Prioritising patients in hyperemesis gravidarum research

Dean, C.R.

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THE CHANCE OF RECURRENCE OF HYPEREMESIS GRAVIDARUM: A SYSTEMATIC REVIEW

C.R. Dean, C.M. Bruin, M.E. O'Hara, T.J. Roseboom, M.M. Leeflang, R. Spijker, R.C. Painter

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ABSTRACT

Around 1 % of pregnancies develop Hyperemesis Gravidarum (HG), causing high physical and psychological morbidity. Reports on HG recurrence rate in subsequent pregnancies vary widely. An accurate rate of recurrence is needed for informed reproductive decision making. Our objective is to systematically review and aggregate reported rates for HG subsequent to index pregnancies affected by HG. We searched databases from inception as per the protocol registered on PROSPERO. No language restrictions were applied. Inclusion was not restricted based on how HG was defined; reports of severe NVP were included where authors defined the condition as HG. We included descriptive epidemiological, case control and cohort study designs. Eligibility screening was performed in duplo. We extracted data on populations, study methods and outcomes of significance. A panel of patients reviewed the results and provided discussion and feedback. Quality was assessed with the JBI (2017) critical appraisal tool independently by two reviewers. We performed the searches on 1st November 2019. Our search yielded 4454 unique studies, of which five (n = 40,350 HG cases) matched eligibility criteria; One longitudinal and four population-based cohort studies from five countries. Follow-up ranged from 2 to 31 years. Definition of HG and data collection methods in all the studies created heterogeneity. Quality was low; studies lacked valid and reliable exposure, and/or follow-up was insufficient. Meta-analysis was not possible due to clinical and statistical heterogeneity. This systematic review found five heterogeneous studies reporting recurrence rates from 15 to 81%. Defining HG as hospital cases may have introduced detection bias and contribute to clinical heterogeneity. A prospective longitudinal cohort study using an internationally agreed definition of HG and outcomes meaningful to patients is required to establish the true recurrence rate of HG.

INTRODUCTION

Hyperemesis gravidarum (HG) is a complication of pregnancy appearing at the extreme end of the pregnancy sickness spectrum. HG affects 1 % of pregnancies. Unlike mild-moderate nausea and vomiting of pregnancy, which is a common, unpleasant, symptom of early pregnancy, HG can cause significant physical and psychological morbidity[1–3] and have a profound effect on quality of life.[4]

The aetiology of HG is largely unknown and as yet there is no biomarker which can diagnose HG or predict the occurrence or severity of the disease in an individual.[5] A genetic aetiology would suggest that people affected would have a high chance of HG recurring in all pregnancies and recently a strong association between HG and genetic variants in two proteins was identified; growth and differentiation factor 15 protein (GDF15) and insulin like growth factor binding protein 7 (IGFBP7).[6] These findings support previous reports identifying familial hereditability causing a threefold increase in HG in people whose mother or sister experienced HG compared to those whose did not.[7]

HG has been reported to recur in subsequent pregnancies following an affected one.[8] Appreciating the risk of recurrence enables families to plan for a prolonged period of maternal illness and evidence suggests that preventative measures such as early treatment may reduce the overall severity of the condition and holistic, practical planning of family life around the illness may reduce the biopsychosocial impacts.[9,10] Additionally, there are reports that people

have terminated otherwise wanted pregnancies believing that they were unlikely to experience HG recurrence in a future pregnancy[11] and conversely, people who curtail future pregnancies believing there is no way to avoid HG in subsequent pregnancies.[12] Such significant life decisions warrant accurate information as a basis. Knowledge enabling advanced planning may help people feel more empowered which in turn may reduce the overall trauma and quality of life consequences of the condition.[10]

The objective of this review is to establish the risk of recurrence of HG in a pregnancy subsequent to an affected one.

METHODS

The review protocol was published in 2017 and followed the Joanna Briggs Institute (JBI) methodology for systematic reviews of descriptive epidemiological studies [13] [Available at: https:// www.ncbi.nlm.nih.gov/pubmed/29135749]. No funding was received for this systematic review.

Patient involvement

Members of the patient advocacy group Pregnancy Sickness Support were first consulted to ensure the review question was considered meaningful and worthwhile, and then throughout the process for continued input. Additionally, two authors of the protocol and review (CD and MOH) are patient representatives for the condition.

Defining HG in the index pregnancy

Without an internationally recognised definition of HG, we included studies in which the authors describe nausea and vomiting in pregnancy as HG, regardless of how that diagnosis was defined or the care setting in which treatment was received. Studies in which people experienced nausea and vomiting during pregnancy, but were not diagnosed with HG were excluded. Subsequent pregnancies were not required to be consecutive and any pregnancy subsequent to the index one was considered.

Eligibility

Studies did not require non-HG pregnancy controls for the index pregnancy. Data on subsequent pregnancies must have been prospective; retrospective data on previous pregnancies were excluded. Inclusion was not restricted by geography, age of study or language.

Search straegy

The following databases were searched from inception using the search strategy outlined in Table 1: Embase, British Nursing Index, CINAHL, MEDLINE, AMED, PsycARTICLES, PsychINFO, Global Health, Cochrane Pregnancy and Childbirth, SCOPUS. In addition to Google, the search for unpublished studies included: Pregnancy Sickness Support website, Hyperemesis Education and Research Foundation website, NHS sites, British Library Explore (for British Theses) and

Google scholar, Grey Literature Report and Open Grey for international Theses. Twitter was used to request knowledge of any relevant grey literature among active researchers and health-care professionals. Key papers were hand searched for backwards citations.

Table 1 SEARCH STRATEGY - OVID MEDLINE(R) IN-PROCESS & OTHER NON-INDEXED CITATIONS AND OVID MEDLINE(R) (1946 TO PRESENT)

Search	Terms
1	Pregnancy/ or pregnancy.mp. or pregnan*.mp. or Gestation*.mp. or Antenatal.mp. or Gravid*.mp.
2	Hyperemesis Gravidarum.mp. or Hyperemesis Gravidarum/ or Nausea/ or Nausea.mp. or Vomiting/ or Vomit*.mp. or Sickness.mp.
3	(Second or Subsequent or Successive or Recur* or Repeat or Next).mp.
4	1 and 2 and 3

Eligibility screening

Titles and abstracts were screened for eligibility by two independent reviewers (CD and CB) using Rayyan software[14] and those fitting the inclusion criteria were retrieved in full text for further eligibility screening by the two independent reviewers. Where possible, foreign language papers were translated with Google translate and then checked for accuracy by bilingual colleagues. Where there was doubt regarding inclusion a third reviewer (RP) was consulted. Data extraction of included studies utilized the standardized data extraction tool from JBI. Where possible authors were contacted for full texts or further information from published abstracts where full papers were not available.

Quality assessment

Methodological quality was assessed using standardized critical appraisal instruments from the JBI System for the Unified Management, Assessment and Review of Information, as available through the JBI (2017) critical appraisal tool downloads.[15] The tool uses 11 questions assessing: similarity of groups; validity, reliability and equality of exposure measurement; confounding factors and how they were dealt with; validity and reliability of outcome measurement; follow up duration and completeness; appropriate statistical analysis. We did not exclude papers based on low methodological scoring.

Data extraction

A data extraction form was generated from the JBI Reviewers Manual. Data extraction was completed by a single reviewer (CD). Authors were approached directly for additional details for data extraction and where possible these were provided.

Statistical analyses

As per the protocol we planned to conduct meta-analysis and assess heterogeneity using Chi-square and I^2. In case of lack of studies or if heterogeneity prohibited meta-analysis, we had predefined that results would be presented narratively.

RESULTS

Flow of in- and exclusion

We performed the search on 01-11-2019. Fig. 1 shows the Prisma flow chart of the selection process. The database searches yielded 8645 hits. Two additional references were obtained from other sources; one from hand searching key reference lists[16] and one from a public call for publications.[17] After removal of duplicates, we were left with n = 4454 unique papers. Eligibility screening of titles and abstract left n = 31 for full text assessment (Fig. 2).

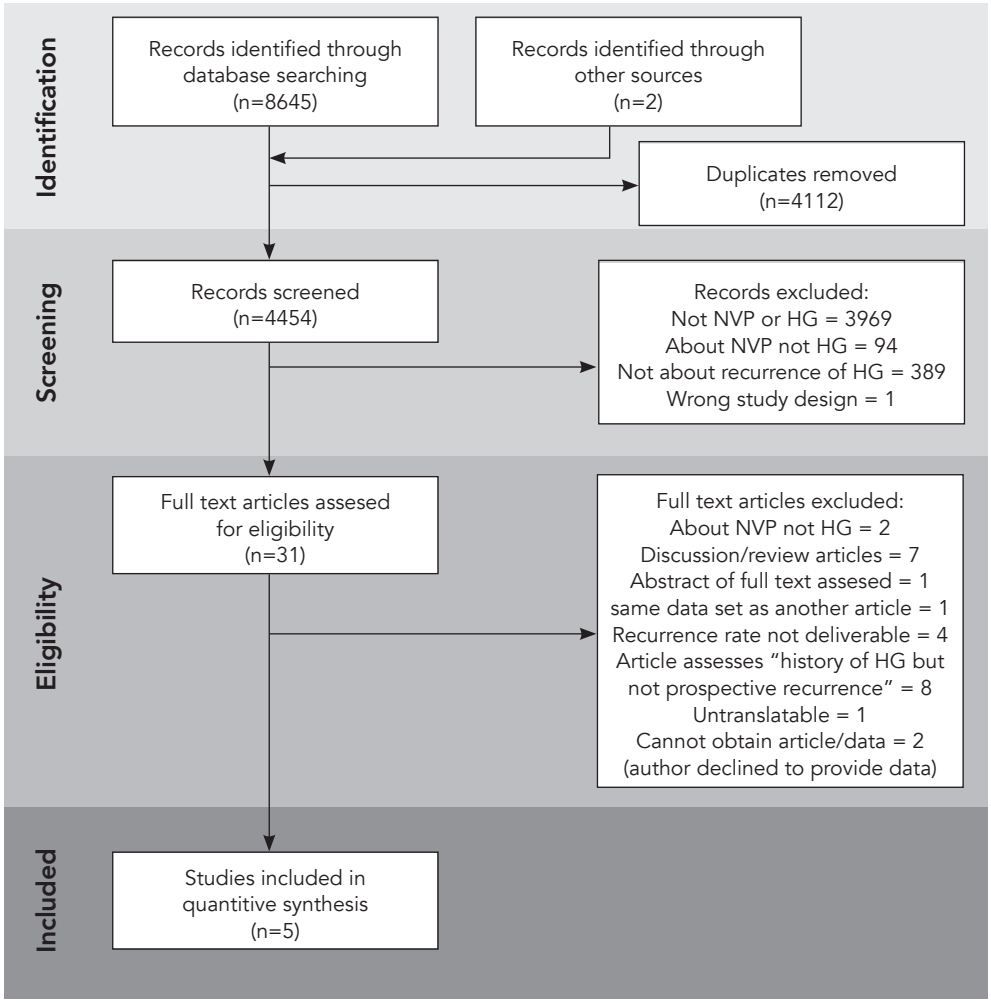

Fig. 1. PRISMA flow diagram of selection process.

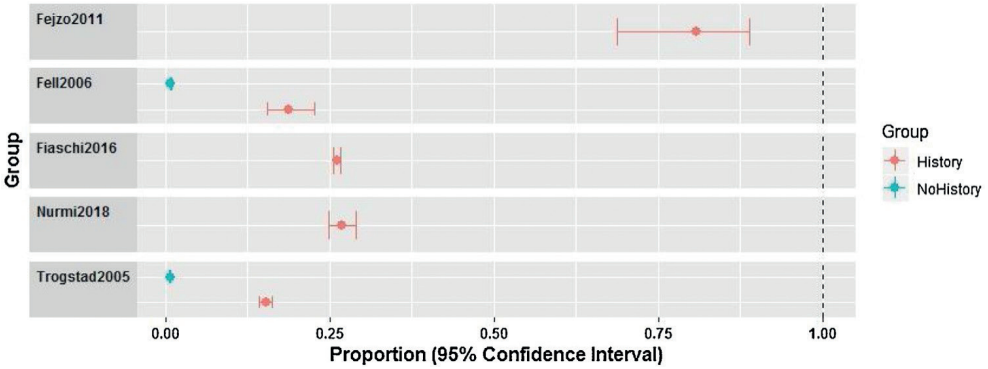

Fig. 2. Forest plot for recurrence rates of hyperemesis gravidarum.

Reasons for exclusion

Two of the 31 articles were translated[18,19] but despite our efforts we were not able to obtain a valid translation of one paper.[20]

Three conference abstracts were identified as for inclusion and the authors contacted for data or full manuscripts.[21–23] One author, of two abstracts, declined to provide further information[22,23] and the other was excluded following provision of further information.[21]

We excluded 12 studies because they collected retrospective data rather than supplying prospective information to calculate a recurrence rate.[19–21,24–32] One reference was an abstract for an already excluded study.[33] One study contained overlapping data with another study from the same authors.[34]

Study characteristics

Of the five included studies (see Table 2), four were large population-based database cohort studies in which three had been derived from documented hospital admissions[16,35,36] and one from a standardised form completed within a week of the birth by the attending midwife or doctor documenting maternal characteristics, pregnancy complications and birth outcomes.[37] The form does not specifically ask about pregnancy sickness or HG and so it is recorded verbatim in section B. The remaining study,[12] was a cohort of people who had self-selected to take part in an online survey of the condition between 2003–2006 and were followed up in 2008 via email to see if they had a subsequent pregnancy.

The chance of recurrence varies from 15.2 % in Trogstad, Stoltenberg[37] to 80.7 % in Fejzo.[12] Confidence intervals (CIs) for Fiaschi, Nelson-Piercy[35] and Nurmi[36] were not reported and so the lead authors were contacted to request further information. Fiaschi was able to provide confidence intervals but not an odds ratio (OR) as the data was no longer available. Nurmi was unable to provide an OR or CIs.

Table 2: Included studies characteristics

Study reference	Trogstad *et al* 2005[37]	Fell *et al* 2006[16]	Fejzo *et al* 2011[12]	Fiaschi *et al* 2016[35]	Fiaschi *et al* 2016[35]
Study design	Population-based database cohort study	Population-based database cohort study	Cohort study using online survey	Population-based database cohort study	Population-based database cohort study
Country	Norway	Canada	United States	United Kingdom	Finland
Data collection period	1967-1998 (31 yrs)	1988-2002 (14yrs)	2008 follow up from 2003-2006 (2-5yrs)	1997-2012 (15yrs)	2004-2011 (7yrs)
Participants	All documented singleton pregnancies > 16 weeks with a 1st and 2nd pregnancy registered	All documented pregnancies >20 weeks with delivery of infant >500g.	Self-selected people who had completed an initial survey 2-5 years previously followed up for subsequent pregnancy	All documented hospital deliveries in UK during study period	All pregnancies ending in delivery with an HG discharge diagnosis within the first 20 weeks of pregnancy
n	HG cases: 4796 Controls: 542442	HG cases: 447 Controls Admission to hospital prior to 24 weeks gestation for HG: 83910	HG cases: 57	HG cases: 33214	HG cases: 1836
HG definition	HG described as pregnancy nausea and vomitng associated with ketosis and >5% weight loss. Also via ICD-8 as 638.0, 638.9 or 784.1.	Admission to hospital prior to 24 weeks gestation for HG	Self-reported symptoms severe enough to cause weight loss and require prescription medication or IV fluids/total parental nutrition/ NG Tube feeding or hospitalisation	Hospital admission coded with ICD-10 for primary diagnosis of HG.	Discharge diagnosis of HG from either hospital or primary care with ICD-10 codes O21, O21.0, O21.1 or O21.9
Data collection	Reported on standardised form completed by midwife/physician within one week of delivery. Form does not specifically ask about HG so would be recorded as verbatim description under "other" and subsequently coded according to ICD-8 as above	The Nova Scotia Atlee Perinatal Database data which records all antepartum admissions during pregnancy. Data abstracted by trained coders.	Self-reported surveys	Hospital Episodes Statistics data.	Medical births register (completed following delivery) and Hospital discharge register

DISCUSSION

Main findings

In this systematic review of five studies reporting 40,350 pregnancies from five countries occurring between 1967 and 2012, we found reported recurrence rate varied from 15% to 81%. We were unable to perform a meta-analysis and provide a summary recurrence rate due to heterogeneity (Fig 2).

Interpretation

The included studies showed significant clinical and statistical heterogeneity. Studies used diverse definitions for HG, which was the major contributor to heterogeneity. Fejzo *et al*.[12] found the highest estimate of recurrence of HG at 81%. The study is a small cohort of self-selected participants followed up from a previous online survey on a charity website in which people reported their symptoms, treatments and outcomes from HG pregnancies. Only 33% of the original cohort responded to the follow up request. HG was defined as symptoms causing significant weight loss and debility, typically requiring medication and/or IV fluids for treatment. The remaining four studies used birth registry data[37] hospital discharge data (ICD-10 codes)[16,35] or a combination of both.[36] Registries and hospital data appear useful for pregnancy research, offering access to large population-based cohorts covering large time spans making them robust and reducing selection bias. However, it is vital that systematic validation of disease specific data is undertaken for credibility of such research.[38] The Medical Birth Registry Data of Norway (MBRN) generates ICD codes as used by Trogstad *et al*.,[37] and has been validated for various birth outcomes such as early pre-term birth and birthweight, but not for medical conditions during pregnancy including hypertension.[39] While attempts have been made to validate the MBRN and ICD codes for HG, such efforts have been hampered by the lack of definition for the condition. While the Norwegian data appears to be valid for milder pregnancy sickness, they were not valid for severe pregnancy sickness or HG and nor were the ICD codes.[40] Validation studies of similar Nordic medical birth registries found that while common procedures, interventions and diagnoses are valid within the registries, occurrence of rarer complications and interventions of pregnancy could not be studied effectively with these registers.[38] Furthermore, MBRN data was collected only on pregnancies progressing past 16 weeks gestation until 1998 and 12 weeks gestation after 1998 which, in the context of HG, would potentially miss cases ending in termination and miscarriage.[40] Fiaschi[35] utilised ICD-10 codes which are hampered by similar challenges around definition and validity. Validation studies addressing use of ICD-10 codes for uterine rupture and second trimester miscarriage found poor positive predictive values and low sensitivity and specificity resulting from a combination of over/under reporting of conditions, multiple codes for the same condition and an inability to secure the accuracy of reported data.[41,42] So, while hospital admission data has been validated for use in birth delivery research and general nausea and vomiting of pregnancy research it cannot be assumed to be valid for use in other early pregnancy complications and specifically HG. In the context of this review the problems with the definitions, data collection methods and ICD codes diminish the validity and internal reliability of these studies and we are unable to use them to generate a reliable rate to predict recurrence of HG.

Hospital admission as an objective definition for recurrence reporting can be further

criticised due to well reported barriers to accessing secondary care specific to HG. In a 2015 charity report on termination for HG many respondents were denied any treatment at primary care level and were never admitted to hospital prior to the termination of pregnancy.[43] Conversely, people who receive high quality treatment in the community may not require admission if symptoms are managed sufficiently. In a recent UK study Gadsby, Rawson[44] found significant variation in treatment of nausea and vomiting of pregnancy between primary care practices and very few secondary care referrals despite multiple presentations to general practice. Members of our patient involvement panel expressed a strong view that hospital admission was an inadequate diagnostic criterion, particularly for second pregnancies where childcare issues meant people would have little choice but to tolerate more severe symptoms without admission to hospital.

External validity

The four large cohort studies[16,35–37] only included cases where the pregnancy continued to either 16 weeks,[37 20] weeks gestation,[16] or delivery,[35,36] and therefore excluded pregnancies ending in earlier miscarriage or termination. The rate of termination for HG has been cited as between 10–25 % which could account for a reduction in the external validity of the cohort studies in which these cases would be excluded.[11,43] The report by Dean and Murphy [43] found the inability to care for other children was given as a key factor in the decision to terminate for over half the participants suggesting that subsequent pregnancies may have a higher termination rate then first pregnancies. Additionally, Fejzo *et al*.[12] found 37 of the 100 respondents to their follow up request said they were not willing to get pregnant again due to the risk of HG. Neither population would be represented by the large data sets used in these studies. However, Fiaschi *et al*. 2016[35] found no difference in the rate of subsequent pregnancy between people with a history of HG and those without.

In 2017 O'Hara[17] explored 172 people's experience of HG and, despite similar levels of symptom severity between pregnancies, she found that hospital admissions were reduced in subsequent pregnancies for a variety of factors. Increased support from healthcare professionals, family and friends in the later pregnancy helped them to cope without hospital admission but also the demands of childcare and a desire to not be separated from their other children meant people were reluctant to be admitted. Additionally, second- and third-line medications, such as ondansetron and steroids, were more commonly used in subsequent pregnancies and so although severe symptoms were still experienced, they were better controlled to avoid the need for admission. Based on the diagnostic criteria which lead to ICD code generation for HG in subsequent pregnancies within the included population-based cohort studies it is likely that recurrence is underestimated due to the lack of early pregnancy loss inclusion and reduced admissions identified by O'Hara.

Strengths and limitations

Among the strengths of this study, are a published protocol, the broad scope, and complete patient involvement throughout the review from inception of the question to interpretation of the finding. A significant limitation of the study is the lack of studies with suitable, homogeneous definitions of HG and data collection methods which decreased external validity through exclusion of potentially important cases.

Conclusion

While this review cannot provide a definitive rate for people to base important reproductive decisions on, a history of HG remains a substantial risk factor and healthcare professionals can advise people that the risk of recurrence is high enough to warrant pre- pregnancy planning.

A large prospective cohort study for HG is needed to follow people through their reproductive lives to establish the nature and course of the condition and the rate of recurrence in subsequent pregnancies. However, recruitment for such a study would need careful consideration and would be significantly aided by an internationally agreed definition for the condition so as not to rely on arbitrary criteria such as hospital admission.[45]

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