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Review Article

Biochemistry Section

Pyridoxine: The 'Ba.Six' of use in Nausea and Vomiting of Pregnancy

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ABSTRACT

Over the centuries, the dietary and biochemical essentiality of pyridoxine in the humans has been well established. Apart from various physiological functions, pyridoxine is therapeutically important in Nausea and Vomiting of Pregnancy (NVP). Pyridoxine on its own or a combination of pyridoxine (vitamin B6) (pregnancy category A) and doxylamine (category B), previously available as Bendectin, is the only medication that is specifically labeled for the treatment of NVP by the Food and Drug Administration. Although various reports claims the efficacy of pyridoxine in NVP, there are a very few studies on its mechanism of action in relieving the symptoms. Therefore, the present review was aimed at revisiting relevant previous data and providing the necessary background to discuss the chemistry, pharmacochemistry, status in pregnancy and mechanism/s of action in NVP of this B-complex vitamin in detail.

Keywords: Deficiency, Fetal uptake, Hyperemesis gravidarum, Supplementation, Vitamin B6

INTRODUCTION

Pyridoxine or vitamin B_6 is a water soluble vitamin of the B-complex group. In human body, the coenzyme form of this vitamin occupies a centre stage in amino acid metabolism in cells. The amino acid catabolism includes catabolism of two components-the carbon skeleton and the amino group. Pyridoxine, in its coenzyme form, is indispensable for both metabolism (transamination and deamination of the amino group, decarboxylation of the carbon skeleton). The coenzyme also plays a major role in glycogen breakdown, neurotransmitter metabolism and hormone metabolism. Beside the dietary and biochemical essentiality, it is also therapeutically important in gynecology. Pyridoxine is believed to be effective in suppression of lactation, however other studies reports similar results to placebo [1-3]. Supplementation of 100 mg vitamin B_6/day have shown to relieved depression and normalised glucose tolerance in women taking contraceptives [4]. Vitamin B_6 administration has also been shown to prevent etretinate induced development of fetal abnormalities [5].

About 70-80% pregnant women experiences nausea and vomiting, while most pregnant women experience it only in the first trimester, a small percentage of women show a prolonged course of symptoms extending until delivery. A combination of pyridoxine (vitamin B6) (pregnancy category A) and doxylamine (category B), previously known as Bendectin commercially, is the only Food and Drug Administration (FDA) approved medication for treatment of NVP [6]. Alternatively, pyridoxine can be taken on its own in NVP. A vitamin B6 supplementation of 1.9 mg per day has been recommended by The American College of Obstetrics and Gynecology recommend for hyperemesis gravidarum [7]. Improvement in nausea scores were obtained in patients with severe nausea who took pyridoxine and a reduction was seen in the vomiting episodes when compared to women taking placebo [8,9].

Biochemistry and Pharmacochemistry of Pyridoxine

Requirements and dosage: Vitamin B6 requirements in the diet are related to protein intake and not to calorie intake. Deficiency of the vitamin precipitates as neurological, dermatological and hematological manifestations. It is considered that 15 µg/g dietary protein is an adequate intake to meet the requirement of most of the population and that 11 µg/g dietary protein is the minimum safe limit. Current Recommended Dietary Allowances (RDAs) range between 1.5-2.2 mg/day. During pregnancy and lactation, the requirement is increased to 2.5 mg/day. Requirement is known to increase in the elderly as well, and the requirement in infants remains undetermined [10]. Vitamin B6 is naturally obtainable from dried yeast, rice polishings, wheat germs, cereals, legumes, oil seeds, egg, milk, meat, fish and green leafy vegetables. The vitamin supplements are also available for use in times of increased demand by the body. However, doses over 100 mg may lead to imbalance, numbness, muscle weakness and nerve damage and extremely high intakes of 500 mg/day leads to neurological damage [10,11]. [Table/Fig-1] shows the limits on the amounts of pyridoxine that can be given nutritionally or for pharmaceutical purposes, as proposed by the UK department of Health Committee on toxicity in June 1997 [12].

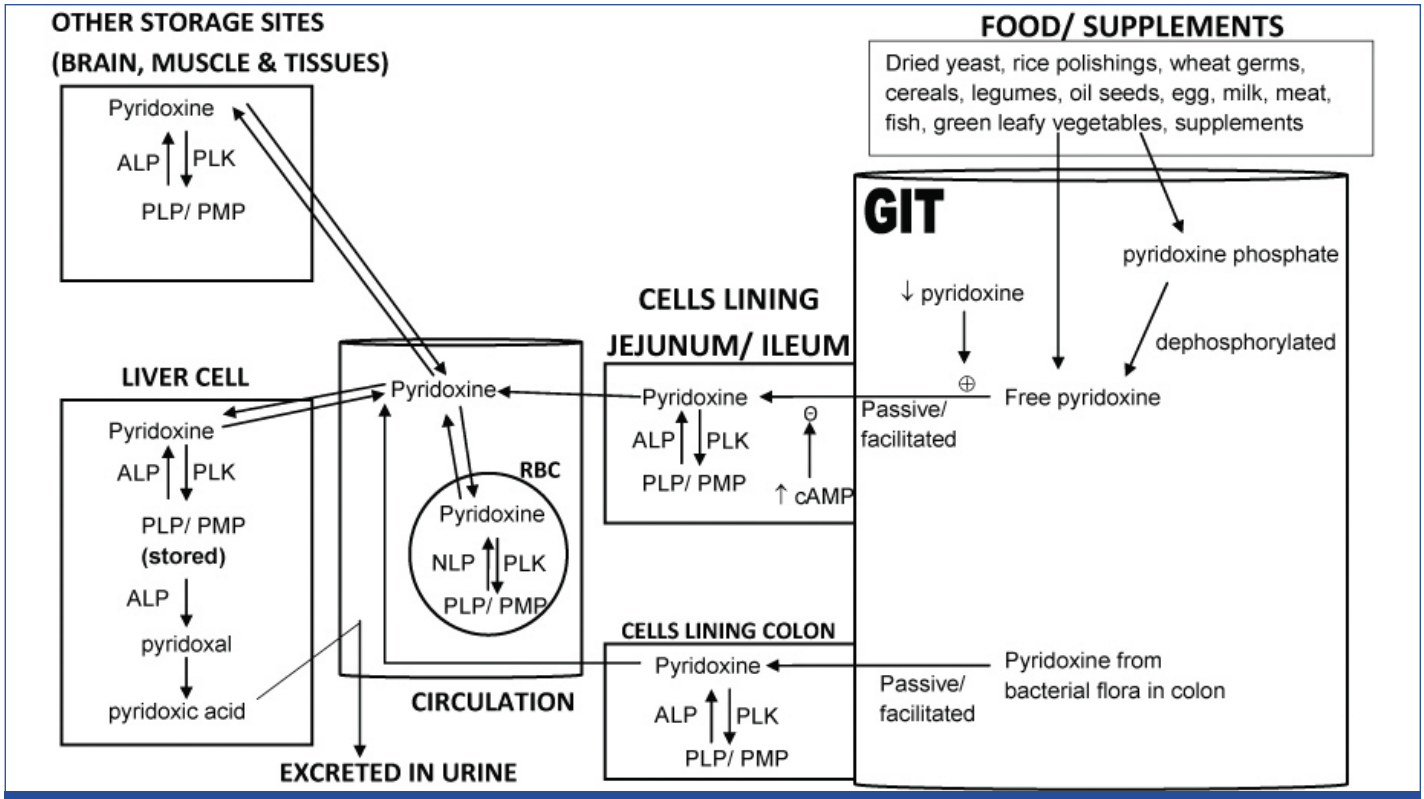
Reference nutrient intake	1.2-1.5 mg/d
Freely sold as nutritional supplement	Upto 10 mg/d
Sold in pharmacy on professional advice	10-50 mg/d
Provided on prescription	>50 mg/d

[Table/Fig-1]: Recommended doses of B6 (UK department of health committee on toxicity, 1997).

Deficiency and toxicity: Vitamin B6 deficiency has been reported to cause seizures in children and rashes; normocytic anemia, cheilitis with scaly lip skin and cracks in the corner of the mouth, non-specific pruritic rash and glossitis in adults. In severe deficiency, it leads to mental status changes or even depression.

More recent studies have implicated the role of B6 deficiency in heart disease, cancer and cognitive decline. Studies also indicate a reduction of symptoms in the premenstrual syndrome (moodiness, irritability, forgetfulness) following B6 supplementation [7,13]. More than 250 mg per day of pyridoxine on a chronic basis, may result in toxic effects on skin, gastro-intestinal, and neurological system [7].

Chemistry: Pyridoxine is one of the three vitamers of the B6 family along with pyridoxal and pyridoxamine. Humans obtain vitamin B6 from diet and from the bacterial microflora of the large intestine [14]. Dietary B6 compounds exist in the free and phosphorylated form that undergoes dephosphorylation to the free form prior to absorption [15-17].



[Table/Fig-2]: Summary of pyridoxine metabolism in the human body.
↑ cAMP: increase in intracellular cyclic AMP; ↓ pyridoxine: decrease in extracellular pyridoxine; ⊕: activates; Θ: inhibits; PLP: pyridoxal phosphate; PMP: pyridoxamine phosphate; PLK: pyridoxal kinase; ALP: Alkaline phosphatase; NLP: Neutral phosphatase

Absorption, metabolism, excretion: The summary of pyridoxine kinetics in the human body is illustrated in [Table/Fig-2]. Pyridoxine is mainly absorbed by passive diffusion in the jejunum. Small amounts are also absorbed in the ileum. Some studies suggests that the intestinal B6 absorbed by a non-saturable mechanism, whole other reports a specific acidic pH (but not Na^+)-dependent carrier-mediated mechanism [15,18-21]. Intestinal absorption is regulated by extracellular as well as intracellular factors. A low vitamin level influences the extracellular regulatory factor causing a transcriptionally mediated up-regulation of intestinal pyridoxine absorption [20]. A Protein Kinase A (PKA) mediated pathway acts as the intracellular regulatory factor; where an increase in intracellular cAMP level leads to a significant decrease in the activity (and/or the number), but not affinity, of pyridoxine uptake [21]. In addition to the absorption of dietary B_6 in jejunum and ileum, humans also absorb pyridoxine from the bacterial flora through an efficient mechanism for vitamin B_6 uptake in the large intestine [19]. The vitamin is freely transported in the blood, primarily stored in the liver and lesser amounts are also stored in the muscle and brain [22]. In mammalian tissues, the Pyridoxal Kinase (PLK) enzyme catalyzes the phosphorylation of pyridoxine to its major coenzyme forms of vitamin B_6, viz. Pyridoxal Phosphate (PLP) and Pyridoxamine 5'-Phosphate (PMP) (note that Pyridoxine Phosphate (PNP) produced from pyridoxine, is immediately converted to PLP). The vitamers of B6 readily diffuse across membranes, phosphorylation to PLP and PMP renders them poorly diffusible and essentially trapped in the cell, since their transport out of the cell requires dephosphorylation by enzymatic hydrolysis. Thus, PLK and the dephosphorylating enzymes of PLP are major factors that control the intracellular PLP concentrations [23,24]. Several nonspecific neutral or Alkaline Phosphatases (ALP) catalyse the dephosphorylation of the phosphorylated forms of vitamin B_6 [24-26]. APL catalyses the conversion of PLP to pyridoxal in most tissues [27,28]. Alkaline phosphatase found in plasma metabolises a small fraction of plasma PLP [28,29]. In human erythrocytes, a neutral phosphatase, appears to be the enzyme primarily responsible for hydrolysing PLP [23]. B6 is metabolised in the liver to the metabolite 4-pyridoxic acid and excreted mostly as 4-pyridoxic acid in the urine. The t ½ of pyridoxine is 15 to 20 days [22].

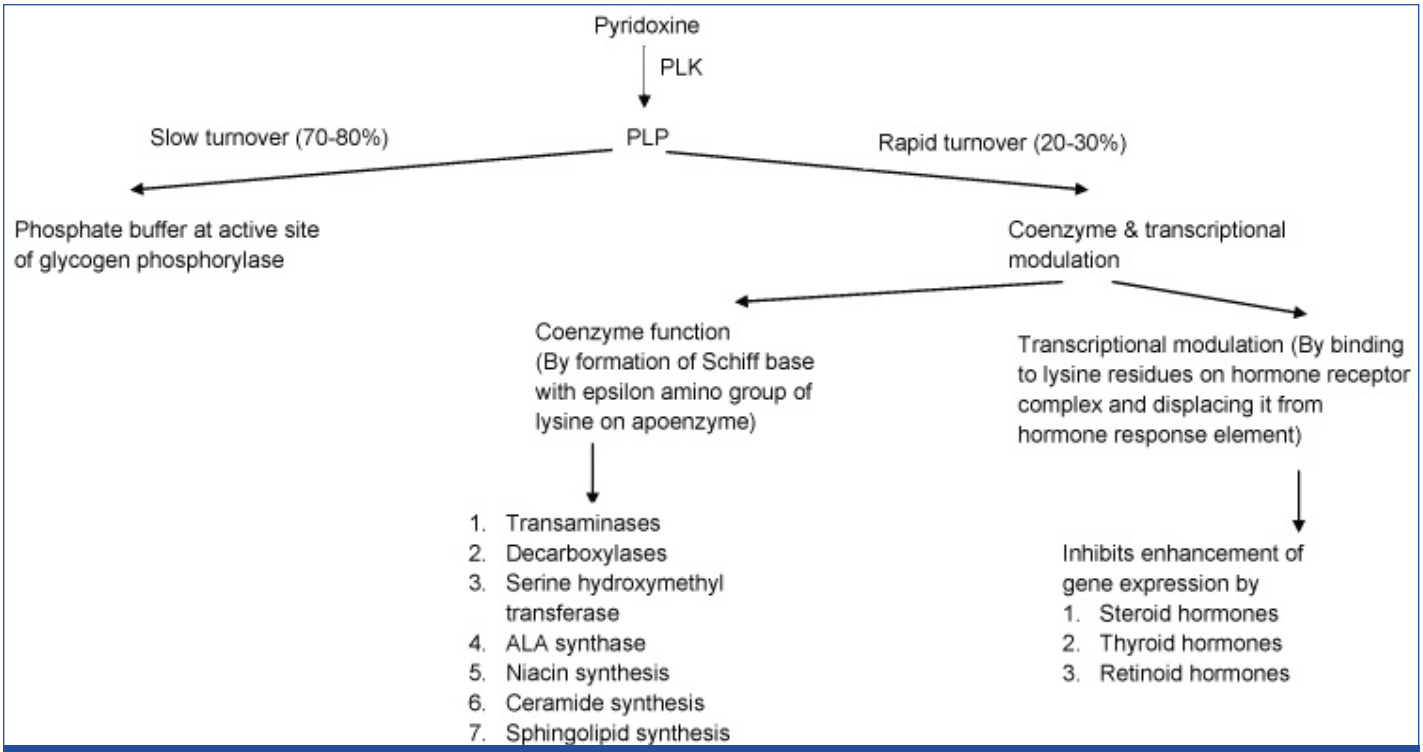
Biochemical functions: The functions of PLP have been summarised in [Table/Fig-3]. The active functional group in pyridoxine is an alcoholic group. Pyridoxal phosphate, the coenzyme form is synthesised from pyridoxine by the enzyme pyridoxal kinase utilising Adenosine Triphosphate (ATP). About 70-80% of PLP is associated with glycogen phosphorylase activity and has a slow turnover; 20-30% is associated with amino acid metabolism and steroid hormone action, and has a rapid turnover [30]. PLP is believed to act as a phosphate buffer at the active site of glycogen phosphorylase [31]. It acts as a coenzyme for various enzymes associated with amino acid metabolism (transaminases, decarboxylases, serine hydroxymethyl transferase), heme synthesis (amino levulinic acid synthase or ALA synthase), niacin synthesis (kynureninase), and also in the formation of ceramide and sphingolipids. In all these reactions, the aldehyde group of PLP forms a Schiff base with the epsilon amino group of lysine residue of the apoenzyme [11].

PLP inhibits enhanced gene expression by steroid hormones, vitamins A and D and thyroid hormones by binding to a lysine residue in the hormone receptor complex and displacing it from the hormone response element [12]. These findings were supported by Symes EK et al., Bowden JF et al., and Bender DA et al., studies in the years 1984, 1986 and 1987 respectively which have reported that B_6 deficiency leads to accumulation of steroid hormones in the nucleus of target tissues [32-35]. Also, experimentally induced acute B6 depletion was found to produce two-fold increase in rate of expression of genes and addition of pyridoxal led to a decrease in gene expression [35-37].

Pyridoxine Levels in Pregnancy

In the recent years, there is a growing consensus that most pregnant women have some level of vitamin B_6 deficiency compared to age matched non-pregnant women [38].

During pregnancy, plasma and erythrocyte pyridoxal 5'-phosphate (PLP) concentrations are altered in humans and laboratory animals [39-41]. In a study by Contractor SF and Shane B in the year 1970, both pyridoxal phosphate and pyridoxamine phosphate levels were found to be significantly lower in the blood of pregnant women as compared to non pregnant women. The pyridoxamine values were



[Table/Fig-3]: Biochemical and signaling functions of pyridoxine.
PLP: Pyridoxal phosphate; PLK: Pyridoxal kinase; ALA synthase: Amino levulinic acid synthase

also lowered in both mother and fetus when compared with those in non pregnant women or men, but there was no difference in 4-pyridoxic acid or in pyridoxal values. Two hours after an oral load of pyridoxine hydrochloride, the values of pyridoxal 5'-phosphate in blood were lower in pregnant women in comparison to non-pregnant women. Higher levels of PLP were found in the cord blood than mother's blood 3.5-10 hours after a pyridoxine hydrochloride load at delivery. The recovery of pyridoxal, pyridoxine and 4-pyridoxic acid (the main metabolite) following the oral load was similar in men, non pregnant women and pregnant women. Therefore it was concluded that the intestinal absorption was unimpaired during pregnancy and the relative deficiency of pyridoxal 5-phosphate was mainly because of the large fetal uptake and not due to metabolic changes in pyridoxine metabolism [42].

Neuroendocrine and Hormonal Factors Contributing to NVP/HG

Nausea and vomiting has been reported in about 50-90% of pregnancies [43]. In a study involving more than 360 pregnant women, nausea limited to the mornings was seen in 2% whereas 80% complained that nausea persisted throughout the day. The condition is usually self-limiting and the symptoms peaks at around 9 weeks of gestation and ceasing at 20 weeks. However, in about 20% cases, both the nausea and vomiting may continue until delivery and this condition is known as nausea and vomiting of pregnancy (NVP) or emesis gravidarum. As long as the affected female leads a normal life, this condition is not pathological [43,44]. In some females, however, it can take a more severe form called Hyperemesis Gravidarum (HG).

Although several factors are believed to contribute to NVP and hyperemesis in pregnancy the present review paper focuses only on the endocrine and hormonal factors [6]. The mechanism of action of pyridoxine as a therapeutic in NVP and pyridoxine is known to inhibit the enhancement of gene expression by steroid hormones. Among the hormonal factors, Human Chorionic Gonadotropin (hCG), progesterone, estrogen, Adrenocorticotropic Hormone (ACTH), cortisol, growth hormone and prolactin have been especially implicated in NVP [45]. These hormones are now well established in the list of circulating chemical agents that stimulate cells of the Chemoreceptor Trigger Zone (CTZ) of area postrema in the medulla oblongata, to initiate vomiting.

Based on the observation that the incidence of hyperemesis is maximum during the peak of pregnancy-induced increase of hCG (around 9 weeks gestation), hCG is considered to be the most likely endocrine factor for the development of HG [46]. The fact that some pregnant women do not experience nausea and vomiting despite elevated hCG-levels, can be explaned on the account of varying biological activity of different isoforms of hCG. An individuals' sensitivity for emetogenic stimuli and hormone receptor interactions modify the effects of hCG leading to hyperemesis in some cases but not in others [47]. The different isoforms of hCG, isoforms without carboxy-terminal portion are short-acting but powerful stimulants of TSH and hyperglycosylated hCG isoforms are long-acting with respect to TSH receptor. Genetic and epigenetic factors attributes to different isoforms of hCG which explains the differences in HG incidence found in different populations and the variability in relationship between hCG and NVP [48,49]. Although the mechanism of emesis by elevated hCG is not well understood, Gadsby and Barnie-Adshead reported that the increased hCG levels causes a receptor mediated increase in PGE2 synthesis, resulting in elevated levels in maternal blood [50]. These findings suggest the role of PGE2 as the causative factor in NVP. Elevated, lowered as well as unaltered progesterone levels have been reported in patients with hyperemesis [51-54]. Increased plasma progesterone in hyperemesis-affected pregnant women is believed to cause a potentially emetogenic elevation of HCG [52]. Progesterone-induced reduced gastrointestinal motility and gastric dysrhythmias (tachygastria, bradygastria) during pregnancy are additional factors contributing to the observed hyperemesis [55,56].

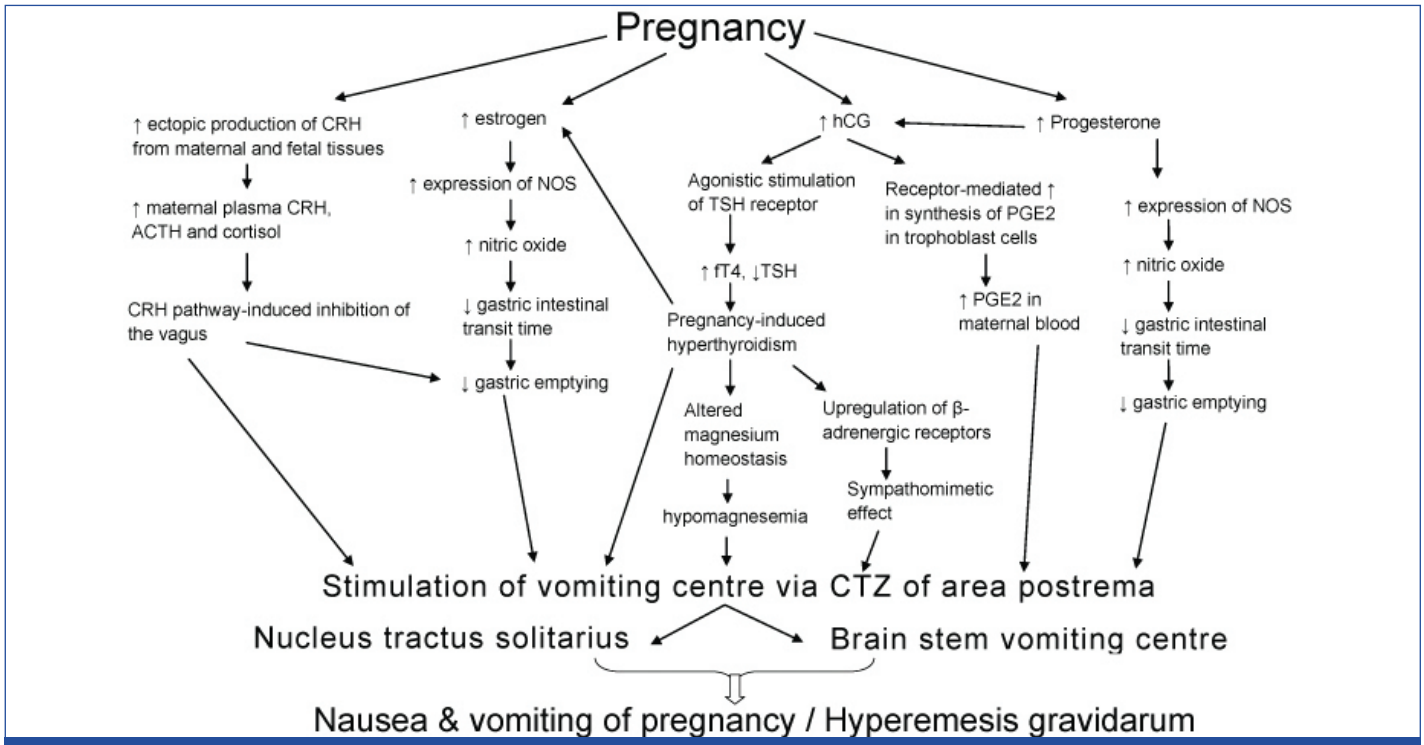
Increased levels of estrogen and estradiol are known to cause nausea and vomiting in pregnancy The observation that oestrogen treatment can cause nausea supports its role in NVP. Conversely, women with hyperemesis seem to be more sensitive to oestrogen effects than asymptomatic pregnant women [52]. Walsh et al., reported that estrogen causes HG by inducing nitric oxide synthase that increasing the production of nitric oxide, that leads to smooth muscle relaxation, which slowes down gastric intestinal transit period and gastric emptying. The study also suggested that progesterone in combination with estrogen may also have a role in NVP since both hormones cause delayed gastric emptying to emetogenic levels [56].

Biochemical hyperthyroidism is prevalent in pregnancy especially in pregnant women with NVP or HG. Goodwin study reports a relationship between hCG and Transient Hyperthyroidism of Hyperemesis Gravidarum (THHG) [48]. Different mechanisms have revealed how hyperthyroidism can trigger vomiting. The first states that the thyroid hormones upregulates β-adrenergic receptors and causes an increase in β-adrenergic activity [57]. Thus, the vomiting in hyperthyroidism may be attributed to sympathomimetic effects of thyroid hormones. Second, it has been speculated that increased thyroid hormones per se can cause emesis by stimulating the CTZ [58]. Third, thyroid hormones alter magnesium homeostasis and the resulting hypomagnesemia affect smooth muscle directly or autonomic innervations of the upper GI smooth muscle [59, 60]. Fourth, since estrogen is increased in patients of both sexes with thyrotoxicosis the raised estrogen could explain the NVP in susceptible patients [58,61,62].

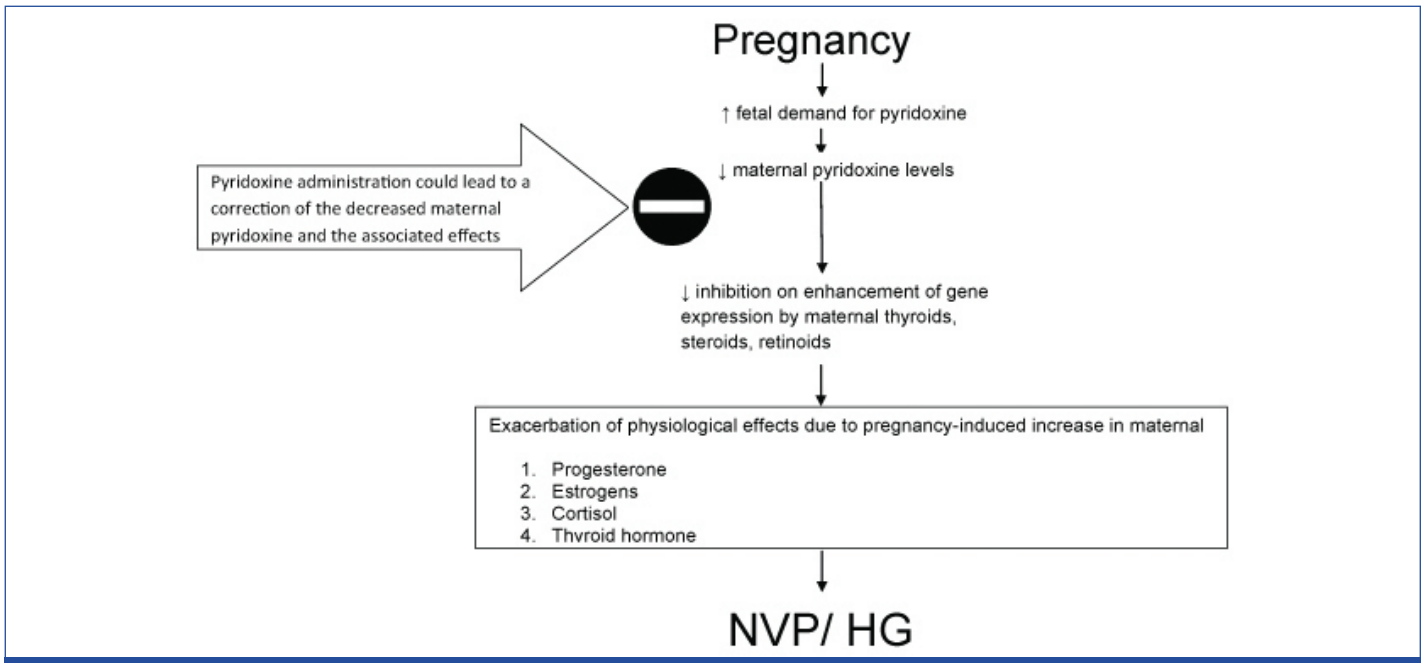
Maternal plasma CRH increases in pregnancy due to its ectopic origin from fetal as well as maternal tissues during pregnancy and a consequential and/or independent increase in plasma ACTH as well as plasma cortisol has also been reported [63]. This peripheral CRF pathway activation has been shown to stimulate inhibitory motor nerves in the dorsal motor nucleus of the vagus, thereby delaying gastric emptying and triggering emesis [64]. The same signal is also seen to trigger area postrema (AP) which is implicated in nausea and vomiting responses) suggesting that elevated peripheral CRF levels modulates the vomiting pathway [65, 66]. The roles of these hormones as causative factors in NVP are summarised in [Table/Fig-4,5].

Pyridoxine-Mechanism of Action in NVP

Currently, the preventive/therapeutic role of pyridoxine in NVP is well accepted. In their review, Nuangchamnong and Niebyl described how NVP is often undertreated partly due to the fear of teratogenic effects of medications on the fetus during early pregnancy. They also gave historical review of the doxylamine-pyridoxine combination drug that obtained FDA approval as a delayed-release combination pill called Diclegis for the treatment of NVP and at present is the



[Table/Fig-4]: Role of neuroendocrine and hormonal factors in etiogenesis of NVP/HG.



[Table/Fig-5]: Maternal pyridoxine levels and pyridoxine administration in nausea and vomiting of pregnancy.

only FDA-approved medication for the indication of NVP. The re-introduction of Diclegis in American market filled up the therapeutic gap created due to removal of Bendectin used for the management of NVP. Based on extensive research, the authors proposed that this combination drug should be first-tier in the hierarchical approach to pharmacological treatment of NVP. Apart from the combination, pyridoxine alone can also be used in NVP [67].

CONCLUSION

Pyridoxine or vitamin $B_{6,}$ the water soluble vitamin of the B-complex group is therapeutically important in gynecology-in suppression of lactation, relieving depression and normalising glucose tolerance in women taking contraceptives, prevent etretinate induced development of fetal abnormalities and in relieving the symptoms of nausea and vomiting of pregnancy induced by increased fetal demand.

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