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The windsor definition for hyperemesis gravidarum: A multistakeholder international consensus definition

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ABSTRACT

Objective: To develop an international definition for hyperemesis gravidarum to assist in clinical diagnosis and harmonize hyperemesis gravidarum definition for study populations.

Study design: A mixed-methods approach was used to identify potential hyperemesis gravidarum definition criteria (i.e. systematic review, semi-structured interviews and closed group sessions with patients and Project Steering Committee input). To reach consensus on the definition we used a web-based Delphi survey with two rounds, followed by a face-to-face consensus development meeting, held in Windsor UK, and a web-based consultation round, in which the provisional hyperemesis gravidarum definition was fed back to the stakeholders. Four stakeholder groups were identified 1) researchers; 2) women with lived experience of hyperemesis gravidarum and their families; 3) obstetric health professionals (obstetricians, gynecologists, midwives); and 4) other health professionals involved in care for women with hyperemesis gravidarum (general practitioners, dieticians, nurses). To reflect the opinions of the international community, stakeholders from countries in all global regions were invited to participate.

Results: Twenty-one identified potential criteria entered the Delphi survey. Of the 277 stakeholders invited, 178 completed round one, and 125 (70%) also completed round two. Twenty stakeholders attended the consensus development meeting, representing all stakeholder groups. The consultation round was completed by 96 (54%) stakeholders, of which 92% agreed with the definition as presented. The consensus definition for hyperemesis gravidarum consisted of: start of symptoms in early pregnancy (before 16 weeks gestational age); nausea and vomiting, at least one of which severe; inability to eat and/or drink normally; strongly limits daily living activities. Signs of dehydration were deemed contributory for the definition for hyperemesis gravidarum.

Conclusions: The proposed definition for hyperemesis gravidarum will help clinical studies to achieve more uniformity, and ultimately increasing the value of evidence to inform patient care.

Introduction

Nausea and vomiting are common in early pregnancy (NVP); approximately 80% of all pregnant women are affected to some degree. [1] When NVP is severe or protracted, the condition is often referred to as hyperemesis gravidarum (HG), affecting up to 3.6% of pregnancies. [1–5] Women with HG may become dehydrated, lose weight or require hospital admission. [6–7] After HG, women more often report anxiety, depression and posttraumatic stress disorder, reflecting the detrimental effect of HG on maternal wellbeing and quality of life. [8–11] HG may increase the chance of preterm birth and small for gestational age, and there is evidence suggesting adverse long term outcomes among offspring and mothers. [11–16]

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Recently there has been progress in understanding disease etiology. The placenta and appetite hormone gene GDF15 has been identified as the greatest genetic risk factor for HG. [17] The hormone activates the vomiting center of the brain, causing nausea and vomiting in animal models. [18] Higher circulating levels of GDF15 are found in pregnant patients hospitalized with HG, patients using antiemetics, patients with 2nd trimester vomiting, and those carrying a female fetus. [19–20] More studies with a clearly defined definition of HG are urgently needed to determine whether GDF15 can be used as a biomarker for HG. Currently, there are no biomarkers that can help diagnose or rule out HG. [21–22] Therefore, HG has remained a clinical diagnosis, which can only be made after other causes of nausea and vomiting have been ruled out.

There is no international consensus on the definition for HG. [23] A recent systematic review demonstrated that the definition for HG used in trials varies widely. [24] The most recent guideline on NVP and HG is the RCOG guideline which describes HG as protracted NVP with the triad of more than 5% pre pregnancy weight loss, dehydration and electrolyte imbalance. [25]

The absence of a uniform definition has led to heterogeneity in research populations on HG. This has further hampered the synthesis of the already scant high-quality evidence on effective treatment for HG, in meta-analyses. [26]

This study aimed to develop an international consensus definition for HG using robust consensus methods engaging all relevant stakeholders. This will help clinical studies achieve more uniformity in HG definition, and ultimately increasing the value of evidence to inform patient care.

Material and methods

The study was prospectively registered on the COMET initiative website (registration number 805) as part of the Definition and Core Outcomes on HG (DCOHG) study. [27] The data collection for the study was carried out between May 2016 and August 2018.

Project Steering Committee

To give guidance and feedback on the different phases of this project a Project Steering Committee was established. The Project Steering Committee consisted of three researchers (MHK, TJR, IJG), two patient representatives (CRD, NG), two obstetricians (WG, RCP), one research midwife (BYG), one general practitioner (JR) and two methodologists (JvH, PMMB).

Recruitment of stakeholders

Four stakeholder groups were identified: 1) researchers; 2) women with lived experience of HG and their families; 3) obstetric health professionals (obstetricians, gynecologists, midwives); and 4) other health professionals involved in care for women with HG (general practitioners, dieticians, nurses).

To reflect the opinions of the international community, stakeholders from countries in all global regions were invited to participate using different type of stakeholder platforms, see Table 1. Participants were asked to provide basic demographic information, for each question participants could choose from a list of options or if they felt our options did not cover their background, to use the option 'other'.

Personal data were managed according to the General Data Protection Regulation.

Table 1
Invited stakeholders.

Invited stakeholders
Speakers at the first World Colloquium on Hyperemesis Gravidarum (NoHype, Bergen, Norway 2015)
Speakers at the hyperemesis gravidarum Associations Satellite meeting of the European Board & College of Obstetrics and Gynaecology (EBCOG) conference (Glasgow, Scotland, 2014)
Speakers at the three Pregnancy Sickness Support (PSS) Conferences (UK, 2013, 2014, 2015)
All corresponding authors of studies referenced in the Cochrane systematic review on treatment of HG
All members of the core outcomes in women's health and newborn health (CROWN) initiative[1]
All members of the Cochrane Pregnancy and Childbirth Group and the Global Obstetrics Network (GONet)
Obstetricians, midwives, general practitioners, dieticians and nurses were invited through (inter-)national professional organisations among others:*The Australian College of Midwives (AUS)*The European Federation of the Associations of Dietitians (EU)*The College of Family Physicians of Canada (CA)_*Dutch General Practitioner Network (Netherlands)*The Royal Australian College of General Practitioners (AUS)*Obstetric health professionals associated with the nationwide Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (Netherlands)
Identification of patient representatives took place by approaching national and international patient organisations who used their social media:* Pregnancy Sickness Support (PSS) (UK)* Hyperemesis Education & Research foundation (HER) (USA)* Zwangerschapsmisselijkheid en Hyperemesis Gravidarum (ZEHG) (Netherlands)
Stakeholders that responded to our initial invitation were also encouraged to forward their invitation to others who might be willing to participate in developing a definition for HG

Stakeholder panel size

There is no robust method for calculating the required sample size of stakeholders in a Delphi survey. Our sample size was based on 2 studies developing a definition using a Delphi method and on 4 studies in the field of obstetrics using a Delphi method for developing a core outcome set. [28–33] Based on previous literature a drop-out rate of 15–21% could be expected. [28,34] We therefore aimed to recruit 245 stakeholders. No minimum number of participants per stakeholder group or per represented country was defined.

Identification of potential criteria

A previously published systematic review on interventions for HG was used to identify potential patient inclusion criteria used for trial entry in published and ongoing randomized clinical trials. [24] To identify additional HG definition criteria, semi-structured patient interviews and closed group sessions through patient fora were conducted and stakeholders were asked during the first Delphi round to list additional HG definition criteria (appendix A).

The Project Steering Committee discussed all potential HG criteria, duplicates were excluded and overarching domains were established through interactive discussion using the thematic clustering of a previously published systematic review. [24]

Consensus process

A 9-point Likert scale, grade 1 to 9, was used to score each criterion. Grade 1 to 3 was defined as of limited importance, grade 4 to 6 as important but not critical, and grade 7 to 9 as critical criterion to include in the HG definition. To be included in the definition, at least 70% of each stakeholder group had to score a criterion as 'critical' and fewer than 15% of stakeholders in each stakeholder group had to score the criterion of 'limited impor-

tance'). To be excluded from the definition, fewer than 70% of each stakeholder group had to score a criterion as 'critical' after round two. In case one or more, but not all stakeholder groups, scored a criterion as 'critical' in the second Delphi round, the criterion was listed as 'undecided' (Table 2). These cut-offs were prespecified and are commonly used in previous published work on the consensus process in women and newborn health research. [28,35–36]

Modified Delphi procedure

A two-round modified Delphi survey was performed followed by a consensus meeting and a consultation round. A Delphi procedure is an iterative process with anonymous consultation and with controlled feedback and quantified analysis of the responses. [37] Stakeholders received an invitation email containing a link to the web-based survey (LimeSurvey GmbH, Hamburg, Germany) for each Delphi round. [38] After accepting the invitation a unique identification code was generated, this identifier ensured future responses to be both linked and anonymous. Weekly reminders were sent to non-responders and after four weeks the survey was closed. Those who had not responded or had stated they were not willing to participate further were not invited to subsequent rounds.

In each round, criteria were presented per domain accompanied by a brief explanation for each criterion. Stakeholders were able to indicate if they felt they were unable to judge a criterion. Prior to rescoring the criteria, scores from round one were presented per criterion in percentages per stakeholder group. On the criteria, for which consensus to include had been reached after the first Delphi round, participants were asked in round two to agree or disagree with inclusion of these criteria in the definition. If consensus to exclude had been reached, or if no consensus was reached in round one, stakeholders were asked to re-score these criteria using a 3-point Likert scale; limited importance, important but not critical and critical.

Consensus development meeting

After the second Delphi round, a consensus development meeting was held during the second International Colloquium on HG (ICHG) conference, in Windsor in October 2017, using a modified nominal group technique. [39] Invitations to participate were sent to all participants of the second Delphi round and the ICHG conference. Results of prior rounds were presented during this face-to-face meeting during a plenary introduction, after which small groups were formed to discuss criteria listed as undecided after the second Delphi round. Stakeholders voted anonymously, through a mobile phone based electronic voting system, to include or exclude criteria listed as undecided after the second Delphi round, after which a provisional definition was formulated.

Table 2
Cut off values.

Limited importance	Grade 1 to 3
Important but not critical	Grade 4 to 6
Critical	Grade 7 to 9
Include	At least 70% of each stakeholder group had to score a criterion as 'critical' and fewer than 15% of stakeholders in each stakeholder group had to score the criterion of 'limited importance'
Exclude	Fewer than 70% of each stakeholder group had to score a criterion as 'critical' after round two
Undecided	In case at least 70% of one or more, but not all stakeholder groups, scored a criterion as 'critical'

Consultation round

A web-based consultation round was held among participants who completed the second round, the purpose was to verify whether participants of the second Delphi round agreed with the provisional definition resulting from the consensus development meeting, which was named as a limitation by another Delphi procedure. [28] The provisional definition was presented and stakeholders were asked to agree or disagree with this definition. In case more than 80% of stakeholders agreed with the provisional definition, we considered the decisions made by stakeholders of the consensus development meeting supported by the participants of the second Delphi round. In case less than 80% agreed with the provisional definition a new Delphi round would take place. In case of disagreement, participants were encouraged to comment in a free text response. These comments were discussed in the Project Steering Committee meeting before a final definition on HG was formulated. This consultation round complements the existing COMET guidelines. [40]

Theory

HG is a clinical diagnosis, which can only be made after other causes of nausea and vomiting have been ruled out. [23] The fact that there is no international consensus on the definition for HG has resulted in heterogeneity in research populations and hampers aggregation of evidence, with only a minority of existing papers using overlapping criteria for trial inclusion. [26]

Results

Identification of criteria

The findings from the systematic review describing variation in HG definition and outcome reporting in randomized clinical trials have been previously published. [24] Briefly, the systematic review yielded thirty-one published trials, reporting data from 2511 women, and three ongoing trials, with a planned total sample size of 360 participants. 15 criteria were identified through the systematic review (appendix B).

Through semi-structured interviews and closed group discussions on patient fora, five additional criteria were added by seven women with lived experience of HG. One criterion was added by the Project Steering Committee. Therefore, 21 criteria were identified, clustered in five overarching domains by the Project Steering Committee, before they entered the Delphi process (Fig. 1).

Modified Delphi survey

Upon the initial invitation, 277 potential participants expressed their willingness to participate in the survey; they received an invitation for round 1 (appendix C). 178 (64%) responded, with respondents from 22 different countries (appendix D and E). Characteristics of participants are shown in Table 3. In the first survey round, consensus on inclusion was reached on four criteria (appendix F). Stakeholders suggested 20 additional criteria in round 1 of the survey. The Project Steering Committee discussed all suggested criteria but decided none of the suggestions were suitable for uptake in the list of definition criteria for round 2. The majority of suggested criteria were in fact examples of criteria that had

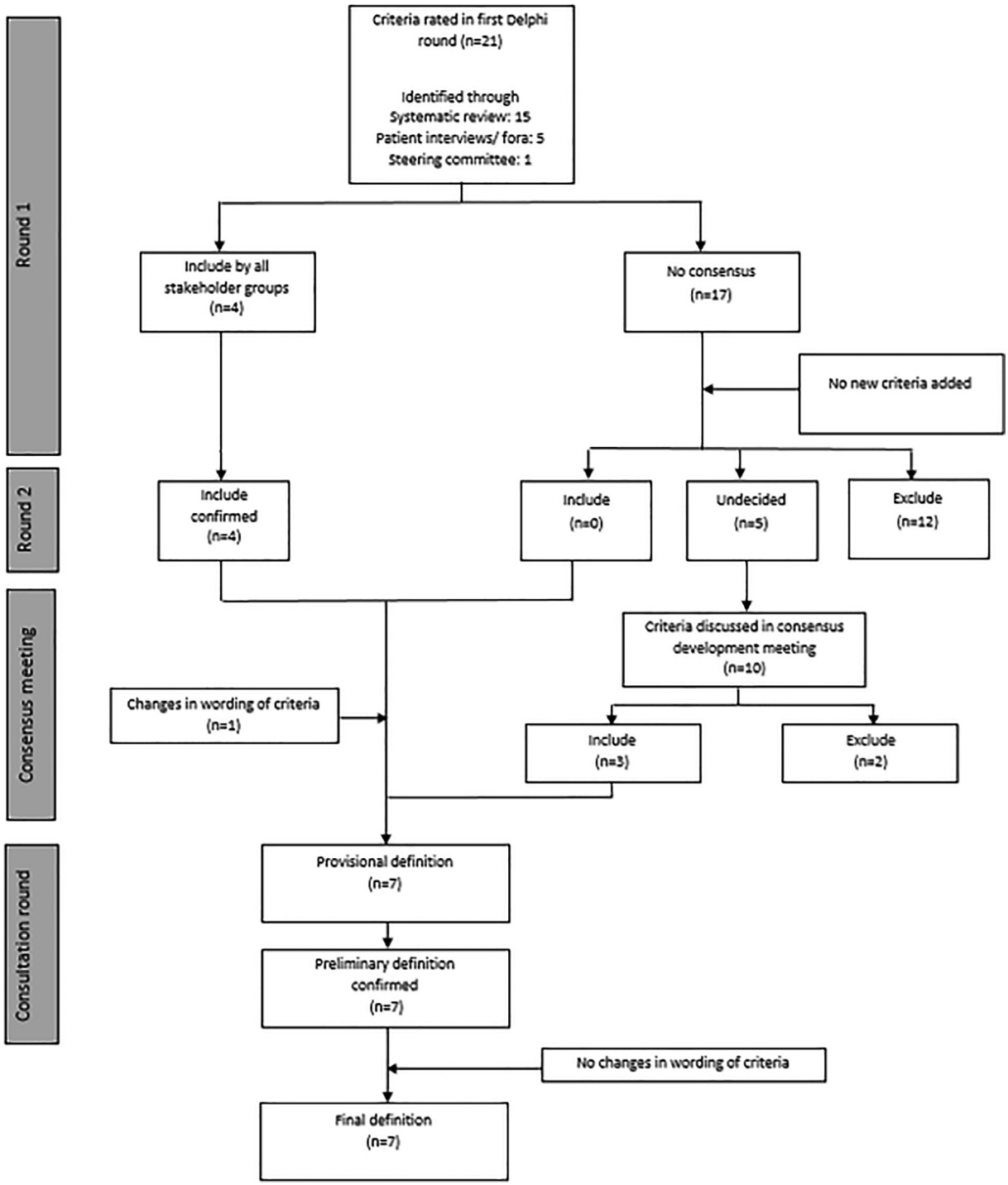

Fig. 1. Flowchart of identification and selection of criteria.

already been included in round one or concerned risk factors for HG rather than new definition criteria (appendix G). Five respondents expressed they were not willing to participate further, without stating their reason.

The second round of the Delphi survey was completed by 125 (72%) of 173 invited stakeholders. Consensus on inclusion was confirmed on all four criteria, which reached 'consensus in' in round 1 (appendix H). 'Consensus out' was reached on twelve criteria. On the five remaining criteria no consensus was reached.

Consensus development meeting

Twenty stakeholders attended the consensus development meeting, representing all stakeholder groups. The five criteria that were undecided after the second Delphi round were discussed and individual voting on the in- or exclusion of these criteria was performed. Three additional criteria were included in the definition and the phrasing of one criteria was changed after discussion (appendix I).

Table 3
Number and Baseline Characteristics of Participants in the Delphi survey and Consensus Meeting for HG definition.

	Round 1	Round 2	Consensus Meeting	Consultation round
	n = 178 (%)	n = 125 (%)	n = 20 (%)	n = 96 (%)
Stakeholder group				
Researchers	21 (12)	14(11)	9 (45)	11 (11)
Women or families with lived experience	56 (31)	35(28)	5 (25)	27 (28)
Obstetric health professionals	62 (35)	50(40)	3 (15)	44 (46)
Other health care professionals	39 (22)	26(21)	3 (15)	14 (15)
2nd stakeholder group	43 (24)	34 (27)	8 (40)	27 (28)
Researchers	16 (9)	12 (10)	3 (15)	10 (10)
Women or families with lived experience	13 (7)	10 (8)	2 (10)	7 (7)
Obstetric health professionals	9 (5)	7 (6)	3 (15)	6 (6)
Other health care professionals	5 (3)	5 (4)	0 (0)	4 (4)
Health care professionals involved in research	97 (54)	72 (58)	15 (71)	59 (61)
Members of CROWN	7 (4)	4 (3)	0 (0)	4 (4)
Part of Cochrane Collaboration	15 (8)	12 (10)	0 (0)	9 (9)
Involved in (inter)national guideline development	45 (25)	35 (28)	10 (48)	32 (33)
Role in allocation of healthcare budgets	10 (6)	7 (6)	1 (5)	6 (6)
Sex				
Male	32 (18)	22 (18)	2 (10)	17 (18)
Female	146 (82)	103 (82)	18 (90)	79 (82)
Personal experience with HG	77 (43)	49 (39)	10 (48)	36 (38)
Patients who participated in a study	14 (8)	10 (8)	3 (14)	8 (8)
Education level				
High	158 (89)	115 (92)	15 (75)	87 (91)
Middle	16 (9)	8 (6)	2 (10)	7 (7)
Low	4 (2)	2 (2)	1 (5)	2 (2)
Missing	0 (0)	0 (0)	2 (10)	0 (0)
Ethnic background				
Asian	8 (4)	5 (4)	2 (10)	5 (5)
Black	2 (1)	2 (2)	0 (0)	1 (1)
Mixed	2 (1)	2 (2)	0 (0)	2 (2)
White	164 (92)	114 (91)	15 (75)	88 (92)
Other	1 (1)	1 (1)	1 (5)	0 (0)
Missing	1 (1)	1 (1)	2 (10)	0 (0)
No. Of countries represented*	22	20	6	18

Consultation round

Of the 125 invited stakeholders that completed round 2, 96 (77%) responded in the consultation round, of whom 92% agreed with the preliminary definition as presented (Table 4). Those who did not agree with the preliminary definition were asked to provide arguments for their disagreement, these were discussed in the Project Steering Committee (appendix J).

Final definition

Each of the following criteria are required for the definition for HG:

- Symptoms starts in early pregnancy, before a gestational age of 16 weeks. More than 70% of stakeholders agreed symptoms had to start before a gestational age of 16 weeks (appendix K)
- Characterized by severe nausea and/or vomiting
- Inability to eat and/or drink normally
- Strongly limits daily activities

Signs of dehydration were deemed contributory but not mandatory for the definition for HG (Appendix L).

Discussion

Principal findings

Through an international consensus process including all relevant stakeholders we present the first international definition for HG. The Windsor definition for HG can be used to decide on eligibility for patients in studies and as a guideline for clinicians diagnosing HG.

Strengths and limitations

Our study has several strengths. First, an important strength of this study lies in its design: a modified Delphi method, combined with a face-to-face consensus meeting and a consultation round. Our methods enabled many geographically distant participants to participate with an equal voice in the consensus process. Face-to-face consensus meetings are known to potentially contribute to underrepresentation of certain stakeholder groups, [28,41] which we tackled by introducing a consultation round. Second, people with lived experience of HG were extensively involved in forming the HG definition which is unique and should be considered another strength of our study [42,43].

Some limitations should be noted. The attrition rate could present a limitation. Our sample size was lower and our drop-out rate was higher than anticipated (36, 28 and 23% for round 1, round 2 and the consultation round respectively) but comparable to other Delphi studies. [36,44] Compared to panel sizes described in other studies on disease definition using the Delphi technique published in the last five years, our study's panel size of 96 participants in the final round was among the largest of its kind, although this fully cannot rule out possible lack of robustness of findings if an even larger panel size had been employed. [29,45–48] Furthermore, there were no differences between those participants that completed all rounds, and those who dropped out, leading us to believe that attrition bias was not a major issue (appendix M). Second, the majority of participants had a high level of education (88%), 92% had a white background, and low- and middle-income countries

Table 4
Presented definition in the consultation round, results of the consultation round and the final definition.

Definition criteria					
Nausea					
Vomiting					
Severe nausea and/or vomiting					
Signs of dehydration					
Inability to drink and/or eat normally					
Strongly affects daily living activities					
Gestational age at beginning of symptoms					
HG definition					
Who?				Pregnant woman Other causes of nausea and vomiting have been excluded	
When?				Beginning of symptoms in early pregnancy	
Symptoms?				Nausea and vomiting. At least one of these should be severe Inability to eat and/or drink normally Strong effect on daily living activities Signs of dehydration contribute to the diagnosis	
Results consultation round:					
		Stakeholder groups			
Agree/disagree with the presented definition	Total	Researchers	Patients and carers	Obstetric health professionals	Other health professionals
	(n = 96)	(n = 11)	(n = 27)	(n = 44)	(n = 14)
Agree	92%	91%	92%	89%	100%
Disagree	7%	0%	8%	11%	0%
Unable to score	1%	9%	0%	0%	0%
Final definition HG:					
Mandatory					**Contributory**
Nausea and vomiting, one of these has to be severe Inability to drink and/or eat normally Strongly affects daily living activities Beginning of symptoms in early pregnancy					Signs of dehydration

were poorly represented, each of which may have reduced the external validity although it is difficult to hypothesise how this could have affected our conclusions.

Interpretation

Developing a definition for a disease has several consequences. In our case there have been concerns, among health care providers and patients alike, that the introduction of an internationally recognized definition for HG could exert harmful side effects on patient care. By delineating HG from non-HG, the definition may lead to a group of pregnant women with some, but not all, hallmarks of HG, who do not meet the criteria for HG and could therefore be denied treatment. However, this is already the case for HG at present: many clinicians consider ketonuria an essential defining attribute to HG, while in fact the evidence underpinning its utility is weak. [23,49–50] The use of ketonuria in delineating HG from non-HG has led to groups of patients being denied HG care, when they would have met the current Windsor definition. [49] Other definitions used in obstetrics, including those for preeclampsia [51] and gestational diabetes [52], have in common with the current Windsor HG definition, that the underlying conditions display signs and symptoms across a spectrum between physiology and disease states. This can frustrate health care professionals who wish to avoid missing a diagnosis when applying stricter diagnostic criteria. In conclusion, the Windsor definition is not intended to be used to include or exclude patients from treatment or, for example, for health insurers to reimburse. As a consequence, the current Windsor definition for HG is broad and therefore may bias future studies toward a less severely affected study population and dilute conclusions. Therefore, identification of women with HG with factors indicating a poor prognosis, e.g. prolonged illness or more severe weight loss, would be of great value. Unfortunately, such factors are yet unknown, but could be uncovered in future research, in which case updating the HG definition should be performed, by adding categories to the definition for severity based on prognosis.

The Windsor definition for HG consists of subjective criteria. Such subjective symptoms could be further quantified using validated scoring systems, e.g. Pregnancy-Unique Quantification of Emesis (PUQE) scoring system [53], or MOS-36 item short form health survey to quantify impact on daily living. [54] However, these questionnaires are likely to present a further burden on clinicians, as they are not part of routine clinical history, and are therefore unlikely to provide benefit in implementation of the Windsor definition. Furthermore, the Windsor definition may prove difficult to ascertain in retrospective or registry studies, as it relies on patient reported measures, which are usually not collected in registries. Such studies are likely to maintain their reliance on ICD-codes, hospital admission, prescription and birth registry data. We recommend the criteria in de Windsor definition be ascertained using routine clinical history and primarily in prospective cohorts and trials.

Conclusions

We propose to define HG as a condition that starts early in pregnancy, before a gestational age of 16 weeks, and is characterized by severe nausea and/or vomiting, inability to eat and/or drink normally and strongly limits daily activities. This Windsor definition for HG can help to standardise inclusion in HG research. When more insight is gained on predicting disease prognosis, this definition needs to be reviewed.

Contribution of authorship

RCP and IJG conceived the idea. The protocol was developed by IJG with help from Jv'tH and MHK. Input for the development of the protocol came from BYG, CD, JMND, JR, NG, RCP, TJR and WG. IJG, LAWJ and MHK executed the project. Expert input at various stages

of the project came from BYG, CD, JR, Jv'tH, NG, PMMB, RCP, TJR and WG. Data were analysed by LAWJ with input from IJG and RCP. LAWJ drafted the manuscript with input from all co-authors.

Details of ethics approval

The ethics board of the Academic Medical Center Amsterdam reviewed the study protocol and provided a waiver for formal ethical approval (dated 11th May 2016, reference number E2-172).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2021.09.004.

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Vitae Larissa Jansen: Larissa Jansen is a 30 year old resident in obstetrics and gynecology in the Netherlands and a pHd student on hyperemesis gravidarum. Together with a team, including Dr. Painter, Dr. Roseboom and Dr. Grooten she already developed a core outcome set for hyperemesis gravidarum. Currently she is also working on systematic reviews on perinatal and long term health outcomes of offspring after pregnancies complicated by hyperemesis gravidarum.