Clinical management of nausea and vomiting in pregnancy and hyperemesis gravidarum across primary and secondary care: a population based study

Running title: Severe nausea and vomiting in pregnancy management

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Abstract

Objectives: To assess how nausea and vomiting in pregnancy (NVP) and hyperemesis gravidarum (HG) are managed and treated across primary and secondary care.

Design: Population-based pregnancy cohort

Setting: Medical records (CPRD-GOLD) from England

Population: 417,028 pregnancies, during 1998-2014

Methods: Proportions of pregnancies with recorded NVP/HG diagnoses, primary care treatment and hospital admissions were calculated. Multinomial logistic regression was employed to estimate adjusted relative risk ratios (aRRRs) with 99% confidence intervals (CIs) for the association between NVP/HG management paths and maternal characteristics.

Main Outcome Measures: NVP/HG diagnoses, treatments and hospital admissions.

Results: Overall prevalence of clinically recorded NVP/HG was 9.1%: 2.1% had hospital admissions, 3.4% were treated with antiemetics in primary care only, and 3.6% had only recorded diagnoses. Hospital admissions and antiemetic prescribing increased continuously during 1998-2013 (trend $p<0.001$). Younger age, deprivation, Black/Asian/Mixed ethnicity, multiple-pregnancy were associated with NVP/HG generally across all levels, but associations were strongest for hospital admissions. Most comorbidities had patterns of association with NVP/HG levels. Among women with NVP/HG who had no hospital admissions, 49% were prescribed antiemetics, mainly from first line treatment (21% prochlorperazine, 15% promethazine, 13% cyclizine) and metoclopramide (10%). Of those admitted, 38% had prior antiemetic prescriptions (34% first-line, 9% second-line, 1% third-line treatment).

Conclusion: Previous focus on hospital admissions has greatly underestimated the NVP/HG burden. Although primary care prescribing has increased, most women admitted to hospital have no antiemetics prescribed before this. An urgent call is made to assess whether admissions could be prevented with better primary care recognition and timely treatment.

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Keywords

Nausea and vomiting in pregnancy, Hyperemesis Gravidarum, antiemeitcs, primary care, secondary care

Tweetable abstract:

The NVP/HG burden is increasing over time and management optimization should be high priority to help reduce hospital admissions

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Introduction

Although nausea and vomiting is a very common symptom in pregnancy (NVP), affecting up to 70% of women [1] who often do not require treatment, in some cases severity can reach critical levels requiring hospital admission and need for continuous monitoring [2]. This severe condition, referred to as hyperemesis gravidarum (HG), has a reported prevalence of around 1.1% worldwide [1] and is responsible for a range of complications due to malnutrition, dehydration and excessive weight loss. Maternal and child health are affected by possible adverse effects of HG [3–5] and pregnancy complications are more likely [6]. These sequelae havesubstantial financial impact on the health services and significant burden on professional health care provision [7–9].

In June 2016, the Royal College of Obstetricians and Gynaecologists (RCOG) published the first national guidelines on the clinical management of NVP and HG for the United Kingdom (UK) [10] providing an accurate handbook for controversial decision making processes in the management of this condition with prescribed medications. Although this is supported by international reviews of HG [11–13], there is no published evidence of how this condition is actually managed by health professionals and what common clinical pathways are followed by affected women. In the UK, research based on surveys [14,15] have shown general dissatisfaction with current clinical care from women experiencing HG, with a claim that many hospital admissions could have been avoided had they received timely antiemetic prescribing to curtail worsening severity. It is unknown whether under-prescribing or late recognition of NVP and HG is widespread as there are no population-based studies showing how this condition is managed between primary and secondary care.

Using the Clinical Practice Research Datalink database (CPRD-HES), we have assessed thespectrum of NVP and HG across primary and secondary care and described how severity and pathways of management vary by maternal and pregnancy characteristics and comorbidities. We assessed the extent to which women are prescribed antiemetics in primary care and how this relates to hospital admissions.

Materials and Methods

Data source

We used primary and secondary care health records linked at individual patient level from the Clinical Practice Research Datalink (CPRD GOLD),[16] which includes over 15 million patients from 684 general practices (GP) across the UK [17]. Recorded information consists of demographics, symptoms and diagnoses coded using the Read coding system [18], clinical tests and drug prescriptions. Over half of CPRD GOLD patients are linked with the Hospital Episodes Statistics (HES) database [19] which consists of all admissions to English hospitals. Information within HES includes diagnoses coded using the International Classification of Diseases system (ICD-10)[21] and hospital procedures coded using the Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS-4)[22]. Maternity data contained in HES includes extensive information on pregnancy, labour and delivery; it is the main datasource for monitoring maternity statistics in England[23] and is used to for perinatal epidemiology research [23,24]. Our previous studies using the CPRD-HES linked population show maternities are representative of those across the English population[25,26]. Patients were not involved in the development of the research.

Study population

Women with pregnancies ending in live birth or stillbirth between October 1998 and April 2014 who had active primary care registration were selected by extracting information from GP and HES records (operational codes of delivery) to obtain the most complete and precise information on each pregnancy. For live births, a probabilistic matching algorithm was employed to link each mother's pregnancy records to the corresponding children by matching each delivery date to a child's estimated birth date or HES birth admission and ensuring they had matching a household code, a unique identifier indicating which individuals in each practice live together. Gestation and pregnancy details were extracted from HES maternity data and, when missing, from the child's HES birth record, the mother's or child's GP records in this order of priority.

Diagnoses and hospital admissions for NVP and HG

To capture the full spectrum of severity, as defined in the national guidelines[10], we identified all primary care diagnoses and hospital admissions for NVP/HG during pregnancy, using specific Read codes for primary care (Table S1) and ICD-10 codes for secondary care (Table S2) that were approved by co-author CNP who is a consultant in obstetric medicine. Due to controversy over a true distinction between NVP and HG and the lack of a standard approach for the diagnosis and clinical management of these conditions [4], the risk that these diagnoses could have been used interchangeably by health professionals to refer to the same condition was taken in to consideration by carrying out a comprehensive analysis considering both diagnoses.

To exclude presentations of nausea and vomiting for specific reasons, a restrictive criterion was applied excluding any NVP diagnoses with evidence of differential diagnoses (Table S3 and S4) recorded in GP data from one week before up to one week after the NVP diagnosis date or in HES data as a secondary reason of admission. This resulted in 1.9% of GP consultations and 17.6% of hospital admissions for NVP being excluded.

Drug treatment for NVP and HG

Antiemetic prescriptions were extracted from primary care records using selected drugs codes (Table S5) according to national recommendations from the RCOG,[10] and grouped in the following drug classes: antihistamines, phenothiazine dopamine antagonists, serotonin antagonists and steroids. As some drugs have multiple indications, differential diagnostic indications were explored to ensure the drugs under analysis were prescribed for the purpose of treating NVP/HG, according to the British National Formulary (BNF) [27].

Grouping women with NVP/HG by their clinical management pathway

We categorised women into 4 mutually exclusive groups (Figure 1), broadly representing their level of NVP/HG burden, according to their presentation and treatment in primary care or occurrence of hospital admissions as follows: a primary care diagnosis only, treatment in primary care, early hospital admissions (>=20 weeks gestation), late hospital admissions. We compared these four groups

to a control group of all remaining women, i.e. those with no evidence of NVP/HG diagnosis nor treatment.

Maternal characteristics

We assessed maternal characteristics and comorbidities based on their previous evidence as risk factors for NVP/HG [28,29] and information currently available in the CPRD-HES source dataset. These were: maternal age at delivery, socioeconomic deprivation as measured by the Index of Multiple Deprivation (IMD 2010) in quintiles [30], ethnicity, smoking status during pregnancy, parity, birth plurality, diabetes, hypertension, pre-eclampsia, parathyroid dysfunction, coronary heart diseases, anaemia, thyroid dysfunction, hypercholesterolemia and asthma.

Statistical analysis

Numbers and proportions of pregnancies for each NVP/HG group (i.e. diagnosis only, antiemetic treatment, early hospital admission and late hospital admission) were presented overall and the change in prevalence of each group was shown over time. To assess whether maternal characteristics differed by NVP/HG group, we used multinomial logistic regression (mlogit[31] with rrr option) to estimate relative risk ratios (RRR) with 99% confidence intervals (CI) for the association of each level of NVP/HG burden with maternal characteristics/comorbidities, compared to the control group. RRRs were adjusted for all the maternal characteristics and pre-existing comorbidities available in the data except for the risk factor of interest (Table 1). In order to account for potential clustering effects from including mothers with more than one pregnancy, a cluster option was set in the analysis. Missing values, present only for three maternal characteristics, namely ethnicity (12.4% missing), smoking (27.8%) and deprivation status (0.2%), were imputed using the multinomial logistic regression imputation method available in Stata MPv15 (Stata Corp, College Station, TX) statistical package [32], applying the mi imp mlogit function[31], setting 10 imputed datasets and using all maternal characteristics available as predictor variables.As a sensitivity analysis to assess whether clear clinical distinctions were actually being made between NVP and HG diagnoses, we conducted stratified analyses by 1) dividing the primary care diagnosis only group into a) those with HG diagnoses and b) those with only NVP diagnoses, and 2) dividing the primary care treatment group into those with a)

antiemetics prescribed for an HG indication and b) antiemetics prescribed for an NVP indication only. We assessed the prevalence of these four groups over time and whether they varied by maternal characteristics.

Results

Within the study period there were 417,028 deliveries ending in live births or stillbirths in 300,858 women. The prevalence of NVP/HG overall was 9.1% (37,856): 3.6% (14,815) pregnancies with primary care diagnoses that did not obtain treatment, 3.4% (14,226) with primary care diagnoses that were administered antiemetic drug treatment, 1.5% (6,390) with first hospital admission before 20 weeks and 0.6% (2,425) with late hospital admissions from 20 weeks onwards. Between 1999 and 2013 (Figure 2) there were statistically significant increases in early hospital admissions and antiemetic prescribing such that by 2013, early admissions occurred in 2.1% of pregnancies and antiemetics were prescribed in primary care in 5.2% of pregnancies compared with 2.5% of pregnancies with recognised NVP/HG that were left untreated ($p<0.001$ for both).

Management variation by maternal characteristics

Maternal characteristics varied across the groups (Table 1). In general, compared with control pregnancies, those among women with NVP/HG had higher proportions of younger women, with higher socioeconomic deprivation, or with Asian or Black ethnicity, and these proportions increased with level of NVP/HG burden with the highest among women with hospital admissions. The prevalence of comorbidities was generally higher in the affected groups compared with control pregnancies, particularly for pre-existing diabetes, gestational hypertension, pre-eclampsia, gestational anaemia and thyroid dysfunctions, asthma, and hypercholesterolemia.

In the adjusted analysis (Table 1), results showed a clear increased risk of NVP/HG with younger maternal age across all levels of burden with the magnitude of risk highest for hospital admissions; whilst women under 25 years were 1.5 times as likely to be treated in primary care compared with women age 30-34 years, they were over twice as likely to be admitted to hospital. Women from more deprived socio-economic groups had a comparable prevalence of NVP/HG diagnoses, however they

were more likely to be treated with antiemetics in primary care, and to have early hospital admission compared with women from the least deprived group (test for trend $p<0.001$ for all groups other than diagnosis only). Asian and Black women had considerable increased risks across all levels of NVP/HG burden, although there was no association between ethnicity and late hospital admission. Current smoking was associated with a decreased risk of NVP/HG across all levels other than late hospital admissions. There was no association with multiparity other than a decreased risk in primary care diagnosis of NVP/HG only. Multiple birth was associated with NVP/HG diagnosed and treated in primary care but the risk was highest in those with early hospital admissions.

Diabetes and hypertension were not associated with NVP/HG diagnosed or treated in primary care, although they were associated with some increase in late NVP/HG hospital admissions and pre-existing diabetes increased the risk of early hospital admissions. Pre-eclampsia was associated with women treated for NVP/HG in primary care, while eclampsia was associated with NVP/HG diagnoses and late hospital admissions. Asthma and anaemia increased the risk of all levels of NVP/HG. There was an increased risk of primary care treatment and hospital admissions in women with thyroid dysfunction or hypercholesterolemia.

Antiemetic prescribing distribution

Distributions of primary care antiemetic prescribing for women with NVP/HG who were and were not admitted to hospital are shown in Table 2. Of those never admitted to hospital (29,041), antiemetics were prescribed in 49% of pregnancies; first, second and third-line treatment was prescribed for 42%, 11%, and 1% of pregnancies respectively. The most commonly prescribed antiemetic was prochlorperazine (21.1%), followed by the other first line drugs promethazine (15.4%) and cyclizine (13%). While ondansetron and steroids were very rarely prescribed to these women, metoclopramide was the most commonly prescribed second line treatment (10%) followed by domperidone (1.5%).

Of the 6,390 pregnancies with early NVP/HG hospital admission (1.5% overall), only 38% had evidence of a primary care prescription of antiemetics before the admission and 50% had antiemetics prescribed following the admission. Overall, 34% received first-line treatment before admission, 9% second-line and 1% third-line treatment. Individual drugs prescribed were similar to those for

unadmitted women, with prochlorperazine being the most common first-line and metoclopramide the most common second-line treatment. Following admissions, cyclizine, metoclopramide and prednisolone prescription rates doubled compared to pre-admission rates and ondansetron increased from 0.4% pre-admission to 4.6% post-admission, reflecting the follow on from the higher level of treatment lines prescribed in secondary care.

Women with late admissions from 20 weeks gestation onwards had even lower prescribing of antiemetics before their first admission (23% of pregnancies treated pre-admission) and only 8% had antiemetics prescribed post-admission. First-line treatment was prescribed in 18% of pregnancies pre-admission, with second and third-line treatment prescribed in 6% and 2% respectively. Prochlorperazine was still the most common drug prescribed pre-admission, followed by cyclizine, metoclopramide and promethazine.

Sensitivity analysis distinguishing NVP from HG diagnoses made in primary care

Among women with recognised NVP/HG who were never admitted to hospital, the proportions of pregnancies receiving an HG diagnosis (rather than an NVP diagnosis) were 21% of those without drug treatment and 41% of those with drug treatment. These proportions remained constant over time (Figure S1) indicating that NVP and HG diagnoses may have been used interchangeably in the medical records. Furthermore, the distribution of key maternal characteristics and comorbidities were very similar between those with HG diagnosed and those with only NVP diagnosed (Figure S2 and Table S6) again providing the rationale for NVP/HG being considered as the same clinical group.

Discussion

Main findings

We found that 9.1% of pregnancies had NVP/HG that was clinically recognised in primary or secondary care; 7% did not result in hospital admission but was treated by GPs with antiemetics half of the time, and 2.1% resulting in hospital admissions. 38% of women admitted to hospital had received previous antiemetics in primary care. The prevalence of affected women prescribed

antiemetics in primary care has increased over time with a turning point at 2008 after which affected women were more likely to be treated than not. Hospital admissions, however, also increased over time, showing an overall increase in the recognised clinical burden of NVP/HG. Moreover, NVP and HG diagnoses were used in a similar way both for antiemetic prescribing and hospital admissions, likely reflecting health professionals considering them on a spectrum of illness, despite distinguishing clinical criteria for hyperemesis gravidarum diagnosis.

Strengths and limitations

The CPRD-HES is a well validated data source [33] widely used for epidemiological research[34] , broadly nationally representative[17,35].and internationally recognised as an extremely meaningful source of clinical information for studying pregnancy complications and prescribed treatments in England.

To our knowledge, this is the first large epidemiological study evaluating the prevalence of clinically recognised and managed NVP/HG within primary and secondary care.

One of the major strengths of this study was the possibility to assess the antiemetic treatments offered to women with NVP/HG in primary care. However, secondary care prescribing was not available and although discharge prescriptions are usually short supply, results on prescribing after admission need to be interpreted cautiously. Whilst it is possible that we overestimated treatments used for NVP/HG, considering antiemetics have multiple indications, we think this is unlikely as we assessed differential diagnoses for each consultation where antiemetics were prescribed and carefully excluded prescriptions referred for treating other conditions including corticosteroids used for asthma, Crohn's disease and other auto-immune conditions. Some antihistamines are available without prescription, however, we do not think this underestimated prescriptions as no antiemetics were licensed for use in pregnancy in England during the study period and pregnant women receive free prescriptions from the GP. We also applied rigorous exclusion criteria for NVP diagnoses that had differential diagnoses for these symptoms, such as gastrointestinal, metabolic or genitourinary conditions, as indicated in RCOG national guidelines for NVP/HG(RCOG, 2016). We acknowledge that NVP is a common symptom in many diseases and potentially also attributable to other conditions such as diabetes or pre-

eclampsia, however, as these are not differential diagnoses, it is also possible that there is co-existence of NVP/HG with other comorbidities.

We have included an extensive analysis of risk factors, however, results could have been affected by residual confounding as we did not include certain factors such as BMI or family support which were not comprehensively recorded in the data and there was sub-optimal recording of certain demographics or life style factors such as ethnicity or smoking status. However quality of data has improved over time [35] and robust information on pre-existing comorbidities and pregnancy complications was available [33]. Moreover imputation of missing values for the affected variables was used to minimise this limitation.

We have included women firstly admitted for NVP/HG after 20 weeks of gestation and although the classic presentation of HG is a hospital admission prior to 20 weeks [36], some women remain symptomatic throughout pregnancy [37] so it was important to capture this group, who may represent a severe and sustained burden of HG. However we acknowledge that those women could have been admitted for excessive NVP due to other underlying conditions such as diabetes, gestational hypertension, eclampsia or hypercholesterolemia, revealed to be strong risk factors of late admissions.

It is important to acknowledge that our findings represent the clinical prevalence of NVP/HG in pregnancies ending in live and stillbirths only, as we did not include pregnancies ending in spontaneous or non-spontaneous abortion. Although some studies have indicated that HG can lead to pregnancy terminations[38], more research is needed to assess how severe NVP and HG may relate to both early or late pregnancy losses.

Interpretation

We have shown that the actual prevalence of clinically recognized NVP/HG is higher than previously reported in agreement with a recently published study based oneight English primary care settings. [39] Using the linked CPRD-HES data source we have been able to provide this important missing information to complete the picture of NVP and HG management. Most of the current literature that describes the prevalence of HG or NVP is either based on medical records of hospital admissions [28,40–

[42] or questionnaires filled in by the affected women to assess the severity of symptoms in an attempt to detect the actual occurrence of HG or NVP, for which women may not always consult a healthcare professional [9,43–45]. We found that overall, HG was diagnosed and managed in primary care alone in 2.5% of pregnancies , of which 75% were treated with antiemetics, showing an higher HG burden than previously reported figures.

In our study the level of NVP/HG burden varied by maternal characteristics and comorbidities consolidating the current knowledge [29] that young mothers, women of Black and Asian ethnic origin, those from more deprived socioeconomic groups, and with multiple pregnancies are generally more likely to be affected across the whole severity spectrum. In particular, women from more deprived backgrounds were much more likely to be admitted to hospital, slightly more likely to be treated with antiemetics, but had similar risk of diagnosis-only to women from less deprived backgrounds, indicating that earlier treatment may prevent later hospital admissions.

An Australian review [46] revealed the suboptimal management offered to women affected by NVP was due to the lack of national standard guidelines, concerns about drug teratogenicity and underestimation of the impact of NVP on women's lives. A pregnancy Sickness Support survey recently published in the UK also reported significant problems accessing treatment and high levels of dissatisfaction with care. [14] General failure of an appropriate HG treatment provision was reported nationally [15,47,48] and internationally [49] with a consequent feeling of isolation and dissatisfaction among the affected women, exacerbated by further evidence of lack of high-quality studies to support any particular intervention. [50] Despite a general consensus that some women are denied access to antiemetics that could help relieve the severe symptoms of these conditions [47], we found that use of antiemetics in pregnancy has increased over time. This could be a sign of rising awareness of the impact of these conditions on the quality of life together with a growing confidence in GPs' prescribing, supported by growing evidence for the safety of antiemetics in pregnancy [10]. However, we also found that women with early hospital admissions were much less likely to be treated in primary care before their admission compared with women who never experienced hospital

admissions (38% versus 49%), potentially supporting the hypothesis that some hospital admissions may be preventable with timely treatment.

Conclusions

The actual burden of clinically recognised NVP/HG is larger than reported figures, currently affecting almost 10% of pregnancies due to a proportion of women reporting clinically relevant symptoms that are managed at primary care level, half of which are treated with antiemetics. Higher NVP/HG severity levels generally confirm the consolidated knowledge of which women are more at risk of developing this condition, with no relevant differences between NVP and HG diagnosis. Doctors' confidence in prescribing antiemetic drugs to pregnant women is increasing, although 62% of women with hospital admissions were not prescribed an antiemetic, raising urgent calls to clarify whether optimal and timely treatments could help prevent hospital admissions.

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Disclosure of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: CNP reports personal fees from Alliance Pharma, during the conduct of the study; personal fees from Sanofi aventis, grants from Leo Pharma, personal fees from warner chilcott, personal fees from UCB, outside the submitted work; she is also one of the co-developers of the RCOG Green Top Guideline on HG.; all other authors did not report any potential conflicts of interest.

Contribution to Authorship

LF conducted data management and the analysis. CNP, SD, RK and LJT contributed to the design and analysis and interpretation of the data; and preparation, critical review, and approval of the manuscript. The corresponding author attests that LF, CNP, SD, RK and LJT meet authorship criteria and that no others meeting the criteria have been omitted.

Details of Ethics Approval

The study was approved by ISAC (Independent Scientific Advisory Committee) for MHRA Database Research (protocol number 14_165R) on the 23rd of September 2014.

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List of Figures:

List of Tables:

Supplemental Material:

514