INTRODUCTION TO A LITERATURE REVIEW OF PREGNANCY SICKNESS

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Introduction

DESCRIBED CLINICAL FEATURES OF NAUSEA AND VOMITING OF PREGNANCY (NVP) AND HYPEREMESIS GRAVIDARUM (HG)

The object of this review is to describe the clinical features of nausea and vomiting of pregnancy (NVP), so that this overlooked, under researched and poorly treated condition can be better understood as a significant medical problem. Using criteria quoted later in this introduction we have culled 144 papers from Medline studies published during the last 35 years under the headings of Nausea and Vomiting of Pregnancy or Hyperemesis Gravidarum (HG) and related papers. NVP has clinical features that can be defined, and NVP can be related to personal and obstetric factors effecting the lives of women at the time of early pregnancy.

The incidence of NVP in normal singleton pregnancies is reported to occur in 73.4% of 39,710 pregnant women. (Review Index RI, 1). Group Literature Review Index references are (abbreviated) to RI plus number. Individual Review references are shown in plain brackets.

Nausea is reported in all women who have NVP except for 0.64% who have vomiting alone (RI 3), making nausea the most frequent symptom. 32.0% of 8,435 pregnant women had nausea only (RI 2a).

EPISODIC NATURE OF NAUSEA

NVP follows a well-defined episodic pattern. 85% of women with NVP have at least two symptom episodes per day, with 70% of episodes lasting 1-4 hours (50). These episodes of nausea have a consistent daily pattern of timing, frequency and duration during the peak symptoms of each individual pregnancy (RI 2c). Recording the pattern of these episodes using a structured daily diary enables women to predict when they will be able to take nourishment at symptom-free intervals each day.

Severity of nausea in a study of 363 women, 292 of whom had NVP, the mean number of hours of nausea per pregnancy was 56 hours and this symptom lasted for a median of 41 days (almost 6 weeks) (50). In 36% of women who had NVP, the nausea lasted for up to 33 hours per pregnancy, but 21% had nausea which lasted for 100-300 hours and a further 10% from 300-700 hours, a thoroughly distressing and depressing experience (RI 2d).

Vomiting is also a significant symptom of NVP, occurring in 47.1% of 19,330 pregnant women (RI 3a) with about 10% of pregnant women experiencing 40 or more vomits during their pregnancy (RI 3c), but women describe nausea as the more distressing symptom (RI 2e).

Absence of NVP. 25% of 24,322 pregnant women who deliver a singleton normal infant did not have any NVP (RI 6). These papers specifically reported the women did not have any NVP, whereas the pregnant women with no NVP which could be inferred from RI 1 mentioned in paragraph 2 above (26.6%), no NVP was not specifically reported.

ONSET, PEAK AND CESSATION OF NVP

The mean day of onset of NVP is day 39 from LMP. (All day dates that are given in this Introduction are measured from the first day of the last menstrual period (LMP)). However 13% of pregnant women start NVP before day 28, which can be the first symptom of their pregnancy. 90% start NVP before day 56, that is the end of week 8 (RI 4). The weeks of peak incidence, that is the weeks when the maximum number of women were experiencing these symptoms, were weeks 7-9. The symptoms rise sharply from week 6 and tail off gradually after week 10 (50). Cessation of NVP was not so well defined as the onset of symptoms (RI 5). The range was 91% of women's NVP ceased by the end of the 16th week in our study (50), but 90% resolved by the 22nd week in another study (80). In our study (50) the mean day of cessation was 84 and occurred at approximately the same day whether NVP began early or late or began severely or mildly, suggesting that possibly a second factor is responsible for the cessation of the condition, a view that is supported by statements of Weigel, M. (31). NVP will stop suddenly in around 30% of women, but will taper off gradually after week 12 in the majority (R15.) About 10% of women find that their NVP symptoms get worse after week 9 from LMP. (R14f)

TIME OF DAY OF NVP, MORNING SICKNESS IS THE WRONG NAME FOR PREGNANCY SICKNESS

Several authors consider the name morning sickness to be inaccurate (RI 7c). Pregnancy sickness or nausea and vomiting of pregnancy give a simple, but far better description of the condition. The symptoms only occur exclusively in the morning in about 14% of women who have NVP (RI 7a), a mean figure of five studies, and symptoms occur after midday in approximately 70% of women with NVP (RI 7b). Dilorio (98) makes the relevant statement that continued references to NVP as morning sickness may be confusing for women pregnant for the first time, when they experience the symptoms at other times of the day. Moreover, frustration can ensue when attempts to seek suggestions for relief from healthcare professionals and self-help books lead only to interventions for morning sickness. In addition, if a woman suffers only from morning sickness she does not have the more severe or most severe symptoms of NVP. In fact the name morning sickness may give the impression that NVP only occurs in the morning, and is therefore not a significant problem. We wish to join the chorus of eight authors in this review asserting that the condition should be called pregnancy sickness or nausea and vomiting of pregnancy rather than morning sickness (RI 7c).

RECURRENCE OF NVP IN SUBSEQUENT PREGNANCIES

Probably one of the questions healthcare professionals will be asked most frequently on the subject of NVP is, “what is the likelihood of similar symptoms of NVP recurring in subsequent pregnancies?” (RI 8). There is surprisingly and disappointingly very little useful information in the literature that sheds light on this problem. There is no doubt that the severity of NVP can vary from one pregnancy to the next in the same individual woman (RI 8a), but that does not answer the question. The best answer that can be given at present, from our own studies and six other investigations, is that about half to two thirds of women will have similar NVP in successive pregnancies, whether these symptoms have been severe or mild in the previous pregnancy (RI 8c). Obviously this leaves one third to one half of women who will have varying degrees of pregnancy sickness symptoms in the pregnancies subsequent to their first. This may mean worse symptoms in subsequent pregnancies after little or no trouble in the first pregnancy, or better symptoms after very troublesome pregnancy sickness in a previous pregnancy. Weigel (31) has stated that the recurrence of NVP pattern is most apparent in women who will have a very low risk of recurrent NVP after infrequent nausea in previous pregnancies. More recent reports suggest that hyperemesis gravidarum has a recurrence rate between 70% and 80% in further pregnancies for the same woman (RI 8C).

HYPEREMESIS GRAVIDARUM (HG)

HG is pregnancy sickness at its most severe. It occurs in about 1% of pregnancies range 0.1% to 1.3% in 16 references (RI 9a). HG develops from NVP in six references (RI 2f). The definition of HG used in nine papers in this review which was written by Fairweather in 1968 states, vomiting occurring in pregnancy starting before the 20th week of gestation, and of such severity to require the patient’s hospital admission, without coincidental medical conditions (10). Other important additions to this definition from various authors include maternal weight loss of more than 5% of pre-pregnancy weight, dehydration, ketonuria, and electrolyte imbalances, most significantly

hypokalaemia. The mean weeks for hospital admission for HG were 10-11 from LMP (RI 9b). The length of stay in hospital for HG varied greatly in different hospitals from 1.8 days to 12.8 days per patient. Annually in the United States more than 50,000 women are hospitalised with the diagnosis of HG with an average hospital stay of 4 days per patient (RI 9c). Readmission to hospital for HG in the current pregnancy again varied for different centres between 8.0% and 31% of patients. After a therapeutic abortion recovery from HG occurred promptly (RI 9e) and after delivery the nausea lifts within a minute or two of the placental circulation closing down (RI 9e).

The importance of Hyperemesis Gravidarum is shown by the incidence of Finished Admission Episodes of Excessive Vomiting in Pregnancy NHS hospitals in England, Years 2004/2005 to 2005/2006 - Hospital Episode Statistics 2004/5 23,738; 2005/6 25,685. "Copyright © 2007 re-used with permission of the information centre. All rights reserved" (RI 9f). When compared to a similar figure for the year 1989/90 of 8,637 finished admission episodes for excessive vomiting in pregnancy shows a nearly threefold increase. The authors of this review agree with eight authors (R142a) and suggest the most significant cause of this increase is the lack of safe pharmacological treatment given for NVP in early pregnancy in England during those years 1989/90 to 2005/6 (RI 42a).

COMPARISON OF NVP WITH VARIOUS FACTORS IN WOMEN'S OBSTETRIC AND PERSONAL HISTORIES

104, marked in references with an asterisk, of the 144 papers assembled in this review relate symptoms of NVP to significant factors in women's personal and obstetric histories, including the findings of our own study (53). The results from each group of papers can be conflicting so that they do not give a definitive answer for the subject, for example, the woman's age did not relate to NVP in 11 references, whereas women of younger age (up to 26 years) were more likely to have increased NVP in another 11 references (RI 18). O'Brien (48) suggests that discrepancies in results of research findings for NVP may be accounted for by the method used to investigate NVP. In this respect, Chin (63) reporting on the symptoms of NVP, states recollection of symptoms and events may be inaccurate. Weigel (78) writes, differences among previous studies of NVP may be due to the following:- population differences; methods of selection; different classification system for NVP and for foetal outcome; or failure to control confounding variables.

The studies used in this review for comparing NVP with various factors in women's personal and obstetric histories do have different methodologies, particularly two. First, the mean time from LMP that information was first collected, the majority of studies collect retrospective information, relying upon memory which is imperfect. Secondly, the method of grading symptoms of NVP. The grading of NVP should be specific, one example being the hours of each day nausea lasted which can be accurately measured using a structured daily diary. This will avoid vague grading such as comparing (1) no NVP with (2) nausea only, or (3) nausea and vomiting. We would suggest that future studies/papers should aim to have the following criteria for the comparing of NVP with any other factors. (1) A well-defined basic population with clearly defined limited exclusions. (2) Be prospective rather than retrospective. (3) If retrospective, include the day from the LMP that information was first collected. (4) Specific grading of NVP with the use of a structured daily diary kept by the pregnant woman of her NVP. (5) An initial questionnaire to obtain relevant personal and obstetric information completed with a trained medical professional. (6) An ultrasound scan to

confirm stage of gestation and the expected date of confinement. (7) Regular follow-up consultations with the medical professional at least once per fortnight until NVP symptoms have ceased for two weeks, and thereafter the facility for further contact to be made if NVP recurs. (8) A post-natal questionnaire completed by the medical professional from hospital or community medical records, confirmed by an interview with the infant's mother. (9) The use of modern statistical methods.

A similar problem of methodology can arise with the studies of Hyperemesis Gravidarum. Here the first problem is the definition of HG. Some papers do not define HG, indeed the diagnosis may only be severe vomiting (66). When multi-centre information concerning women with HG are brought together into one study, the diagnosis of HG did vary considerably between centres (29). The definition used by Fairweather and modified by other authors quoted in RI 9 may be acceptable. Four authors have compared mild HG and severe HG. Mild HG referred to those women simply admitted to hospital with HG. Severe HG was defined as admission to hospital accompanied by either loss of more than 5% of pre-pregnancy weight (42) or one of the following:- ketonuria, electrolyte disturbances (28) (62), or single compared to multiple admissions for HG in the current pregnancy (33). The other standard criteria for the comparison of HG with any other obstetric or personal factor should be the same as those for a NVP study.

These suggested criteria for comparison of NVP with any other obstetric or personal factor have only been completed by two authors in this review. However, all the information obtained throws some light on the specific subject being studied. Therefore, the information should not be ignored but used profitably, especially where a majority report the same result. We agree with the statement of Pettigrew "A stainless steel law of systematic reviews also generally applies that is, the more rigorous the review, the less evidence there will be to prove a point". (111)

The objectives of the studies in this review were either to find some clues to the aetiology of NVP, or to find an association between NVP with conditions that might arise later in pregnancy or at its outcome. In the summary of the present review (RI 44) the probability of NVP was found to be independent of (not related to) a woman's marital status (RI 11), ethnic origin (RI 13), pre-pregnancy diabetic state (RI 22), pre-eclamptic toxaemia in the current pregnancy (RI 28), delivery before 37 weeks (RI 30), stillbirth or perinatal mortality in the current pregnancy (RI 36). The probability of NVP was also found to be not related to (RI 45), a wanted or unwanted pregnancy (RI 12), genetic factors (RI 14), alcohol use (RI 17), maternal age (RI 18), parity (RI 19), sex of the baby (RI 31) and any specific fetal abnormality (RI 35).

The probability of NVP was higher (or greater) (R1 44) when the woman had NVP in a previous pregnancy (R1, 8b, 8c) was a non-smoker (RI 16), had nausea when previously taking an oral contraceptive (RI 21), with a hydatidiform mole (RI 24), with a twin pregnancy (RI 33), with an increase of food cravings (RI 37) and with excessive caffeine intake (RI 38). The probability of NVP was lower (the only negative association) for spontaneous abortion (RI 26). However, the present review has shown that 25% of women who have a normal singleton delivery also have no NVP (RI 6). Therefore, the absence of NVP should not be viewed as a negative consideration for the outcome of a pregnancy. On the other hand, provided a hydatidiform mole or twin pregnancy are excluded by an ultrasound scan, the presence of NVP, even severe NVP or HG may be viewed as an encouraging sign for a successful outcome of the pregnancy.

Hyperemesis Gravidarum alone, but not NVP other than HG, was associated with young age, up to 25 years (RI 18), nulliparity (primiparity in earlier papers) (RI 19), a previous unsuccessful pregnancy (abortion, stillbirth or neo-natal death) (RI 25), reduced maternal weight gain in the current pregnancy (RI 27) and a reduced sex ratio (female excess) of offspring (RI 31). It is difficult to explain the reason that only HG should be associated with these pregnancy related subjects but it may be of interest to the clinician. Severe HG, included loss of 5% or more of pre-pregnancy weight or multiple admissions for HG, can be associated with intra uterine growth retardation (RI 29), reduced birth weight of the baby (RI 32), but not with delivery before 37 weeks of gestation (RI 37).

OTHER SIGNIFICANT FACTORS RELATING TO NVP AND HG

Natural Ways to Improve NVP

Eating during nausea free episodes, which can be anticipated by using a structured daily diary, especially eating immediately she feels hungry, or nibbling food even if she feels nauseous (RI 39). The usual advice of small meals often is still important but eating any time the nausea goes off is even more relevant. Stop eating as soon as she feels full, don't eat the last crust. Let them eat their cravings, for women with severe NVP will still have cravings (RI 37), or whatever she fancies with certain important exceptions such as paté, liver, soft cheeses, under cooked eggs and peanuts. Whether she can eat or not encourage plenty of drinks in small frequent quantities avoiding all alcoholic drinks or more than a total of 3 cupfuls of either tea or coffee per day (RI 38).

Rest (RI 39) The experience of ladies with severe NVP shows that rest, lying down to avoid positional changes especially after meals or when feeling nauseous is the second most important way of naturally relieving the nausea.

Minimising all odours (RI 39 & RI 40) is also so important for her. Associated with her nausea increased or altered olfactory sensation (sense of smell) is her problem (RI 40). The most troublesome odours are fried or fatty cooking smells and other cooking odours. Even usually inoffensive odours such as perfumes or deodorants can be most troublesome. Some women experience increased severity to many different odours causing them to make statements such as "I can smell odours in a room nobody else can smell". (RI 40)

Adverse effects of severe NVP on the quality of women's lives. As yet no acceptable method for analysis of descriptive papers has been identified. Therefore, all the papers describing the clinical features of NVP (RI 1-9), the time lost from work (RI 41) and the adverse effects of the mother-to-be's quality of life (RI 42) were accepted for analysis. Certainly the studies related to these two latter subjects are retrospective, sometimes the severe symptoms occurred a long time earlier, and may be considered subjective depending upon the woman's reaction to her NVP. These studies also contain the reports of a selected group of women suffering from the more severe symptoms of NVP. Nevertheless, they are significant because they give a relevant picture of the adverse effect NVP has on the mother-to-be's lifestyle, a most important but often neglected subject.

These women with severe NVP reported the following adverse effects to their lives (RI 42), 52% said they felt depressed always or most of the time; 40% said NVP had an adverse effect on the

relationship with their partner; 50% of women feared that NVP would harm their baby. Even mild to moderate NVP caused depression most of the time in 21% of women (RI 42). NVP can impose substantial lifestyle limitations on pregnant women, interfering with cooking, shopping and interaction with their children (81). Severe NVP caused 14% of women to state they would be less likely to consider having more children (91), and 25-59 legal abortions per year in England and Wales from 1979 to 1992 were performed due to "excessive vomiting of pregnancy" (100). This figure in 2002 - 2006 was less than 10 annually in England (R142). The authors of eight studies have stated that the time lost from work due to NVP is significant (RI 41), in fact it has been estimated that 8.5 million hours per year in England and Wales are lost from paid employment due to pregnancy sickness symptoms (50).

These facts and figures show the distress nausea and vomiting of pregnancy can cause. NVP is an under-researched and poorly treated condition. Further investigation into its aetiology, and safe effective treatment which is currently available, and extensively used in Canada, please see our website www.pregnancysicknesssupport.org.uk given early in the condition (R142a), can be of great benefit to women suffering from NVP.