What causes nausea & vomiting of pregnancy?

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Conference presentation 5th September 2013

Introduction

We have presented the case that nausea and vomiting of pregnancy (NVP) has an organic cause by applying our own work and the work of 143 other researchers working in the field of early pregnancy. Professor Gadsby and I have assessed all the information from these references over many years. The full document may be accessed on the website of www.pregnancysicknesssupport.org.uk under sections health care professionals, then causes. For the purpose of this shortened presentation the first name author of each relevant article is included in the text with a separate list of all 24 author groups at the end of the presentation.

I am pitching this talk for people with both a medical background and those without. I can give more medical details to anyone who is interested and I will be very happy to answer questions or discuss our theories.

Summary of our thesis

Nausea and vomiting of pregnancy is caused by the release of hormones from the cells of the early chorionic villi, that is the early placenta.
The hormones in which we are particularly interested are human chorionic gonadotrophin (hCG), progesterone and locally acting eicosanoid hormone, prostaglandin E_2 (PGE_2).

It has been the usual practise at present to say that hCG or βhCG are the main cause of nausea and vomiting of pregnancy (NVP) because they have a temporal (time based) relationship with NVP and as there are receptors in the human brain for hCG which can result in sickness COLE (1).

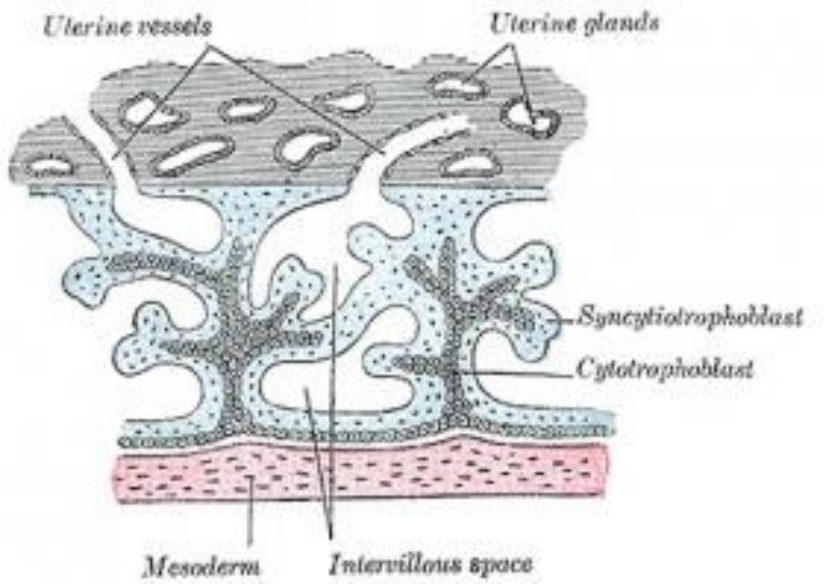
We agree that hCG plays a significant part in causing NVP. Our theory is that hCG is one factor which increases the production of prostaglandin E_2 from early trophoblast (or placental) cells. We will show that PGE_2 is a very emetic eicosanoid (locally acting hormone that makes women very sick) and is also produced from early trophoblast (placental) cells.

There is an enzyme named Prostaglandin dehydrogenase (PGDH), that is also produced by these early placental cells which breaks down prostaglandins E_2 abolishing its emetic capability. This PGDH, which is under progesterone control, thereby reduces NVP. Our theory is that the prostaglandins E_2 is a key factor causing NVP.

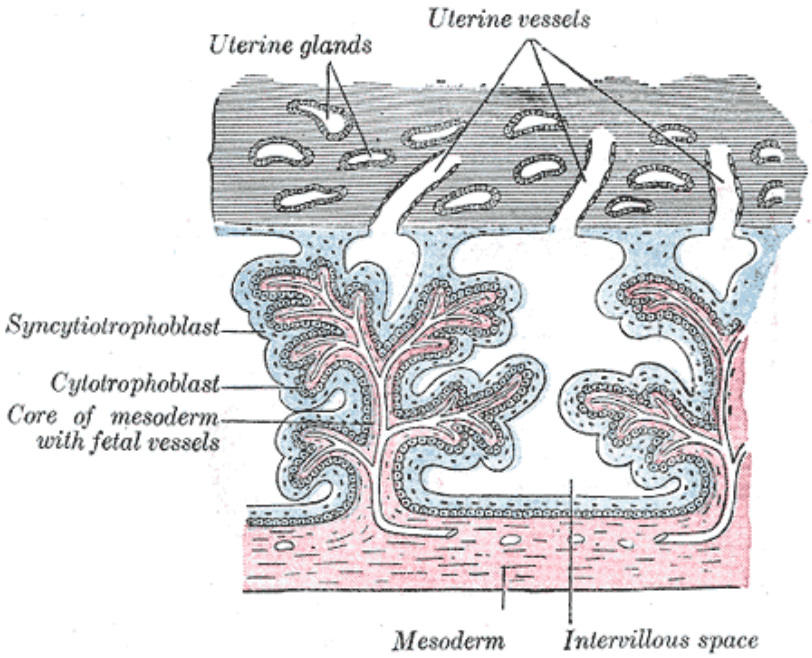
Early Development of Human Trophoblast

Formation of Chorionic Villi

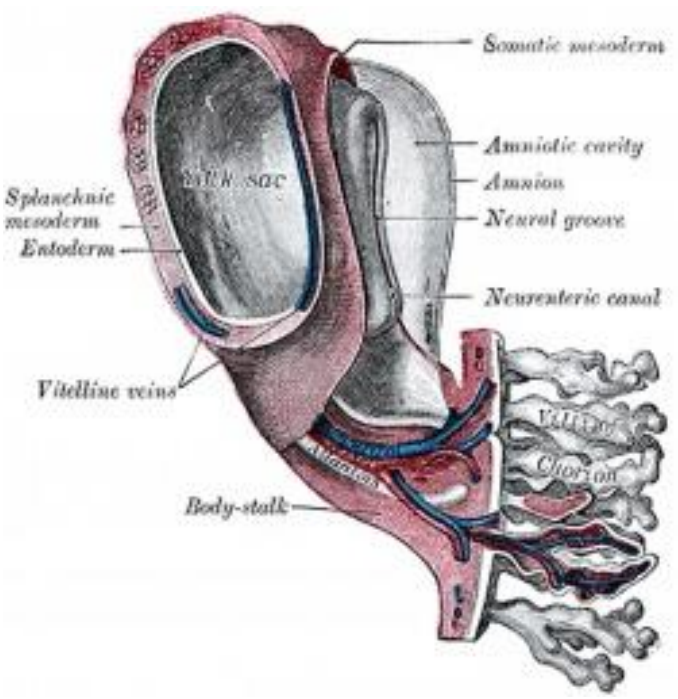
Primary villi, week 2 from LMP (first day of last menstrual period) which equals week of gestation, composed of a central mass of cytotrophoblast cells surrounded by syncytiotrophoblast cells.



During week 4 these villi develop a central core and so become branched villi.



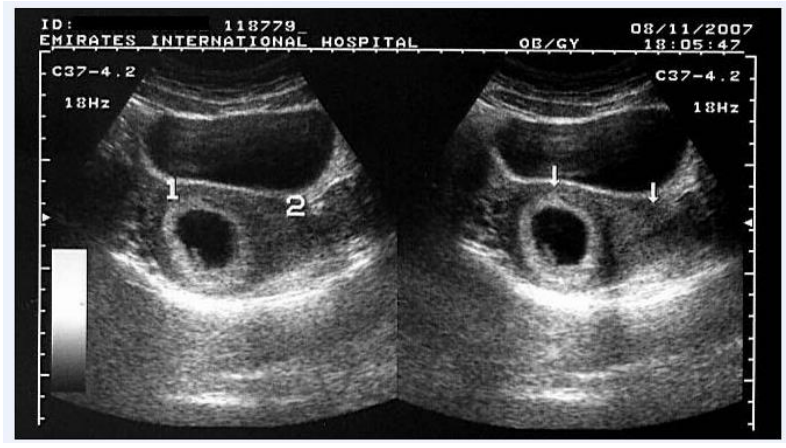
During week 5 the appearance of blood vessels in the central core produces tertiary villi.



By 6 weeks gestation the majority of these villi are tertiary in type. Usually NVP starts about day 35 (end of week 5) to 42 (end of week 6). So we need to study the hormones coming from these chorionic villi when looking for the cause of NVP.

<u>Ultrasound features of early gestational sac</u>

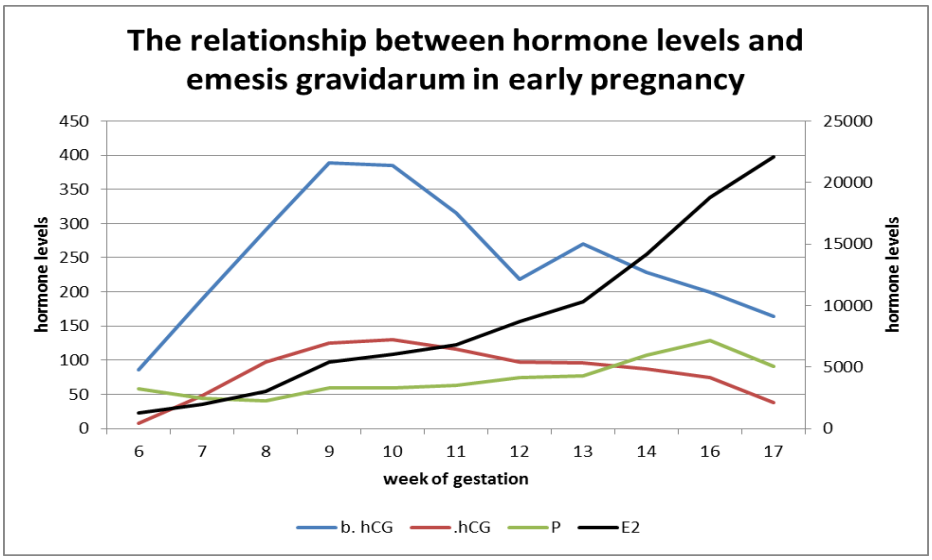
These chorionic villi surround the whole gestational sac as a complete circle at 5 weeks gestation.



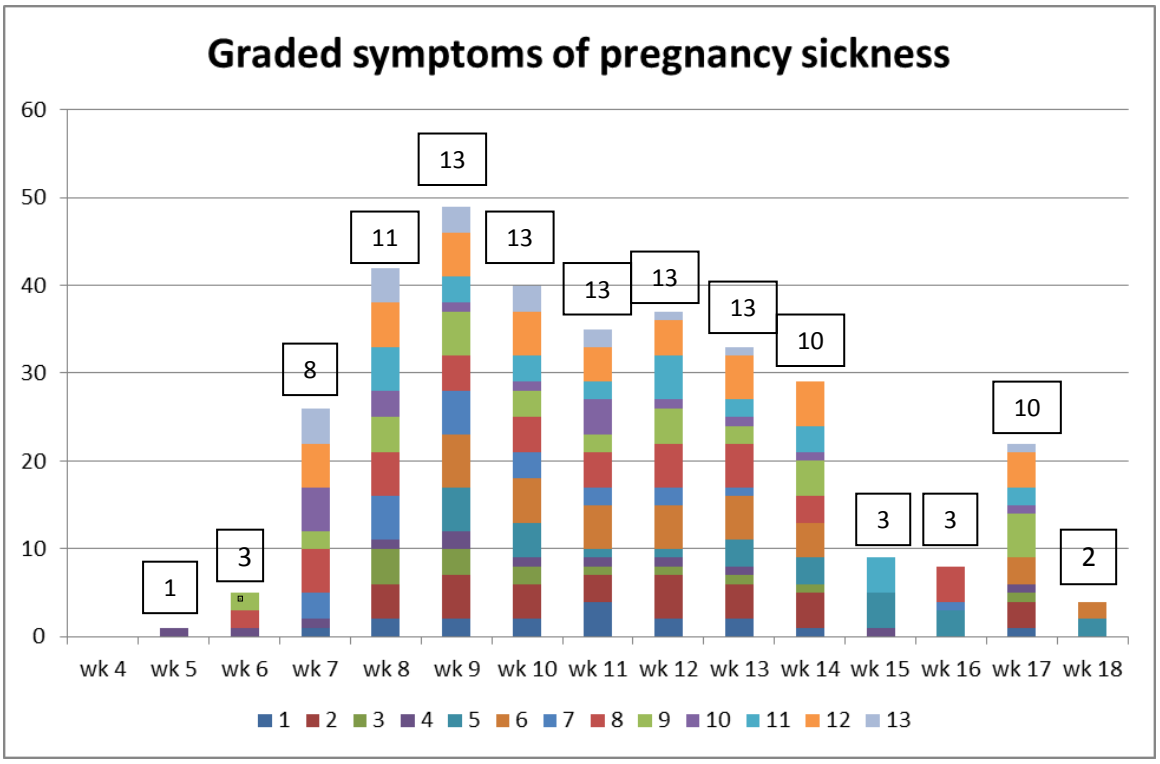
At 5 weeks the ring covering the sac is 3-4 cm thick and triples in size in the next 2 weeks.

Weeks 6-9 of gestation are typically the worst weeks for NVP. By 10 weeks of gestation the ring ceases to grow (typically the NVP can begin to improve at 10 weeks). After 10 weeks, two-thirds of the ring ceases to grow while one-third becomes the definitive placenta.

The cytotrophoblast cells of the chorionic villi fuse together to form the syncytiotrophoblast cells. These syncytiotrophoblast cells as they develop, become multi-nucleated, containing any number of nuclei from 2-50 per cell COLE L (1). They become the most active cells of the chorionic villi. The syncytiotrophoblast cells secrete hormones including human chorionic gonadotrophin (hCG). Maternal serum (blood) hCG levels rise sharply in the weeks 4-8 of gestation to reach a maximum between weeks 8-10 of gestation.



Therefore the hCG synthesis depends upon the differentiation of cytotrophoblast into syncytiotrophoblast cells. hCG in maternal blood has been estimated and is typically related to the severity of NVP COLE (1) & HOLDER(2) both graphs on this page are HOLDER'S (2).



Number of patients that week

There's much more to think about with the hCG story, some of which shows an even closer relationship between certain types of hCG as the whole molecule is secreted in up to seven separate types. Two acidic types are related to the peak severity of NVP, and two basic types to the reduction of NVP or HG, but we will not consider these in detail this morning.

Problems when relating maternal serum hCG to NVP or Hyperemis Gravidarum (HG)

We have to consider hCG is the most significant hormone in relation to the severity of NVP or HG. There are two problems; first an individual women's severity of NVP is not always related to the level of her maternal serum hCG. There is a solution to this called the spare receptor syndrome COLE L (1). Secondly, after 14 weeks gestation the maternal serum level of hCG remains fairly constant throughout the remainder of pregnancy, but in women with severe NVP or HG awful symptoms can continue to 22 weeks of gestation or even sometimes throughout pregnancy.

In our opinion the answer to these problems could be to consider a locally acting eicosanoid hormone called prostaglandins E_2 (PGE_2).

Prostaglandins E_2 is known to cause nausea and vomiting in early pregnancy when used for treatment to obtain a legal abortion

Nausea and vomiting were the most troublesome side effects when PGE_2 was first used to procure a termination of pregnancy in the early 1970s. These side effects were clearly and persistently described when PGE_2 was given by intravenous infusion KARIM SM (3). The oral route was quite unsuitable because of the severity of side effects. It was shown that raised maternal plasma levels of prostaglandins were associated with an increased incidence of nausea and vomiting GILLETT PG (4) and that these side effects regressed rapidly when the infusion was reduced (WIQVIST M, BYGDEMANN M (5)) or stopped JEWELEWICZ R (6).
Another investigation showed that the dose which produced side effects varied considerably from one woman to another WIQVIST M (5). It has been shown in another experiment that suitable dose levels of intravenous prostaglandins vary within a wide range and have to be adjusted to suit an individual woman (WIQVIST M, BEGUIN P (7)).
The effects of nausea and vomiting occur more readily when PGE_2 and PGF_2 alpha are given in the first or second trimester of pregnancy, in the third a much lower dose is required to induce labour BEAZLEY B (8).
In 1987 the use of PGE_2 pessaries given pre-operatively before termination of pregnancy, were found to be associated with an unacceptably high incidence of nausea and vomiting. This nausea and vomiting is only too apparent to those providing anaesthetic service to patients who have received prostaglandins MILLAR J M (9).

Production of PGE_2 in syncytiotrophoblast cells

When any cell activators activate their receptors on a cell wall arachidonic acid is released from that cell wall. The ability of the cytokine IL-1 to initiate prostaglandin synthesis is perhaps one of its most important biological properties accounting for many systemic effects. DINARELLO CA (10).

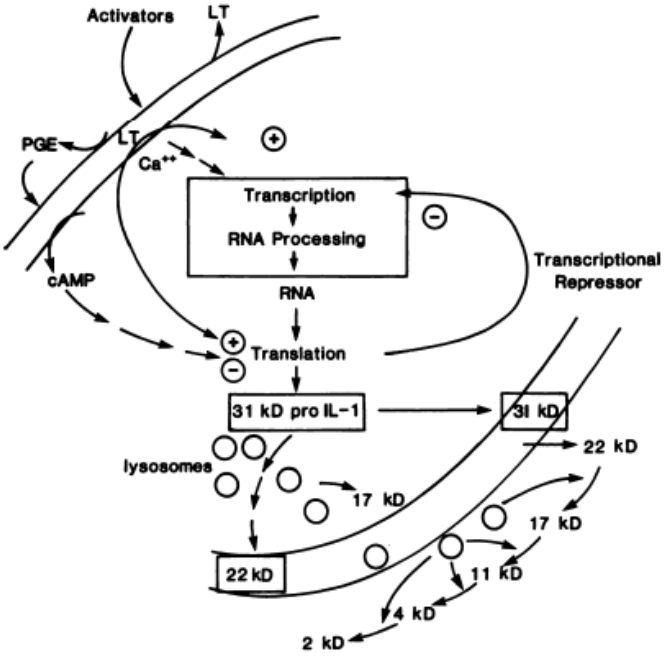


Figure 2. Steps in the transcription, translation, and processing of IL 1. Cell activators stimulate PGE, leukotrienes (LT), and intracellular calcium levels. Transcription and translation are enhanced by calcium and LT. Transcription is short-lived because of the synthesis of a transcriptional repressor protein (or proteins), and translation is reduced by PGE-induced cAMP. The 31,000-Da IL 1 precursor (pro IL 1) undergoes limited cleavage into 22,000- and 17,000-Da peptides that can be found associated with the cell as well as in the extracellular compartment. Membrane-bound IL 1 can be the 31,000-Da precursor or the 22,000-Da product. Lysosomal enzymes and serine proteases are responsible for cleavage of pro IL 1 into various peptides with molecular masses of 17,000 (the prominent extracellular form) and also of 11,000, 4000, and 2000 forms as determined by gel electrophoresis.

Various molecules, such as hCG, act as local chemical messengers binding to specific receptors in adjacent cells to give a concerted tissue response. This cell stimulation will result in the release of arachidonic acid from the cell wall which after further oxidative metabolism via eicosanoid pathways can result in the production of prostaglandins NORMAN R (11).

A further investigation shows hCG itself can stimulate PGE2 synthesis in 9-12 week placentas at physiological conditions. The rate of PGE_2 synthesis increased with a longer incubation period particularly in placentas of younger gestation. There was considerable variation of PGE_2 production between placentas of the same gestation NORTH RA (12).

An additional investigation demonstrated the cytokine interleukin-1 (IL-1) induced a five- fold increase in PGE_2 production which was density, time and dose dependent in first trimester 8-10 weeks human placenta SHIMONIVITZ S (13).

There is then plenty of PGE_2 produced in early placentas (Professor SINCHA YAGEL personal communication 1998). More information is available in our full paper on our website.

Prostaglandin E_2 receptors

Prostaglandin E_2 acts via 4G protein coupled receptors EP1-EP4. PGE_2 receptor analogue the drug gamepost has been demonstrated to possess EP3 receptor agonist activities. Gamepost, a prostaglandins derivative was used to promote a legal abortion.

An Association between symptoms and maternal prostaglandin E_2

We have found an association between hCG and pregnancy sickness for weeks 7-17 weeks of gestation and an association between hCG and PGE_2 synthesis in early trophoblast cells. It seemed reasonable to make further investigation of the possible relationship between maternal PGE_2 synthesis and early pregnancy nausea and vomiting.

In this study GADSBY R (14) took blood samples from pregnant women in the community between 7-9 weeks of pregnancy whilst 1) women are nauseated (symptomatic sample) and 2) within the same 24 hour period when they were not nauseated (control sample).Women were this able to be their own controls. Maternal serum IL-1B, TNF alpha and PGE_2 were measured and related to the presence or absence of NVP at a time each sample was taken.

None of the women received any medication for nausea and vomiting or any other medical condition. Their mean age was 27.4 years. All 18 went on to deliver a normal single live baby. There were no significant differences between control and symptomatic samples for the cytokines IL-1B or TNF alpha.

There was a statistically significant difference ($p<0.001$) between the mean symptomatic and control results for PGE_2. Moreover, the PGE_2 was always higher in the symptomatic sample, than the control sample. This was independent of the time of day that the symptomatic samples were taken. Eight symptomatic samples were taken in the morning, whereas ten were taken after midday.

Decidua and Decidualisation

The formation of a specialist decidua from endometrium the lining of the non-pregnant uterus is called Decidualisation

Decidualisation includes the process of differentiation of spindle-shaped stroma cells of the endometrium into plump secretory decidual cells which create a pericellular and matrix rich in Fibronectin and laminin

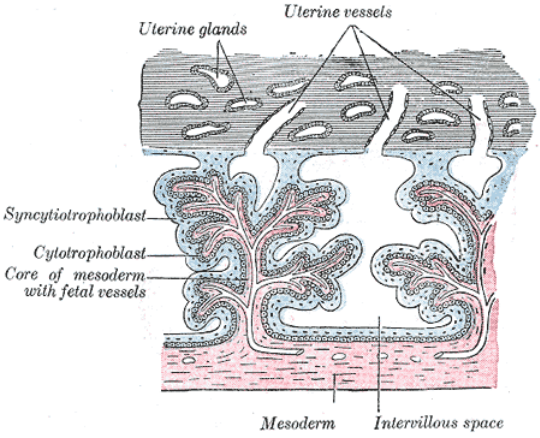
Vascularity as well as vascular permeability is enhanced in decidualised endometrium

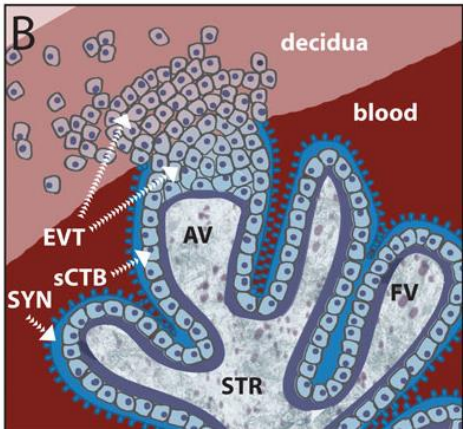
The leukocyte (white blood cells) population in the decidua is distinct with the presence of large numbers of endometrial granular leukocytes. These are called uterine NK cells. (Wikipedia Human Decidua and Decidualisation).

Role of the human decidua

At the maternal interface the decidua participates in the exchanges of nutrition, gas and waste with the embryo. It also protects the pregnancy from the maternal immune system. Further the decidua has to allow a very controlled invasion by extra villous trophoblast cells from the chorionic villi (Wikipedia).

As extra villous trophoblast cells (EVT cells), which will possess paternal or fetal genes, enter the maternal decidua they will be exposed to possible destruction by decidual (maternal) NK cells, which are present in large numbers





These NK cells, only become killer cells when they are stimulated by a cytokine IL-2 interleukin -2 (15). Therefore there needs to be suppression of IL-2 cytokine at the baby-mother interface in the decidua (15).

The Presence of PGE_2 in the Decidua

Early decidual stroma cells at 6.5 – 9.5 weeks of gestation seem to contain an important suppressor of interleukin -2, which was identified as PGE_2 (16). First trimester human placental macrophages also secrete large amounts of PGE_2 YAGEL S (17).

Therefore Prostaglandin E_2 is one important factor in the immunosuppression of the expected attack by mother's decidual cells into the invading cells of the genetically dissimilar baby.

Prostaglandin Dehydrogenase Activity in Trophoblast cells of the early human placenta

Prostaglandin dehydrogenase is an enzyme required for the first step of prostaglandin metabolism (breakdown) KIERSE M (18). In human uterine and intra-uterine tissues, oxidation of the 15-hydroxyl group of prostaglandins is catalysed almost entirely by a NAD-linked 15-hydroxyprostaglandin dehydrogenase (PGDH) (18).
PGDH activity was measured in homogenates of 25 human placentae between 7 and 10 weeks of gestation. Between 7 and 8 weeks of gestation and 15 and 16 weeks, mean values for PGDH increased 10 fold. There was a large variation in PGDH activity between individual placentae of each of the early gestational stages KIERSE M (18).

JARABAK J also states there was a wide variation in the PGDH content in individual placentas (19).

FALKAY (20) states in early human placentae 15-OH PGDH activity decreases between 5 and 9 weeks and then gradually increases in week 9. On regression analysis, there is a fairly close correlation (r2=0.69) between PGDH activity and the concentration of progesterone in the placenta. Cheng L (21) writes after administration of Mifepristone (RU-486) in vivo the levels of PGDH in uterine tissues fall. Such results support earlier suggestion that PGDH is under progesterone control.
In another study Cheng L (22) writes, PGDH controls the level of PGE_2 in the decidual stroma cells and decidual small arteries and veins. The use of antiprogesterone reduces progesterone and therefore PGDH in these tissues so that PGE_2 is able to filtrate to the myometrium making miscarriage more likely.
There are two ways of controlling progesterone in early pregnancy. First Epostane, the competitive inhibitor of the enzyme 3B Hydroxysteroid dehydrogenase, or secondly Mifepristone (RU-486) a competitive progesterone receptor agonist. The RU-486 papers show that the (RU-486) treatment causes far less nausea than Epostane. Therefore reducing the levels of progesterone in early pregnancy causes more sickness than blocking progesterone receptors STITES (23). Progesterone also stabilises cell membranes reducing phospholipase A_2 a precursor of prostaglandin synthesis SCHWARZ (24).
It seems reasonable to suggest that the cause of this increased nausea and vomiting after treatment with Epostane or RU-486 is due to lowered preogesterone activity in decidual and chorionic tissues, associated with lower prostaglandin dehydrogenase and raised prostaglandin E_2 in the tissue, thence raised maternal serum levels of prostaglandin E_2.

Clinical features which can be associated with PGE_2 and PGDH causing NVP/HG

1. The variation in NVP from pregnancy to pregnancy, indeed no two pregnancies have exactly the same symptoms, and the variation in NVP from one pregnancy to the next in the same mother, which occurs in at least 33% of pregnant women (pregnancysicknesssupport.org.uk/healthcare-professionals/ literature review section 8a)
    - We have seen that maternal serum hCG and prostaglandin E_2 vary considerably from one pregnancy to another. In a similar way, the Prostaglandin dehydrogenase activity varies between individual placentas at the same stage of gestation
2. The finding that whether NVP begins early or late, severely or mildly, it usually ceases at 12-14 weeks of gestation GADSBY R (25) suggests that another substance, possibly PGDH activity is required to reduce or stop NVP
3. The median week of peak NVP is week 9 from LMP interquartile range 8-10 weeks GADSBY R (25). This week corresponds with the week of peak maternal hCG serum levels and the nadir of maternal serum progesterone. High serum hCG gives maximum stimulation of maternal PGE_2 synthesis. Low maternal progesterone leads to reduced placental PGDH. Both raised PGE_2 and low PGDH will be related to increased NVP at week 9 of gestation
4. The positive correlation between decreased NVP and increased cigarette smoking status agreeing with the finding of 10 other authors (pss.org.uk/healthcare-professionals/, literature review section 16) can be due to the damage cigarette smoking in pregnancy causes to the placental cells, with resultant marked decrease of maternal hCG and PGE_2 (pss website, Healthcare Professionals, Literature Review, Section 16)
5. We have published the paper Nausea and Vomiting of Pregnancy : An Association between symptoms of NVP and maternal serum Prostaglandin E_2, already described in this article. 18 women with daily episodic symptoms of NVP gave two samples of blood in one 24 hour periods, 16 of them between 7-9 weeks from LMP. The maternal serum level for the control (no NVP)and symptomatic (with NVP) samples for maternal serum PGE_2, along with time of day and the day from LMP were recorded. None of these women received treatment for NVP or other medical conditions. All 18 went on to deliver a normal baby. There was a statistically significant difference between the mean symptomatic and mean control for maternal serum PGE_2
    - Moreover for each woman the symptomatic PGE_2 level was always higher than the control sample. This was independent of the time of day the symptomatic sample was taken Eight symptomatic samples were taken before midday, whereas 10 were taken after midday.

Conclusion

We have presented evidence that NVP and HG have a biological cause. hCG is the hormone that has the closest relationship with NVP/HG in weeks 6-17 from LMP.

However, we have presented evidence that rather than hCG itself, the eicosanoid locally acting hormone prostaglandin E_2 (PGE_2) is a candidate agent to be considered because it is known to cause NVP. PGE_2 is involved in the immune suppression occurring at the materno foetal interface, and both its production by syncytiotrophoblast cells and destruction by PGDH offer an explanation for the variation in symptoms, their episodic nature and cessation of symptoms that happen in women with NVP/HG.

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