Adverse maternal and birth outcomes in women admitted to hospital for hyperemesis gravidarum: A population-based cohort study

L. Fiaschi,[a] C. Nelson-Piercy,[b] J. Gibson, [a] L. Szatkowski,[a] L. J. Tata[a]

Author affiliations

a. Division of Epidemiology & Public Health, University of Nottingham, Clinical Sciences Building Phase 2, City Hospital, NG5 1PB Nottingham, UK

b. Women's Health Academic Centre, Guy's & St Thomas' Foundation Trust, St Thomas' Hospital, SE1 7EH London, UK

Corresponding author

Linda Fiaschi

Division of Epidemiology and Public Health

University of Nottingham, NG5 1PB Nottingham, UK

Email: linda.fiaschi@nottingham.ac.uk

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Abstract

Background: Evidence for risks of adverse maternal and birth outcomes in women with hyperemesis gravidarum (HG) is predominantly from small studies, unknown or conflicting.

Methods: A population-based cohort study using secondary healthcare records (Hospital Episode Statistics covering all of England from 1997-2012) was used to calculate odds ratios (OR) with 99% confidence intervals (CI) for the association between HG hospital admission and adverse outcomes, adjusting for maternal and pregnancy confounders.

Results: Within 8,211,850 pregnancies ending in live births or stillbirths, women with HG had increased odds of anaemia (OR 1.28, 99% CI 1.23,1.33), preeclampsia (OR 1.16, 99%CI 1.09,1.22), eclampsia (OR 1.84, 99% CI 1.07,3.18), venous thromboembolism antenatally (OR 1.94, 99% CI 1.57,2.39 for deep vein thrombosis and OR 2.54, 99% CI 1.89,3.40 for pulmonary embolism) and post-partum. Odds of stillbirth (OR 0.77, 99% CI 0.66,0.89) and post-term (OR 0.86, 99% CI 0.81,0.92) delivery were decreased. Women were more likely to be induced (OR 1.20, 99% CI 1.16,1.23), to deliver preterm (OR 1.11, 99% CI 1.05,1.17), very preterm (OR 1.18, 99% CI 1.05,1.32) or by caesarean section (OR 1.12, 99% CI 1.08,1.16), to have low birthweight (OR 1.12, 99% CI 1.08,1.17) or small-for-gestational-age (OR 1.06, 99% CI 1.01,1.11) babies and, although absolute risks were small, their offspring were more likely to undergo resuscitation or neonatal intensive care.

Conclusion: HG may have important antenatal and postnatal consequences that should be considered in communications between healthcare professionals and women to best manage HG and prevent progression during pregnancy.

Keywords

Hyperemesis Gravidarum, adverse pregnancy outcomes, stillbirth, birthweight, preterm,

pregnancy complications

Introduction

Hyperemesis gravidarum (HG) is the most severe form of nausea and vomiting in pregnancy (NVP) and in many cases requires hospital admission and continuous treatment. [1] It affects up to 2% of pregnancies, causing other maternal and child morbidities responsible for further hospital admissions and adverse social, psychological and economic impacts in affected women.[2] In England in 2010 alone, HG was the primary diagnosis for over 17,500 hospital admissions in pregnancy.[3] While maternal dehydration,[1,4,5] weight loss and anaemia[1] are the most evident consequences of HG, severe NVP can also trigger central nervous system complications,[4] liver and renal failure,[6] and antenatal venous thrombosis (VTE).[7] There is some evidence of a higher risk of placental dysfunction and preeclampsia[8] in women first admitted with HG in the second trimester, whilst associations with complications such as gestational diabetes and hypertension[9–11] or postnatal VTE[12,13] are less clear. There is conflicting evidence on how HG may directly affect the health of the unborn child in terms of birthweight or being small for gestational age. Although some studies suggest that HG is not associated with adverse pregnancy outcomes,[9,10] others have found associations with preterm birth[14] and lower birthweight[15,16]. Moreover, little evidence has been reported on the occurrence of stillbirth[8] and need for neonatal care for babies born to women affected by HG. The burden of HG likely remains grossly underestimated by the medical community[5] and urgent calls for large population studies on this topic have been raised.[17]

We assessed the risk of adverse maternal, pregnancy and birth outcomes for women admitted to hospital for HG, using a cohort of over 8 million pregnancies identified from anonymised electronic hospital records in England. Outcomes investigated included

stillbirth, low birthweight, preterm birth and delivery complications for both the mother and the baby.

Materials and Methods

Study population

A cohort of pregnancies was built by extracting data on each delivery recorded in the English maternity Hospital Episode Statistics (HES) dataset between April 1997 and March 2011, including only pregnancies ending in live birth or stillbirth, as previously described.[3] A probabilistic matching algorithm was used to link a mother's delivery record to one or more children's birth records. A hierarchical approach used the following 6 variables in a priority order: delivery date, unique hospital identifier, postcode of residence, unique general practice identifier, gestational age at birth and birthweight. Overall 86.3% of the total HES pregnancies were matched to one or more children. Of the matched pregnancies, 32.1% had a unique match to children on all variables, providing the highest degree of certainty; inability to match on all variables was mainly due to missing information primarily for gestation or birthweight in either the mother or child's record. The following 57.2% were matched on 4-5 variables. The remaining 10.7% were matched with the minimum requirement of the first 3 variables, still providing a robust assumption. Whilst our probability matching algorithm will have a margin of error we expect this to be small and this is a standard approach with routinely-collected anonymised datasets for health research.[18,19] HES data are anonymised such that individual patients as well as the location of residence cannot be identified by researchers. Ethical approval for this study was obtained from The Health & Social Care Information Centre (DSA Reference: DARS-NIC-25516-N5Q7T)

Hyperemesis gravidarum

A pregnancy was considered affected by HG if at least one admission with an ICD-10 code
(International Classification of Diseases version 10, used to define diagnoses) for HG (O210
or O211) was recorded as the primary diagnosis, excluding admissions on the date of
delivery, in line with a previous published study.[3] Pregnancies with a first admission for HG
in the third trimester were excluded as HG usually peaks at 8 weeks' gestation and a later
first admission could be a misdiagnosis of other pregnancy complications such as
preeclampsia or acute fatty liver of pregnancy.[8] We grouped women as having only one HG
admission during pregnancy (i.e., HG admission), having at least one re-admission (i.e., HG
readmission) or no HG admissions during pregnancy.

Adverse maternal, pregnancy and birth outcomes

Outcomes were selected based on the literature[9,14,17] and availability in HES data. Maternal
and pregnancy outcomes included birth status (live birth or stillbirth); gestational age at
delivery grouped as very preterm (24-31 weeks), preterm (32-36 weeks), term (37-41
weeks) and post-term (over 42 weeks); type of delivery (spontaneous, assisted or breech
extraction, emergency or elective caesarean section); haemorrhage (ante, intra and post-
partum); induction of labour (surgical, medical, both, unspecified); placental dysfunction
(malformation, praevia, abruption); anaemia occurring after the first trimester; pre-
eclampsia (with or without eclampsia); gestational diabetes; gestational hypertension; and
venous thromboembolism (VTE) during pregnancy, at delivery and in the first 12 weeks
postpartum, distinguishing between deep vein thrombosis (DVT) and pulmonary embolism
(PE). Delivery and postpartum VTE analysis without history within the current pregnancy or

delivery was also assessed to distinguish a first event from (previously treated) recurrences. The recorded prevalence of delivery type was comparable to published HES statistics [20] and other published work. [21] Comorbidities were extracted from diagnostic codes according to ICD-10 code lists and relevant procedures (e.g. caesarean section) from OPCS-4 codes (Office of Population Censuses and Surveys Classification of Interventions and Procedures, used to define procedures). The maternity HES dataset provided information whenever missing from the two previous sources. This priority reflects the ordered level of data quality, where procedure recording is expected to have the highest accuracy due to the original purpose of hospital data recording. Gestational age at birth, birthweight, neonatal care and resuscitation are only available from maternity HES.

Live births or stillbirths were obtained mainly from recorded diagnoses (97.5% for live outcomes and 97% for stillbirths) and then from maternity HES. Induction of labour was obtained in a priority order from recorded information on procedures from OPCS-4 used during delivery (85%) which were largely in agreement with the maternity HES dataset (except for surgical induction which was underreported in maternity HES), recorded ICD-codes (0.6%) and maternity HES (14%).

We assessed the following adverse birth outcomes among live matched singletons: need for neonatal care (special, intensive and very intensive); resuscitation method (drugs, drugs and mask, tube, tube and drugs); birthweight (<2500, 2500-3999 and $\geqslant$4000 g). Small or large for gestational age (SGA/LGA), defined as less than the 10th centile and more than the 90th centile respectively, were estimated using the Global Reference standard that accounts for mean differences in birthweight by maternal race. [22,23]

Potential confounding factors identified a priori were those previously shown to be associated with HG as well as with adverse maternal and neonatal outcomes.[3] They were year of delivery, English region of secondary care setting, maternal age, parity, ethnicity, socio-economic group as measured by quintile of the Index of Multiple Deprivation (IMD 2010), maternal comorbidities (anaemia, thyroid and parathyroid dysfunctions, hypercholesterolemia, pre-existing diabetes or hypertension), sex of the baby and birth plurality. Details and methods to obtain these factors are described elsewhere.[3]

Statistical analysis

We calculated the percentage of pregnancies affected by HG hospital admission and readmission (as a proportion of all pregnancies) and assessed variation across different values of each outcome. For the binary outcomes gestational anaemia, diabetes and hypertension, we performed logistic regression to estimate odds ratios (OR) with 99% confidence intervals (CI) for the associations with HG admission and HG readmission, both compared with a baseline of no admission. As all other maternal, pregnancy or birth outcomes had 3 or more possibilities (e.g., low, normal or high birthweight), we used multinomial logistic regression with the relative risk ratio (RRR) option in Stata to produce similar effect measures. The RRR is sometimes interpreted as a conditional odds ratio or called a multinomial odds ratio and so for the purposes of this paper we report model output as an OR from here forward. We applied a cluster correction to all analyses to account for potential clustering effects from women who had more than one pregnancy during the study period. Analyses were adjusted for maternal confounders and different sets of relevant outcomes other than the outcome under analysis, depending on the time of

onset of the factor and the potential confounding effect that those outcomes could have in each risk assessment analysis. Table 1 shows the list of covariate factors for each analysis. Missing values for gestational age groups (32%) were imputed using an ordered logistic regression imputation method in Stata MPv14 (Stata Corp, College Station, TX) statistical package, with 10 imputed datasets and the predictor variables in Table 2. Sensitivity analysis was also conducted excluding all pregnancies with missing information. A similar method was used to impute small or large for gestational age.

Results

We obtained a cohort of 8,211,850 pregnancies from 5,329,101 women, where 0.53% (n= 43,766) of pregnancies ended in stillbirth, and 1.6% (n= 130,138) were multiple deliveries (Table 2). The prevalence of HG admission and readmission was 1.02% (n=83,679) and 0.42% (n=34,518), respectively. The prevalence showed that hospital admission and readmission for HG were more common in women under the age of 30, of Black or Asian ethnicity, with higher socio-economic deprivation, carrying multiple babies or a female baby, and with pre-existing anaemia, thyroid or parathyroid dysfunction, hypercholesterolemia or type 1 diabetes in the current pregnancy.

Table 3 shows the numbers, proportions and adjusted odds ratios for each adverse maternal outcome for women with one HG admission and HG readmission, compared to women without HG admissions. Compared with women from the referent group, women with one admission for HG had an increased relative odds of developing anaemia, preeclampsia and eclampsia during the current pregnancy. These women also showed an increased relative odds of antepartum VTE for DVT and for PE, VTE recorded during the delivery admission (OR

2.11, 99% CI 1.37,3.26 for DVT) and postpartum VTE (OR 1.49, 99% CI 1.03,2.14 for DVT and OR1.61, 99% CI 1.08,2.38 for PE). A generally higher relative odds was shown for women with more than one admission for HG, particularly for antepartum DVT (OR 2.64, 99% CI 2.00,3.48) and delivery and postpartum PE (OR 3.47, 99% CI 1.53,7.89 and OR1.92, 99% CI 1.11,3.34 respectively). Confidence intervals of effect estimates overlapped between HG admission and readmission for most outcomes, other than for anaemia and gestational hypertension, the odds of which were both significantly higher for HG readmission.

Although the odds ratios for preeclampsia and VTE were high for admitted women, the absolute increased risks were generally low (absolute risks of preeclampsia were 2.2%, 2.7% and 3.1% in women without HG admission, with HG admission and with readmission respectively; for antepartum DVT absolute risks were 9, 18 and 25 per 10,000 pregnancies respectively; for postpartum DVT absolute risks were 4, 6 and 7 per 10,000 pregnancies respectively).

The adjusted analysis for adverse delivery outcomes (Table 4) showed a decreased relative odds of stillbirth (OR 0.77, 99% CI 0.66, 0.89), in pregnancies affected by a single admission for HG. There was not significant variation for haemorrhage and placental dysfunction, though elective caesarean section and induction of labour were more likely in women with HG (OR 1.12, 99% CI 1.08,1.16 for caesarean section, OR 1.20, 99% CI 1.16,1.23 for surgical and medical induction). Although the analyses of HG readmission were affected by limited statistical power, the results described above were largely similar.

The prevalence of HG admission and readmission and the distribution of maternal characteristics within the 6,835,060 singleton pregnancies were the same as for the whole population shown in Table 2, indicating that the restricted matched population was not different from the original one. The risk of adverse birth outcome also varied between women with and without HG (Table 5). Women with a single admission for HG were more likely to deliver very preterm (OR 1.18, 99% CI 1.05,1.32), preterm birth (OR1.11, 99% CI 1.05,1.17) and less likely to deliver post-term (OR 0.90, 99% CI 0.85,0.96). The relative odds of neonates being in need of resuscitation with drugs or drugs and mask, and intensive neonatal care were also higher (OR 1.13, 99% CI 1.05,1.21, OR 1.19, 99% CI 1.06,1.33 and OR 1.18, 99% CI 1.04,1.33 respectively) however the absolute increased risks were generally low. Moreover, babies from pregnancies affected by HG were more likely to have a low birthweight (<2500 gr) and to be small for gestational age (OR 1.12, 99% CI 1.08,1.17 and OR 1.06, 99% CI 1.01,1.11 respectively) compared to children from the referent group. They were also less likely to have a high birthweight ($\geq$4000 g) (OR 0.88, 99% CI 0.85,0.91).

Excluding pregnancies with missing data on gestational age, resulted in a distribution of gestational age and birthweight categories more similar to those from national statistics. Reassuringly the findings relating to HG, however, showed very similar relative odds for adverse neonatal outcomes to the overall analysis (Table S1).

Comment

Main findings

We assessed the risk of adverse maternal, delivery and birth outcomes in women with one or more hospital admissions with a primary diagnosis of HG using the full inpatient hospital records dataset for England (HES) collected from 1997 to 2012. Within a cohort of over 8 million pregnancies we found that hospital admission for HG was associated with a relative increase of developing anaemia, preeclampsia and eclampsia, hypertension during pregnancy and DVT and PE antenatally, at delivery and up to 12 weeks postpartum. Women with HG admissions were more likely to be induced, have a caesarean section and deliver preterm. Although the relative odds of stillbirth was reduced for women with HG admissions, their babies were more likely to be small for gestational age and have low birthweight.

Interpretation

While a general association between HG and preeclampsia has been previously reported,[34] another large study [8] found that women with a first admission for HG in the second trimester were more likely to develop preeclampsia. We found that this association was true also for eclampsia and for both HG admission and readmission, regardless of the time of admission. Although we had no evidence that HG is responsible for minor placental dysfunctions, it could be an early warning of severe problems associated with placental function such as eclampsia or the two conditions could share a common aetiology reflecting for instance different aspects of faulty immunology of pregnancy.

The Royal College of Obstetricians and Gynaecologists' (RCOG) green-top guidelines consider HG a transient risk factor for VTE[27] according to evidence of a general increased

risk of VTE for women with HG.[7,35] However, while a higher VTE risk during the antepartum period and at delivery was confirmed in other studies,[7,12] evidence for VTE in the post-partum period alone was not reported.[12,13] Whilst the absolute risk was very small, in our study women with HG showed a higher relative odds of VTE antenatally, at delivery and up to 12 weeks post-partum for both DVT and PE. This could be due to an ante-partum DVT either diagnosed only postnatally or causing a later postpartum PE. Clinical reviews and previous studies[1,36] have shown anaemia as a likely consequence of HG due to malnutrition and this was confirmed by our results. The current largest study on the topic so far[14] showed an inverse association with large for gestational age (OR 0.95, [0.90,99]), in agreement with our results (OR 0.97, 99% CI 0.93,0.99 and OR 0.92, 99% CI 0.87,0.98 respectively) although we found a positive association with very preterm birth, in contrast with their results. In addition we showed an increased relative odds of SGA especially for HG readmission, as confirmed by other studies. [8,17] We found HG to be significantly associated with preterm birth and low birthweight, which was also confirmed in a previous systematic review.[17]

Of the very few studies that have looked into the risk of stillbirth for women with HG, lack of statistical power was a common limitation even for the largest of these.[9,10,14] In contrast, our study population size allowed us to show an inverse association with stillbirth in agreement only with a previous study from 1985.[37] This finding is somewhat counter-intuitive; the risk of SGA is increased in women with HG (probably due to placental dysfunction or maternal nutritional deficits), and SGA is known to be one of the main causes of stillbirth.[38] A possible explanation is that the increased rate of spontaneous and elective preterm deliveries among women with HG outweighs this effect, such that the children at the greatest risk of stillbirth if carried to term are typically delivered before they become

fatally malnourished, leading to a lower risk of stillbirth overall. We did not find any association between HG and gestational diabetes and contrasting results are reported in previous studies.[9–11] HG was not a risk factor for gestational hypertension in previously published work,[9,10] in contrast with our results showing higher effect estimates for HG readmission. Higher rates of induction of labour and caesarean section have been demonstrated previously in women with HG,[39] in agreement with our results; however for the nature of our data we were unable to establish why these medical interventions were chosen by the doctor. Children born to mothers with HG were also more likely to need neonatal care and/or resuscitation although the absolute increased risks were low; this is to our knowledge the first study to look into these specific adverse outcomes.

Strengths of the study.

To our knowledge this work represents the largest study so far carried out on this topic. The quality of the HES dataset has improved over time[24] and its validity has been demonstrated in different studies including in the area of perinatal epidemiology.[3,21] Over 97% of deliveries in England and Wales in the 1997-2011 time window took place in National Health Service (NHS), maternity units and maternity wings[25] and all delivery information is recorded in inpatient data. Moreover, in the UK, all women are offered free antenatal care and entitled to free NHS prescriptions during pregnancy therefore we believe that our population capture the vast majority of pregnant women in the UK. The data are comprehensive, nationally representative,[21,26–29] and prospectively recorded so free from recall bias. The size of our population and the assessment of significance at the 1% level reduce the possibility that results were due to chance alone.

Limitations of the data

Although data on some possible confounding factors, such as smoking or body mass index (BMI), weight loss or treatment, were not available, information on a large number of other basic demographic characteristics and common comorbidities allowed for a robust adjustment for important confounders. Hospital data will miss milder complications, such as mild anaemia for which women are not admitted to hospital. The prevalence of hypertension and diabetes was on the lower range of those reported in the literature. [30,31] However, we would expect maternity HES data to capture significant acute morbidity such as VTE cases which are treated in secondary care in the UK.[7,13]

Where gestation data were missing a multiple imputation was applied however we also conducted a sensitivity analysis excluding pregnancies of unknown length and results were similar to the original analysis. The amount of missing data for other variables was generally low apart from specific birth outcomes such as resuscitation and neonatal care. However, the sensitivity analysis showed unchanged results with a much lower missing value rate (2% missing for birthweight and 6.4% for SGA in the highest prevalence group).

We assessed HG readmission as a way of assessing severity, though we acknowledge that the probability of being readmitted could be influenced by other factors, such as external support or socio-cultural factors, not available from this data source.

The current largest study on the topic,[14] based on the Medical Birth Registry of Norway, a validated dataset for epidemiological research[32], includes all births in Norway, compared with an estimated 97% of English births included in HES. The Norwegian study had information on maternal smoking, which is not available in HES, however, MBRN has been reported to underestimate cases of severe HG due to a codification change to less specific

codes for data recorded from 1999.[33] It also does not include details such as onset an

duration of HG. It is likely that we have captured a good estimation of the starting time of

this condition and a potential duration according to the dates of hospital admissions in the

HES data. On the other hand, our study is based only on hospital admission for HG, which

will skew the analysis towards the higher level of HG severity, excluding women who may

only consult their GP or midwife, or obtain private support.

Conclusions

HG is associated with adverse health outcomes for the affected mother and child. Although

for certain outcomes such as preeclampsia or VTE the absolute increased risks are low, HG

can represent a warning sign of possible imminent complications, such as anaemia or

dehydration. Recognition of early symptoms of HG and improvement in provision of timely

support to women at high risk could help prevent and control complications such as

anaemia, or VTE secondary to dehydration. Future research should assess effects of

different treatments for HG offered in primary or secondary care settings on adverse

pregnancy and birth outcomes, considering the low-quality evidence currently available.[40]

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Disclosure of Interests

CNP reports personal fees from Alliance Pharma relevant to the submitted work and from Sanofi Aventis, Warner Chilcott, Leo Pharma, UCB and Falk, outside the submitted work and she is one of the co-developers of the RCOG Green Top Guideline on Hyperemesis Gravidarum; all other authors did not report any potential conflicts of interest.

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Supplemental Table

Table S1 - Relative odds of adverse outcomes for 4,757,713 live singletons births in women with HG admission and readmission and known gestational age at birth, between April 1997 and March 2011.

Table 1 - Selected confounders for each outcome under analysis

Outcomes:	Adjusted for:
Antenatal Complications	
Gestational Diabetes[1]	
Gestational Hypertension[1]	
Gestational Anaemia	Standard & mutual
Antenatal VTE	
Pre-eclampsia	
Perinatal complications	
Placental dysfunction	Standard & mutual
Haemorrhage	
Delivery factors	
Induction of labour	Standard
Gestational week at delivery	
Pregnancy outcome	Standard & mutual
Type of delivery	
Delivery VTE	
Birth factors	
Birth weight	Standard
SGA/LGA	
Postnatal complications	
Neonatal care	
Resuscitation	Standard
Postnatal VTE[2]	

Standard adjustments: maternal age, maternal ethnicity, socio-economic status, year of delivery, region of treatments, parity, pre-existing anaemia, pre-existing and gestational diabetes, pre-existing and gestational hypertension, hypercholesterolemia, thyroid dysfunction, parathyroid dysfunction, sex of the baby and plurality

Mutual indicates adjustment for other factors within the group (e.g. other antenatal complications)

[1] Gestational diabetes or hypertension are not adjusted for the same pre-existing condition

[2] Post-natal VTE was also adjusted for pregnancy outcome, induction of labour, gestational week at delivery and mode of delivery.

Table 2 -Maternal characteristics for 8,211,850 pregnancies in women with hyperemesis gravidarum admission and readmission, between April 1997 and March 2011.

Maternal characteristics	Pregnancies in women with					
	no HG admission N= 8,093,653		HG admission N= 83,679		HG readmission N=34,518	
	n	%	n	%	n	%
Maternal age at delivery (years)						
< 20	545,291	6.7	6,997	8.4	2,392	6.9
20-24	1,515,108	18.7	21,981	26.3	8,700	25.2
25-29	2,187,967	27.0	25,298	30.2	10,992	31.8
30-34	2,334,278	28.8	19,458	23.3	8,290	24.0
35-39	1,245,589	16.4	8,245	9.9	3,492	10.1
40-44	252,929	3.1	1,609	1.9	615	1.8
≥ 45	12,491	0.2	91	0.1	37	0.1
Maternal Ethnicity[a]						
White	5,579,842	68.9	51,768	61.9	19,986	57.9
Black and white	98,936	1.2	1,579	1.9	664	1.9
Asian	738,389	9.1	13,258	15.8	6,721	19.5
Black	384,520	4.8	8,101	9.7	3,600	10.4
Chinese	41,296	0.5	221	0.3	85	0.3
Other	168,194	2.1	1,867	2.2	805	2.3
missing	1,082,476	13.4	6,885	8.2	2,657	7.7
Maternal socio-economic status						
1 (least deprivation)	1,305,784	16.1	9,465	11.3	3,694	10.7
2	1,328,418	16.4	10,775	12.9	4,318	12.5
3	1,461,670	18.1	13,738	16.4	5,489	15.9
4	1,728,277	21.4	18,903	22.6	7,813	22.6
5 (most deprivation)	2,216,406	27.4	30,415	36.4	13,049	37.8
missing	53,098	0.7	383	0.5	155	0.5
Multiple delivery						
singleton	7,932,988	98.0	81,086	96.9	33,230	96.3
twins	121,083	1.5	2,184	2.6	1,102	3.2
triplets and more	5,613	0.1	95	0.1	61	0.2
unknown	33,969	0.4	314	0.4	125	0.4
Sex of the baby						
Male	3,868,562	47.8	35,988	43.0	14,243	41.3
Female	3,814,614	47.1	42,613	50.9	18,112	52.5
not sepcified	8,663	0.1	64	0.1	29	0.1
Multiple males	26,352	0.3	436	0.5	203	0.6
Multiple mixed	34,577	0.4	614	0.7	322	0.9
Multiple females	26,027	0.3	490	0.6	264	0.8
missing	314,858	3.9	3,474	4.2	1,345	3.9
Parity[b]						
0	4,231,003	52.3	42,975	51.4	17,479	50.6
≥1	3,862,650	47.7	40,704	48.6	17,039	49.4
Pre-existing Anaemia[c]	391,268	4.8	5,783	6.9	2,787	8.1
Pre-existing Diabetes[c]						
type 1	29,072	0.4	580	0.7	245	0.7
type 2	8,968	0.1	107	0.1	50	0.1
unspecified	17,026	0.2	136	0.2	75	0.2
Pre-existing Hypertension[c]						
pre-existing	28,942	0.4	299	0.4	120	0.4
unspecified	241,491	3.0	2,859	3.4	1,189	3.4
Thyroid dysfunction[c]	46,619	0.6	802	1.0	482	1.4
Parathyroid dysfunction[c]	255	<0.01	11	0.0	10	<0.01
Hypercholesterolaemia[c]	1,085	<0.1	31	0.0	20	0.1

HG = Hyperemesis Gravidarum. Pregnancies are defined as HG admisson if there was only one hospital admission with primary diagnosis of HG in the current pregnancy or HG readmission if there was more than one hospital admission in the current pregnancy.

[a]Categories reflect HES definitions: Asian includes Indian, Pakistani, Bangladeshi and other Asian ethnicity other than Chinese

[b] Parity defined as combination of diagnostic codes information, original HES variable and number of previous recorded deliveries.

[c] Diagnosis recorded at any admission during the current pregnancy. For pre-existing anaemia only diagnoses recorded up to the end of the first trimester were considered

Table 3 -Adverse maternal outcomes for 8,211,850 pregnancies in women with hyperemesis gravidarum admission and readmission, between April 1997 and March 2011.

Maternal outcomes	Pregnancy in women with						Odds ratios of adverse outcomes in women with	
	no HG admission N=8,093,653		HG admission N= 83,679		HG readmission N= 34,518		HG admission	HG readmission
	n	%	n	%	n	%	aOR (99% CI)	aOR (99% CI)
Gestational Anaemia								
None	7,704,232	95.2	78,087	93.3	31,857	92.3	1.00 (Reference)	
Present	389,421	4.8	5,592	6.7	2,661	7.7	1.28 (1.23, 1.33)	1.43 (1.35, 1.51)
Gestational Diabetes								
None	7,916,410	97.8	81,528	97.4	33,582	97.3	1.00 (Reference)	
Present	122,177	1.5	1,328	1.6	566	1.6	0.96 (0.89, 1.03)	0.91 (0.82, 1.02)
Gestational Hypertension[a]								
None	7,583,268	93.7	77,902	93.1	31,926	92.5	1.00 (Reference)	
Present	239,952	3.0	2,619	3.1	1,283	3.7	1.08 (1.03, 1.14)	1.27 (1.18, 1.37)
Preeclampsia								
None	7,911,740	97.8	81,381	97.3	33,448	96.9	1.00 (Reference)	
Preeclampsia	180,853	2.2	2,275	2.7	1,062	3.1	1.16 (1.09, 1.22)	1.27 (1.17, 1.39)
Eclampsia	1,060	<0.1	23	<0.1	8	<0.1	1.84 (1.07, 3.18)	1.50 (0.60, 3.76)
VTE antepartum								
None	8,083,232	99.9	83,444	99.7	34,394	99.6	1.00 (Reference)	
Deep vein thrombosis	7,572	0.1	155	0.2	88	0.3	1.94 (1.57, 2.39)	2.64 (2.00, 3.48)
Pulmonary Embolism	2,849	<0.1	80	0.1	36	0.1	2.54 (1.89, 3.40)	2.69 (1.75, 4.15)
VTE at delivery								
None	8,091,250	99.9	83,629	99.9	34,493	99.9	1.00 (Reference)	
Deep vein thrombosis	1,771	<0.1	38	0.1	15	<0.1	2.11 (1.37, 3.26)	2.00 (1.03, 3.92)
Pulmonary Embolism	632	<0.1	12	<0.1	10	<0.1	1.75 (0.82, 3.71)	3.47 (1.53, 7.89)
VTE at delivery with no prior antepartum VTE								
None	8,081,640	99.9	83,418	99.9	34,381	99.9	1.00 (Reference)	
Deep vein thrombosis	1,139	<0.1	20	<0.1	6	<0.1	1.74 (0.97, 3.12)	1.24 (0.43, 3.56)
Pulmonary Embolism	453	<0.1	6	<0.1	7	<0.1	1.21 (0.42, 3.49)	3.36 (1.25, 8.98)
VTE 12 weeks postpartum								
None	8,087,784	99.9	83,584	99.9	34,472	99.9	1.00 (Reference)	
Deep vein thrombosis	3,356	<0.1	51	0.1	24	0.1	1.49 (1.03, 2.14)	1.69 (0.99, 2.86)
Pulmonary Embolism	2,513	<0.1	44	0.1	22	0.1	1.61 (1.08, 2.38)	1.92 (1.11, 3.34)
VTE 12 weeks postpartum with no prior VTE antepartum or at delivery								
None	8,076,197	99.9	83,332	99.9	34,346	99.9	1.00 (Reference)	
Deep vein thrombosis	3,088	<0.1	48	0.1	18	0.1	1.54 (1.05, 2.24)	1.39 (0.75, 2.55)
Pulmonary Embolism	2,355	<0.1	38	0.1	17	0.1	1.50 (0.98, 2.28)	1.61 (0.86, 3.01)

HG = Hyperemesis Gravidarum. Pregnancies are defined as HG admisson if there was only one hospital admission with primary diagnosis of HG in the current pregnancy or HG readmission if there was more than one hospital admission in the current pregnancy.

aOR= adjusted conditional odds ratio from multinomial logistic regression other than for gestational anaemia, diabetes and hypertension where binary logistic regression was used; see Table 1 for model covariate adjustments. Baseline comparions for all models are pregnancies with no HG admission.

CI= confidence interval

[a] Not adjusted for hypercholesterolaemia due to lack of variability

Table 4 -Adverse delivery outcomes for 8,211,850 pregnancies in women with hyperemesis gravidarum admission and readmission, between April 1997 and March 2011.

Delivery outcomes	Pregnancy in women with						Odds ratios of adverse outcomes in women with	
	no HG admissions N=8,093,653		HG admission N= 83,679		HG readmission N= 34,518		HG admission	HG readmission
	n	%	n	%	n	%	aOR (99% CI)	aOR (99% CI)
Haemorrhage at delivery								
None	7,264,425	89.8	75,143	89.8	31,035	89.9	1.00 (Reference)	
Ante-partum	116,528	1.4	1,274	1.5	483	1.4	1.08 (0.99, 1.17)	1.00 (0.88, 1.14)
Intra-partum	126,660	1.6	1,173	1.4	470	1.4	0.93 (0.87, 1.01)	0.89 (0.79, 1.00)
Post-partum	586,040	7.2	6,089	7.3	2,530	7.3	0.95 (0.92, 0.99)	0.93 (0.88, 0.99)
Placental dysfunctions[a]								
None	7,930,210	98.0	82,110	98.1	33,880	98.2	1.00 (Reference)	
Malformation	85,849	1.1	771	0.9	326	0.9	0.93 (0.85, 1.02)	0.97 (0.84, 1.12)
Previa	48,032	0.6	458	0.6	166	0.5	0.99 (0.87, 1.13)	0.88 (0.70, 1.10)
Abruption	29,562	0.4	340	0.4	146	0.4	1.08 (0.93, 1.24)	1.11 (0.90, 1.38)
Induction of Labour								
None	4,112,131	50.8	40,850	48.8	16,867	48.9	1.00 (Reference)	
Surgical only	970,265	12.0	10,914	13.0	4,509	13.1	1.10 (1.07, 1.13)	1.13 (1.08, 1.18)
Medical only	949,439	11.7	9,862	11.8	3,978	11.5	1.08 (1.05, 1.11)	1.09 (1.04, 1.14)
Surgical and medical	1,049,463	13.0	12,771	15.3	5,478	15.9	1.20 (1.16, 1.23)	1.29 (1.23, 1.34)
Other/ unspecified	14,630	0.2	144	0.2	60	0.2	1.22 (0.98, 1.51)	1.28 (0.91, 1.79)
Unknown	997,725	12.3	9,138	10.9	3626	10.5	1.00 (0.97, 1.03)	0.99 (0.95, 1.05)
Pregnancy outcome								
Live birth(s)	8,050,475	99.5	83,277	99.5	34,332	99.5	1.00 (Reference)	
Stillbirth(s)	39,443	0.5	355	0.4	157	0.5	0.77 (0.66, 0.89)	0.82 (0.66, 1.01)
Live birth and Stillbirth[b]	3,735	0.1	47	0.1	29	0.1	0.97 (0.66, 1.43)	1.20 (0.73, 1.99)
Type of delivery								
Spontateous	5,177,860	64.0	53,640	64.1	22,022	63.8	1.00 (Reference)	
Emergency C-Section	1,189,153	14.7	12,670	15.1	5,314	15.4	1.01 (0.98, 1.04)	0.97 (0.92, 1.03)
Elective C-Section	725,164	9.0	7,192	8.6	2,921	8.5	1.12 (1.08, 1.16)	1.07 (0.99, 1.16)
Assisted	958,641	11.8	9,674	11.6	4,044	11.7	1.02 (0.99, 1.05)	1.02 (0.95, 1.09)
Breech	42,835	0.5	503	0.6	217	0.6	1.04 (0.92, 1.17)	1.04 (0.81, 1.35)

HG = Hyperemesis Gravidarum. Pregnancies are defined as HG admisson if there was only one hospital admission with primary diagnosis of HG in the current pregnancy or HG readmission if there was more than one hospital admission in the current pregnancy.

aOR= adjusted conditional odds ratio from multinomial logistic regression; see Table 1 for model covariate adjustments. Baseline comparions for all models are pregnancy with no HG admission.

CI= confidence interval
[a] Diagnosis recorded at delivery admission and mutually exclusive
[b] at least one live birth and one stillbirth

Table 5 - Relative odds of adverse outcomes for 6,835,060 live singletons births in women with HG admission and readmission, between April 1997 and March 2011.

Birth outcomes	Live singleton births[a] in women with						Odds ratios of adverse outcomes in women with	
	no HG admission N= 6,737,892		HG admission N= 68,858		HG readmission N= 28,310		HG admission	HG readmission
	n	%	n	%	n	%	aOR (99% CI)	aOR (99% CI)
Gestational week at birth								
<32	30,285	0.5	431	0.6	171	0.6	1.18 (1.05, 1.32)	1.16 (0.96, 1.39)
32-36	235,562	3.5	2,926	4.3	1,357	4.8	1.11 (1.05, 1.17)	1.19 (1.09, 1.28)
37-41	4,206,797	62.4	44,341	64.4	18,485	65.3	1.00 (Reference)	
≥42	214,804	3.2	1,882	2.7	672	2.4	0.90 (0.85, 0.96)	0.81 (0.73, 0.90)
Missing	2,050,444	30.4	19,278	28.0	7,625	26.9	[e]	
Birth weight of singletons								
<2500 gr	312,276	4.6	4,087	5.9	2,004	7.1	1.12 (1.08, 1.17)	1.30 (1.22, 1.38)
2500-4000 gr	4,471,198	66.4	47,796	69.4	19,719	69.7	1.00 (Reference)	
≥4000 gr	627,045	9.3	5,147	7.5	1,955	6.9	0.88 (0.85, 0.91)	0.83 (0.78, 0.88)
unknown	1,327,373	19.7	11,828	17.2	4,632	16.4	0.95 (0.93, 0.99)	0.92 (0.88, 0.96)
SGA/LGA								
normal	3,290,224	48.8	35,427	51.5	14,827	52.4	1.00 (Reference)	
sga	393,594	5.8	5,202	7.6	2,460	8.7	1.06 (1.01, 1.11)	1.13 (1.07, 1.20)
lga	704,297	10.5	6,408	9.3	2,473	8.7	0.97 (0.93, 1.00)	0.92 (0.87, 0.98)
Missing	2,349,777	34.9	21,821	31.7	7,625	26.9	[e]	
Resuscitation method[b]								
none	3,727,988	55.3	37,954	55.1	15,873	56.1	1.00 (Reference)	
drugs	136,910	2.0	1,645	2.4	645	2.3	1.13 (1.05, 1.21)	1.03 (0.92, 1.15)
mask	273,953	4.1	2,893	4.2	1,188	4.2	1.09 (1.04, 1.14)	1.06 (0.98, 1.15)
drugs and mask	44,086	0.7	545	0.8	221	0.8	1.19 (1.06, 1.33)	1.13 (0.94, 1.34)
tube	30,532	0.5	296	0.4	129	0.5	1.06 (0.91, 1.23)	1.09 (0.87, 1.37)
tube and drugs	14,098	0.2	128	0.2	61	0.2	0.97 (0.77, 1.22)	1.12 (0.80, 1.55)
unknown	2,510,325	37.3	25,397	36.9	10,193	36.0	1.06 (1.03, 1.08)	1.03 (0.99, 1.07)
Neonatal care[cd]								
normal	4,771,428	70.8	48,159	69.9	19,664	69.5	1.00 (Reference)	
special care	362,677	5.4	4,283	6.2	1,845	6.5	1.14 (1.09, 1.18)	1.18 (1.11, 1.26)
intensive care	36,345	0.5	440	0.6	146	0.5	1.18 (1.04, 1.33)	0.93 (0.75, 1.16)
very intensive care	54,146	0.8	665	1.0	299	1.1	1.16 (1.05, 1.28)	1.22 (1.05, 1.42)
unknown	1,513,296	22.5	15,311	22.2	6,356	22.5	0.98 (0.96, 1.01)	0.99 (0.96, 1.04)

HG = Hyperemesis Gravidarum. Pregnancies are defined as HG admisson if there was only one hospital admission with primary diagnosis of HG in the current pregnancy or HG readmission if there was more than one hospital admission in the current pregnancy.

aOR= adjusted conditional odds ratio from multinomial logistic regression; see Table 1 for model covariate adjustments. Baseline comparions for all models are pregnancy with no HG admission.

CI= confidence interval

[a] only live children matched to their mothers.

[b] The HG analysis is not adjusted for hypercholesterolemia, diabetes and parathyroid dysfunction due to lack of variability

[c] Neonatal level of care according to HES definition

[d] The HG analysis is not adjusted for diabetes due to lack of variability

[e] Missing values for these variables are estimated in the regression models using multiple imputation, therefore no OR is given.

Table S1 - Relative odds of adverse outcomes for 4,757,713 live singletons births in women with HG admission and readmission and known gestational age at birth, between April 1997 and March 2011.

Birth outcomes	Live singleton births[a] in women with						Odds ratios of adverse outcomes in women with	
	no HG admission N=4,687,448		HG admission N= 49,580		HG readmission N= 20,685		HG admission	HG readmission
	n	%	n	%	n	%	aOR (99% CI)	aOR (99% CI)
Gestational week at birth								
<32	30,285	0.7	431	0.9	171	0.8	1.30 (1.14, 1.47)	1.28 (1.05, 1.57)
32-36	235,562	5.0	2,926	5.9	1,357	6.6	1.15 (1.09, 1.21)	1.30 (1.21, 1.40)
37-41	4,206,797	89.8	44,341	89.4	18,485	89.4	1.00 (Reference)	
≥42	214,804	4.6	1,882	3.8	672	3.3	0.81 (0.76, 0.86)	0.69 (0.62, 0.77)
Birth weight of singletons								
<2500 gr	253,169	5.4	3,384	6.8	1,674	8.1	1.13 (1.08, 1.19)	1.31 (1.22, 1.40)
2500-4000 gr	3,807,676	81.2	41,027	82.8	17,082	82.9	1.00 (Reference)	
≥4000 gr	533,093	11.4	4,419	8.9	1,652	8.0	0.88 (0.84, 0.92)	0.81 (0.76, 0.87)
unknown	93,510	2.0	750	1.5	277	1.3	0.92 (0.84, 1.02)	0.82 (0.70, 0.97)
SGA/LGA								
normal	3,290,224	70.2	35,427	71.5	14,827	71.7	1.00 (Reference)	
sga	393,594	8.4	5,202	10.5	2,460	11.9	1.07 (1.03, 1.11)	1.16 (1.10, 1.23)
lga	704,297	15.0	6,408	12.9	2,473	12.0	0.95 (0.91, 0.98)	0.89 (0.84, 0.94)
unknown	299,333	6.4	2,543	5.1	925	4.5	0.86 (0.82, 0.91)	0.76 (0.69, 0.83)
Resuscitation method[b]								
none	3,223,667	68.8	33,347	67.3	14,076	68.1	1.00 (Reference)	
drugs	119,326	2.6	1,483	3.0	592	2.9	1.14 (1.06, 1.22)	1.05 (0.93, 1.17)
mask	234,215	5.0	2,521	5.1	1,048	5.1	1.09 (1.03, 1.15)	1.07 (0.98, 1.16)
drugs and mask	37,642	0.8	484	1.0	198	1.0	1.21 (1.07, 1.36)	1.15 (0.95, 1.38)
tube	25,534	0.5	251	0.5	108	0.5	1.06 (0.90, 1.26)	1.08 (0.83, 1.38)
tube and drugs	12,230	0.3	111	0.2	48	0.2	0.97 (0.76, 1.24)	1.01 (0.70, 1.47)
unknown	1,034,834	22.1	11,383	23.0	4,615	22.3	1.09 (1.06, 1.12)	1.07 (1.02, 1.12)
Neonatal care[cd]								
normal	3,454,494	73.7	35,921	72.5	14,852	71.8	1.00 (Reference)	
special care	272,985	5.8	3,365	6.8	1,497	7.2	1.16 (1.10, 1.21)	1.23 (1.14, 1.32)
intensive care	26,298	0.6	331	0.7	110	0.5	1.21 (1.05, 1.40)	0.95 (0.75, 1.22)
very intensive care	38,973	0.8	498	1.0	220	1.1	1.18 (1.05, 1.33)	1.22 (1.02, 1.46)
unknown	894,698	19.1	9,465	19.1	4,006	19.4	0.98 (0.95, 1.01)	0.99 (0.95, 1.05)

HG = Hyperemesis Gravidarum. Pregnancies are defined as HG admisson if there was only one hospital admission with primary diagnosis of HG in the current pregnancy or HG readmission if there was more than one hospital admission in the current pregnancy.

aOR= adjusted conditional odds ratio from multinomial logistic regression; see Table 1 for model covariate adjustments. Baseline comparions for all models are pregnancy with no HG admission.

CI= confidence interval

[a] only live children matched to their mothers.

[b] The HG analysis is not adjusted for hypercholesterolemia, diabetes and parathyroid dysfunction due to lack of variability

[c] Neonatal level of care according to HES definition

[d] The HG analysis is not adjusted for diabetes due to lack of variability