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RESEARCH ARTICLE

"WHAT BEHIND THE SCENE OF HYPEREMESIS GRAVIDARUM: AN ARTICLE REVIEW"

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Abstract

Background: Hyperemesis gravidarum is a complicated medical condition characterized by persistent severe nausea and vomiting. The incidence of hyperemesis gravidarum is about 0.5% of live births and thought to be of higher incidence in hydatidiform mole, multiple pregnancies and other medical conditions associated with elevated hormonal levels.

Objectives: The aim of this article is to provide evidence-based data that summarize the causes and treatment regimens of Hyperemesis Gravidarum.

Review of literature: Hyperemesis gravidarum is a multifactorial condition with various etiological factors have been identified such as hormonal, psychological, genetic and infectious factors, the exact cause and pathogenesis still unknown. The management of this medical condition involves psychological treatment in addition to antiemetic drugs, pyridoxine and vitamin replacement. We performed this literature review with focusing on articles published over the last 10 years, to examine the recent theories of possible causes and management in hyperemesis gravidarum.

Conclusion: Hyperemesis gravidarum could be a life-threatening condition that occurs during the first trimester. It is a treatable condition, mostly by supportive means such as vitamins, IV Fluids, bland diet and family support. These patients can get rapidly into shock, fluid loss or electrolyte imbalance, there for pregnant women with suspected hyperemesis gravidarum must not go on without a well-developed treatment plan.

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Introduction:-

Nausea and vomiting of pregnancy (NVP) are quite common problem that women experience in early pregnancy. The prevalence of pregnant women who have nausea with vomiting is approximately 50–55% and 25% have nausea alone, but the majority are self-management suffices (Matthews et al, 2014). NVP is found more typically in Western countries and urban populations, but it is rare among Native Americans, Africans, Eskimos and most Asian populations (Lee et al, 2011).

The severe end of continuous nausea and vomiting during pregnancy is called Hyperemesis Gravidarum (HG), which complicate about 0.3% to 2% of pregnancies causing pathological changes that affect both mother and fetus. HG cases may experience acetonuria, dehydration, electrolyte imbalance and the most serious complication is Wernicke's encephalopathy. Fetus also could be affected by low birth weight, small for gestational age, prematurity

and a 5-minute Apgar score (Apgar stands for "Appearance, Pulse, Grimace, Activity, and Respiration.") of Less than seven (Clark et al, 201).

HG is most prevalent during the first trimester when both the placenta and the corpus luteum are producing hormones and the body is trying to adapt to the pregnancy state. Although HG is a serious medical condition, the etiology of it still not clear and is explained by few theories. Hormonal theory is the most accepted one which proposed that human chorionic gonadotrophin hormone (HCG) plays a critical role in addition to Helicobacter Pylori (H-Pylori) infection theory and the psychological theory (Lee et al, 2011).

The goal of the treatment of HG is to decrease the symptoms and the complications for mother and fetus and to enhance the quality of her life. While the pathogenesis is still unclear, therefore the treatment can be challenging for the health providers (Bustos et al, 2017). However, since HG reported to be linked with serious complication that affect both mother and fetus, this review will highlight the current evidence on the etiology and treatment modalities of hyperemesis gravidarum.

Objectives:-

The aim of this review article is to increase the awareness of this problem with the following objectives:

1. To recognize the causes and clinical manifestation of hyperemesis gravidarum.
2. To explore the approaches of diagnosis of hyperemesis gravidarum.
3. To establish the treatment options of hyperemesis gravidarum.

Review Of Literature:-

Definition of hyperemesis gravidarum (HG):

Hyperemesis Gravidarum (HG) is a medical condition, which is characterized by severe nausea, and vomiting of pregnancy that is not confined to the morning, not responding to regular medications and affects the patient's general condition (requires hospitalization). Also, it is associated with weight loss and electrolyte disturbance in many cases (Gillott et al, 2005).

It affects nearly 0.3–2% of pregnancies especially in primigravida and it is linked with maternal and fetal morbidity. while previously known as a common cause of death in pregnancy, with proper treatment this is now very rare (Yeh et al, 2018).

Hyperemesis Gravidarum etiology:

The causes underlying this medical condition are not clearly understood (McCarthy et al, 2014). There are a number of suggested hypotheses that are include:

Endocrine theory:

The severity of HG has a positive correlation with the levels of HCG. This theory explains the higher incidence of HG in multifetal pregnancies and hydatidiform moles, and the drastic improvement after 12 week gestation (Cole et al, 2010), because HCG naturally reaches a maximum serum concentration at 8-10 weeks of pregnancy (50000 mIU/ml) and then slightly decrease till 20th week of pregnancy (5000 mIU/ml) and continues at around that level till the end of pregnancy where it disappears 1-2 weeks after delivery. The mechanism of how HCG could cause HG still unclear, but some proposed hypotheses state that HCG has a stimulatory effect on the secretory processes (hormonal and digestive enzyme secretion) in the Upper Gastrointestinal Tract (GIT) (Gillott et al, 2005).

Other studies suggest that as HCG structure is similar to thyroid stimulating hormone (TSH) (both have identical α subunit), so it may cause a stimulation of the thyroid gland. Among 15 studies on the relation between HG and Gestational Transient Thyrotoxicosis (GTT), 11 of them confirmed the significantly higher thyroxin (T4) levels in the hyperemesis group whereas 9 out of 13 showed significantly higher TSH levels (Gillott et al, 2005).

Infection with Helicobacter Pylori theory:

Recent studies found that, there is an association between H-pylori and HG, and they have found a serological evidence for this association. They thought, that H-pylori infection among pregnant women could be due to changes in the gastric acid secretion phase (increased steroid hormone levels during pregnancy leads to accumulation of fluid and thus changes in the gastric pH) or induced by pregnancy-related changes in the immune system (changes in

humoral and cell mediated immunity in order to protect the fetus may lead to de novo H-pylori infection) (Golberg et al, 2007). This may lead to activation of a latent infection with H-pylori that in turn cause the clinical manifestations of hyperemesis. Non-pregnant patients with H-Pylori infection may develop gastric or duodenal ulcers with abdominal pain and periodic vomiting according to type of ulcer, but here there is the most recent accepted theories for HG that include H-Pylori infection as an accepted one. A systematic review which included 14 case-control studies published between 1998 and 2006, concluded that there is an association between hyperemesis and H-Pylori reflected in an overall odds ratio (OR) of 4.45 (95% CI: 2.31-8.54). This finding is further supported by an even more recent, although partly overlapping, meta-analysis of 25 case-control studies published from 1966 to 2008, showing an overall OR of 3.32 (95% CI: 2.25-4.90) there is still a debate about whether H-Pylori is a cause or a consequence of HG. On the other hand, H-pylori infection could be secondary to hyperemesis as excessive vomiting could itself lead to increased risk of H-pylori infection (Sandven et al, 2008).

Psychological theory:

Psychological and psychiatric factors have been strongly implemented in association with hyperemesis gravidarum (Faramarzi et al, 2015). Frequent occurrence of hyperemesis gravidarum has been linked to stress and emotional tension. Hyperemesis gravidarum appears more common among immature, dependent, hysteric, depressed, or anxious women. Hyperemesis is considered a possible protest reaction against the pregnancy as a result of psychological conflicts especially from within the familial and home environment. The importance of psychological factors in the etiology of hyperemesis gravidarum is emphasized by the disappearance and recurrence of symptomatology in relation with separation or return to the family environment and by the fact that this disease is amenable to treatment with hypnosis and other forms of suggestion.

Eating disorders have been associated with hyperemesis gravidarum. A series of 13 women in whom an eating disorder was precipitated during pregnancy, including 4 with hyperemesis gravidarum were described indicating that the interaction between the two entities is variable and dependent upon the individual psychological characteristics of the patient (Eliakim et al, 2000).

Genetic theory:

A recent theory suggests that there is a link between the two genes (GDF15 and IGFBP7) and HG. These two genes (encoding two proteins GDF15 and IGFBP7) are important during pregnancy for the development of human placenta and the control of appetite. One study provides an evidence of abnormal rise of these proteins in the blood of hospitalized patients with HG. However, the underlying mechanisms by which these two proteins induce the symptoms of HG is unknown (Fejzo et al, 2018).

Hyperemesis Gravidarum Clinical Presentation:

HG usually present with vomiting, that is repetitive and not related to meals, it bilious in color and may associate with bloody drops at the end of episodes. Dehydration also is one of the signs, and it may be associated with weakness, fainting and loss of weight, and in severe cases circulatory collapse. In some cases of uncontrollable conditions, it can lead to jaundice, hepato-renal failure, Wernicke's encephalopathy, delirium and coma (Goodwin et al, 2008).

Hyperemesis Gravidarum diagnostic approach:

Mainly, HG is a diagnosis of exclusion for other medical conditions, but no confirmatory test is available. Investigations are directed to identify the causes of vomiting and assess maternal and fetal conditions (Practice Bulletin Summary, 2015).

Laboratory investigation:

Firstly, in all conditions doctor starting with blood sample to perform complete blood count (CBC) to check for anemia and hemoconcentration (Lee et al, 2011).

Then, urine analysis for ketones, specific gravity, renal functions and volume status. Presence ketones in urine are a red flag sign because it is harmful to fetus and can lead to delay development. High specific gravity of urine reflects the in-body volume depletion. Serum electrolytes and ketones, to assess the electrolyte status for low potassium (hypokalemia) and sodium (hyponatremia), and evaluation of variations in blood potential hydrogen (pH) either metabolic acidosis or alkalosis (Lee et al, 2011).

In addition, liver enzymes and bilirubin are essential in any lab test, elevated transaminase levels may occur in approximately 50% of pregnant women diagnosed with HG. Mild transaminase elevation often subsides once the nausea has resolved. The significant elevation of liver enzymes may be a sign of another underlying liver condition, such as hepatitis (viral, ischemic, autoimmune), or some other etiological factors of liver injury (Goodwin et al, 2008).

The thyroid function shall to be obtain involving; TSH and free thyroxine. HG is often associated with a transient state of hyperthyroidism and suppressed TSH levels in approximately 50-60% of pregnant women. However, the elevated free thyroxine may indicate that overt hyperthyroidism is present, thus necessitating further workup and treatment, so further workup and investigations are needed such as neck ultrasound, family history of thyrotoxicosis, repetition of thyroid hormone profile in second trimester (HG peak is during the first trimester), third trimester and after labor to follow-up thyroid hormones and decide wither it's a transient case of thyrotoxicosis or there was an underline thyrotoxicosis (Tan et al, 2002).

Finally, in rare cases reported the associated between HG and calcium level. Some female suffering from hypercalcemia period being with HG, resulting from hyperparathyroidism. In addition, there is a list of important markers included; Hematocrit, Amylase and lipase. the elevated amylase level is noted in about 10% of patients with HG (Johnson et al, 2015). Urine culture and sensitivity, this investigation is to exclude urinary tract infection (UTI), because it is common in pregnant lady and it is often associated with nausea and vomiting (Goodwin et al, 2008).

Radiographical uses:

The radiation is harmful on case of pregnant women, the only imaging we can use is ultrasonography (US). Is usually needed in pregnant women diagnosed with HG for evaluation of multiple pregnancies, gestations or trophoblastic disease and to assess the fetal growth. Additional imaging procedure are not needed unless the symptoms and sings are not resolved after the expected period or if the presentation is atypical such as nausea and vomiting in pregnancy beginning after 8-10 weeks of gestation and persists after 20-22 weeks. In such cases upper abdominal ultrasonography would be indicated to evaluate pancreas and/or biliary tree (Poursharif et al, 2007).

Hyperemesis Gravidarum Management:

The goal of the treatment of HG is to decrease the symptoms and the complications for mother and fetus and to increase the quality of her life (Gazmararian, et al, 2002). While the pathogenesis is still unclear, therefore the treatment can be challenging for the health care providers (Abramowitz et al, 2017).

Initial Therapy:

Intravenous (IV) fluids immediately start to treat the dehydration. The fluid often includes supplementation of electrolytes as persistent vomiting frequently leads to severe electrolyte and vitamin deficiency. Prolonged period with vomiting can cause a shock known as hypovolemic shock to the patient with marked decrease in blood pressure (hypotension) and an increase in the pulse rate (tachycardia). Unfortunately, most patients do not seek treatment in the hospital or outpatient clinics until they are in trouble, so it is considered as an emergency case and the action must be taken quickly (Wegrzyniak et al, 2012).

Pharmacological therapy:

Starting by antiemetic drugs like chlorpromazine, phenothiazines and prochlorperazine, which are central and peripheral dopamine antagonist that have been proved effective in treating the symptoms of NVP and HG (Wegrzyniak et al, 2012). If antiemetic drugs are not effective, then oral Methylprednisolone is indicated. The mechanism of action is assumed to be through direct effect on the vomiting center in brain. In some cases, IV hydrocortisone can be used for patients not responding to therapy with fluids and antiemetic drugs (Fejzo et al, 2012).

Supplement like vitamins A and B are thought to be depleted two weeks of malnutrition associated with severe vomiting of HG only. Patients with HG fear from eating because of vomiting so they avoid eating and worsen their nutritional status. So, they need a detailed nutritional assessment for evaluation and supplementation. In addition, serum electrolyte levels should be monitored and supplemented; of particular concern are sodium and potassium (Abramowitz et al, 2017). Supplementation for the lost Vitamin B1 (thiamine) must be considered to reduce the risk of Wernicke's encephalopathy. Taking multivitamins at the time of conception is considered to decrease the severity

of symptoms of HG as recommended by American College of Obstetricians and Gynecologists (ACOG) (ACOG Practice Bulletin, 2018). Table 1 shows the drugs that can be used to treat HG (Thomas et al, 2015).

Nonpharmacological therapy:

Dietary modifications include recommendations to have small and frequent meals, avoid spicy or fatty foods, and drink fluids regularly. Lifestyle modifications include avoiding noxious sensory stimuli, eating crackers in the morning after waking, and increasing rest. Although these are common recommendations, there are few published studies evaluating the efficacy of these changes for prevention or treatment of HG (Gillott et al, 2005).

In herbal medications, Ginger for example, is believed to inhibit the growth of H-Pylori (about 19 strains) through the extracted methanol group with evidence of beneficial effects (Mahady et al, 2003). In addition, some studies have proved that taking Ginger in quantities of 1 g/day for four days has been shown to significantly reduce nausea and vomiting compared with a placebo (Vutyavanich et al, 2001).

There are few studies that examined the effect of psychotherapy in treatment of HG and reported that it is effective. Also, psychological support from the medical care team and family has shown to reduce the severity of HG (Faramarzi et al, 2015). Consultation with a psychiatrist or psychologist may be indicated because psychological assessment may be needed. Early during pregnancy with HG, behavioral therapy may be beneficial (Al-Ozairi et al, 2009).

Follow-up care:

Follow up of both fetal and maternal conditions are recommended. The fetal condition by serial US, the maternal condition by observation of vomiting number, content and vital signs (Pulse, Temperature, standing and lying Blood Pressure and Respiratory Rate), volume status (mucous membrane condition, skin turgor, neck veins and mental status). Fluid chart (record the fluid input and output to early diagnose oliguria which is an important sign of dehydration, a common complication of HG). Daily analysis of urine (for ketones and specific gravity) and blood chemistry (to detect metabolic changes and electrolyte disturbances). Weekly examination of fundal level (Campbell et al, 2016).

Therapeutic (induced) abortion:

All therapeutic measures should have been tried before offering termination of a wanted pregnancy. It is indicated in cases showing the following criteria: Severe vomiting persisting for more than one week after treatment. Worsening of vital data (systolic blood pressure below 100 mmHg, plus above 100 beat/min and temperature is persistently exceeding 38°C. Affection of liver pointing to impending liver functions with appearance of jaundice and bile in urine. Impairment of kidney functions with anuria. Absence of chloride (Cl-) in urine with or without persistent albuminuria or high blood urea. Retinal hemorrhage or Wernicke's encephalopathy. Severe dehydration with oliguria and circulatory collapse without good response to treatment (Mitchell-Jones et al, 2017).

Methods of termination of pregnancy include, vaginal evacuation which is indicated when the gestational age is less than 12 weeks. While surgical suction and evacuation is indicated if the gestational age exceeds 12 weeks. Nitric oxide and oxygen are used for anesthesia instead of halothane to not affect the liver or prostaglandins that aggravate the vomiting (Poursharif et al, 2007).

Hyperemesis Gravidarum Complications:

Whereas prior to the 1940s (at which time fluid and electrolyte dynamics were not clear) maternal death complicating hyperemesis was not uncommon. In the distant past, due to the severity of potential complications of hyperemesis gravidarum, at times pregnancy termination was advocated. Currently, hyperemesis gravidarum is rarely associated with death. Notwithstanding, serious life-threatening complications may occur (Eliakim et al, 2000).

Medical Complications:

There is an evidence of an increased incidence of depression, anxiety and fear in patients with HG about the next pregnancies (Poursharif, et al, 2008). Wernicke's encephalopathy which is a degenerative change in the brain related to B1 (thiamine) deficiency and manifested by delirium, ataxia, nystagmus. Women can suffer from atrophy of the heart leading to heart failure, peripheral neuropathy with retinal hemorrhage and detachment. Metabolic and hematological disturbances like dehydration, hemoconcentration, hypokalemia, hyponatremia, starvation and

Disseminated Intravascular Coagulopathy (DIC) due to prolonged dehydration (Practice Bulletin Summary, 2015). HG has been reported in many studies to be associated with increased risk of adverse pregnancy outcomes such as abortion (spontaneous and induced), low birth weight, preterm birth and small-for-gestational age infants (McCarthy et al, 2014). On the other side, a systematic review identified no association between HG and Apgar scores (other studies said HG is associated with low APGAR score), congenital anomalies, or perinatal death (Veenendaal et al, 2011).

Social and financial complications:

In addition to the medical complications, there are financial complications. Over 55% of pregnant women with NVP required some investment off work. Working pregnant women need time off from this work which is legally paid, in addition their medical care may be also paid in most cases so the work will lose financially and also their efforts (Tan et al, 2018). HG is one of the most common indications for hospitalization in the first trimester of pregnancy (Boelig et al, 2018).

Conclusion:-

HG could be a life-threatening condition that occurs during pregnancy mostly in the first trimester. In order to explore the causes and consequences of HG, there is need for a universally agreed definition of the condition and more researches to be done. It is a treatable condition, mostly by supportive means such as vitamins, IV Fluids, bland diet and family support. These patients can get rapidly into shock, fluid loss or electrolyte imbalance, therefore for pregnant women with suspected HG must not go on without a well-developed treatment plan.

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Conflict of interest:

The authors declare that there is no conflict of interest.

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Annex:

Table 1:- Drugs that can be used to treat HG .

| Drug Name | Usual Dosage Range | Main Side Effects | FDA | Pregnancy |
|-----------|--------------------|-------------------|-----|-----------|
|-----------|--------------------|-------------------|-----|-----------|

| | | | Category |
|-----------------------------------|---|---|----------|
| Vitamins and Antihistamines | | | |
| Pyridoxine | 25 mg q 8 h PO | - | A |
| Thiamine1 | 250 mg IV 3-5 days | - | A |
| Doxylamine | 12.5 mg q 12 h PO or 12.5 mg am and 25 mg pm PO | - | A |
| Doxylamine pyridoxine combination | 10/10 mg up to 4 tablets (1 tablet am, 1 tablet afternoon, 2 tablets bedtime) PO | - | A |
| Diphenhydramine | 50-100 mg q 4-6 h PO/IM/IV | Drowsiness | B |
| Dimenhydranate | 50-100 mg q 4-6 h PO/PR 50 mg q 4-6 h IV | Drowsiness | B |
| Meclizine | 25 mg every q 4-6 h PO | Drowsiness | B |
| Dopamine Receptor Antagonist | | | |
| Promethazine | 25 mg q 4-6 h PO/IM/IV/PR | Sedation, dry mouth, EPS | C |
| Prochlorperazine | 5-10 mg q 4-6 h (maximum 40 mg/day) PO/IM/IV, 25 mg q 12 h PR | Sedation, dry mouth, EPS | c |
| Metoclopramide | 5-10 mg q 8 h PO/IM/IV | EPS | B |
| Chlorpromazine | 10-25 mg q 4-6 h PO/IM 50-100 mg q 6-8 h PR 25-50 mg q 4-6 h IV | EPS, orthostatic hypotension (IM route), sedation | c |
| Droperidol | 0.625-2.5 mg IV over 15 minutes, then 1.25 mg or 2.5 mg IM as needed; can be given IV continuously at 1-1.25 mg/h | EPS, black box warning (QT prolongation and torsade's de pointes) | C |
| Serotonin Antagonist | | | |
| Ondansetron | 4-8 mg q 6-8 h PO | Headache, constipation | B |
| Glucocorticoids2 | | | |
| Prednisolone | 40-60 mg/day PO (then taper) | Cleft palate | C |
| Methylpred-nisolone | 16 mg q 8 h PO/IV (2-3 days, then taper over 2 weeks) | Cleft palate | C |

PO: oral, am: morning, pm: night, IM: intramuscular, IV: intravenous, PR: rectal, EPS: extrapyramidal symptoms.