Hyperemesis gravidarum
Definition, treatment, prognosis and offspring outcome
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General discussion
Hyperemesis gravidarum: a diagnostic dilemma

The work presented in this thesis focuses on different aspects of hyperemesis gravidarum (HG) care and research. A common thread throughout this thesis is the lack of a standardised definition for HG. To date, the understanding of the likely multifactorial aetiology of HG is limited. No test is available to confirm the presence or severity of the condition. This implies that diagnosis relies on clinical characteristics. In chapter 8 we illustrated that currently, a wide variety of characteristics is being used to qualify a women as having HG. This variety results in a large heterogeneity in study populations, which hampers study compatibility and generalizability of results; a problem we have emphasised in multiple chapters of this thesis.

In order to overcome these hurdles it is important to reach consensus on the definition of HG. The systematic review presented in chapter 8 will form the basis for the Definition and Core Outcome for Hyperemesis Gravidarum (DCOHG) project; an international consensus project to identify a minimum set of clinical criteria for HG diagnosis and which core outcomes are important to measure in intervention studies (https://www.hgresearch.org/dcohg/). The project is designed to harmonize and improve clinical research of HG and engages multiple stakeholders including health care professionals, patients and researchers from all over the world. To develop the consensus statement, a modified Delphi method is used, which includes several survey rounds and a consensus meeting. A Delphi procedure is a well-established instrument for reaching consensus between a panel of experts for research questions that cannot be answered by empirical evidence with a high degree of certainty. Various international consensus projects have shown that it is possible to reach consensus on a clinical definition for multifactorial diseases with the use of a (modified) Delphi procedure. The Delphi method has several advantages: the possibility to include a large number of participants; substantial amount of time to express ideas, reflect on answers and make changes and the possibility to express opinions freely and anonymously. Moreover, it is a great way of involving patients and caregivers, which enhances quality and appropriateness of the results and possibly implementation. However, the Delphi method also has some disadvantages; participants may be influenced by questionnaire design, there is a potential bias in participant selection and viewpoints and judgements that are collected are subjective in nature. Other consensus methodologies include Nominal Group Techniques, RAND/UCLA Appropriateness Method and a consensus development conference. All of these methods have their own advantages and disadvantages.
Lessons from other fields of medicine

HG is not the only disease that faces definition challenges. There are numerous conditions that cannot be diagnosed with one test and, in some cases, reaching consensus on definition has been an ongoing process spanning several decades. An example is sepsis; a syndrome of pathologic, physiologic and biochemical abnormalities induced by infection. Although it is one of the leading causes of mortality worldwide, clinicians and researchers have been struggling with its definition for years. In 1991, a first effort was made to achieve consensus: a conference was held with the goal of agreeing on a set of criteria that could define a patient with sepsis. Although the application of a consistent and easy to use set of criteria resulted in declined mortality rates, limitations in the list of criteria were recognised and revisions have been made. Recently the third international consensus on the definition for sepsis was published. Consensus was reached through analysis of electronic health record databases, meetings, Delphi processes and voting. Although considerable effort was made to reach agreement, shortly after the consensus statement was published, various parties rejected the consensus definition due to its disadvantages. It was, for example, suggested that a sudden change in definition could reduce early recognition of sepsis without certainty that the new criteria would lead to improved outcomes.

Also, within the field of rheumatology clinicians and researchers have repeatedly faced the challenge of defining diagnoses. Various consensus projects have been held to define rheumatologic syndromes. However, the disadvantages of a standardised diagnosis have also been a point of discussion within this specialty and recently, the American College for Rheumatology stated that they no longer consider funding or endorsement of diagnostic criteria but that they recommended the use of classification criteria. In the same paper, they give a thorough explanation of the differences between diagnostic and classification criteria. Diagnostic criteria are a set of signs and symptoms for use in clinical practice. They are usually broad and reflect different features of the disease with a goal of identifying as many individuals with the disease as possible. Classification criteria, on the other hand, are standardised definitions that are designed to create a well-defined, homogeneous cohort of patients for research. They do not need to identify all possible patients with the disease but rather identify the majority of patients with similar clinical disease features. Therefore, the purpose of diagnostic criteria is to have a high positive predictive value of a specific diagnosis, whereas the purpose of classification criteria is to create a clearly defined group of patients with a similar condition.
The medical specialty that makes the most use of diagnostic criteria is undoubtedly psychiatry, with the Diagnostic and Statistical Manual of Mental Disorders (DSM) being probably the best-known set of diagnostic criteria worldwide. Within psychiatry, there has been a great deal of discussion about the pros and cons of diagnostic criteria, especially from the patient perspective.\textsuperscript{23-25} Often mentioned disadvantages are that diagnostic criteria enhance diagnostic labelling, which might lead to stereotyping and can create stigma. Moreover, there is a risk that patients who are in need for help but cannot be categorised will not get the treatment they need.\textsuperscript{26,27} On the other hand, a diagnostic label itself can provide the patient with meaning and acknowledgement for the symptoms; which may generate comfort, emotional relief, acceptance and credibility.\textsuperscript{28} Diagnosis can lead the way to treatment and to patient organizations and may protect from the feeling of guilt.\textsuperscript{27}

Within HG research, there are many things we can learn from the debates and discussion about diagnosing, classifying and labelling in other fields of medicine. We cannot ignore the fact that HG research has been hampered by the large heterogeneity in research populations, limiting the interpretation and comparability of study results.\textsuperscript{29} One of the main goals in HG research therefore remains to ensure that a more clearly defined population of HG patients will enter future clinical trials. Whether a set of diagnostic criteria for use in clinical practice is beneficial for HG patients is unknown. Qualitative research has suggested that health care professional sometimes hold ambivalent attitudes toward women with HG, perceiving them as problematic patients.\textsuperscript{30} Similar literature showed that an ambivalent attitude of practitioners may adversely affect access of HG patients to timely and appropriate care.\textsuperscript{30,31} A diagnostic label might help HG patients and their care providers accept that they are sick and that ‘just getting over the morning sickness’ is unlikely to be an effective therapeutic strategy.\textsuperscript{32} However, similar disadvantages with the risk of women in need of treatment, but not meeting diagnostic criteria and therefore not receiving treatment are possible and of an unknown magnitude.

**Value of diagnosing in current medicine**

While the discussion about the use of diagnostic criteria and labelling it not over, there have been suggestions that not disease diagnosis, but patient prognosis should be the starting point in clinical practice.\textsuperscript{33} This idea mainly comes from fields of medicine where technological development has resulted in the introduction of new, more accurate diagnostic tests.\textsuperscript{34} Even diseases that always seemed to have an objective pathological definition, such as thyroid cancer, have had a substantial ‘diagnostic drift’ over the recent years, caused by the increase of the specificity of (new) tests. This results in more and more patient with a diagnosis of a disease.\textsuperscript{34}
A diagnosis classifies a patient as having or not having a specific disease and is generally the guide in treatment and management decisions. A diagnostic label is therefore particularly useful if it is given to patients that will benefit from a specific clinical intervention. This however, requires information about prognosis; the likely course of the given disease in that particular patient. Patient prognosis is not only dependent of the disease diagnosis and the given treatment but is also influenced by biological and social factors. Focusing on improving prognosis, regardless of the diagnosis may provide a more effective approach to improving health outcomes. Shared understanding between patients and health care providers of which outcomes are needed or wanted is an important and indispensable part of this framework.

**Predicting prognosis of hyperemesis gravidarum**

The concept that prognosis can replace diagnosis in the framework for clinical practice would, theoretically, be a very good option in HG care. HG may have detrimental effects on maternal and offspring health and is accompanied with high health care costs. It is likely that different parties involved may hope for different outcomes of treatment. It might be that a ‘good outcome’ for a patient is being able to take care of her children after treatment, whereas a doctor might want to reduce weight loss or the chance of readmission. Focusing on what outcomes should be achieved rather than choosing which symptoms should be treated may be beneficial for both HG patient and their doctors.

However, to apply such a framework in clinical practice, clinicians should be able to make an estimation of the prognosis of their individual patient. A well established and increasingly common way of predicting an outcome, is by using an outcome prediction model. An ideal outcome prediction model incorporates all known features that are independently predictive for the outcome of the disease in question. This requires background knowledge about the course of the disease and risk factors of poor outcomes. Unfortunately, this knowledge is very limited in the field of HG. High quality research assessing indicators that predict poor maternal and neonatal outcomes is currently lacking. Moreover, it is unknown whether outcomes currently measured in HG research are most relevant for women with HG and their offspring. Herein lies an important future goal of HG research, although this might be easier said than done. To study prognosis, ideally an entire population with a particular disease is studied, starting at the onset of the disease and throughout the entire course. Obviously it is impossible to study an entire population and therefore, a representative sample of patients must be studied. However, as emphasised earlier in this discussion, defining what a representative sample of HG patients is, is already a challenge on its own.
Implications for hyperemesis gravidarum research and care

We have illustrated that HG care and research can be very challenging for all parties involved. Clinicians and patients may feel powerless by the lack of good treatment options while researchers face the challenge of a very heterogeneous study population. This may be enhanced by the fact that, in the field of HG, there is not always a clear ‘starting point’ from where to go; we do not know the underlying cause of the disease nor can we predict its course. This is not something we should just accept, but, in order to create more guidance in HG care and research, should be explored. A good step is currently being taken with the DCOHG project, a modified Delphi survey designed to identify a minimum set of clinical criteria for HG diagnosis, as explained earlier. After the last Delphi round, classification criteria for HG research can be established. The use of classification criteria will enhance homogeneity of the research population, which will significantly improve HG research. We have illustrated that classification criteria may also have shortcomings and that it can be necessary to update them over time. It is therefore important to evaluate the performance of the classification criteria. The DCOHG project is designed to harmonize and improve HG research and is not designed to develop a set of diagnostic criteria for use in clinical practice. It is however possible that the consensus definition of HG for research purposes will be extrapolated to clinical practice via, for example, guidelines. We have illustrated that diagnostic and classification criteria serve different purposes and that they cannot be used interchangeably. Therefore, caution should be taken with the use of the formulated criteria in clinical practice and treatment should not depend upon whether a patient ‘fits’ the consensus definition.

We have also illustrated that it may not always be necessary to have a well-defined diagnosis to deliver good patient care. Prognosis could serve as a good starting point in clinical practice as well. Especially in a condition as HG, that lacks diagnostic tests, such a framework can be of great benefit. In order to implement such a framework in HG care, studies on prognosis are very much needed. Ideally, large prospective studies would be set-up which aim to identify risk factors for specific, predefined adverse outcomes. The classification criteria formulated by the DCOHG project will be of great value in this studies, as it will help to select a well-defined, representative sample of HG patients. Moreover, the DCOHG project will also evaluate which outcomes are important to measure in studies on HG. The outcomes the different stakeholders will select during the Delphi processes can serve as a guidance in which outcomes should be measured in prognostic studies. After risk factors for (adverse) outcomes have been identified, they should be taken into consideration when choosing treatment options. Researchers, on their term, can use the identified risk factor to design more targeted trials.
Conclusion
To date, the etiology of HG is largely unknown and there is no single marker that can diagnose or predict disease severity. We have however, illustrated that HG is not the only condition which faces this challenge and that there are numerous diseases from which we can learn how to handle the lack of a well-defined diagnosis. We have given several examples of frameworks for research and clinical care that bypass the use of the traditional disease diagnosis, among which the use of classification criteria in research. Currently, a very important step in HG research is being taken by reaching consensus on HG classification criteria with the DCOHG project. We have suggested that a next important step in HG research is to set-up studies focusing on patient prognosis, as prognosis can serve as an important starting point in clinical care. By carrying out these steps and implementing them in HG research and care, we can create more guidance for researchers and caregivers and thereby, improve HG patientcare. It is however important to keep evaluating the frameworks being used in research and clinical practice, as the process of defining, diagnosing and predicting the course of disease will always be dynamic, depending on acquired knowledge and technological developments.
References


