Nausea and vomiting in pregnancy

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Abstract

Nausea and vomiting during pregnancy, or “morning sickness” are very common, though not well understood. The extreme form, hyperemesis gravidarum can lead to severe complications. We analyzed articles which were published in the last years in this field in MEDLINE. Various etiologies have been suggested, including elevated levels of human chorionic gonadotropin, thyroid hormone or association with Helicobacter pylori infection. Despite the nausea and vomiting, patients are usually able to maintain adequate nutrition. The management of the condition involves symptomatic treatment along with antiemetics, pyridoxine and thiamine, however few studies have evaluated its effectiveness and safety.

Key words: nausea, hyperemesis gravidarum, pregnancy

Definition and incidence

Nausea and vomiting are some of the early symptoms which might suggest a woman the presence of pregnancy, as they affect up to 80% of pregnant women; 50% have both nausea and vomiting and 25% have nausea. Nausea is considered to be one of the most arduous symptoms connected with pregnancy. Their character and inconvenience are similar to the ones which occur in oncological patients during chemotherapy [1].

It is estimated that during the first three months of pregnancy every third woman experiences nausea and about 37-56% complains about nausea and vomiting. Only about 20% of pregnant women do not suffer from these ailments during the first three months of pregnancy [10, 21, 22, 41]. Although it is popularly known as “morning sickness” the study done by Jewell and Young [16] demonstrated than less than 2% of women experience nausea only in the morning and 80% reported nausea throughout the day. The problem is generally time-limited with onset about the fifth week after the last menstrual period, a peak at 8-12 weeks and resolution by 16 to 18 weeks for most women; approximately 5% of women will have symptoms throughout the pregnancy [38]. In a prospective study carried out on 160 pregnant patients with nausea and vomiting only half of the women reported relief by 14 weeks, but 90% had relief by 22 weeks [21].

A small percentage of women experience a severe form of nausea and vomiting known as hyperemesis gravidarum (HG). Estimates of incidence of HG vary from 0.3 to 1.5% of all live births. The principal condition to diagnose HG is the presence of three or more vomiting episodes during the day, weight loss of over 5% (or 3 kg) and ketonuria [12, 19]. Electrolyte, thyroid and liver abnormalities also may be present. Therefore it is necessary to exclude other illnesses which could cause similar symptoms, like for example hypertyreosis.

Hyperemesis gravidarum is the most common indication for hospitalization in the first trimester of pregnancy [11].

Risk factors

Uncontrollable vomiting of pregnant women occur more often during the first pregnancy or with previous pregnancy complicated by HG, in non-smokers, in women with lower body weight, with hepatopathy, lipid disturbances as well as in multiple (increased placental mass) and molar pregnancies. Genetic factor play also an important role; daughters and sisters of women who had HG are more likely to have the same problems [4]. Mother’s more advanced age (> 30 years), smoking and supplementation of vitamins before pregnancy turned out to be a good protection [17].

Etiology

The etiology of unstoppable vomiting remains unclear. However, there are many hypotheses concerning the etiopathogenesis of this affection.

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The most popular hypothesis concerning uncontrollable vomiting in pregnant women is the influence of hormonal changes connected with developing pregnancy. The maternal and placental hormones are considered to play a meaningful role in fragrance intolerance, nausea and vomiting. The correlation between nausea and vomiting with total concentration of human chorionic gonadotrophin (HCG) is meaningless. It was noticed that the level of its subentity (β-HCG) correlates with both the occurrence and the intensity of these ailments. The symptoms usually develop simultaneously with increasing β-HCG concentration and most intensive ailments are connected with the time of the highest concentration of this hormone in 10-12 weeks of gestation [13].

Attention should be paid to more intense vomiting in pregnancies, where the β-HCG concentration is increased, for example in multiple and mole pregnancies, pregnancies with Down syndrome as well as in pregnancies with female fetuses [22, 37]. Also estrogens might influence the occurrence of vomiting. Various researches have shown a higher concentration of estradiol in women suffering from HG in comparison to the control groups. Moreover, the connection of the increased β-HCG concentration with estradiol has been proven [7, 22].

As far as progesterone is concerned the data are contradictory. Lagiou et al. estimated higher estradiol level and lower prolactin level in women with HG, but there is no connection between estradiol and progesterone. Increased levels of steroid hormones, responsible for for slowing down the intestinal passage, might cause HG symptoms. These scientific results are not unequivocal [36].

In the course of uncontrollable vomiting, about 50-70% pregnant women suffer from transient hyperthyroidism of hypermethesia gravidarum. As the degree of stimulating the thyroid gland changes, so does the intensity of vomiting. This suggests that HCG isoforms are characterized by increased thyreotropic effect and simultaneously they show a greater connection with uncontrollable vomiting in pregnant women. The condition of making such a diagnosis is the lack of previous thyroid diseases, lack of thyroid goiter and also absence of thyroidal antibodies in blood serum. In women with HG an increase in biochemical exponents of hyperthyroidism might correlate with the seriousness of clinical picture [14].

In laboratory research done on patient with HG the TSH level was lower, the concentration of thyroxin was considerably increased and the concentration of an active thyroidal hormone (triiodothyronine) was only slightly increased. It comes to hyperstimulation of thyroid gland by β-HCG, because its structure is very similar to TSH. Both hormones belong to groups of glycoproteins; they have identical subentity α and only slightly different subentity β. In the group of patients suffering from HG and hyperstimulation of thyroid gland the vomiting and the electrolyte disturbances are more intensive, and the liver function tests show abnormalities [14, 40].

Another research shows that in women suffering from HG there might be certain immune disturbances; IgG and IgM are considered to increase, the same tendency is observed in components C3 and C4 of complement system, leucocytosis may appear and also there might be an increase in α TNF level and lymphocytes T-helper 1/T-helper 2 balance can be disturbed [24, 43]. With hyperthyroidism these changes are even more visible. However, it has not been resolved yet if the described changes are the cause or the results of vomiting.

In the literature there are also some other possible patomechanisms of development of uncontrollable vomiting in pregnant women, for example Helicobacter Pylori, changes in leptin output, possible influence of serotonine, hormonal changes, (e.g. hypocorticism, hypotuitarism), malfunction of yellow body or intensification of gastroesophageal reflex as a result of decreased pressure in lower esophageal sphincter [40].

For several years the scientists study the connection between HG symptoms and H. pylori infection. The results are contradictory. Bagis et al. [3] confirmed a positive outcome in about 95% pregnant women with H. pylori in histological examination of gastric biopsies. Sandeven et al. [36] showed a doubled risk of HG in women, who had been infected with H.pylori (HpIpG+). In the research done by Aytac et al. [2], using tests to detect the antigen H.pylori in the stool, there was no proof that the number of disease incidents is higher in women with positive test results. This bacteria occurs much more frequently in general population (about 80%), therefore the infection might be secondary to the changes which take place in pregnant women’s organism (changes in immune system and the hormonal system) [2, 3, 36, 40].

Sometimes HG is treated as an ailment connected with psychosomatic diseases. It is commonly believed that particular female features of character or mental disturbances might predispose to their occurrence. Nausea and vomiting tend to be treated as a result of female immature personality or they might mean her not being prepared for maternity [40]. On the other hand it should be stressed that only the inconvenience of this ailments itself might be so enormous that secondarily it might evoke unbenefficial phenomena in the sphere of mind,
increased tension, anxiety or fear of the pregnant woman [39]. Buckwalter et al. [5] tested it on a woman with HG history (from a psychological point of view) and they did not find any meaningful differences either in the psychological sphere or in the sphere of personality disturbances.

Scientists took also the attempt to systematize HG in the evolutionary process. The creation of such an immune mechanism could protect the fetus from an unprofitable influence of potentially harmful substances. The taste and the smell as result of refusal to eat by pregnant women might be a beneficial evolutionary process, which could protect an unborn child from the toxicity of mother’s metabolites. A passive acceptance of this affection might considerably decrease the pregnant woman’s quality of life and in extreme forms it might lead to the limitation of intrauterine growth of the fetus [38].

Differential diagnosis

The diagnosis of uncontrollable vomiting is made by exclusion of other disease entities. HG gives not specific symptoms; therefore an accurate differential diagnosis should always be done. Vomiting occurs without any relations to time of the day, always before 9 week of pregnancy and it disappears usually between 16 and 22 week of pregnancy [38, 40]. It is necessary to exclude many chronic diseases such as with:

- digestive system – such as inflammation of abdominal mucosa, intestinal inflammation, hepatitis and pancreatitis, appendicitis, chronic peptic ulcer disease, diseases of biliary tree;
- urinary system – infection and urolithiasis, uremia;
- chronic endocrinological diseases – diabetic ketoacidosis, hyperthyroidism, Addison disease and porphyria;
- neurological diseases – brain tumors, migraine, dis-equilibrium, drug-induced damages;
- other states connected with pregnancy – fatty degeneration of the liver and preeclampsia [24, 38].

The suspicion of uncontrollable HG in pregnant women recommends to search for some risk factors such as multiple pregnancy or hydatid mole.

Laboratory results indicate dehydration (increased hematocrit and urine specific weight), electrolytic disturbances (hyponatremia, hypokalemia, metabolic hypochloremic alkalosis) and ketonuria. It often comes to moderate increase in aminotransferase activity, increase in concentration of bilirubin, amylase and lipase [40].

Maternal risks

Frequent vomiting might be the cause of metabolic disturbances in pregnant women such as dehydration, acidosis as well as electrolytic disturbances with hypokalemia, acid-alkaline disturbances. It might cause anemia, disturbances in heart rhythm, convulsions and even decay of muscle proteins or muscular atrophy [26]. Long-lasting, very intensive vomiting, might in rare cases lead to Mallory-Weiss syndrome, rupture of esophagus or spleen, choroid bleedings, pneumothorax as well as neurological complications such as mielinolysis of cerebellum or Wernicke encephalopathy caused by lack of vitamin B1 [36].

Fetal risks

The influence of vomiting on the condition of the fetus depends on intensification of the ailments. Various researches showed that the women, in whom the vomiting occurred in the early pregnancy, have lower risk of miscarriage in comparison to the control groups [12]. Most likely high concentration of placental hormones has a protective influence on the early pregnancy. The frequency of fetal abnormalities does not change, although there is information concerning increased risk of malformations in the central nervous system [7, 12]. The group of children born by women who were hospitalized because of HG and improper result of biochemical examinations had lower birth weight and there were more frequently delivered prematurely [8].

Management options

The first and general recommendation for all the women suffering from nausea and vomiting in the early pregnancy is to lead a regular peaceful lifestyle, to stay in bed longer, to rest and to avoid intensive odors and sights of meals that might cause vomitory reflexes. It is also recommended to eat frequently, not abundant meals, as well as to drink small amounts of liquids rather cool and sour sweet. It was turned out that meals rich in proteins can soothe the nausea more than food rich in fat or carbohydrates [15].

In the recent literature a great attention was put to supplementing vitamin preparations [9]. A widely quoted Levichecka algorithm recommends firstly the evaluation of patient’s clinical state and depending on it to choose of form in which the medicines are supplied. If the patient is not dehydrated and can take the preparation orally, initially it is recommended to supply pyridoxine (vitamin B6) three times a day 10-25 mg, up to maximal
dose 100 mg/24 hours. The treatment is considered to be safe and its efficiency has been confirmed in three randomized clinical trials [23, 35, 42]. When the treatment is unsuccessful, then a medicine which acts antiemetically should be added. Furthermore, it is suggested to supply: metoclopramide 5-8 mg every 8 hours, promethasine (12-25 mg every 4 hours), trimetobenzamide 200 mg every 6-8 hours orally or rectally [23]. However, in the Polish market there is lack of the preparation, which has been well tested and recently most widely applied in other countries – doxylamine (12.5 mg 3-4 times a day).

The management at dehydrated women is different. If the patient does not react to ambulatory treatment, and most importantly if she does not tolerate supplying any liquids, it is recommended to hospitalize her in order to hydrate, equalize electrolytic and metabolic disturbances. Intravenous supplement of liquids is recommended. There has been no research concerning fluid therapy applied in women with HG. There are various combinations dependant on medical center. Our department uses successfully a hydrating set, which consists of: NaCl, PWE and glucose solution supplemented with vitamin C, vitamin B1, potassium chloride and insulin; in total it contains 2 liters of liquid. The hydration should be started with supplying isotonic salt solution and Ringer lactate [29]. It is advised to be careful in applying glucose solution at the beginning of liquid supplementation because of the risk of Wernicke encephalopathy [25]. Moreover, due to the risk of this complication in women, in whom the vomiting last for over 3 weeks, it is advised to supply vitamin B1 (100 mg) intravenously. In the next stage intravenous supplementation with one of following medicaments is recommended: diphenhydramine 50 mg in 50 ml NaCl isotonic solution, metoclopramide 5-10 mg every 8 hours or promethasine 12.5-25 mg every 4 hours and as supplement methylprednisolone 16 mg every 8 hours or ondasetron 8 mg in a 15-minute intravenous infusion for 3 days [23]. The present data in the literature do not indicate that commonly applied antiemetic might have teratogenic activity. However, for the time being the safety of application in pregnant women has been defined only for first generation antihistamine medicaments [23].

The treatment of uncontrollable vomiting may also include the combination of droperidol and diphenhydramine [28]. The preceding was considered to be effective; a shorter period of hospitalization and reduction of rehospitalisation was observed [20]. Unfortunately, there are doubts if such a therapy is safe. The are some descriptions of side-effects like cardiac rhythm disturbances of torsades de poites type. Lacasse et al. [20] in comparative research by means of therapy with droperidol 0.5-1 mg/h plus diphenhydramine 25-50 mg every 6 hours and metoclopramide 1,2-1,8 mg/h plus diphenhydramine 50 mg every six hours observed a better effectiveness in regression of symptoms and smaller amount of side effects in women who took metoclopramide with diphenhydramine [20].

In women who do not react to antiemetic medication and in whom the weight loss is stable it is recommended to give glycocorticosteroids. Such treatment is considered to be applied as the last resort in women who require enteric or parenteral nutrition. The most commonly methylprednizolon is applied in the dose of 48 mg/24h for three days. In patients, in whom the treatment will have a positive effect, the therapy will still be applied in smaller dosage for two weeks [26, 29, 34]. The effectiveness, good tolerance, quick regression of symptoms and lower risk of rehospitalisation in such treatment has been proved. Taking into consideration the information about increased risk of chilo-alveolo-schisis, the application of steroids before the 10th week of pregnancy should be avoided [28, 30].

It is suggested that patients with uncontrollable vomiting in the second trimester of pregnancy, who do not react on antiemetic treatment should be diagnosed for ulcerous illnesses. If the H. pylori infection is confirmed, the physician should apply eradication [2, 3, 36]. The treatment with amoksycilin, metronidazole, blockers of proton pump and even H2 receptor blockers is considered to be safe [18, 32].

In cases of weight loss despite of the applied treatment, it is recommended to apply one of the methods of supported feeding. Initially it is recommended to apply internal nutrition by means of intestinal tube. The tube is placed in the area of pylorus to prevent food subsidence into the abdomen. If the woman does not tolerate such a method, then parenteral feeding should be applied. If we need only to complete the lack of calories, a peripheral access can be used. Such an access is also chosen when the intravenous seems to be necessary only for several days as an intermediary before the introduction of intravenous feeding program. The necessity of parenteral feeding for a long time happens quite rare. In such cases it is required to put on central catheter, which is associated with a great number of side-effects [33].

Rosen et al. [31] in a randomized controlled trial evaluated the effectiveness of low-level nerve stimulation therapy over the volar aspect of the wrist at the P6 point
in therapy of nausea and vomiting in early pregnancy. They concluded that nerve stimulation therapy is effective in reducing nausea and vomiting and promoting weight gain in symptomatic women in the first trimester of pregnancy.

Prevention

Prevention of nausea and vomiting should be one of the elements of perinatal care. Czeizel et al. [6] and Emelianova et al. [9] demonstrated that women who were taking a multivitamin at the time of conception were less likely to require medical attention for vomiting. Such prevention should be specially advocated women with a history of nausea and vomiting or hyperemesis gravidarum in a previous pregnancy.

Recommendations

American College of Obstetricians and Gynecologists presented management guidelines of nausea and vomiting in pregnancy [1]. They are summarized in two points:

1) Intravenous hydration should be used for the patient who cannot tolerate oral liquids for a prolonged period or if clinical signs of dehydration are present. Correction of ketosis and vitamin deficiency should be strongly considered. Dextrose and vitamins, especially thiamine, should be included in the therapy when prolonged vomiting is present.

2) Enteral or parenteral nutrition should be initiated for any patient who cannot maintain her weight because of vomiting.

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