Nausea, pregnancy sickness and the role of dietary protein

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Abstract

Nearly 80% of mothers suffer from pregnancy sickness, primarily in the first trimester. Many theories have been developed to account for this condition and these have suggested that varied aetiologies are involved. However, no clear cause has been established that has led to the alleviation or reduction of the majority of the symptoms of pregnancy sickness.

It is proposed that pregnancy sickness nausea, in line with other instances of nausea, will occur when the ability of the organism to maintain homeostasis is impaired. Moreover, it is suggested that pregnancy sickness nausea should be recognised as a warning sign that the maternal body is experiencing a protein deficiency of rapid onset.

Examination of relevant clinical findings has revealed that protein reduces pregnancy nausea and gastric dysrhythmias. It has also been shown that protein metabolism is aided by two of the dietary aids widely used by pregnant mothers to combat nausea. Conversely protein synthesis is inhibited by several substances common to the initial food aversions of pregnancy.

Pregnancy sickness and other instances of nausea may share the same aetiology, and might be similarly resolved.

Introduction

Pregnancy sickness is characterized by symptoms that include either nausea alone, or both nausea and vomiting, and is associated with between two-thirds (Flaxman &

Sherman, 2008) and 80 per cent of all pregnancies (Quinlan & Hill, 2003). Thus, the majority of mothers experience some degree of nausea and vomiting and this occurs mainly during the first trimester (Lacasse, Rey, Ferreira, Morin & Berard, 2008). Pregnancy sickness can range from slight nausea occurring briefly during parts of the day, to feelings of continual nausea, retching and vomiting throughout each day (Gadsby, Barnie Adshead & Jagger, 1993). This study showed that 28% of mothers had nausea only, whilst 52% had both nausea and vomiting. In a small number of cases, where women have had extreme nausea and vomiting, this has prompted the mothers to request legal abortions (Office of Population Censuses and Statistics, 1995).

Although the effects of pregnancy sickness are well documented, its causative factors have not been satisfactorily resolved (Jewell & Young, 2003; Koch & Frissora, 2003; Swallow, Lindow, Masson & Hay, 2005). Many different theories have been suggested to explain why pregnancy sickness occurs. These theories cover both the psychological and physical aspects, such as the endocrine, psychosomatic, immunological, genetic incompatibility, carbohydrate metabolism, vitamin B6, gastric dysrhythmia, and hyperolfaction factors (von Dadelszen, 2000). Recent work hypothesizes roles for *Heliobacter pylori* (Shirin, Sadan, Shevah, Bruck, Boaz, Moss, et al., 2004), an obstetric syndrome (Goodwin, 2002) and an evolved adaptation for maternal and embryo protection (Flaxman & Sherman, 2000).

Because insufficient evidence is available to indicate a shared aetiology with many of the other clinical features that occur in the first trimester concurrently with pregnancy sickness, no universal theory has yet been put forward to explain pregnancy sickness in its entirety. Other clinical features can include food aversions (Bayley, Dye, Jones, DeBono & Hill, 2002), food cravings (Whitehead, Andrews & Chamberlain, 1992), fatigue (van Lier, Manteuffel, Dilorio & Stalcup, 1993), anxiety and depression (Koken, Yilmazer, Cosar, Sahin , Cevrioglu & Gecici, 2008), gastrointestinal motility disorders and constipation (Baron, Ramirez & Richter, 1993) and gastric dysrhythmias (Koch, Stern, Vasey, Botti, Creasy & Dwyer, 1990).

Many of the investigations carried out into the aetiology of pregnancy sickness have concentrated on a single aspect or one area of the effects experienced by mothers. With so

many aspects involved, it is proposed to seek for and investigate the possibility of a common denominator responsible for initiating the symptomatology of pregnancy sickness.

In searching the literature, of particular interest was a study demonstrating that protein meals reduced nausea and gastric slow wave dysrhythmic activity in first trimester pregnancy (Jednak, Shadigan, Kim, Woods, Hooper, Owyang & Hasler, 1999). Protein meals were shown to be more effective in reducing nausea than those predominately of carbohydrate or fat. Given that protein is essential for the health and growth of the human body, this study seems to point the way to possible control over the severity of nausea. Elsewhere similar suggestions were made by Levine, Muth, Williamson and Stern (2004), who found that liquid protein-predominant meals were most effective in suppressing the development of gastric tachyarrythmia and nausea. Previously dysrhythmic activity has been linked with nausea in pregnancy (Koch et al., 1990*)* and dysrhythmias have been shown to commence before nausea is experienced (Jednak et al., 1999).

Hypothesis

Herein it is proposed that pregnancy sickness nausea occurs when the protein requirements of the embryo and maternal body exceed the resources immediately available for protein synthesis. In this instance the maternal body has difficulty in maintaining homeostasis, and will require an increased quantity of protein from its own resources, or from the diet, to regain homeostatic balance. Without sufficient protein becoming rapidly available, the maternal body malfunctions. The resulting nausea, often preceded by gastric dysrhythmias, should be recognised as a warning sign that a protein deficiency of rapid onset is occurring. Ingestion of protein in the first trimester, appropriate to the maternal requirements dictated by the experience of nausea, would suppress the nausea and the gastric dysrhythmic disturbance. It is also proposed that pregnancy sickness nausea is not unique, but is similar to many other instances of nausea, in that it is the result of a protein deficiency initiated when the body is subjected to acute physiological stress.

Supporting evidence

Any universal underlying cause of pregnancy sickness nausea should be able to explain the many physiological responses in the first trimester. These physiological responses include the detrimental actions on the embryo caused by substances such as alcohol, tobacco and caffeine, and the often beneficial actions produced by Vitamin B6 and ginger in helping to reduce pregnancy nausea. The protein deficiency hypothesis provides a universal explanation for these and for many of the clinical features occurring concurrently with pregnancy sickness.

Beneficial effects : Vitamin B6 and ginger

Vitamin B6 and ginger are two well known and researched natural remedies that mothers turn to in order to mitigate the severity of their pregnancy sickness. Vitamin B6 and ginger have both been shown, as detailed below, to have links with protein metabolism.

During pregnancy, vitamin B6 (pyridoxine) has been shown to reduce nausea in symptomatic women in the first trimester (Jamigorn & Phupong, 2007) and vitamin B6 also diminishes vomiting (Sahakian, Rouse, Sipes, Rose & Niebyl, 1991). Interestingly, not only were nearly 60% of all pregnant women found to be deficient in vitamin B6 (Heller, Salkeld & Korner, 1973), but vomiting also was significantly associated with a lack of vitamin B6 in the first six weeks of gestation (Emelianova, Mazzotta, Einarson & Koren, 1999). The close association of vitamin B6 with the nausea and vomiting in pregnancy is of note as it also has a role of central importance as a co-enzyme in the metabolism of amino acids (Institute of Medicine of the National Academies (IOM), 1998, p.150). Vitamin B6 has been shown to have a definite influence on liver protein synthesis during pregnancy in the rat (Ross & Pike, 1956).

Ginger also has the ability to reduce pregnancy-induced nausea (Willetts, Ekangaki & Eden, 2003), nausea and vomiting (Vutyavanich, Kraisarin & Ruangsri, 2001; Chaiyakunapruk, Kitikannakorn, Nathisuwan, Leeprkobboon & Leelasettagool, 2006), nausea and gastric dysrhythmias (Lien, Sun, Chen, Kim, Hasler & Owyang, 2003), and diminish or eliminate symptoms of hyperemesis gravidarum (Fischer-Rasmussen, Kjaer, Dahl & Asping, 1991). Ginger has also been found to reduce plasma vasopressin, which

increases in nausea and dysrhythmias (Koch et al., 1990). Ginger has a beneficial action in pregnancy for some mothers and can be linked to protein in that ginger contains proteases, with high proteolytic activity, which promote the digestive processes. (Thomson, Wolf & Allen, 1973).

Vitamin B6 and ginger have both been shown to reduce pregnancy nausea, and both aid protein metabolism. As protein reduces pregnancy nausea (Jednak et al., 1999), the supplementation of Vitamin B6 or ginger to the diet will improve protein metabolism and enable a faster reduction in the nausea, if sufficient protein is available to meet amino acid requirements at that time.

Dietary Aversions.

Food and dietary aversions are common in early pregnancy, and amongst those foods or substances most commonly avoided by mothers in the first trimester are coffee, alcohol and tobacco (Demissie, Muroki & Kogi-Makau, 1998). As coffee/caffeine, tobacco and alcohol have been shown to have a detrimental effect on the embryo, it was of interest to find that they also decreased or inhibited protein synthesis.

Coffee

Caffeine has been shown to inhibit both DNA and protein synthesis of the cells (Kanemaru, Rossowska, Yoshino, Yazdani, Narayanan & Nakamoto 1992), and also decreases protein synthesis in the rat brain (Felipo, Portoles, Minana & Grisolia, 1986). In 2009 Wendler, Busovsky-McNeal, Ghatpande, Kalinowski, Russell and Rivkees found that caffeine exposure during embryogenesis results in both short-term effects on cardiac development and long-term effects on cardiac function. It has also been shown that maternal caffeine ingestion during pregnancy causes a reduction in cerebral but not in body weight, and a decrease in protein content per wet weight of fetal cerebrum (Tanaka, Nakazawa & Arima, 1983), suggesting that protein synthesis is affected.

Tobacco

Tobacco smoke exposure has long been known to have a detrimental effect on the fetus. Studies have shown that maternal smoking depresses the active uptake of amino acids by

human placentae and lowered their levels in the placenta and umbilical vein (Sastry, Horst & Naukam, 1989), affects the placental and fetal protein metabolism and enzyme activity (Jauniaux, Gulbis & Acharya Gerlo, 1999), and significantly alters mitochondrial function and DNA in the placenta, possibly impairing nutrient transfer to the fetus and protein synthesis (Bouhours-Nouet, May-Panloup, Coutant, Boux de Casson, Descamps, Douay, et al., 2005). In addition, smoking in non-pregnant subjects has been shown to impair muscle protein synthesis (Winther Petersen, Magkos, Atherton, Selby, Smith, Rennie, et al**.,** 2007) and induce an unfolded protein response in the human lung (Kelsen, Duan, Ji, Perez, Liu & Merali, 2008).

Alcohol

Chronic exposure to ethanol during pregnancy has been shown to have a strong inhibitory effect on DNA and protein synthesis in palate cells (Weston , Greene, Uberti & Pisano, 1993) and acute alcohol intoxication also impaired protein synthesis in the liver and skeletal muscle (Lang, Frost, Kumar, Wu & Vary, 2000). Acute alcohol exposure also had an inhibitory effect of on myocardial protein synthesis (Vary, Lynch & Lang, 2001) and reduces brain protein synthesis (Bonner, Dalwai, Marway & Preedy, 2003).

The dietary aversions experienced by the majority of mothers are significantly concentrated in the first trimester, at the time of organogenesis (Flaxman & Sherman, 2000). These might now be recognized as an aversion to those substances that interfere with the protein synthesis required for the rapid cell division taking place in the embryo at this time.

Protein Synthesis

Protein synthesis might be aided or inhibited by choices made in early pregnancy. The introduction of high protein meals into the diet of a mother, who is nauseous, has also been shown to be beneficial (Jednak et al., 1999). It is suggested herein that the relationship of protein with nausea is an inverse relationship. An insufficient supply of protein, and/or insufficient nutrients to synthesise protein, could cause pregnancy nausea to occur early in pregnancy. Demand for an increase of protein might be from either the increased requirements of the maternal body and/or from the embryo.

Although a significant positive correlation has been shown between the week of onset of nausea and the week of onset of aversions (Bayley et al., 2002), Demissie et al. (1998) noted that it was difficult to establish the view that an aversion to coffee was mainly due to nausea, and Lawson (2002) reported that a decrease in coffee consumption due to coffee aversion may be a phenomenon independent of nausea and appetite loss.

It is therefore suggested that some aversions will occur early in the first trimester without connection to pregnancy nausea, and before pregnancy nausea has commenced in those mothers later affected. These aversions would be to those substances that inhibit protein synthesis, for example coffee/caffeine, tobacco and alcohol. As previously suggested, the avoidance of these substances, due to aversions, would promote an optimal environment for the rapid cell division of organogenesis. Many more food aversions are experienced only after gastric dysrhythmias and nausea have commenced. These food aversions, closely correlated to pregnancy sickness, are often to previously favoured foods which have become distasteful. It is suggested that these food aversions might be to those substances unacceptable to a now compromised digestive system.

Protein Deficiency

The consideration that a protein deficiency is occurring in many mothers only a few weeks after conception is unusual, unprecedented and needs investigation. Protein deficiencies generally occur at times of chronic malnutrition and semi-starvation. Initially, it was thought that the human body could adjust to the changes in resources, having adaptive mechanisms for slowing some of the body's physiological activities, although Shetty (1999) states that this cannot be assumed to be part of a beneficial adaptation. Continued protein deficiency will negatively impact on the body.

Similarities between the symptoms of semi-starvation and the symptoms concurrent with pregnancy sickness are clearly apparent. Generally accepted symptoms in early pregnancy include tiredness, irritability, faintness, constipation, depression, muscle cramps, nervousness, decrease in gastric motility, feeling cold, restless, anxiety, mood swings, psychological problems, dizziness, trouble sleeping and loss of concentration. Additionally eating was noted as helpful in pregnancy sickness, and this was obviously the

same in semi-starvation. The 1950 study by Ancel Keys best documents the symptoms of semi-starvation over a six month period. From this can be seen that many of the same symptoms occur in both pregnancy sickness and semi-starvation. Such similarities are not conclusive, but are of interest.

Pregnancy sickness symptoms can occur before the first missed period (Vellacott, Cooke & James, 1988), with the mean number of days from the last menstrual period being 39 (Gadsby et al, 1993), or 14-15 days post conception. This is a fast rate of onset and different from the usual rate of onset of semi-starvation symptoms in non pregnant subjects.

It has been asserted that during the first trimester, as maternal weight gain is low, little overall growth occurs and energy requirements increase negligibly. As a consequence, it has been advised that the mother needs minimal extra energy intake as a nutritional requirement (King, 1981; FAO/WHO, 2004; Food and Nutrition Board, 2005).

Maternal dietary requirements for pregnancy are estimated to total 85,000 additional kilocalories over the course of 40 weeks, approximating to an average of 300 extra kilocalories per day (Ritchie & King, 2008). Although recent guidelines recommend there be no increase in energy intake during the first trimester, because total energy expenditure changes little and weight gain is minor during the first trimester (Food & Nutrition Board, 2005), other studies do not support this. It has been shown that maternal weight gain in the first trimester is a significant predictive of birth weight (De Carvalho Padilha, Accioly, Chagas, Portela, Silva & Saunders, 2009), correlates with newborn weight and ponderal index more than in other trimesters (Brown, Murtaugh, Jacobs Jr., & Margellos, 2002) and is the most important predictive of fetal linear growth (Neufeld, Haas, Grajeda & Martorell, 2004). Recent findings suggest that a high quality diet in the first trimester favours fetal growth, increases birth size and reduces fetal growth restriction (Rodrıguez-Bernal, Rebagliato, Iniguez, Vioque, Navarrete-Munoz, Murcia, et al., 2010).

It is herein suggested that the first trimester low maternal energy requirement theory is incorrect, and that there is a high demand from the embryo for amino acids involved in the processes of cell division during organogenesis. If there is a continuous high demand

for amino acids, which remains unsatisfied, the result would be to produce symptoms of protein deficiency.

As the growth of the embryo is exponential, the demand for amino acids could increase over the first 8 – 10 weeks of pregnancy. The pregnant mother would be in an unprecedented situation as her normal food intake, or even a slightly increased food intake, might not satisfy the sudden and rapid onset of higher nutritional needs. This could also be exacerbated if the food intake of the mother was also not supplying the necessary nutrients for optimum protein synthesis.

In the literature it has been shown that 52% of women, who suffered nausea, reported that eating improved their symptoms (Whitehead, Andrews, & Chamberlain, 1992). Ninety-one per cent of midwives suggest that frequent small meals be eaten for relief from nausea and vomiting in pregnancy (Wills & Forster, 2008). In another study, women who had eaten food high in protein reported that this gave them immediate relief from nausea in most circumstances (Voda & Randall, 1982). 'One woman had a high protein snack before going to bed and found this decreased her morning nausea immensely' (p.155). A highly significant correlation between the number of daily vomiting episodes and mean weight loss has been observed (Emelianova et al., 1999). One third of mothers who vomited said eating had improved their symptoms (Whitehead et al., 1992).

However, if the maternal diet does not satisfy the demand for foods high in protein, and the demand for amino acids in the first trimester might be increasing continuously, then symptoms of protein deficiency would manifest rapidly. This might account for the rapid onset of pregnancy sickness and nausea in some mothers that previously has not been understood.

Snow (1981) gives an indication of the increasing speed of cell proliferation in the embryo. Snow points out that there is an acceleration in growth rate during gastrulation. Gastrulation begins between 14-16 days after conception. Based on tissue volume estimates (taken from textbook descriptions of early embryology), the human embryo increases some 40-fold in size in 4 days. Snow goes on to state 'From the neural plate stages through organogenesis various regions of the embryo establish their own growth

profiles, characteristic of the organs into which they will develop. Little is known of these growth profiles, but it seems that the origination of an organ primordium may be a fairly catastrophic event involving an initial period of very rapid cell proliferation.'

The hypothesis of a higher requirement for amino acids during organogenesis could explain the early onset of pregnancy sickness in a minority of mothers. The sudden increase in the size of the embryo in 4 days, during gastrulation, would take place around the time of the first missed menstrual period. Pregnancy sickness symptoms can occur around the time of the first missed period (Gadsby et al., 1993).

Beyond pregnancy

If this hypothesis, linking pregnancy nausea to a protein deficiency of rapid onset, is the body's physiological reaction to a homeostatic imbalance, this might not be restricted to pregnancy. Is it feasible that this could be an extreme example of a widely occurring phenomenon? A search of the literature indicates that there are other instances of nausea with similarities in symptomatology, where the same methods of helping to reduce the nausea are as beneficial as in early pregnancy.

Post Operative Nausea & Vomiting

A meta-analysis by Chaiyakunapruk, Kitikanakornn, Nathisuwan and Leelasettagoo (2006) concluded that ginger was more effective than placebo in reducing post operative nausea and vomiting.

Chemotherapy nausea

High protein meals with ginger have been shown to reduce the delayed nausea of chemotherapy and also reduce the use of antiemetic medications (Levine, Gillis, Yanchis, Koch, Voss, Stern & Koch. 2008).

After injury or surgery the catabolic stress response often contributes to the loss of muscle mass and function, and potentially to impaired immune function and delayed healing. This indicates an immediate need for amino acids in the repair and reconstruction of damaged parts. It is herein hypothesized that in the case of post

operative nausea and vomiting, and chemotherapy nausea, the rapid surge in the demand for useable protein, because of the catabolic depletion of skeletal muscle, might account for the nausea that can occur and is not accountable to the anaesthetic or medication used.

Motion sickness

Protein-predominant meals were more effective than carbohydrates for inhibiting the development of nausea and the symptoms of motion sickness. (Levine, Muth, Williamson & Stern, 2004).

The nausea of the different instances of motion sickness, further examples of which are shown below, does not obviously accord with the hypothesis of a protein deficiency initiating the nausea. If, as might be conjectured, there is a link, then it could be assumed that cell creation is the cause. In types of motion sickness, such as sea sickness, space sickness and cyber sickness, the causative factor for a protein deficiency might be neurogenesis. There is evidence that adult generated hippocampal cells may function in learning and memory formation (Gould, 1999; Gross, 2000), and that new learning is often dependent on *de novo* protein synthesis (Helmstetter, 2010). It is therefore suggested that nausea associated with motion sickness could indicate a period of rapid neurogenesis involved in learning and new memory formation at times of acute physiological stress.

Seasickness

One study compared the effects of powdered ginger rhizome and seven over-the-counter prescription anti-emetic drugs on the prevention of sea sickness on 1489 subjects. It concluded that ginger was as effective as the other anti-emetic drugs tested (Schmid, Schick, Steffen, Tschopp, & Wilk, 1994).

Simulator sickness/Cybersickness

High protein meals were found to be important in attenuating the nausea specific to optokinetic motion. (Williamson, Levine & Stern, 2005).

Space sickness

Gastric slow wave changes associated with space motion sickness are consistent with laboratory induced motion sickness. (Harm, Sandoz & Stern, 2002). It is also known that human spaceflight is associated with a loss of body protein. (Stein & Gaprindashvili, 1994).

The above instances of nausea outside of pregnancy also indicate a possible increased requirement for protein, which is similar to that shown in pregnancy sickness nausea. There is also a similarity in the beneficial introduction of protein meals and ginger to reduce nausea. The possibility that pregnancy sickness nausea is one manifestation of a response to an acute physiological stress, which might be occurring in other instances of nausea, needs further investigation.

Conclusion

In summation, it is hypothesised that the creation of new cells, in response to an episode of acute physiological stress, whether it be in pregnancy or elsewhere in the life cycle, will induce a protein demand of extremely rapid onset. This will result in a protein deficiency, if resources for fulfilling the demand are not readily available. Any protein deficiency of rapid onset will cause gastric dysrhythmias, and in turn these will produce the feelings of nausea we are all familiar with.

In the case of pregnancy sickness nausea, the repeated acute physiological stresses due to the increasing needs of organogenesis, would require a plentiful and frequently replenished supply of protein.

Therefore the nausea associated with pregnancy sickness is an indication of a disruption in the homeostatic balance of the maternal body. This imbalance would be initiated by the necessity to synthesise sufficient protein for cell division and growth at a time when the resources immediately available to the maternal body and the embryo are inadequate for this process to be satisfactorily achieved.

It is hoped that this hypothesis will resolve the nausea associated with pregnancy, provide an optimal environment for future embryos during the period of organogenesis, and in its wider application indicate more precisely the needs of the body during times of acute physiological stress.

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