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Recurrence rates of hyperemesis gravidarum in pregnancy: a systematic review protocol

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The recurrence rate of hyperemesis gravidarum from one affected pregnancy to the next: a systematic review protocol

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Review question/objective

The quantitative objective is to identify the recurrence rate of Hyperemesis Gravidarum (HG) in pregnancies subsequent to one affected by HG

Background

Definition of Hyperemesis Gravidarum

Nausea and vomiting is an unpleasant yet common symptom in early pregnancy.[1] For most women it does not cause significant morbidity, symptoms can be managed with self-help techniques and are self-limiting. However, nausea and vomiting of pregnancy (NVP) appears on a spectrum of severity and at the severe end women may be diagnosed with the serious complication of pregnancy called Hyperemesis Gravidarum (HG).[2] Diagnosis of NVP and HG requires excluding other potential causes of severe sickness both pregnancy related and non-pregnancy related.[3] Although there is currently no international consensus on the definition of HG, there are commonly used diagnostic criteria. The Royal College of Obstetricians and Gynecologists (RCOG) published the first national guideline for NVP and HG in 2016 stating that HG should be diagnosed when NVP symptoms are protracted and include weight loss greater than 5%, dehydration and electrolyte imbalance.[4] However, other criteria have also

been used such as the patient requiring hospital admission or the presence of ketonuria.[5] Both criteria have been criticized and the latter has recently been disputed as a systematic review found no association between ketonuria and HG severity.[6]

Epidemiology and complications of HG

Unlike NVP, which affects up to 80% of pregnant women, HG only affects around 1-1.5% of women. Additionally, for around 30% of women, NVP symptoms will be severe enough to impact normal life, require time off work and reduce food and fluid intake, yet not warrant the diagnosis of HG.[7] The biopsychosocial impacts of both NVP and HG have been well documented in the literature.[8-11] However, HG carries additional risks and potential complications for both mother and fetus including Wernicke's encephalopathy, and low birth weight and premature labour.[12,13] Hyperemesis gravidarum is also associated with perinatal death and accounts for significant levels of pregnancy loss through therapeutic termination.[14,15] Treating HG can be challenging and costly. The single most frequent reason for hospital admission in the first half of pregnancy is HG, which is associated with significant health care costs, and lacks an effective treatment supported by high quality evidence.[16,17]

Etiology and recurrence rate

The etiology of HG in unclear, although it is likely to be multifactorial and almost certainly contains a genetic element.[18,19] It is well documented that daughters and siblings of affected women have a 30% risk of experiencing HG compared to the normal population,[19] and some pilot studies have identified possible target genes involved in HG heritability.[18] Unlike "normal" pregnancy sickness many women report experiencing HG in multiple pregnancies and it has been found to limit family size as a result, although there is conflicting evidence on this topic.[20,21] The risk of recurrence in subsequent pregnancies is currently reported as being anywhere from 15% to around 80%.[20-23]

Relevance of evidence on recurrence rates of HG

Anecdotal reports, via the Pregnancy Sickness Support (PSS) charity helpline for the condition, suggest women are being told by their healthcare provider (HCP) that "Every pregnancy is different" and their risk of having HG in a subsequent pregnancy is as low as the general population, i.e. 1-1.5%. This is despite published evidence to the contrary dating back as far as 1964.[24] This is important for a number of reasons including: women needing this information to make important life decisions; the opportunity for pre-pregnancy planning; and the impact on their relationship with their HCP, all of which shall be addressed.

First, there are reports of women seeking termination for an HG affected pregnancy under the illusion that, in a future pregnancy, they are unlikely to experience it again.[25] Even for those anticipating a risk of recurrence, the discrepancy in the literature is so large it is possible it could factor in a couple's decision as to whether or not to conceive, maintain, or end a pregnancy. Yet, if the true recurrence figure is not as high as reported in other literature, such as 80+% then women may be limiting their family size based on incorrect information.[20] It is essential, therefore that a definitive answer is sought to this question to enable women to make life altering decisions based on an accurate evidence base.

Secondly, there is a growing body of evidence that when subsequent pregnancies are planned in conjunction with the HCP, and treatment for HG is started early, the pregnancy outcomes are improved for both mother and foetus.[26] For women to make informed autonomous decisions about their reproductive and family planning options they must have accurate and accessible information to assist them. Recent research into the detrimental effects of maternal malnutrition and weight loss in pregnancy shows potentially lifelong impacts for the infant,[27-29] while the risk for long-term morbidity for the mother is also attracting increasing attention, particularly with the increased awareness of conditions such as Post Traumatic Stress Disorder.[30,31]

Multigravidas women, as previously described, may have the opportunity to prepare and plan if a reasonably accurate prediction of risk is available. Dean [26] suggests a number of ways in which women with a history of HG can prepare for subsequent pregnancy and describes the use of an holistic pre-emptive care plan to include:

- Physical preparation, such as establishing a healthy pre-pregnancy weight and fitness level
- Prophylactic medication
- Criteria for assessing deterioration
- Further treatment options planned in advance
- Psychosocial management, such as arranging childcare and emotional support.

It is well documented that during such severe levels of sickness, previously independently minded, autonomous women can feel disempowered and unable to advocate effectively for themselves.[14,32-34] With advanced planning women may feel more empowered to cope with the condition and therefore experience less associated trauma despite recurring physical symptoms.[26]

A randomized control trial (RCT) in 2013 found that starting treatment prior to symptom onset significantly reduced the overall severity and duration of symptoms for women with a previous history of HG.[35] Despite some methodological concerns, the results are promising and further prophylactic RCTs would be beneficial for women with a history of HG but may only be warranted if, indeed, recurrence is likely. Therefore it is vital that a definitive recurrence risk is established and the information disseminated widely to the population it affects.

Anticipated methodological limitations

Through an initial review of the literature exploring the recurrence of HG it is striking that the discrepancy in the estimates of recurrence may be due to the definition of hyperemesis Gravidarum used. For example, admission to hospital is commonly used as an inclusion criteria, such as in the case of Trogstad et al.[23] However, it is increasingly recognized that in subsequent pregnancies women may know what to expect and access earlier intervention in the community precluding the need for hospital admission, despite symptoms as severe as the previous pregnancy.[26] It could also be argued that women subjected to poor hospital treatment in a first pregnancy, such as the isolation and psychological interrogation, that was still occurring as recently as 2004 in Paris, could deter women in subsequent pregnancies from accessing medical treatment.[36] This is supported by Sykes et al. who found that some

women avoided returning to their doctor for help after they had been met with ineffective communication and dismissive attitudes while seeking initial treatment.[32] Furthermore Dean et al. found that some of the women in their survey of termination for HG had not accessed hospital treatment because of obstacles at primary care level.[14] We will discuss methodological steps necessary to deal with these issues in the following section.

Listening to the patient's voice within clinical research processes is vital to ensure that the questions asked are meaningful and relevant to those they seek to benefit.[37] Members of the patient advocacy group for HG, PSS, were invited to comment on the review question. Support for the review question was strong and they felt that by establishing a definitive recurrence risk for HG women, their families and their HCPs will be better placed to make life altering decisions and plans according to solid, evidence based information.

Methods

Keywords

Hyperemesis Gravidarum

Recurrence; Subsequent pregnancy; Risk factors

Inclusion criteria

Defining Hyperemesis Gravidarum

Grooten et al. highlight that the lack of clinical definition for HG is a serious barrier to all aspects of HG research on an international level and to that end are undertaking a Delphi Study to develop an international consensus definition and set of core outcomes for HG studies.[5,38] However, until such a definition is established we must work with those available. A number of experts including the authors of the definition Delphi study, two consultant obstetricians from the UK, one midwife, one GP, and seven patients and trustees of the patient support group Pregnancy Sickness Support were consulted about the challenges of the definition in the context of this review. It was agreed that, despite the challenges surrounding definition and outcome measures, a definitive recurrence rate based on current literature would have a practical benefit to patients and their HCPs. Previous authors of systematic literature reviews have dealt with this issue pragmatically by including all papers about HG regardless of how they have been defined and assessing heterogeneity statistically as measured by I^2.[6,12,39] This review will take the same pragmatic approach and wherever possible, we will stratify the aggregated data according to the HG (recurrence) definition applied. By employing sensitivity analyses, we will be able test the hypothesis that differences in reported recurrence HG rates are dependent on the method used to define HG recurrence.

Types of participants (population)

This review will consider studies that include women who have had more than one pregnancy and who have experienced hyperemesis gravidarum in at least one of those pregnancies regardless of

pregnancy outcome, duration or treatment. Studies that include women with NVP and not diagnosed with HG will be excluded.

Condition

This review will consider studies that evaluate recurrence of hyperemesis gravidarum, regardless of how it is defined. Studies which evaluate the recurrence of NVP will be excluded.

Context

This review will not limit inclusion by geography, care setting such as primary or secondary care.

Types of studies

This review will consider descriptive epidemiological study designs including case series, RCTs and descriptive cross sectional studies for inclusion. Individual case reports will be excluded. To address issues regarding prevalence and incidence, epidemiological studies, such as those classified under the term “observational and descriptive” studies, are required. These designs address questions such as: How many people have a disease? Who is getting the disease? Where is the disease occurring?.[40]

Search strategy

An initial search of systematic review registers and databases, including Cochrane Database of Systematic Reviews, PROSPERO International prospective register of systematic reviews and Joanna Briggs Institute Database of Systematic Reviews found that no previous systematic review of the recurrence rate for Hyperemesis Gravidarum has been undertaken or is underway currently.

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all relevant reports and articles will be searched for additional studies. Studies will not be limited by publication date. Where possible foreign language publications will be translated to English for inclusion.

The databases to be searched include:

Embase, British Nursing Index, CINAHL, MEDLINE, AMED, PsycARTICLES, PsychINFO, Global Health, Cochrane Pregnancy and Childbirth, SCOPUS

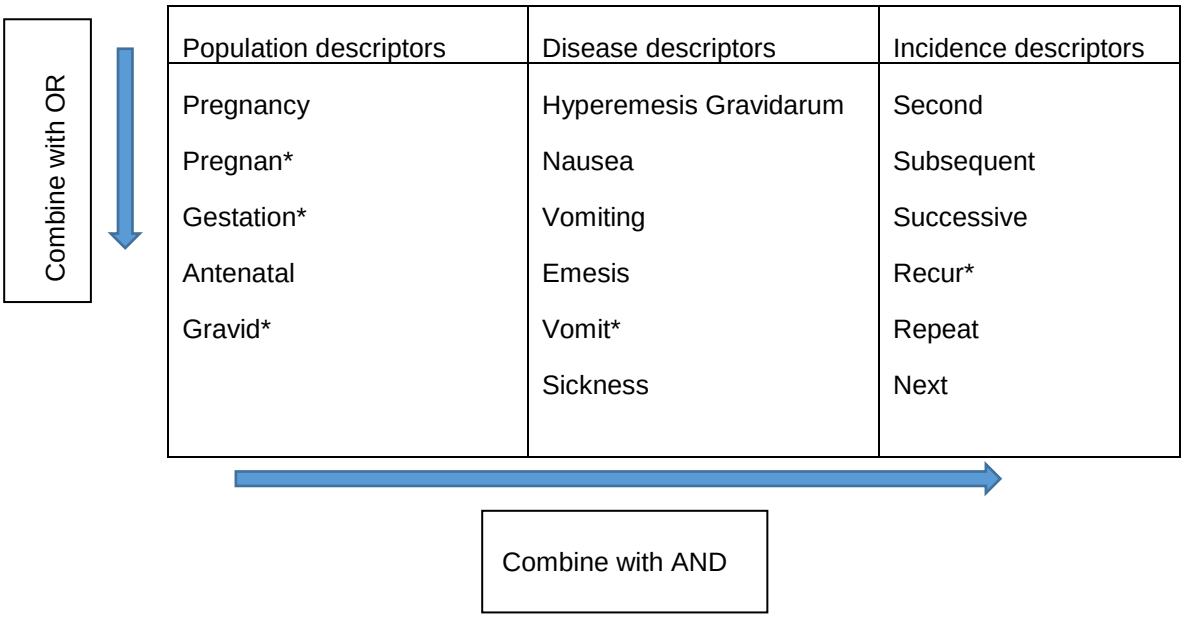
In addition to Google, the search for unpublished studies will include:

Pregnancy Sickness Support website, Hyperemesis Education and Research Foundation website, Motherisk Website, Blogs and parenting forums, NHS sites, British Library Explore (for British Theses) and Google scholar, Grey Literature Report and Open Grey for international Theses. Social media, such as Twitter will be used to request knowledge of any relevant grey literature among active researchers and healthcare professionals.

Additionally reference lists of key papers will be hand searched for backward citations.

Initial keywords to be used are summarized in Table 1:

Table 1: A summary of the key words to be used in the search strategy.



Initial searches will be limited to title and abstract only. Results will be checked to ensure key references are found in order to ensure the key words are correct. Additionally the Medical Subject Headings (MeSH) terms will be checked to ensure all relevant terms are covered in the search.

An example initial search strategy is presented in Appendix 1.

Assessment of methodological quality

Titles and abstracts will be assessed for relevance and papers fitting the above inclusion criteria will be retrieved. Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI), as available through the JBI (2017) Critical appraisal tool downloads.[41] Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data extraction

Qualitative and quantitative data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI. The data extracted will include specific details about populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Quantitative data will, where possible be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated. Heterogeneity will be assessed statistically using the standard Chi-square and also with I^2. Further sensitivity analysis will be conducted based on study design. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

Conflicts of interest

There is no conflict of interest to declare. The review has not received funding.

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Appendix I: Search Strategy Example

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (1946 to Present)

Search	Terms	Hits
1	Pregnancy/ or pregnancy.mp. or pregnan*.mp. or Gestation*.mp. or Antenatal.mp. or Gravid*.mp.	982065
2	Hyperemesis Gravidarum.mp. or Hyperemesis Gravidarum/ or Nausea/ or Nausea.mp. or Vomiting/ or Vomit*.mp. or Sickness.mp.	127423
3	(Second or Subsequent or Successive or Recur* or Repeat or Next).mp.	2118437
4	**1 and 2 and 3**	**1345**