Introduction

Hyperemesis gravidarum (HG) complicates around 0.3–2% of pregnancies and is characterized by severe nausea and vomiting due to pregnancy resulting in dehydration and electrolyte imbalance, metabolic disturbance and the need for hospitalization.[1] HG typically arises between the 4th and the 10th week of gestation with resolution usually by 20 weeks of gestation.[2] in 10% of cases symptom may persist throughout pregnancy.[3] Hormonal relationships with HG are often reported particularly the association with high levels of human chorionic gonadotropin. The aetiology of HG remains unclear and may be multi-factorial with biologic, psychological and socioeconomic antecedents.[2] Historically, a pregnant woman’s vomiting was thought to represent various psychological conflicts but it is also plausible that psychological symptoms are a result of the stress and the physical burden of HG rather than a cause.[2] Women with prior psychiatric or medical conditions are more likely to develop HG when pregnant.[4] The prevalence of major depression, generalized anxiety disorder, avoidant personality disorder and obsessive-compulsive personality disorder has been shown to be higher in women with HG.[5] In contrast, women with HG were no more likely than controls to have psychological morbidity after birth.[6]

A study at our centre indicates that anxiety and depression were common in HG women when assessed at their first hospitalization with caseness rates of 46.9% and 47.8% respectively.[7] These rates compare unfavourably with anxiety and depression rates of 36.3% and 22.1% in the first pregnancy trimester, 32.3% and 18.9% in the second trimester and 35.8% and 21.6% in the third trimester from a longitudinal study of Chinese women in Hong Kong.[8]

We sought to evaluate the evolution of nausea, vomiting, depression, anxiety and stress in the HG cohort from hospitalization into the third trimester of pregnancy. We hypothesize that

Depression, Anxiety, Stress and Hyperemesis Gravidarum: Temporal and Case Controlled Correlates

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Abstract

Objective: To evaluate the temporal and case-controlled correlations of anxiety, depression and stress with hyperemesis gravidarum

Study Design: We performed a longitudinal cohort study of women with hyperemesis gravidarum using the Depression, Anxiety and Stress Scale (DASS-21) to evaluate psychological distress at hospitalization and in the third trimester of pregnancy (from 28 weeks gestation). Third pregnancy trimester controls were recruited from routine antenatal clinic attendees who were matched to gestational age at the second DASS-21 assessment in the HG cohort.

Results: The prevalences of nausea and vomiting, depression, anxiety and stress caseness in newly hospitalised hyperemesis gravidarum women were 100% and 100%, 49% and 21% respectively by the second trimester, which by the third trimester had fallen to 15.7% and 9.9%, 4%, 19% and 3% and in third trimester controls were 15.9% and 14.2%, 14%, 61% and 20% respectively. Within the hyperemesis gravidarum cohort, nausea, vomiting depression, anxiety and stress reduced significantly by an absolute 84.3% (95% CI 76.2%–89.8%), 90.1% (82.8%–94.2%), 14.9% (7.2%–23.0%), 49.6% (38.6%–58.7%) and 18.2% (10.4%–26.4%) respectively between hospitalization for hyperemesis gravidarum and at the third trimester. In the third trimester, when comparing the hyperemesis gravidarum cohort to controls, the risk of nausea or vomiting was similar but depression, anxiety and stress were significantly lower: adjusted odds ratio AOR 0.10 (95% CI 0.03–0.5), 0.11 (0.05–0.23) and 0.08 (0.02–0.33) respectively.

Conclusion: Our study revealed a reassuring pattern of a strong rebound from depression, anxiety and stress in women with hyperemesis gravidarum such that by the third pregnancy trimester the level of psychological distress was even lower than in controls. This observation imply that much of the psychological distress in acute hyperemesis gravidarum is self-limiting and probably in the causal pathway of hyperemesis gravidarum. Care in women with hyperemesis gravidarum should focus on the relief of nausea and vomiting.

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Participation was made for the missing information but if a deliberate choice was made for the missing information. If the questionnaire or data sheet was incomplete, another request for completion was made. Study data was not routinely made available to providers.

**Data collection**

Inpatient data from the HG hospitalization were transcribed to the case report form from clinical notes and on-line laboratory records. Ketonuria, hyponatraemia, hypokalaemia and high haematocrit on admission and prolonged hospital stay were selected as measures of severity of HG at hospitalization. Standard inpatient care of HG was provided to participants: comprising initial rehydration with intravenous fluids (typically normal saline), an intravenous anti-emetic (typically metoclopramide) and oral thiamine. Oral intake was resumed when tolerated. Patients were discharged once they were rehydrated, electrolyte repleted and tolerating sufficient oral intake. Participants who wished to deliver in our centre were referred to the antenatal care clinic for subsequent care. Our pregnancy care system is open to local women of all risk categories who choose our services on their own volition.

**Controls**

Controls matched for gestational age ≥ 28 weeks (at timing of second DASS-21 assessment in the HG cohort) were recruited on a 1 to 1 ratio from amongst routine antenatal clinic attendees by a co-author (SNZ). The inclusion criteria for the controls were the same as HG cases i.e. women with multiple pregnancies, thyroid disease or overt history of psychological illness were excluded. We could not recruit controls from the early first trimester at a similar threshold gestational age for reassessing nausea, vomiting, depression, anxiety and stress as it represents the conventional cut-off for the third pregnancy trimester. HG typically would have resolved by 20 weeks[2] allowing two or more months for psychological distress to respond and to minimize dropouts due to preterm delivery.

Controls that had probable HG (i.e. severe nausea and vomiting requiring medical treatment) in the current pregnancy were excluded.

**Sample size calculation**

Study population sample size for the HG cohort, comparing depression caseness in early and late pregnancy was calculated thus. Depression caseness was found in 47.8% at hospitalization for HG[7] and present in 21.6% of the unselected third trimester.
Table 1. Characteristics of women with hyperemesis gravidarum at hospitalization stratified according to their depression, anxiety and stress status as assessed by the 21-stem Depression Anxiety and Stress Scales.

|                          | Depression* | P Value | Adjusted P | Anxiety* | P Value | Adjusted P | Stress* | P Value |
|--------------------------|-------------|---------|------------|----------|---------|------------|---------|---------|
|                          | Yes n = 23  | No n = 98|             | Yes n = 83 | No n = 38|             | Yes n = 26 | No n = 95|
| Age (years)              | 28.4±4.5    | 28.8±4.8| P = 0.67    | 28.9±4.8 | 28.5±4.5| P = 0.69    | 29.5±4.6 | 28.6±4.7| P = 0.39 |
| Gestational age (weeks)  | 9.4±3.4     | 9.3±2.2 | P = 0.87    | 9.0±2.5 | 10.1±2.4| P = 0.03    | 9.3±2.8 | 9.4±2.4| P = 0.99 |
| Weight (kg)              | 55.5±11.4   | 55.5±10.7| P = 0.98    | 55.9±10.3| 54.6±11.9| P = 0.53    | 54.5±11.2| 55.8±10.7| P = 0.60 |
| Gestational age at start of vomiting (weeks) | 7.2±3.1 | 7.1±1.9 | P = 0.85 | 6.8±2.1 | 7.9±2.2 | P = 0.01 | 6.8±2.6 | 7.2±2.0 | P = 0.36 |
| Duration of vomiting (weeks) | 2.2±1.4 | 2.2±1.3 | P = 0.94 | 2.2±1.3 | 2.2±1.4 | P = 0.58 | 2.5±1.4 | 2.1±1.3 | P = 0.16 |
| Vomiting episodes (per day) | 8 [5–10] | 6.5 [5–10] | P = 0.15 | 8 [5–10] | 6 [5–8.25] | P = 0.15 | 8 [5–10] | 7 [5–10] | P = 0.15 |
| Parity                   | 1 [0–1]     | 0 [0–1] | P = 0.55    | 1 [0–1] | 0 [0–2] | P = 0.55    | 1 [0–1] | 0 [0–1] | P = 0.55 |
| Miscarriage              | 4 (17.4)    | 17 (17.3) | P = 0.99 | 14 (16.9) | 7 (18.4) | P = 0.80 | 4 (15.4) | 17 (17.9) | P = 0.99 |
| Ethnicity                |             |         | P = 0.40    |         |         |             |         |         | P = 0.61 |
| Malay                    | 17 (73.9)   | 79 (80.6) | 68 (81.9) | 28 (73.7) | 20 (76.9) | 78 (80.0) |         |         |         |
| Indian                   | 3 (13.0)    | 10 (10.2) | 10 (12.0) | 3 (7.9) | 4 (15.4) | 9 (9.5) |         |         |         |
| Chinese                  | 2 (8.7)     | 2 (2.0) | 2 (2.4) | 2 (5.3) | 0 (0.0) | 4 (4.2) |         |         |         |
| Others                   | 1 (4.3)     | 7 (7.1) | 3 (3.6) | 5 (13.2) | 2 (7.7) | 6 (6.3) |         |         |         |
| Previous hyperemesis gravidarum | 6 (26.1) | 25 (25.5) | P = 0.99 | 20 (24.1) | 11 (28.9) | P = 0.66 | 9 (34.6) | 22 (23.2) | P = 0.31 |
| Planned pregnancy        | 12 (52.2)   | 52 (53.1) | P = 0.99 | 42 (50.6) | 22 (57.9) | P = 0.56 | 11 (42.3) | 53 (55.8) | P = 0.27 |
| Married                  | 21 (91.3)   | 97 (99.0) | P = 0.09 | 80 (96.4) | 38 (100) | P = 0.55 | 26 (100) | 92 (96.8) | P = 0.99 |
| Local family support     | 20 (87.0)   | 79 (80.6)| P = 0.57 | 67 (80.7) | 32 (84.2) | P = 0.80 | 23 (88.5) | 76 (80.0) | P = 0.40 |
| Low income               | 9 (39.1)    | 44 (44.9) | P = 0.65 | 36 (43.4) | 17 (44.7) | P = 0.99 | 7 (26.9) | 46 (48.4) | P = 0.07 |
| Housing                  |             |         | P = 0.01 | P = 0.06 | P = 0.72 | P = 0.48 |         |         |         |
| Owned                    | 6 (26.1)    | 39 (39.8) | 29 (34.9) | 16 (42.1) | 11 (42.3) | 34 (35.8) |         |         |         |
| Rented                   | 12 (52.2)   | 55 (56.1) | 48 (57.8) | 19 (50.0) | 12 (46.2) | 55 (57.9) |         |         |         |
| Living with extended family | 5 (21.7) | 4 (4.1)| 6 (7.2) | 3 (7.9) | 3 (11.5) | 6 (6.3) |         |         |         |
| Tertiary Education       | 10 (43.5)   | 60 (61.2) | P = 0.16 | 49 (59.0) | 21 (55.3) | P = 0.70 | 15 (57.7) | 55 (57.9) | P = 0.99 |
| Paid employment          | 20 (87.0)   | 83 (84.7) | P = 0.99 | 71 (85.5) | 32 (84.2) | P = 0.99 | 22 (84.6) | 81 (85.3) | P = 0.99 |
| Regular exercise         | 2 (8.7)     | 22 (22.4) | P = 0.24 | 15 (18.1) | 9 (23.7) | P = 0.47 | 2 (7.7) | 22 (23.2) | P = 0.10 |
| Ketonuria                | P = 0.42    | P = 0.75 | P = 0.57 |         |         |         |         |         |         |
| Nil                      | 1 (4.3)     | 3 (3.1) | 2 (2.4) | 2 (5.3) | 1 (3.8) | 3 (3.2) |         |         |         |
| 1+                       | 0 (0)       | 4 (4.1) | 2 (2.4) | 2 (5.3) | 0 (0) | 4 (4.2) |         |         |         |
| 2+                       | 0 (0.0)     | 1 (1.0) | 1 (1.2) | 0 (0.0) | 0 (0) | 1 (1.1) |         |         |         |
| 3+                       | 7 (30.4)    | 15 (15.3) | 16 (19.3) | 6 (15.8) | 7 (26.9) | 15 (15.8) |         |         |         |
| 4+                       | 15 (65.2)   | 75 (76.5) | 62 (74.7) | 28 (73.7) | 18 (69.2) | 72 (75.8) |         |         |         |

Hyponatraemia* $15 (65.2)/76 (77.6)$ = 0.2861 (73.5)/30 (78.9)/P = 0.6520 (76.9)/71 (74.7)/P = 0.999 Hypokalaemia* $0.0 (0.0)/16 (16.3)$ = 0.04/P = 0.9910 (12.0)/15.8)/P = 0.573 (11.5)/13 (13.7)/P = 0.99Long Hospital stay ≥ 4 days **$4 (17.4)/8 (18.4)$ = 0.9917 (20.5)/13.2)/P = 0.444 (15.4)/18 (18.9)/P = 0.78High Haematocrit ≥ 0.41**$5 (22.7)/20 (20.6)/P = 0.7819 (23.6)/16.2)/P = 0.47 (15.4)/1 (22.6)/P = 0.59

Data presented as mean ± standard deviation, median [interquartile range] and number (%). Bivariate analyses are with Student t test for continuous data set, Mann Whitney U test for ordinal or non-parametric data, Fisher Exact test for 2×2 categorical dataset and Chi Square test for larger categorical dataset. All tests are 2-sided.
Statistical Analysis

Statistical analysis was performed using the SPSS 15 (SPSS Inc., Chicago IL, USA). The one sample Kolmogorov-Smirnoff test was used to assess normality of data distribution. Fisher’s exact test was used for 2x2 categorical data, Chi-Square test for larger than 2x2 categorical data sets. The means of normally distributed continuous data was assessed by Student t-test. The Mann Whitney U test was used for non-normally distributed data and ordinal data. McNemar’s test was used to analyse change in nausea, vomiting, depression, anxiety and stress at hospitalization for HG compared to at the third trimester. Multivariable logistic regression analysis was used to control for co-variables with P<0.05 on bivariate analysis. P<0.05 on 2-sided tests was taken as a level of significance for all tests.

Results

129 women were recruited at hospitalization for HG. All completed the DASS-21 questionnaire and also provided personal information as requested in our standardised data collection form. Eight participants (five could not be contacted or did not respond and three had miscarried) did not complete the DASS-21 questionnaire in the third trimester leaving 121 women in the HG cohort. Nausea, vomiting, depression, anxiety and stress caseness were all far less prevalent (AORs 0.1 [95% CI 0.03–0.5], 0.11 [95% CI 0.05–0.23], and 0.08 [95% CI 0.02–0.33]), respectively in the HG cohort compared to controls.

In Table 3, we compared the characteristics of the HG cohort and that of controls recruited in their third trimester (DASS-21 assessment performed at a mean±standard deviation gestational age of 30.5±1.6 weeks gestation) in the HG cohort. Nausea, vomiting, depression, anxiety and stress caseness all declined significantly (P<0.001, McNemar’s test) as anticipated: absolute percentage reductions by the third trimester were 84.3% (95% CI 76.2–89.8%), 90.1% (95% CI 82.8–94.2%), 14.9% (95% CI 7.2–23.0%), 49.6% (95% CI 38.6–58.7%) and 18.2% (95% CI 10.4–26.4%) respectively.

Discussion

Currently, the 2-way etiologic relationship between HG and psychological distress remained unresolved. We performed a longitudinal study on a cohort of women with HG assessing the evolution of depression, anxiety and stress from diagnosis of HG into the third pregnancy trimester when in tandem with the typical natural history of HG; full recovery can be anticipated. We also compared the HG cohort against controls (without a history of potential predictors using bivariate analysis. The rates of depression, anxiety and stress caseness were 19%, 69% and 21% respectively. We adjusted for all characteristics with P<0.05 on bivariate analysis in a multivariable logistic regression analysis model to identify independent risk factors for depression, anxiety and stress caseness. No significant independent predictor for depression, anxiety and stress was found after adjustment.

Table 2 shows the magnitude of the evolution of symptoms of nausea, vomiting, depression, anxiety and stress over time from hospitalization to the third trimester (on or after 28 weeks gestation) in the HG cohort. Nausea, vomiting, depression, anxiety and stress caseness all declined significantly (P<0.001, McNemar’s test) as anticipated: absolute percentage reductions by the third trimester were 84.3% (95% CI 76.2–89.8%), 90.1% (95% CI 82.8–94.2%), 14.9% (95% CI 7.2–23.0%), 49.6% (95% CI 38.6–58.7%) and 18.2% (95% CI 10.4–26.4%) respectively.

In Table 3, we compared the characteristics of the HG cohort and that of controls recruited in their third trimester (DASS-21 assessment performed at a mean±standard deviation gestational age of 30.5±1.6 weeks). Compared to controls, the HG cohort was significantly (P<0.05) younger, more likely to have had HG in a previous pregnancy and be of Malay ethnicity and less likely to have had a tertiary level education. Adjustment was made for these variables when comparing the risk of nausea, vomiting, depression, anxiety and stress between the HG cohort and controls in the third trimester (displayed in Table 4).

Table 4 shows the bivariate relative risks and adjusted odds ratios (AOR) of nausea, vomiting, depression, anxiety and stress in the third trimester of the HG cohort compared to controls. There was no difference in nausea and vomiting. The overall nausea and/or vomiting rates were 17.4% compared with 15.9% (95% RR 1.1 95% CI 0.8–1.4; p = 0.86) for HG women against controls in the third trimester. However, depression, anxiety and stress caseness were all far less prevalent (AORs 0.1 [95% CI 0.03–0.5], 0.11 [95% CI 0.05–0.23], and 0.08 [95% CI 0.02–0.33]), respectively in the HG cohort compared to controls.

As HG women of Chinese ethnicity seemed to have a higher rate of depression caseness (Table 1) though numbers were few and the control group has a higher proportion of Chinese women (Table 3), post hoc we performed a sensitivity analysis excluding Chinese women. The results of this sensitivity analysis are not materially changed compared to the original findings as described above.
HG) in the third trimester to address the hypothesis whether psychological distress is driven by the symptoms of HG.

In our study of women hospitalised for HG, using DASS-21, 19%, 69% and 21% were classified as having depression, anxiety and stress caseness respectively. No independent risk factor was identified for these components of psychological distress in our cohort. By the third trimester, the rates had fallen to 4%, 19% and 3%, a substantial and significant decrease in tandem with a sharp fall in the symptoms of nausea and vomiting. The HG cohort’s adjusted odds ratio for depression, anxiety and stress was only about one-tenth that of controls recruited in the third trimester whilst nausea and vomiting prevalences were similar. The reduction in depression, anxiety and stress was a surprise finding particularly in terms of magnitude; the expectation was that psychological distress in the HG cohort should fall to about the background rate in tandem with the expected fall in the symptoms of nausea and vomiting as HG resolved. The large fall in psychological distress in the HG cohort is not likely to be consistent with psychological distress being a major driver of HG as psychological distress is similar in the first and third trimester of pregnancy [8] and far more supportive of psychological distress being a reaction to the debilitating physical effects of HG, with a

| Characteristics | Hyperemesis Cases n = 121 | Controls n = 113 | P Value |
|-----------------|--------------------------|-----------------|---------|
| Age (years)     | 28.8 ± 4.7               | 30.7 ± 4.5      | <0.001  |
| Parity          | 1 [0–1]                  | 1 [0–1]         | 0.95    |
| Miscarriage     | 21 (17.4)                | 28 (24.9)       | 0.19    |
| Ethnicity       |                          |                 | >0.001  |
| Malay           | 96 (79.3)                | 77 (68.1)       |         |
| Indian          | 13 (10.7)                | 12 (10.6)       |         |
| Chinese         | 4 (3.3)                  | 24 (21.2)       |         |
| Others          | 8 (6.6)                  | 0 (0.0)         |         |
| Previous hyperemesis gravidarum | 31 (25.6) | 3 (2.7) | <0.001  |
| Planned pregnancy | 64 (52.9)               | 48 (42.5)       | 0.12    |
| Married         | 118 (97.5)               | 113 (100)       | 0.25    |
| Local family support | 99 (81.6)             | 90 (79.6)       | 0.74    |
| Low income*     | 53 (43.8)                | 53 (46.9)       | 0.69    |
| Housing         |                          |                 | 0.43    |
| Owned           | 45 (37.2)                | 50 (44.2)       |         |
| Rented          | 67 (55.4)                | 53 (46.9)       |         |
| Living with extended family | 9 (7.4)     | 10 (8.8)        |         |
| Tertiary Education | 70 (57.9)               | 84 (74.3)       | 0.01    |
| Paid employment | 103 (85.1)               | 95 (84.1)       | 0.86    |
| Regular exercise | 24 (19.8)               | 31 (27.4)       | 0.22    |

Data presented as mean ± standard deviation, median [interquartile range] and number (%). Bivariate analyses are with Student t test for continuous data set, Mann Whitney U test for ordinal or non-parametric data, Fisher Exact test for 2×2 categorical dataset and Chi Square test for larger categorical dataset. All tests are 2-sided.

*Month income of less than RM3000 (approximately US$950)
very strong rebound in psychological wellbeing after physical recovery from HG. Women with HG also regard HG as being biologically determined.[16] These findings suggest that as perceived by the patients themselves, specific psychological assistance maybe of limited value during acute HG and when recovery from HG. Women with HG also regard HG as being psychologically determined.

In HG severity using laboratory and clinical parameters did not impact further on the risk of depression, anxiety and stress scores in HG. That study also reported a calculated score of at least 15 on the summated (then doubled) scores of the stress component of the 21-stem Depression, Anxiety and Stress Scales.

A calculated score of at least 10 on the summated (then doubled) scores of the anxiety component of the 21-stem Depression, Anxiety and Stress Scales.

A calculated score of at least 8 on the summed (then doubled) scores of the anxiety component of the 21-stem Depression, Anxiety and Stress Scales.

A calculated score of at least 10 on the summed (then doubled) scores of the depression component of the 21-stem Depression, Anxiety and Stress Scales.

When assessed at 15 weeks and again at 20 weeks gestation, depression, anxiety and stress scores have been shown to be higher in 164 nulliparous HG women than in 3259 nulliparous controls with an even greater difference observed in women with severe (defined as requiring hospitalization) HG. That study also reported that elevated stress, depression and limiting response to pregnancy scores occurs secondary to the HG and normalise when the HG improves, although this effect may take weeks to occur. In contrast, more than five weeks following the cessation of vomiting, anxiety scores remain elevated in women with HG.[17] Our data of women hospitalised with HG showed that further differentiation in HG severity using laboratory and clinical parameters did not impact further on the risk of depression, anxiety and stress (Table 1).

The nausea and/or vomiting rates in the third trimester of 15.9% in our control group (which was similar to that in the HG group of 17.4%) may seem high and a potential contributor to psychological distress in controls. We did not exclude women with mild NVP from our control group. A recent meta-analysis of the worldwide literature taking into account data from 59 studies found an average NVP rate of 69.4% with NVP symptoms continuing into the third trimester in 23.5%[9] which would suggest that the 15.9% NVP rate in our controls and 17.4% rate in HG cases were consistent with the global experience.

There were strengths and limitations to our study. Our HG cohort was exclusively of women with the most severe clinical presentation that needed hospitalization. Hospitalization is a useful and pragmatic demarcator of HG from the much milder nausea and vomiting of pregnancy which can affect up to 90% of pregnancies.[18] Our HG cohort sample size was properly powered to observe a drop in depression caseness to the background rate in tandem with expected resolution of HG by the third trimester. The drop-out rate in the study was low and there were few missing data. We presented a hybrid analysis with cohort and case controlled elements which we believed best describe the temporal and case-control correlation between HG and depression, anxiety and stress. However, the Malay language version of DASS-21 has not specifically been validated in HG even though it has been validated against HADS in infertility patients.[13] Longitudinal data starting from prepregnancy to term is required to best define the etiological relationship between psychological distress and HG. This type of data is difficult to obtain as the incidence of HG can be as low as 0.3%, requiring a very large prepregnant sample size for a powered study. We did not take into account factors which might have arisen by the third trimester that might have contributed to depression, anxiety and stress in controls e.g. gestational diabetes, pregnancy induced hypertension, fetal growth restriction. However, HG is not associated with gestational diabetes or hypertension; any positive association that HG might have with fetal growth restriction would tend to move the effect to null instead of a reduction in psychological distress when compared to controls. Also, we took only gestational age into account when selecting our controls which resulted in the control group having a number of characteristics significantly different from the HG cohort. However, we used multivariable logistic regression to adjust for these differences in the eventual analysis. Sensitivity analysis excluding women of Chinese ethnicity also did not materially alter our findings.

### Conclusion

Depression, anxiety and stress in HG are probably in the causal pathway of HG as a response to the deleterious physical effects. The psychological distress appears to be self-limiting in tandem

| Table 4. Nausea, Vomiting, Depression, Anxiety and Stress in the Third Trimester in Women Previously Hospitalised with Hyperemesis Gravidarum Compared to Controls. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Hyperemesis Gravidarum**      | **Controls**    | **Relative Risk 95% Confidence Interval** | **Adjusted P value** | **Adjusted Odds Ratio (95% Confidence Interval)** |
| n = 121                         | n = 113P value  | P = 0.99        | RR 1.0 95 CI 0.5–2.0 | P = 0.43 AOR 1.4 (0.6–3.0) |
| Nausea*                         | 19 (15.7)       | 18 (15.9)       | P = 0.99       | RR 1.0 95 CI 0.5–2.0 | P = 0.43 AOR 1.4 (0.6–3.0) |
| Vomiting†                       | 12 (9.9)        | 16 (14.2)       | P = 0.42       | RR 0.7 95 CI 0.3–1.4 | P = 0.49 AOR 0.7 (0.3–1.8) |
| Depression§                     | 5 (4.1)         | 16 (14.2)       | P = 0.011      | RR 0.3 95 CI 0.1–0.8 | P = 0.003 AOR 0.1 (0.03–0.5) |
| Anxiety†                        | 23 (19.0)       | 69 (61.1)       | P < 0.001      | RR 0.3 95 CI 0.2–0.5 | P < 0.001 AOR 0.11 (0.05–0.23) |
| Stress†                         | 4 (3.3)         | 23 (20.4)       | P = 0.001      | RR 0.2 95 CI 0.1–0.5 | P < 0.001 AOR 0.08 (0.02–0.33) |

Data expressed as number (%). Analyses are by Fisher Exact test. All tests are 2-sided. Adjustment made for maternal age, ethnicity, educational attainment and hyperemesis gravidarum in a previous pregnancy as these characteristics are significantly different between the hyperemesis gravidarum and control groups.

*At least one day of nausea in the last week.

†At least one day of vomiting in the last week.

‡A calculated score of at least 10 on the summated (then doubled) scores of the depression component of the 21-stem Depression, Anxiety and Stress Scales.

§A calculated score of at least 8 on the summed (then doubled) scores of the anxiety component of the 21-stem Depression, Anxiety and Stress Scales.

‖A calculated score of at least 15 on the summated (then doubled) scores of the stress component of the 21-stem Depression, Anxiety and Stress Scales.

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with symptoms of HG. Care in HG should arguably be focused on relieving the symptoms of nausea and vomiting.

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Author Contributions

Conceived and designed the experiments: PCT SNZ NA SZO SYK. Performed the experiments: SNZ. Analyzed the data: PCT SNZ NA SZO SYK. Contributed reagents/materials/analysis tools: PCT NA SZO SYK. Wrote the paper: PCT SNZ.