ORIGINAL RESEARCH

Retrospective analysis of haemolytic uremic syndrome in pregnancy and during postpartum period in patients: Retrospective analysis in a tertiary care clinical setting

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ABSTRACT
Pregnancy is associated with various forms of thrombotic microangiopathy, including hemolytic uremic syndrome (HUS). Pregnancy outcomes in patients with HUS are not well-documented. In this article, we go over the traits and prognoses of HUS-affected women who got pregnant while receiving perinatal care at the hospital. This was a retrospective single-center study conducted in India in 57 pregnant women. Different pregnancy outcomes and characteristics of HUS were recorded during different trimesters of pregnancy and also during the postpartum follow-up. The average age at the time of pregnancy-related HUS was 28±4.5 years. The risk for HUS occurrence was higher for the first pregnancy and it was lowered in subsequent pregnancies. HUS was diagnosed mainly in the third trimester. While in HUS presenting patients acute kindly injury was significant and thrombocytopenia was mild. There was no maternal death but neonatal or fetal deaths took place in 5 (8.8%) cases. Overall, 45 of 57 (79%) pregnancies resulted in a live birth and 5 (8.7%) pregnancies resulted in miscarriage. Progression of HUS to ESRD and CKD was progressive and occurred within 3 months. While streroid therapy brings kidney functions to the normal, relapse occurs in 65% patients and that lead to ESRD. Compared to patients with HUS in the postpartum period, patients presenting with HUS during pregnancy had a more frequent personal history of CKD or HUS. In conclusion, atypical HUS associated with pregnancy is a very serious condition that, if untreated, has a poor prognosis for the health of the mother's kidneys. In patients who are at risk for the disease, pregnancy appears to be a significant trigger.

Keywords: Pregnancy, Hemolytic uremic syndrome, Retrospective study, Diagnosis

INTRODUCTION

When red blood cells are broken down and obstruct the kidneys' filtering system, it results in hemolytic uremic syndrome, or HUS [1]. HUS is a medical condition characterized by the triad of thrombocytopenia, thrombotic microangiopathy, and acute kidney injury [2]. The symptoms of HUS include nausea, bloody diarrhea (loose stools or poop), fever, chills, stomach pain, and headache. Most frequently, HUS happens after a severe bowel infection caused by some toxic strains of the bacteria E. coli. It can also happen due to specific medications, autoimmune diseases, or pregnancy. If pregnancy causes thrombotic microangiopathy (TMA), the condition is referred to as pregnancy-associated atypical hemolytic syndrome (p-aHUS). It impacts one

out of every 25,000 pregnancies, primarily the postpartum period, and it is associated with poor maternal outcomes [3]. There is a high risk of developing thrombotic microangiopathy during pregnancy, including HUS and ADAMTS13 deficiency-associated thrombotic thrombocytopenic purpura [4,5]. There are instances of severe postpartum hemorrhage presenting with features that are similar to those of HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelet count) syndrome and pregnancy-associated HUS [6,7].

Pregnancy in patients with aHUS is considered high risk because some patients have underlying chronic kidney disease (CKD) and aHUS recurrence

during or after pregnancy is a possibility. Adverse pregnancy outcomes in high-risk patients with CKD are significantly increased due to risk factors including kidney

dysfunction, proteinuria, hypertension, and poorly controlled diseases [8,9]. Qualitative evidence shows that pregnancy in patients with CKD may be discouraged by the physician, or patients themselves may decide against becoming pregnant due to the possibility of adverse outcomes [10].

There are increasing numbers of statistics on maternal and fetal outcomes in women with a history of HUS [11–12]. These reports were based on a pharmacovigilance database; pertinent patient medical histories, such as dialysis or transplantation status, kidney function (estimated glomerular filtration rate), familial aHUS history, and genetics, were not systematically characterized. Also, gestational age and birth weight were not reported. In this retrospective study, we describe traits in women with aHUS who got pregnant or who developed aHUS while pregnant, including those who were deemed high-risk for pregnancy. We also examine the results of pregnancies in this population.

MATERIALS AND METHODS

STUDY DESIGN

This was a retrospective single-center study conducted in India, in which a HUS registry has been established. Through computerized databases, we identified all women with pregnancy-related HUS included in these registries between 2020 and 2022.

PATIENTS

Patients of all ages with a clinical diagnosis of HUS were eligible for enrollment. There are 57 pregnant women on the list as of the time of this analysis. The current analysis included women who became pregnant after being diagnosed with a HUS, enrolled in the a HUS Registry, and had evaluable pregnancy data. The term "pregnancy-associated HUS" refers to HUS that develops either during pregnancy or in the postpartum stage (up to 12 weeks after delivery). Mechanical hemolyticanemia (hemoglobin1.1 mg/dl or >25% increase from baseline value) or the signs of thrombotic microangiopathy in a kidney biopsy sample (endothelial cell swelling and detachment from the basement membrane, double contours) were used to define HUS. HUS that happened during pregnancy or in the first 12 weeks after delivery was called HUS which was linked to pregnancy. Mechanical hemolyticanemia (hemoglobin 1.1 mg/dl or >25% increase from baseline value) or typical features of thrombotic microangiopathy in a kidney biopsy sample (fibrin/platelet thrombi, endothelial cell swelling, detachment from the basement membrane, double contours) were linked to at least three of the following signs of HUS.

The exclusion criteria included showing signs of an E. coli infection that produces Shiga toxin, ADAMTS13 activity below 5%, or a subsequent diagnosis of thrombotic thrombocytopenic purpura [13]. Individuals with a missing pregnancy outcome and patients with preeclampsia (defined by hypertension >140/80 mmHg and proteinuria >300 mg/d [8] after 20 weeks of gestation) before the development of thrombotic microangiopathy features, HELLP syndrome (defined by aminotransferase >70 U/L, lactate dehydrogenase >600 U/L, and platelet count) were excluded.

DATA COLLECTION AND ANALYSIS

Per protocol, pregnancy outcome data for all patients was collected during this study.

RESULTS

There were 57 patients with pregnancy-related HUS who were registered during the study period. The main characteristics of these patients are summarized in Table 1.

PATIENT CHARACTERISTICS AT PRESENTATION

The average age at the time of pregnancy-related HUS was 29±6 years (Table 1). Atypical HUS was present in the families of 14 patients (24.5%), with at least one affected member. Prior to presenting with pregnancy-associated HUS, seven (12.3%) patients had a personal history of atypical HUS and had either one (n=4) or multiple (n=3) episodes that were unrelated to pregnancy. Five patients had already had plasma exchanges for atypical HUS, and two of them had stage 3 CKD because of it. The risk for HUS occurrence was higher for the first pregnancy (53%) and lower for subsequent (second, third, or subsequent) pregnancies (24.6%, 12.3%, and 10.5%, respectively). HUS occurred mainly in the pregnancy period (n=43, 70.2%; meantime of 24.5±6.6 weeks of gestation). This is mainly in the third trimester of pregnancy. Twenty patients (24%) presented with HUS during the postpartum period. AKI was severe, with 43 (75.5%) patients requiring dialysis at presentation. In contrast, thrombocytopenia was mild (mean platelet count: 95.6±45.3×10 /μl) and even absent in six (10.6%) patients. Extrarenal symptoms were noted in 10 patients (17.5%). When kidney

biopsies were done on eight patients, most of whom had normal platelet counts, the typical signs of thrombotic microangiopathy were found.

Table 1:Characteristics of 57 patients with the pregnancy-associated hemolytic uremic syndrome

Characteristics	Number (%)/Mean±SD
Number of patients	57
Age at HUS onset, yr	28±4.5
Number of previous pregnancies	0.8±0.8
Rank of pregnancy HUS was diagnosed in (*n*=57)	
First	31 (53.45)
Second	14 (24.6)
Third	7 (12.3)
Fourth or subsequent	6 (10.5)
Preeclampsia during pregnancies	7 (12.3)
Fetal loss during previous pregnancies	10 (17.5)
Familial history of atypical HUS	14 (24.6)
Personal history of atypical HUS	11 (19.3)
Timing of HUS	
Postpartum	20 (24)
During pregnancy	40 (70.2)
Features of hemolytic uremic syndrome	
Serum creatinine, mg/dl	5.8±3.4
Dialysis	34 (60.6)
Platelet count $\times 10^3$, per µl	95.6±45.3
Hemoglobin, g/dl	7.5±1.7
Lactate dehydrogenase, U/L	2138±745
Neurologic involvement	6 (10.5)
Other extrarenal manifestations	4 (7)
Treatment	
Number of patients who underwent plasma exchange	31 (53.45)
Number of patients who received plasma infusion	14 (24.6)
Number of patients who received therapy for HUS	20 (35.0)

OUTCOME

No maternal deaths have been documented. Neonatal or fetal deaths took place in 5 (8.8%) cases. Overall, 45 of 57 (79%) pregnancies resulted in a live birth. Out of 9 pregnancies with CKD and ESRD, two (22% of the total) resulted in premature births. The median (range) gestational age was 37.3 (28–41) weeks. Nine low-birth-weight newborns were recorded. Elective terminations were reported in 2 (3.5%) pregnancies, one because of a health reason and the other as per patient choice. Five (8.7%) pregnancies resulted in miscarriage.

Within three months of the first signs of pregnancy-associated HUS, 20 patients (35.1%) progressed to ESRD, and 14 (24.6%) developed CKD. There was no difference in the risk of ESRD and CKD between patients who went through plasma exchanges and those who did not. Fifteen of the twenty people who were treated with therapy had their kidney function return to normal. The remaining patient treated remained dialysis-dependent.

A relapse of HUS occurred in 37 patients out of the 57 (65%) who did not reach ESRD within 3 months of pregnancy-associated HUS. In four out of 10 relapsing patients, HUS relapse led to ESRD. At last follow-up (5.6±3.5 years), 12 out of 57 (21%) patients had an eGFR>60 ml/min per 1.73 m^2, 9 had CKD, and 20 (35.1%) had progressed to ESRD.

Table 2:Outcome of 57 patients with pregnancy-associated hemolytic uremic syndrome

Outcome	Number (%)/Mean±SD
Duration of follow-up, Yr	5.6±3.5
Patients with an eGFR<60 ml/min per 1.73 m^2 without ESRD	12 (21.0)
Patients with an HUS relapse	10 (17.5)
Patients who reached ESRD	20 (35.1)
ESRD within 3 mo of pregnancy HUS (*n*=78)	25 (43.8)
Relapse in the native kidneys	
Number of relapses	2.4±1.1
Patients reaching ESRD after a relapse	12 of 20 (60)

PATIENTS' CHARACTERISTICS AND OUTCOME DEPENDING ON THE TIMING OF HUS

Compared to patients with HUS in the postpartum period, patients presenting with HUS during pregnancy had a more frequent personal history of CKD or HUS (31% versus 8%). They tended to require less frequent dialysis in the acute phase, even though this difference was not statistically significant (Table 3).

Table 3: Main characteristics of 57 patients who presented with hemolytic uremic syndrome during pregnancy (n=23) or in the postpartum period (n=35)

Characteristic	HUS during Pregnancy (*n*=23)	HUS Postpartum (*n*=35)
Medical history		
Personal history of HUS	6 (26.1%)	4 (11.2%)
At onset		
Age, yr	28.5±4.7	30.1±3.1
Need for dialysis	8 (34.8%)	24 (68.6%)
Neurologic involvement	0 (0%)	2 (5.7%)
Plasma exchange	5 (21.8%)	28 (80%)
Outcome		
Duration of follow-up, yr	1.2±0.4	2.4±0.5
HUS relapse	3 (13.0%)	12 (34.9%)
CKD	3 (13.0%)	9 (25.7%)
ESRD	5 (21.8%)	16 (45.7%)

DISCUSSION

According to the findings, pregnancy-related HUS has a severity at onset (50 percent of patients experience CKD and ESRD). A previous study [14] discovered that pregnancy can cause pregnancy-associated HUS, a rare form of HUS. It is still not clear why a lot of women get HUS in their second or later pregnancies but not in their first, and it is also not clear how pregnancy causes HUS. Complement activation happens in the placenta at the mother-fetal interface during a healthy pregnancy [15], so it makes sense that pregnancy-associated HUS would primarily happen during this time. In the research we did, the number of miscarriages was statistically the same as in the whole population. In England, a two-year prospective community study found that 12% of 657 pregnancies ended in miscarriage prior to the 20th week [16]. The Centers for Disease Control and Prevention in the USA estimate that in 2008, out of a total of 6,578,000 pregnancies, 17% resulted in fetal loss [17]. In our study, fetal loss (miscarriage plus late fetal death) occurred in 17.5% of pregnancies.

The postpartum period of uneventful pregnancies was the setting for 60% of the cases in this study, and in this situation, the diagnosis of HUS is relatively simple. The differential diagnosis for the remaining 40% of cases during pregnancy (mostly in the third trimester) is more difficult because many illnesses, such as preeclampsia, HELLP syndrome, or severe bleeding, can mimic HUS [18]. Additionally, one-fourth of pregnant women with HUS had a history of CKD/HUS, and the possibility of renal vascular damage prior to gestation may account for the development of HUS early in pregnancy and prior to delivery. Lastly, pregnant women with HUS and women who had HUS after giving birth had the same severe renal outcome (risk of ESRD). This was a big difference from how patients with preeclampsia and HELLP syndrome usually got their kidney function back to normal.

This research highlights a number of problems related to pregnancy-related HUS. First, plasma exchanges did not improve the kidney outcome of HUS caused by pregnancy, and the risk of end-stage renal disease (ESRD) remained high for both patients who had plasma exchanges and those who did not. Second, the current data will help doctors give advice to people who want to start a pregnancy but have a history of atypical HUS or who are healthy but carry variants of the complement gene. In our study, the risk of HUS was highest during the first pregnancy, but it remained fairly high during subsequent pregnancies and may even rise as eculizumab rescues patients from ESRD and thereby maintains their ability to carry a pregnancy. Patients should be informed of the risks associated with potential clinical or subclinical chronic kidney damage due to prior episodes of atypical HUS, including hypertensive complications of pregnancy that may occur despite treatment with eculizumab, before deciding whether or not to become pregnant (although this risk is estimated based primarily on studies in atypical HUS unrelated to pregnancies). In order to quickly identify and thus treat the early manifestations of HUS in these patients, pregnancy necessitates close collaborative monitoring by nephrologists and obstetricians in level 3 maternity hospitals beginning in the first weeks of pregnancy and continuing for up to 3 months after delivery.

CONCLUSION

Pregnancy-related atypical HUS is a very severe disease, with a poor prognosis for maternal kidney function if left without specific, effective treatment. Pregnancy seems to be an important trigger for the disease in at-risk patients. Prospective studies are needed in order to specifically assess the etiological factors correlating pregnancy and HUA and find safe

therapeutic options for the treatment of HUS during pregnancy.

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