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**Nausea and Vomiting in Pregnancy (NVP) is not just
"Morning Sickness": Data from a prospective cohort study**

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5 NAUSEA AND VOMITING IN PREGNANCY (NVP) IS NOT JUST “MORNING SICKNESS”:
6 DATA FROM A PROSPECTIVE COHORT STUDY
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Abstract

Background: Nausea and vomiting in pregnancy is usually called “morning sickness”. This is felt by sufferers to trivialise the condition. Symptoms have been described as occurring both before and after noon, but daily symptom patterns have not been clearly described and statistically modelled to enable the term “morning sickness” to be accurately analysed.

Aim: To describe the daily variation in nausea and vomiting symptoms in early pregnancy, in a group of sufferers.

Design and Setting: Prospective cohort with women recruited from 15 May 2014 to 17 Feb 2017 by SPD Ltd, who were researching hormone levels in early pregnancy and who extended the study to include the description of pregnancy symptoms

Methods: Daily symptom diaries of nausea and vomiting were kept by these women who were trying to conceive. They also provided daily urine samples which when analysed enabled the date of ovulation to be determined. Data from 256 women who conceived during the first month of the study were included in this paper. Daily symptom patterns and changes in daily patterns by week of pregnancy were modelled. Functional data analysis was used to produce estimated symptom probability functions

Results: There is a peak of probability of nausea in the morning, a lower but sustained probability of nausea throughout the day and a slight peak in the evening. Vomiting has a defined peak incidence in the morning.

Conclusion: Referring to nausea and vomiting in pregnancy as simply “morning sickness” is inaccurate, simplistic and therefore unhelpful.

INTRODUCTION

Nausea and vomiting have been known to be early signs of pregnancy for several thousand years, (1) The phrase to describe it as “morning sickness” has been in widespread use for nearly two hundred years (2). The use of the term is felt by many women who have suffered from it, to trivialise the condition (3). This is especially felt by women who have experienced severe symptoms (3).

Although nausea and vomiting of pregnancy (NVP) is now rarely life threatening, it can have a profound effect on the quality of women’s lives. Severe NVP can cause feelings of depression, (4) difficulties between partners (4) less effective parenting (5) and concern for the health of the unborn child.(4) Some women have such severe NVP that they are less likely to have another child, (4) or they consider termination of subsequent pregnancies. (6) In some women the condition is so intolerable that they actually elect to have a termination of the current pregnancy, even if it was very much wanted (6).

The condition also has significant economic impact. It has been recently estimated that the annual costs to the NHS in England and Wales of managing nausea and vomiting of pregnancy are around £62 million (7)

The condition also has an economic impact through time lost to paid work by women suffering from the condition. In one study around 35% of women in paid work lost time from the condition, causing an estimated loss of 8.6 million hours to paid work per year. (8)

Several studies have reported that women say that the symptoms of nausea and vomiting occur before and after 12 midday (8) and in severe cases can go on throughout the waking hours (9). In spite of this the widespread use of phrase morning sickness persists.

In this paper we have used a dataset of daily NVP symptom diaries kept by 256 women who were trying to conceive and were participating in a cohort study. The dataset also recorded demographic details of the women, their date of LMP, date of ovulation, and daily Human Chorionic Gonadotrophin (hCG) urine levels.

We recently described the onset of NVP from the day of ovulation (10), and in that publication , argue that it is a much more accurate way of describing the onset of pregnancy than is the usual method of using day of the last menstrual period (LMP). Therefore this paper also uses time from the day of ovulation to date the onset of pregnancy.

We have modelled the daily symptom patterns, as well as daily and weekly variation to provide a better understanding of the symptom patterns of NVP, to further understand whether the term “morning sickness” is valid.

METHODS

The cohort study was carried out by SPD Development Company Limited, a company that focuses on home diagnostic testing such as pregnancy testing, ovulation testing and fertility monitoring under the Clearblue brand (trial registration number; clinical trials.gov NCT01577147). The study was originally designed to investigate hormone levels in early pregnancy but was extended to include the study of pregnancy symptoms. Recruitment for the study was through advertisement on the company's website and study was open for recruitment from 12 May 2014 to 25 November 2016. First volunteer was recruited on 15 May 2014 and final volunteer for the cohort reported here completed the study on 17 February 2017. Each volunteer was interviewed and only included in the study if she fitted the inclusion criteria, which were: age over ≥ 18 years old, seeking to become pregnant and has regular menstrual periods. Exclusion criteria were medical conditions that contra-indicate pregnancy, known infertility or having treatment for infertility or women who were currently pregnant. The study was approved by SPD ethics committee on 9th April 2014 (Protocol-0400 Revision 8).

Initially, 1443 women who were planning to become pregnant were recruited into the study. 1073 of those women did not achieve pregnancy in a one-month period, and 82 women had pregnancy losses. Out of the remaining 288, who successfully conceived, 32 dropped out of the study. Hence, the study population includes 256 women.

Volunteers were recruited preconception, and began the study on day 1 of their next menstrual cycle. On enrolment to the study, participants provided their demographic and menstrual cycle information and previous pregnancy-related medical history. Throughout the study they provided information about their symptoms by completing a daily diary and also provided a daily urine sample which provided hormone levels. Lutenising hormone (LH) was measured (AutoDELFI, Perkin Elmer) in order to determine the day of LH surge, which precedes ovulation by approximately 1 day.(11,12) Day of ovulation provides the most accurate method for determining pregnancy duration (13). Human Chorionic Gonadotrophin (hCG) was measured (AutoDELFI, Perkin Elmer) in late luteal phase and throughout early pregnancy, in order to identify viable pregnancy and early pregnancy loss.

Women recorded in their symptom diaries whether they had experienced each of nausea and vomiting for each hour in the day. They started their pregnancy diaries once they had notified the researchers of a positive pregnancy test and were instructed to finish completing the diaries at day 60 of the pregnancy, measured from LMP (date of last menstrual period). If a woman did not achieve pregnancy, she was instructed to collect urine samples and complete the symptom diaries only up to day 7 of her next cycle. 194 of the participants also responded to a follow-up questionnaire on the outcome of their pregnancy, including the gender and weight

of their baby/babies, the type of delivery, and information about any complications during the delivery

Statistical methods:

The anonymised dataset was transferred to the Department of Statistics at the University of Warwick and examined by DI and ET using R Studio statistical Software. Daily symptom patterns and changes in daily patterns by week of pregnancy were modelled Functional data analysis was used to produce estimated symptom probability functions. For this a Fourier basis system was used with 23 basis functions. The roughness penalty method was used to smooth the discrete data with an integrated squared second derivative roughness penalty. Then Principle Component Analysis was used to investigate the main deviations of individual's symptom patterns from the mean pattern (14) .

RESULTS

Insert Table 1: Demographic characteristics of 256 women

The study population had a mean age of 30.4, which precisely corresponds to the mean age of mothers in England and Wales in 2016, according to the Office for National Statistics' latest publication on the subject [15]. The youngest volunteer was 18 and the eldest 43.

The mean BMI of the whole study population was 27.02 kg/m². Almost all (95%) of the women were white, with 90% of those being European. The study population does not reflect a broad range of ethnicities or races. There is a high education level in the population with 75% of women having an education level of A levels or higher.

More than half, 60%, of the women had previously had children with 68% of those women having only had 1. One volunteer had already had 7 live births. Almost half, 43%, of the cohort had previously suffered at least one miscarriage. Before conceiving during this study, the volunteers had been trying to conceive for a mean of 8.42 months, median 5 months.

Symptom Diaries

A total of 7584 daily diaries were completed with a mean of 30 diaries per participant. The mean start day of the diaries was day 30 of pregnancy measured from LMP and day 13 measured from ovulation. A sixth (44, 17%) of the 256 participants stopped filling in diaries before day 60 from LMP. For the following analysis, start of pregnancy was measured from ovulation and not LMP as it is a more accurate measurement [7]. Table 2 shows the number of participants that completed diaries in each week. Week 4 had the highest completion rate with 99%

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6 of participants. Weeks 2 to 7 are the only weeks in which symptoms can be reliably
7 reviewed as weeks 1 and 8 have few participants. There are only recordings up to
8 week 8 of pregnancy from ovulation, therefore only symptoms in early pregnancy
9 are considered
10

11 **Insert Table 2: Number of completed diaries in each week of pregnancy, dated** 12 **from ovulation** 13

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15 A participant was said to have symptoms if they had experienced at least one hour of
16 nausea or vomiting during the days they completed diaries. Out of the 256
17 participants who completed diaries, 15 (5.8%) had no symptoms, 89 (34.8%) had
18 nausea only, 150 (58.6%) had both symptoms and 2 (0.8%) just had vomiting with
19 no nausea. This brings the symptom prevalence to 94.2% of participants, much
20 higher than found in previous studies. Volunteers who experienced nausea had
21 symptoms a mean of 3.4 (median 2.7) hours per day, with 23% averaging at least five
22 hours per day. Only 17 of the 152 (11%) women who experienced vomiting did so
23 during more than one hour per day. The mean day of onset of symptoms was day 34
24 measured from LMP and 18 from ovulation, which is in week 3 of pregnancy
25 (measured from ovulation).
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30 **Daily Symptoms Patterns**

31 Despite the term being “Morning Sickness”, the data shows at least one participant
32 experienced both nausea and vomiting in all hours of the day except between 11pm-
33 12pm for nausea and 11pm-1am for vomiting. The most common hour for
34 volunteers to experience nausea and vomiting was between 9-10am with 82%
35 experiencing nausea in this hour and 29% experiencing vomiting. In each hour of the
36 day between 7am -10pm more than 60% of participants experienced nausea and
37 more than 13% experienced vomiting. In general vomiting is most common between
38 the hours of 7am-1pm but nausea is highly likely throughout the whole day time, not
39 just the morning. Although these statistics are not individual symptom patterns it
40 shows there is a very large proportion of women who have symptoms throughout
41 the whole day. See figure 1
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Weekly Nausea and Vomiting Pattern

Insert Figure 1: Estimated probability functions for Nausea by week of pregnancy from Ovulation

In order to look at how the daily pattern changes by week, the percentage of nausea and vomiting experienced for each hour of the day for each week was calculated for the participants collectively. Weeks 2 to 7 are considered, as at least 141 women recorded a diary (Table 2). Data from all participants who completed diaries in each week were included. The probability functions shown in Figure 1 and 2 were estimated using functional data analysis. Figure 1 shows the estimated probability of nausea throughout the day for each week of pregnancy as measured from ovulation. There is a similar pattern in each week of pregnancy, with a peak of probability of nausea in the morning then a lower but sustained probability of nausea throughout the day with a slight peak in the evening. The general probability of nausea throughout the day is different between weeks of pregnancy. Week 2 and week 3 have the lowest likelihood of nausea, with an increase in week 4 then weeks 5,6,7 have the highest probability of nausea symptoms with similar patterns. For all weeks from 2 to 7 of pregnancy, nausea was experienced at all hours in the daytime, not confined to the morning.

For vomiting there is a defined peak of probability in the morning for each week (Figure 2). The later the week, the higher probability of vomiting, with the highest being in week 7, when about 10% of women vomited. Similar to the nausea patterns shown in Figure 1, there is still a sustained probability of vomiting throughout the day until the evening, however for week 2 and 3 the probability of vomiting is very low. The rise in symptom probability in the morning is more defined for vomiting than nausea.

Nausea Patterns at an individual level

Although Figure 1 represents the estimated probability of nausea for all participants collectively, it does not necessarily represent an individual participant. At an individual level the most common daily pattern was found to be similar to that of the collective pattern but with a much higher (e.g 50%-60%) or lower < 10%) probability of nausea throughout the whole day. This accounted for 67.1% of variation. Some individuals also exhibited a pattern close to the collective pattern but with an increased or decreased probability of nausea in the morning. A small proportion of volunteers showed to have a peak of symptoms in the middle of the day.

Insert Figure 2: Estimated probability functions for Vomiting by week of pregnancy from ovulation

DISCUSSION

We have been able to gather information from a well described, representative cohort of women who have prospectively collected information on their NVP symptoms from the onset of pregnancy to describe their daily and weekly symptom patterns. For the first time in the literature we have used statistical modelling techniques to accurately describe the variations seen in these symptom patterns.

This paper shows that it is not appropriate to call NVP “morning sickness”. Our data describes in detail the daily and weekly pattern of NVP from its early onset. It clearly shows nausea and vomiting symptoms can occur throughout the day. Vomiting does mostly occur in the mornings. Nausea, which many sufferers describe as the worst aspect of their symptoms (8) , can occur throughout 24 hours. The continued use of the term “morning sickness” could imply that symptoms only rarely occur in the afternoon and evening so that sufferers will have significant parts of the day symptom free and so be able to do housework, paid work and look after their families for the majority of any 24 hour period. This study shows that this is an incorrect assumption and that symptoms, particularly nausea can occur at any time of day.

Our results confirm and amplify findings from other studies. In their paper from 1993 (8) Gadsby and Barnie-Adshead report that 92.5% of women with NVP symptoms experienced them both before and after noon. In a review of the literature on NVP, a total of 13 papers covering 7904 women were found that describe some information about daily symptom patterns. All describe symptoms occurring both before and after midday. (16)

The strengths of our study are that it is based on a sizable cohort of women who are broadly representative of women becoming pregnant in the UK. The data on NVP symptoms was collected prospectively from the onset of pregnancy and we can pinpoint the day of ovulation through the measurement of the LH surge, so we can accurately date the pregnancy. We have used statistical methodology to accurately describe daily and weekly symptom patterns for the first time.

Some weaknesses of the study are that the dataset has a under representation of women from lower socio-economic (educational) backgrounds and black and minority ethnic backgrounds. We assumed that days without diary entries were days without symptoms. Women in the study stopped recording NVP symptoms at around week 9 of pregnancy when a number were still experiencing symptoms so that this dataset cannot be used to reliably describe NVP symptom cessation. As volunteers were instructed to start collecting NVP data on day 30 following LMP, there is some heterogeneity in start date relative to day of ovulation. As these

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6 results use true pregnancy duration from ovulation, week 4, for example, might be
7 weeks 6 to 9 from LMP.
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10 This paper further reinforces the idea that calling NVP just “morning sickness” is
11 inaccurate, simplistic and unhelpful. We wonder what further data could be needed
12 for the media and general public to stop using the term “Morning sickness” and for
13 them to refer to the condition as “Nausea and Vomiting of Pregnancy (NVP) “
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15
16 **Funding:** Study was funded by SPD and SJ is employee of SPD Development
17 Company Limited, a fully owned subsidiary of SPD Swiss Precision Diagnostics GmbH,
18 Geneva; the manufacturer of Clearblue pregnancy and fertility tests.
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21 **Ethical Approval** The study was approved by SPD ethics committee on 9th April 2014
22 (Protocol-0400 Revision 8).
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25 **Competing Interests** RG, DI, ET and JLH have no conflicts of interest to declare
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28 **Acknowledgements.** We would like to thank all the women who took part in this
29 study
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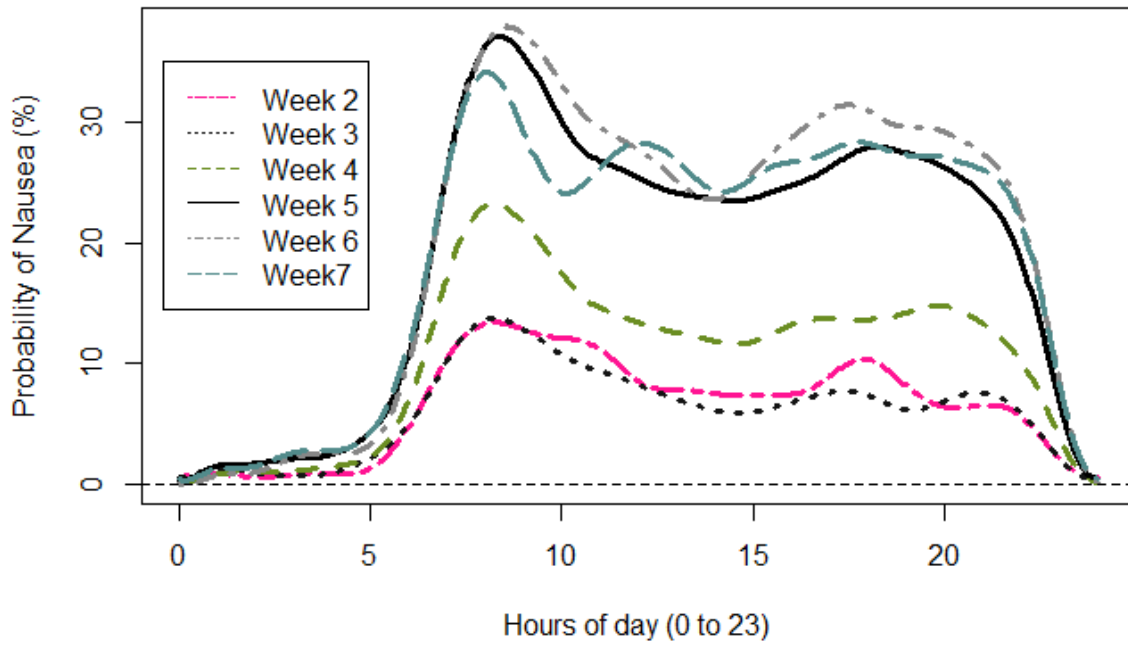
Symptoms	No (%)
	Nausea n=255
Age	
≤ 25	35 (0.14)
[25,30]	97 (0.38)
[31,max)	124 (0.48)
BMI*	
≤ 25	119 (0.46)
(25,30]	63 (0.25)
(30,max)	73 (0.29)
Smoking status	
Prev & Curr	100 (0.39)
Never	156 (0.61)
Live Births	
0	103 (0.4)
1	105 (0.41)
> 1	48 (0.19)
Miscarriages	
0	145 (0.57)
1	68 (0.26)
>1	43 (0.17)
Education level	
level 1, 2 or lower	82 (0.32)
A Levels	65 (0.25)
Higher	109 (0.43)

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Week from Ovulation	1	2	3	4	5	6	7	8
No. volunteers	2	195	249	254	242	225	141	7
Percentage of sample population	1%	76%	97%	99%	95%	88%	55%	3%

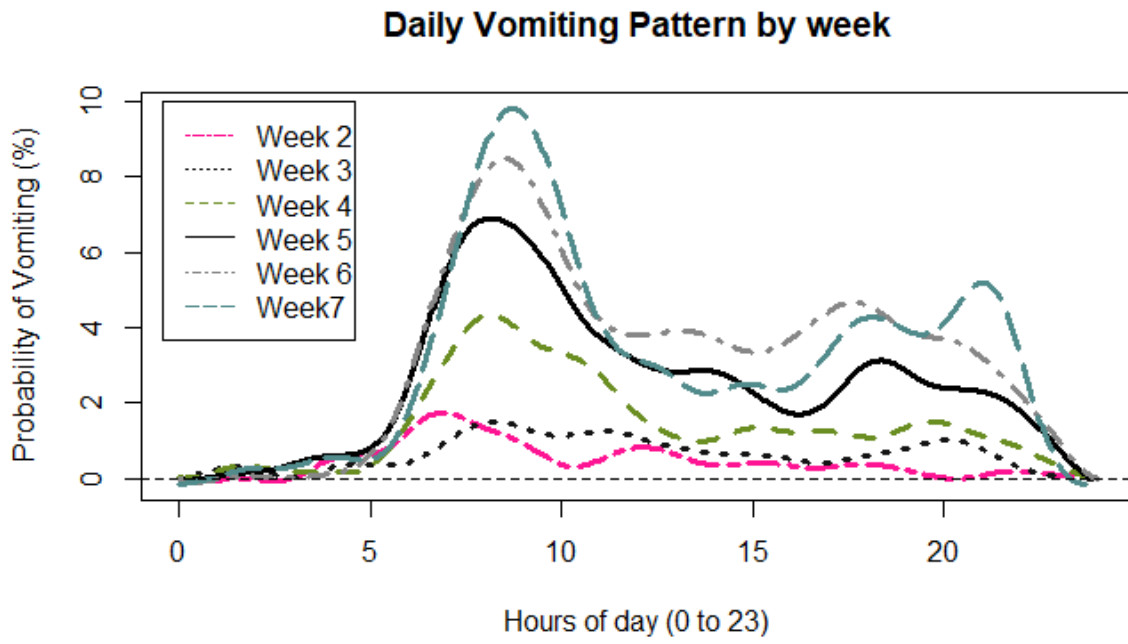
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Daily Nausea Pattern by week



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