also hope for a cure, because HG's effects outlast **delivery**: Children of mothers with HG are more likely to have neurobehavioural and mental problems.
1:5 mothers exhibit signs of post traumatic stress disorder: the worse the HG had been, the higher this rate is, even more so if there had been more pregnancies affected by HG.
The majority of women who have had HG will curtail further pregnancy plans for fear of the high recurrence rates (>80%). Women with HG have thoughts of suicide and 1:4 will think about termination while they are pregnant with a very much wanted baby.

Let me translate, as difficult as I find this: Today, someone in Holland is considering terminating their wanted and planned pregnancy, because they feel it is their only way of surviving HG. In the USA, 1 in 10 women with HG actually will have a termination for the sole reason of HG.

From that perspective, there are few pregnancy disorders with a higher fetal lethality rate than HG. I fear that, as medication is the only option available to lessen the burden of symptoms, any barriers to access will lead to increased rates of terminations. For example, recent medicine shortages have huge repercussions for women with HG, who have fewer alternatives 'because they are pregnant'. Even more concerningly, the recent reluctance of clinicians to prescribe ondansetron (one of our more powerful medications for HG), was the direct result of cautionary messages issued by the EMA on the risk of orofacial clefting linked to ondansetron. Just let me put these risks into perspective: the risk of cleft lip is normally 11: 10000. With ondansetron use this goes up to 14:10000. We do not know whether the 3:10000 extra cases of clefting are caused by ondansetron, or whether nutritional deficiencies common to HG could be causing these effects. Consider how those numbers compare to 1:10 women ending their much-desired pregnancy because of HG.

When the EMA advised limiting metocloperamide prescription to just 5 days, this already led to increases in termination rates in Norway. In collaboration with University of Bergen's Jone Trovik, my PhD student Lois vd Minnen will soon quantify the effects of EMA's

messaging on ondansetron on pregnancy termination rates among women with HG. I fear this will not be good news.

Audience, it is inappropriate for regulatory bodies to issue cautionary messaging for medication use in pregnancy without considering the context and ultimate effects such messages.

So let me summarize what is needed to take the field of HG forward

- ***Find a cure.*** The ICHG community is as ready as ever to take this forward.
- In the meantime, consider ***'there is no such thing as a free lunch'***. HG has long term effects on mother and baby. Consider this when weighing the pros and cons of medication.
- ***Both cautionary messaging and poor drug availability*** can have grave repercussions for HG patients. Regulatory bodies who create barriers to appropriate medication 'in the interest of the fetus' may in fact be contributing increased risks for the fetus.

On that note, I will finish talking about HG by calling on the **Art of Medicine.** My trade, obstetrics, derived from the Latin obstare, literally means to standing by your patient. Interestingly, this is exactly what midwife means. From the Old Dutch 'MED WIJF': this also means standing by women's side. While we are working to find a cure, we can stand by our patients.

In this lecture, I hope to have shown you that the pivotal lessons, learned early on, still hold:

- Firstly: **That good health takes far more than good hospitals**. Maternal obesity, but also undernutrition, and the specific issue of hyperemesis gravidarum, require involvement of many parties outside the hospital.
- Secondly: **That 'There is no such thing as a free lunch'.** I have shown you that both under- and overnutrition in pregnancy lead to repercussions both in mothers and their children, that outlast the duration of pregnancy. We, as carers for pregnant women, have great responsibilities, holding the key for lifelong health.
- **And finally, Medicine is after all an Art.** 'Medicine the Science' does not always have have all the answers. Paraphrasing Tammy Wynette: "Stand By Your Woman".

Words of thanks

It is a blessing to work among such inspiring people! Both in my clinical work as well as in the research community I feel privileged to be part of this team.

I thank the Board of the Vrije Universiteit and the Board of the Amsterdam UMC for their trust and support in endowing me with this chair. I thank the head of the Division, Christianne de Groot, and head of Obstetrics, Eva Pajkrt, for their support and patience throughout.

Standing on the shoulders of giants is what they say. Thanks to my giant promotors: Otto Bleker and Patrick Bossuyt. My co promotor and collaborator, a giant in her own right, Tessa Roseboom, I admire your direction and poise as you go exactly where you aim to go. You never lose track of what it is really about. Thanks for bringing the field so much value, and thank you for your support and friendship.

On the eve of your own farewell: Thank you Joris van der Post, for your generosity and for being the compass of the department for so long.

And my PhD students past, present and future: all of you work so hard, and with so much passion. You are an incredibly important cog in the big wheel of science. The fact that I didn't mention all your work in my talk today is simply because you have been so prolific. Keep in inspiring me with your talent and drive!

My co-workers at Amsterdam UMC Vrouwenkliniek.
I hold each and every one of you *'my Family at work'* close to my heart. We have each other's backs at all times.

Family, friends and colleagues from all over the world. Thank you for making the trip, your presence today is the best gift of all.

Gailtaler familie und Freunde. Danke dass es do seits! Und danke dass i bei enk Daham sein kon.

Dad, I know you would have been glowing with pride today, and you would have loved that this title comes with its own special outfit and beret!

I come from a long line of strong women. Both my grandmothers I thank for showing me the value of an education they would have wanted, but could not have. And that a woman needs to be independent no matter what. Mum, made of pretty strong stuff yourself. And you have great legs! Now don't ruin your make up!

Kids. Jacob, Sam, Juno.
You are my one and only true mark on the world.
It fills me with pride to see how you are growing into such interested and interesting individuals, each with your own drive and confidence.

Herwig.
Thanks for your patience and support always! I don't tell you enough how grateful I am to have you as my wing man. Who would have thought, on that fateful December 2nd night in 1994 at the Tennant Creek 'Shaft', that this is where the future was heading? Time for a celebration, I am in my best 'little black dress' as you can see.

Thank you all!

'Ik heb gezegd'