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Updates in Management of Hyperemesis Gravidarum

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Abstract

Hyperemesis gravidarum is the most severe form of nausea and vomiting during pregnancy and is characterized by intractable nausea and vomiting that leads to dehydration, electrolyte and metabolic disturbances, and nutritional deficiency that may require hospitalization. Hyperemesis gravidarum is a clinical diagnosis; most of physicians diagnose it by its typical presentation and exclusion of other causes of nausea and vomiting in the pregnant woman. Onset of vomiting typically starts between 6 and 8 weeks' gestation and peaks by 12 weeks. It is a disease of high prevalence among pregnant women. It is a common experience affecting 50% to 90% of all women. It is the most common indication for hospitalization during the first half of pregnancy. Nausea and vomiting are usually limited to first trimester but 20% of women continue throughout pregnancy. It causes economic burden upon families and countries. There are many lines of treatment of Hyperemesis gravidarum, some lines are well studied. Studies regarding drug safety were done to determine incidence of congenital anomalies in babies of mothers received these drugs. Other lines are still experimental. Recent literature regarding management of Hyperemesis gravidarum support using saline or ringer's fluid as a first line for fluid replacement, Antihistamines are the main antiemetic that used in the treatment of those cases, Ondansetron is a promising drug regarding its safety and its efficacy. Use of Proton pump inhibitors should be taken in mind in cases that are resistant to treatment with evidence of H. pylori infection. No current evidence support use of pyridoxine but thiamine and Folic acid should be replaced to avoid consequences of their deficiencies. Steroids are given only in refractory cases. Termination of pregnancy is the last line of treatment in these cases. Actually those patients need psychotherapy especially when they consider termination of pregnancy. Many experimental lines need further researches; ginger and acustistimulation are the most promising experimental lines of treatment.

Keywords: Hyperemesis gravidarum; Catabolic; Ondansetron; Embryogenesis

Introduction

Hyperemesis gravidarum is the most severe form of nausea and vomiting during pregnancy and is characterized by intractable nausea and vomiting that leads to dehydration, electrolyte and metabolic disturbances, and nutritional deficiency that may require hospitalization. Hyperemesis gravidarum is a clinical diagnosis; most of physicians diagnose it by its typical presentation and exclusion of other causes of nausea and vomiting in the pregnant woman. Onset of vomiting typically starts between 6 and 8 weeks' gestation and peaks by 12 weeks. It is a disease of high prevalence among pregnant women. It is a common experience affecting 50% to 90% of all women. It is the most common indication for hospitalization during the first half of pregnancy. Hyperemesis gravidarum are usually limited to first trimester but 20% of women continue throughout pregnancy. It causes economic burden upon families and countries. There are many lines of treatment of Hyperemesis gravidarum, some lines are well studied. Moreover, studies regarding drug safety were done to determine incidence of congenital anomalies in babies of mothers received these drugs. Other lines are still experimental. In this article, we are going to discuss those lines using recent statistics and studies regarding each line of treatment.

Fluid therapy

The most important intervention is fluid and electrolyte replacement. This pregnant woman is in a catabolic condition and sufficient caloric requirements must be administered through our treatment strategy [1]. The volume of fluid should be enough to replace the deficit and continuing loss through vomiting as well as to meet normal fluid and electrolyte requirements. RCOG guidelines of 2016 recommend that saline with potassium chloride with daily monitoring of electrolytes is the most beneficial parenteral hydration. Dextrose solutions are not preferred except if the serum sodium levels are normal and thiamine has been given to avoid precipitation of Wernicke's encephalopathy. A randomised controlled trial comparing the use of 5% dextrose and 0.9% sodium chloride with 0.9% sodium chloride in women with Hyperemesis gravidarum showed no difference after 24 hours in terms of persistent ketonuria, quality of life, nausea, vomiting or resolution of electrolyte imbalance [2]. But higher concentration sodium chloride (for

example 1.8%) should be avoided even if the patient is significantly hyponatraemic because too rapid correction of serum sodium level may cause osmotic demyelination syndrome. Potassium intake is often necessary and should be given according to the serum potassium level.

But higher doses should be given slowly and under monitoring especially ECG due to risk of arrhythmia [2].

Scarcely amino acid as well was fat solutions can be needed for refractory and resistant cases [1]. Fluid replacement can be monitored by ketonuria, electrolytes and urea and creatinine levels. Fluids should be stopped once these reach normal range and a normal diet has resumed [2,3].

Antiemetics – their Safety and efficacy

Antihistamines: They are the most commonly used medication for Hyperemesis gravidarum [4]. Antihistamines are the earliest group of drugs that have been used for the treatment of those patients [5]. Drowsiness is the most common side effect reported with antihistamines; it can lead to noncompliance to treatment and it may affect quality of life [4]. Regarding the fetus, no studies to date have demonstrated any teratogenic side effects of doxylamine and dimenhydrinate [5]. In order to confirm these findings, a meta-analysis was performed on 24 controlled studies published between 1964 and 1991, and included more than 200,000 first-trimester exposures to antihistamines. This meta-analysis found that there was no increased risk for congenital defects in babies whose mothers had used antihistamines during the first trimester [5].

Phenothiazines, butyrophenones and benzamides: The use of phenothiazines for the treatment of Hyperemesis gravidarum may be linked to the fact that they have a wide range of neurotransmitter receptor blocking activity, including histamine, dopamine, muscarine, serotonin, and alpha-adrenergic receptors. Activation of dopamine receptors in the stomach inhibits gastric motility [4]. Dopamine also plays a role in emetic signalling through the chemo receptor trigger zone [5].

Regarding their safety, a follow-up study was conducted in Hungary in children exposed to promethazine in utero to assess measurements, such as weight and head circumference, at birth and at 8 months of age. There were no differences in the children exposed to promethazine compared with children who were not exposed to teratogen [5]. In a cohort study of 264 women treated with a low dose of chlorpromazine for Hyperemesis gravidarum in the first trimester of pregnancy, infants did not have any increased incidence of congenital anomalies. Animal studies regarding the teratogenic potential risk of prochlorperazine have found conflicting results. At high doses, prochlorperazine has been found to increase the incidence of cleft palate in mice and rats but this risk has not been observed in rabbits. Some human case reports have reported fetal anomalies in babies born to mothers who had used prochlorperazine but these anomalies have not been consistent and include newborns with cleft palate , a congenital heart defect , a skeletal and a limb anomalies [5]. So we need further studies with adequate sample size to investigate its safety. Regarding metoclopramide, several prospective studies have confirmed its safety. In one study involving 309 women exposed to metoclopramide during the first trimester of pregnancy, there was no increased risk for birth defects and furthermore, there were no significant differences in the average birth weight and the rate of premature labor in exposed and unexposed babies [5].

Serotonin receptor antagonists: It has been found that serotonin receptor antagonists are the most effective antiemetic drug, based on patients' recall of their own symptoms. In the United States, these agents are preferred to be used more for the treatment of Hyperemesis gravidarum than in other countries. Putting in mind equal effectiveness of Ondansetron compared with promethazine, and no sedative effect, it may be the preferred antiemetic in women who have responded to antiemetics especially who experience significant drowsiness and sedation with Antihistamines [4]. Regarding its safety, two studies have been conducted to determine the safety profile of Ondansetron use during pregnancy. The first study was done in Sweden in which 45 women were exposed to Ondansetron throughout the whole pregnancy, with 21 exposed in the first trimester. No major fetal anomalies were reported in this study. The second study was done at the Mother risk Program in Toronto, Canada, and involved a comparison between women who were exposed to either Ondansetron or other antiemetic medications or other non-teratogens. 176 women were included in each group, and no differences were found among those groups. Because of these recent studies, there is increased evidence for the safety of the use of Ondansetron during pregnancy [5].

Proton pump inhibitors

Because nowadays reviews support the relationship between H. pylori and Hyperemesis gravidarum, proton pump inhibitors should be put in mind during its management. Pregnancy studies with Lansoprazole or Pantoprazole are very limited but more data exist on the safety of omeprazole in pregnancy [6]. In a controlled cohort study, the rate of major fetal anomalies was compared between pregnant women exposed to Omeprazole, Lanzoprazole, or Pantoprazole during first trimester and a control group who were counselled for non-teratogens. The study design is a multi-centric prospective controlled study of the European Network of Teratology Information Services. Authors followed up 295 women exposed to Omeprazole, Tolansoprazole and Pantoprazole during pregnancy, and compared pregnancy outcome to that of 868 European Network of Teratology Information Services controls. The rate of major fetal congenital anomalies did not differ between the exposed and control groups so they concluded that there is no difference when exposure was limited to the first trimester of pregnancy after exclusion of other genetic, cytogenetic or infectious anomalies [6]. In another large cohort study, done in Denmark showed that exposure to proton pump inhibitors during the first trimester of pregnancy was not associated with a significantly increased risk of major fetal anomalies [7].

Vitamins

A Cochrane review concluded that there is a lack of consistent evidence supporting that pyridoxine is an effective therapy for Hyperemesis gravidarum [8,9]. Furthermore, a placebo-controlled trial of this drug in Hyperemesis gravidarum did not demonstrate any improvement in nausea, vomiting or re-hospitalisation in 46 women given 20 mg orally three times a day in addition to standard treatment.

On the other hand, all women with Hyperemesis gravidarum should be prescribed thiamine, especially if the symptoms have been present for three weeks or more [2]. Thiamine can be given intravenously and certainly in those who are vomiting this is the most appropriate route of intake [9]. Regarding Folic acid, requirements increase in pregnancy and supplementation is recommended in all pregnant women until the end of the first trimester to decrease incidence of congenital neural tube defects especially with vomiting loss [2].

Corticosteroids therapy

There is insufficient evidence to support steroids in the treatment of Hyperemesis gravidarum. This is attributed to small study size, inconsistent diagnosis definition, publication bias, low study quality. Although in severe refractory cases, steroids treatment might still be considered as the last line treatment [1,10].

If steroids are needed because of failure to respond to standard treatment as mentioned by RCOG guidelines of 2016, the usual dose is 100 mg intravenous hydrocortisone, twice daily. If symptoms are improved, this is followed by oral intake of prednisolone 40-50 mg daily; the dose should be gradually tapered until the lowest maintenance dose that continues to control vomiting is reached [3].

Termination of pregnancy

Women suffering Hyperemesis gravidarum have an increased likelihood of considering termination of pregnancy. Consideration of termination or actual termination due to vomiting is associated with psychosocial circumstances, which should be taken in mind when managing such patients [2].

In a survey study, conducted to know characteristics of patients who terminated their pregnancies due to Hyperemesis gravidarum, authors found that of 808 women who completed the survey, 123 (15.2%) had at least one termination due to Hyperemesis gravidarum, and 49 (6.1%) had multiple terminations. Prominent reasons given for the terminations were inability to care for the other family members and herself (66.7%), fear that she or her fetus could die (51.2%), or that the baby would be abnormal (22.0%) [11]. Steroids is a choice which should be taken in mind before therapeutic termination of pregnancy, but the decision to use steroids requires careful counselling session with the patient [12]. RCOG guidelines of 2016 recommend that all therapeutic measures should have been done before offering termination of a wanted conception.

Psychotherapy

There are few studies examining psychotherapy treatment for Hyperemesis gravidarum. Indeed, Psychological support from family and the medical team has been found to reduce symptoms of Hyperemesis gravidarum and enhanced patients' compliance to treatment, therefore it improves clinical outcomes [13].

By providing care and support of those patients, and by encouraging family members including her spouse to do the same, these can relieve the psychological burden of the disease and enhance clinical outcomes [9]. If the patient works, a tolerable schedule or working conditions will be beneficial. She should be counselled that an adverse perinatal outcome is not expected due to this disease when adequate weight gain is achieved and sufficient treatment is given [1]. Psychotherapy may involve dialogues between the physician and the pregnant woman to evaluate the psychosocial situation in her marital relationship and provide support regarding acceptance of the pregnancy and the disease [14].

Experimental Treatment

There are many experimental lines of treatment, one of them is hypnotherapy. There seems to be currently insufficient evidence to support using hypnosis in the management of Hyperemesis gravidarum. So RCOG guidelines of 2016 mentioned that Hypnotic therapies should not be recommended to treat this condition. Moreover, there is very limited evidence that would suggest that hypnosis for this condition is not harmful [15].

Because of concerns about teratogenic effects, drugs usually are avoided during the critical embryogenesis period by some patients. So RCOG guidelines of 2016 mentioned that women may be reassured that acustimulations are safe in pregnancy and acupressure may improve Hyperemesis gravidarum. Therefore, many women try these alternative therapies such as acupuncture or acupressure [16]. Some clinical trials' data showed a protective effect of acupuncture, but the continuous data, that taking in mind the whole effect of acupuncture on the treatment outcomes, did not show significant effect. It is unclear what is responsible for this inconsistency of the results. More studies need to be done to determine dose, characteristics of responders, differences among modalities, or other factors that determine response to acusti-stimulation [17]. Regarding ginger, the methanol extract of ginger rhizome has been found to suppress the growth of 19 strains of H. pylori. The fraction containing the gingerols is found to be inhibiting the growth of all H. pylori strains with significant action against the cytotoxin-associated gene (Cag A) positive strains, one of the important stains causing infection. Ginger is available in a number of forms such as tea, biscuits, and crystals or sugared ginger [8]. There is evidence suggesting that ginger is effective in reducing nausea and vomiting experienced during pregnancy. Regarding its safety, the studies used divided doses ranging between 500 and 1500 mg per day with no higher incidence of birth defects, miscarriages, or deformities than in the statistics of general population. But actually there are small numbers of studies that

investigate its safety [18,19]. That is why, RCOG guidelines of 2016 mentioned that Ginger may be used by women wishing to avoid antiemetic therapies in mild to moderate NVP. Patients should be counselled regarding the limits of the currently available literature [18]. In USA, it has not been approved yet by the United States Food and Drug Administration (US FDA) with concerns of potential effect on testosterone binding and thromboxane synthetase activity [8].

Summary

Recent literature regarding management of Hyperemesis gravidarum support using saline or ringer's fluid as a first line for fluid replacement, antihistamines are the main antiemetics that are used in the treatment of those cases. Ondansetron is a promising drug regarding its safety and its efficacy. Use of PPI should be taken in mind in cases that are resistant to treatment with evidence of H. pylori infection. No current evidence support use of pyridoxine but thiamine and Folic acid should be replaced to avoid consequences of their deficiencies. Steroids are given only in refractory cases. Termination of pregnancy is the last line in management of those patients. Actually those patients need psychotherapy especially when they consider termination of pregnancy. Many experimental lines need further researches; ginger and acustistimulation are the most promising experimental lines of treatment.

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