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Case Report

Surgical Management of Underlying Biliary Disease in Refractory Hyperemesis Gravidarum

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Introduction

Hyperemesis gravidarum (HEG) is the most common cause of hospitalization during the first half of pregnancy. It affects approximately 0.3-3% of all pregnancies [1]. There is no one accepted definition or diagnostic criteria for HEG. The most commonly cited criteria include persistent vomiting not related to other causes, measure of acute starvation (most commonly ketonuria), and weight loss; most often loss of at least 5% of pre-pregnancy body weight [2]. Symptoms typically begin in the late first trimester and are rarely associated with abdominal pain. HEG is managed a stepwise fashion by adding pharmacotherapy sequentially until symptom resolution [3, 4]. Patients who present with classic signs and symptoms of HEG but are non-responsive to all levels of therapy present a therapeutic challenge. In these cases, the search for other causes of nausea and vomiting should be undertaken. In the current report, we review 10 cases of refractory HEG. Eight patients were incidentally diagnosed with biliary disease by abdominal ultrasound (US) during workup for refractory symptoms. These patients underwent surgical consultation and were subsequently offered laparoscopic cholecystectomy. Here, we review the pregnancy courses from initial presentation until delivery to explore the incidence of underlying biliary disease and role of cholecystectomy in refractory HEG.

Methods

From July 2015 to August 2016, we conducted a retrospective review of patients with HEG refractory to standard stepwise management. All patients were admitted to the antepartum service at our institution and managed by a team of obstetricians and maternal-fetal medicine specialists. We defined refractory HEG as failure to improve with standard multi-agent pharmacotherapy, in some cases ultimately requiring supplementary parenteral nutrition. Standard pharmacotherapy regimen included the following, which were added in stepwise fashion: intravenous fluid (IV) hydration containing vitamins and electrolyte solution, IV pyridoxine and anti-histamine, metoclopramide, promethazine, ondansetron, and finally corticosteroids (Table 1). From this cohort, we identified patients with biliary pathology on abdominal US, including cholelithiasis or gallbladder sludge. These patients underwent surgical consultation and were then offered laparoscopic

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cholecystectomy. Surgery was performed by the same surgeon, using the same techniques under general anesthesia. Specific surgical techniques included abdominal insufflation with the veress needle in the left upper quadrant, followed by abdominal entry under direct visualization with opti-port superumbilically, and maintenance of intra-abdominal pressure of 10 mmHg. These cases were then reviewed from hospital presentation to completion of pregnancy. Outcomes included resolution of symptoms, delivery of viable infant, delivery at term, infant birth weight, neonatal intensive care unit (NICU) admission, hospital readmission and need for parenteral nutrition post-operatively. Patients with diagnosis of nausea and vomiting in pregnancy related to other causes were excluded; included patients with febrile illness, gastroenteritis and diabetic ketoacidosis.

Table 1: Stepwise management of hyperemesis gravidarum.

Step	Pharmacotherapy	Dosing	Considerations
1	IV Fluid hydration with electrolyte and vitamins	Maintenance fluid requirements	Fluids used contained potassium, thiamine, magnesium
2	Pyridoxine	Oral pyridoxine 25 mg every 8 hours	If not tolerating oral, 25 mg added to IV fluid solution
3	Anti-histamines	Benadryl 25 mg IV every 8 hours	
4	Ondansetron	4 mg IV every 8 hours	Prolonged QT interval
5	Metoclopramide	10 mg IV in 50 mL D5W administered IVPB	Extra-pyramidal side effects
6	Promethazine	25 mg rectal suppository every 6 hours	
7	Corticosteroids	Methylprednisone 16 mg every 8 hours for 3 days, followed by 2-week taper to lowest effective dose	Concerns regarding birth defects with first trimester use

IV: Intravenous; D5W: dextrose and water; mL: IVPB: Intravenous piggyback

Table 2: Patient demographic characteristics.

Race	**N (%)**
Caucasian	3 (30)
Hispanic	4 (40)
African American	3 (30)
Age (years)	**Mean (**Range)
	30.3 (22-39)
BMI (m^2/kg)	**Mean** (Range)
	28.2 (22.5-40.2)

Results

We identified 10 patients meeting criteria for refractory HEG. All patient presented in the late first and second trimester (11.5 to 18 weeks gestational age). The mean age of presentation was 30.3 years (range: 22 – 39) and the mean BMI was 28.2 (range: 22.5 – 40.2) (Table 2). The most common presenting symptoms were severe nausea (100%), vomiting (90%) and weight loss of at least 5% pre-pregnancy body weight (90%). Interestingly, no patients presented with complaint of abdominal pain, although two (20%) were found to have right upper quadrant tenderness on physical examination. All patients underwent abdominal US during hospitalization and work for refractory disease. Eight (80%) were diagnosed with cholelithiasis or sludge on abdominal US and subsequently underwent surgical consultation. All patients were evaluated by the same surgical team, specializing in advanced minimally invasive and general surgery. After surgical consultation and consultation with maternal fetal medicine specialist, all patients with biliary pathology on US were offered laparoscopic cholecystectomy for refractory HEG. Six patients elected to proceed with laparoscopic cholecystectomy. The six laparoscopic cholecystectomies were performed under general anesthesia. All patient received standard one-time dose of preoperative antibiotics prior to skin incision; cefazolin 2g IV. Preoperative and postoperative auscultation of fetal heart sounds were performed by obstetricians. There were no intra-operative or immediate post-operative complications.

Postoperatively, symptoms improved in 5 patients (83.3%), with 4 patients (66.7%) experiencing complete resolution of symptoms. These 4 patients required no further antiemetic therapy beyond post-operative day 2, resumed regular diet and continued to term uneventfully. No patients required parenteral nutrition beyond post-operative day 2. One patient experienced partial resolution of symptoms; residual intermittent nausea was successfully managed with oral anti-emetic therapy as an outpatient. This patient resumed regular diet on postoperative day 3 and continued on oral anti-emetic into the third trimester. She did not require re-hospitalization or further IV pharmacotherapy (Table 3). All 5 patients who experienced symptom improvement continued on post-operatively to delivered viable infants at term.

One patient failed to experience significant improvement following cholecystectomy. Immediately postoperatively, her symptoms improved, and she resumed oral intake. However, she continued to experience intermittent nausea and vomiting requiring multiple IV medications and continued hospital admission. Despite this, her oral intake improved after surgery, and weight remained stable. Unfortunately, while admitted, she was diagnosed with intra-uterine fetal demise at 20.0 weeks gestation, 19 days postoperatively. Of note, this patient suffered intra-uterine demise at 19 weeks in her prior pregnancy. She declined genetic testing and autopsy in both instances. Of the 5 live-born term infants, all birth weights were appropriate for gestational age (AGA). There were no cases of growth restriction ($<10^{th}$%) or large for gestational age ($>90^{th}$%). There were no NICU admissions. The mean time to hospital discharge following laparoscopic cholecystectomy was 2.6 days, excluding the patient with fetal demise at 19 days post-operatively. There were no hospital re-admissions following discharge post-operatively.

Table 3: Outcomes.

	N (%)
Delivery of viable infant:	5 (83.3)
Delivery at term: [a]	5 (83.3)
Birth weight:	
AGA [b]	5 (100)
IUGR [c]	0 (0)
LGA [d]	0 (0)
NICU admission:	0 (0)
Hospital readmission:	0 (0)
Mean time from symptom onset to initial presentation:	8.5 days (range: 3-14)
Mean time from admission to surgery:	8.3 days (rang: 5-18)
Mean time from surgery to hospital discharge [e]:	2.6 days (range: 2-4)

[a]Term define as > 36.6 weeks gestational age.

[b]AGA: appropriate for gestation age.

[c]IUGR: intrauterine growth restriction, define as weight <10th% for gestational age.

[d]LGA: large for gestational age, define as weight >90th% for gestational age.

[e]Excluding one case of patient with intra-uterine demise who remained in the hospital until 22 days post-operatively

Discussion

Up to 85% of women will experience some degree of nausea and vomiting during pregnancy. Its most severe form, HEG only affects 3% of pregnancies. Despite its overall low incidence, HEG is the single most common cause of hospitalization during the first half of pregnancy [1, 5]. Although no definitive mechanism of action is universally accepted, several factors are agreed to play a role in the pathogenesis of HEG. The hormones estrogen, progesterone and human chorionic gonadotropin (HCG) are elevated in early pregnancy and known to have emetogenic properties [4]. Additionally, progesterone is known to play a role in slowing gastric motility and impairing gallbladder contractility by inhibiting cholecystokinin-mediated smooth muscle stimulation [2]. Traditional management of HEG entails a step wise approach of sequential pharmacologic interventions. At our institution, we use the approach detailed in Table 1. Failure of traditional management should prompt investigation into underlying causes that may contribute to nausea and vomiting in pregnancy.

The most commonly used modality for imaging the biliary system is US. The sensitivity and specificity of 80 and 88%, respectively for acute cholecystitis [6, 7]. US exposes the fetus to no ionizing radiation and can safely be used in pregnant patients [8]. Cholelithiasis is identified in up to 8% of all pregnant women undergoing abdominal US [9]. Therefore, we do not advocate routine abdominal sonogram in all patients initially presenting with HEG. We estimate there is a significant percentage of patients with HEG and concomitant cholelithiasis, who would benefit from routine stepwise therapy and ultimately do not require cholecystectomy. We suggest that abdominal US should be reserved for those patients who are refractory to traditional management. However, in patients presenting with symptoms of nausea and vomiting in pregnancy with concomitant abdominal pain, imaging should not be delayed ruling out alternative diagnosis. Of note, there are documented cases in the literature of patients with symptomatic biliary disease and normal imaging studies [10]. In the event of refractory HEG and normal abdominal US, biliary dyskinesia should still be considered, and cholecystectomy should be offered on a case-by-case basis. Laparoscopic cholecystectomy in pregnancy has been associated with improved maternal and fetal side outcome compared to open cholecystectomy [11]. It is unlikely that our patient with intrauterine fetal demise 19 days postoperatively was related to cholecystectomy. Interestingly, no patients in our cohort presented with epigastric and right upper quadrant pain traditionally associated with biliary disease. Based on these findings, we suggest that biliary disease may manifest different symptomatology in pregnancy. The major limitation to our case series is the small sample size and absence of control group. Despite these limitations, this is the first report of successful surgical management of HEG. Our positive pregnancy outcomes indicate the need for large prospective study to confirm our findings.

Conclusion

In the present report, we observed resolution of symptoms of HEG with cholecystectomy in patients with ultrasonic evidence of biliary disease. Patients presenting with HEG refractory to standard pharmacotherapy present a therapeutic challenge for physicians. In these patients, the search for underlying etiology for nausea and vomiting should be undertaken. Identification of biliary pathology on abdominal ultrasound should prompt surgical consultation and consideration of cholecystectomy even in the absence of abdominal pain.

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