Original Article

# Frequency of Thrombotic Microangiopathy in Patients with Pregnancy Related Acute Kidney Injury



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## ABSTRACT

**Objective:** To determine the Frequency of thrombotic micro-angiopathy in patients with pregnancy related acute kidney injury.

**Study Design:** Cross-sectional study.

**Place and Duration of study:** This study was conducted out at Department of Nephrology, Baluchistan Institute of Nephro-Urology, and Department of Obs and Gynae, BMCH Quetta from July 2016 to December 2017.

**Material and Methods:** A heterogeneous disease called Pregnancy-related acute kidney injury (P-AKI that occurs due to a large number of important etiologies. Although a rare but a fatal cause of P-AKI ispregnancy associated Thrombotic microangiopathy (TMA), with very poor consequence. Patient survival pregnancy and kidney outcome is dependent on early diagnosis and prompt treatment. The two most common disorder of thrombotic microangiopathies (TMA) are TTP (thrombotic thrombocytopenic purpura) and HUS (hemolytic uremic syndrome). In this study we would determine the frequency of thrombotic microangiopathy in patient with pregnancy related acute kidney injury. Among the patients admitted in department of gynecology and obstetrics during this period, who developed AKI, MAHA and unexplained thrombocytopenia were enrolled. Modified Jaffe's technique was used to measure serum creatinine whereas Modification of Diet in Renal Disease (MDRD) equation was used to measure glomerular filtration rate. Acute Kidney Injury was defined as when the urine output decreased to less than 400 mL for more than 6 h or serum creatinine increased about 1.5 times from the baseline or both. Thrombotic microangiopathy was further classified into TTP and a HUS. ADAMS-TS-13 levels were sent. . Data was collected on predesigned Performa. Non-probability consecutive sampling technique was used for sample collection. After accomplishment of data of required sample, a statistics was established on SPSS version 22.0 for data analysis. For continuous variables such as age the mean, median and standard deviation was calculated. For qualitative variables Pearson Chi- square test ($\chi 2$) was applied whereas t-test was applied for all continuous variables. P-value < 0.05 considered as significant.

**Results**: 2763 patients were admitted in department of Gynecology, 221patients (8%) were diagnosed as pregnancy related AKI (P-AKI).among them 26 patients (11%) had pregnancy related thrombotic microangiopathy (P-TMA) as a cause of AKI. 19 patients were having TTP and 7 had HUS.15 Patients were nulliparous while 11 were multiparous. The mean age was 29.5±3.8 years. Most of TTP patients 15/19 presented antepartum while 4/19 postpartum. HUS developed in all patients in postpartum period.50 % of the patients with TTP required dialysis initially but only 10 % developed ESRD. In HUS group 90 % required dialysis initially and 80 % remained dialysis dependent .thrombocytopenia was more severe in TTP group while renal failure in HUS.

**Conclusion:** The spectrum of thrombotic microangiopathies (TMA) during pregnancy has very complex presentation .Although very difficult to differentiate from acute fatty liver of pregnancy and HEELP syndrome yet is very necessary as each of them have entirely different management. Early identification and prompt treatment with plasmapharesis, plasma exchange, pulsed steroid therapy and if required dialysis can decreases the maternal and neonatal mortality risk and improve the outcome of both.

**Key Words:** Pregnancy, pregnancy related acute renal injury, pregnancy related Thrombotic microangiopathy, TTP, HUS

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## INTRODUCTION

Pregnancy related acute kidney injury (P-AKI) is considered as an entity of heterogeneous disease that happens due to a large number of underlying etiologies[1]. A very uncommon and lethal medical condition known as Thrombotic Microangiopathy (often known simply as TMA)[2]. Which damages the body's vital organs like kidney and brain by involving there smallest blood vessels[3].

TMA in pregnancy is important although rare cause of P-AKI. The patient may present during pregnancy or postpartum with low platelets (<150) usually less than 50K, hemolysis as evident by MAHA, raised LDH and indirect bilirubin. Sometimes neurological symptoms like fits, decreased conscious level may also be seen. TTP usually present in second or third trimester and HUS usually in postpartum period[4].

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Normal pregnancy is a procoagulant state. in order to protect hemorrhage at the time of labor few haemostatic changes occur, which are hormonally mediated.

TTP is caused by deficiency of ADAMTS 13 (a disintegrin and metalloprotease with thrombospond in type 1 motif, member 13) (5).ADAMS TS 13 is mandatory to cleave von Willebr and factor (VWF) .Lack of ADAMSTS13 either acquired or inherited (IgG autoantibodies to ADAMTS13) results in accumulation of ultra large VWF multimers leading to platelet aggregation and thrombosis in micro vessels. Von Willebr and Factor (VWF) levels increases during pregnancy, returning back to normal 6 weeks postpartum. VWF and ADAMTS13 have a reciprocal relationship. In second and third trimesters of normal pregnancy, ADAMTS13 activity decreases both because of excess substrate (vWF) and effect of estrogen, while VWF levels increases[6]. This is the reason that TTP is seen more commonly in pregnancy[7].

In HUS mutation occurs in complement genes of the alternative complement pathway, such as CD46 (also termed MCP),CFH (Factor H), CFI (Factor I)[7], Factor B or C3,complement-activating genes[8].

Approximately 15–30% of all cases of a HUS is due to CFH mutations(8).10-13% of CD46 mutations occurs in a HUS patients, the mostly being heterozygous and these patients have a milder clinical sequence[9].

Inmedical practice it becomes sometimes hard to distinguish clinically among TTP, HUS, PE, and HEELP but yet is very important as the management is entirely different.

Severe thrombocytopenia very high LDH ,second or third trimester presentation, prominent neurological symptoms ,less severe renal failure, failure of resolution of thrombocytopenia and high LDH three days after delivery, ADAMSTS 13 levels <10% all suggest TTP.

In contrary more severe renal failure ,postpartum presentation, ADAMTS 13 level >10%,mutatoins of factors involved in alternate complement pathway, persistence of hematological abnormalities and renal dysfunction after delivery, failure of resolution of renal failure with plasmapharesis, rapidly progressive postpartum acute kidney injury without an apparent cause for acute tubular necrosis , all suggest HUS

In this study we would determine the frequency of thrombotic microangiopathy in patient with pregnancy related acute kidney injury.

# MATERIALS AND METHODS

Cross-sectional study was conducted in Department of Nephrology, Baluchistan Institute of Nephro-Urology, Quetta, and Department of Obstetrics and Gynecology BMCH in a period of 18 months from month of July 2016 to December 2017. Ethical committee approval was obtained before conducting the study. Among 2763 patients admitted in department of gynecology and obstetrics during this period, 26 patients were enrolled. The inclusion criteria comprise all patients with evidence of AKI,MAHA ,thrombocytopenia, raised LDH, normal coagulation profile, neurological abnormalities without another apparent cause like HEELP,AFLP,PE .TMA was categorized as TTP and HUS.ADAMTS 13 levels were sent. Patients with MAHA, more severe thrombocytopenia and neurological involvement, ADAMTS 13 levels <10% were categorized as TTP, while patients with more severe renal failure, less severe thrombocytopenia and neurological involvement and ADAMS TS 13 level >10 % were labelled as HUS[10].

For Data collection predesigned Performa was used. In which patient's medical registration no, age, complete history, physical examination and laboratory tests were included. Informed consent was obtained from all participants. The non-probability consecutive sampling was used for sampling technique. After accomplishment of data of required sample, a statistics was established on SPSS version 22.0 for data analysis. For continuous variables such as age the mean, median and standard deviation was calculated. For qualitative variables Pearson Chi- square test ($\chi 2$) was applied whereas t-test was applied for all continuous variables. P-value < 0.05 considered as significant.

# RESULTS

Of 2763 admitted patients in department of Gynecology, 221 patients(8%) were diagnosed as pregnancy related AKI(P-AKI).among them 26 patients (11%) had pregnancy related thrombotic micro-angiopathy (P-TMA) as a cause of AKI. The mean age of patients is 29.5±3.8 years. Of those 26 females, 15 were nulliparous and 11 were multiparous. With respect to thrombotic microangiopathies, 19 patients were found TTP, and 7 were diagnosed as aHUS which constitute of 73.1% and 26.9 % respectively (Table 1).

**Table No. 1: Thrombotic Microangiopathies**

| | | |
|---|---|---|
| **Thrombotic Microangiopathies** | 19 | 73.1 % |
| • TTP | 7 | 26.9 % |
| • HUS | | |

**Table No.2: Frequency and their percentage**

| | **Frequency** | **Percentage** |
|---|---|---|
| **Parity** | | |
| Nulliparous | 15 | 60% |
| Multiparous | 11 | 40 % |

Concerning parity, out of 7 nulliparous, 5 of them had TTP and remaining 2 had HUS. On the other hand, of total 19 multiparous, 14 were found to have TTP and remaining 5 were diagnosed as a HUS.

15/19 (80%) of the patients presented with TTP presented in second or third trimester and only 4/19 (20 %) postpartum, while all HUS 7/7 (100%) patients present after delivery.

**TableNo. 3: Time of presentation**

| TMA (26) | Time of presentation | |
|---|---|---|
| | 2nd or 3rd time | Post-partum |
| TTP(19) | 80% (15/19) | 20%(4/19) |
| HUS(7) | 0% (0/7) | 100% (7/7) |

All patients in our study developed AKI, less severe in TTP group, more severe in HUS arm. in patients with TTP 9/19 patients( 50 % )required dialysis,17/19 ( 90% )gained their renal functions back within 3 weeks but 2/19 patients( 10 %) remained dialysis dependent. While in HUS 6/7 patients (90%) patients required dialysis and 5/7 patients (80%) got ESRD.

**Table No. 4: Out Come**

| **TMA (26)** | **Out Come** | |
|---|---|---|
| | **Initial requirement of dialysis** | **Dialysis dependent** |
| **TTP (19)** | 50 % (9/19) | 10 % (2/19) |
| **HUS (7)** | 90 % (6/7) | 80% (5/7) |

**Table No.5: Laboratory investigations in patients with pregnancy related acute kidney injury**

| | Microan-giopathies | N | Mean ± Std. Deviation | P-value |
|---|---|---|---|---|
| TLC | TTP | 19 | 12.52 ± 5.13 | 0.93 |
| | aHUS | 7 | 12.71 ± 4.71 | |
| Hb | TTP | 19 | 11.26 ± 1.62 | 0.56 |
| | aHUS | 7 | 10.85 ± 1.34 | |
| Platelets | TTP | 19 | 75.71 ± 8.38 | 0.03* |
| | aHUS | 7 | 84.68 ± 6.60 | |
| PT | TTP | 19 | 13.47 ± 1.95 | 0.81 |
| | aHUS | 7 | 13.28 ± 1.38 | |
| APTT | TTP | 19 | 33.78 ± 3.58 | 0.89 |
| | aHUS | 7 | 34.00 ± 4.04 | |
| AST | TTP | 19 | 136.47 ± 6.72 | 0.62 |
| | aHUS | 7 | 126.28 ± 43.70 | |
| ALT | TTP | 19 | 137.68 ± 49.04 | 0.92 |
| | aHUS | 7 | 135.57 ± 48.33 | |
| Total Bilirubin | TTP | 19 | 6.53 ± 4.24 | 0.46 |
| | aHUS | 7 | 5.18 ± 3.47 | |
| Direct bilirubin | TTP | 19 | 3.87 ± 2.34 | 0.18 |
| | aHUS | 7 | 5.37 ± 2.83 | |
| Indirect bilirubin | TTP | 19 | 2.93 ± 1.12 | 0.89 |
| | aHUS | 7 | 3.00 ±.93 | |
| serum creatinine | TTP | 19 | 2.40 ± 1.35 | 0.04* |
| | aHUS | 7 | 4.30 ± 2.43 | |
| SBP | TTP | 19 | 125.73 ± 26.14 | 0.83 |
| | aHUS | 7 | 123.57 ± 9.16 | |
| DBP | TTP | 19 | 82.73 ± 11.11 | 0.80 |
| | aHUS | 7 | 83.85 ± 4.98 | |

# DISCUSSION

The study determines the frequency of thrombotic microangiopathy in patients with pregnancy. Pregnancy related acute kidney injury is a life-threatening condition.TMA is one of the important cause of pregnancy related acute kidney injury.TMA is defined as the presence of fibrin and/or platelets thrombi in the arterioles and capillaries of vital organs, mostly affecting the brain and kidney histologically. TMA presents with swelling of endothelial cells, sub endothelial accumulation of protein and cell debris, and in certain cases, splitting of the glomerular basement membrane[4].

TMA presenting with predominantly renal failure is usually called hemolytic uremic syndrome (HUS), while more severe thrombocytopenia with neurological involvement is defined as thrombotic thrombocyto-penicpurpura (TTP), but overlap may occur: 10% cases of TTP patients have AKI, and neurologic involvement is not uncommon in typical HUS or aHUS[11] .

TMA in pregnancy still has increase morbidity and mortality (up to 10%) rates[12]. ADAMTS13 deficiency-related TMA (TTP) happens mostly during the second and third trimesters of pregnancy. In our study, most patients with TTP15/19(80%) presented in either second or third trimester of pregnancy while 4/19 (20%) presented postpartum. this finding in our study is consistent with the literature review, where pregnancy triggered TTP in 23 cases in which 83% of cases were seen in second or third trimesters[13]. These finding may be due to progressive decrease in ADAMTS13 and the similar increase in vWF antigen during normal pregnancy[12].

HUS mainly presents in post-partum period ,our patients with HUS 7/7 (100%) developed it postpartum, but it may be develop prepartum during second or third trimester as observed by Bruel et al (14),where 24% patients developed HUS before delivery and 76% patients presented postpartum . Dysregulation of the alternative complement pathway during postpartum period is caused bygene mutation encoding complement proteins. Numerous factors which leads to trigger the complement activation in an already genetically susceptible individual such as, preeclampsia, drugs, cancer, maternal–fetal hemorrhage, inflammation and infections. Most of our patients with TTP (14/19) and HUS (5/7) had TMA presentation in either first or second pregnancy while TMA developed in few multiparous women. This finding is consistent with retrospective study from the Spanish registry[15] where they found that 73% patients had TMA presentation in first pregnancy.

While Fadifa khouri et al[16] found that most patients presented in second pregnancy. The exact etiology that patients are more prone in first and second pregnancies is not known.

TTP presents with less severe renal failure and rarely becomes dialysis depedent.in our study 100% patients had renal failure with mean serum creatinine(2.40mg/dl ),but only 50% required dialysis and only 10% (2 patients) landed up on permanen themodialysis-HUS has a very dismal renal outcome. Most of the patients develop CKD and becomes dialysis dependent. in our study among 7 patients with HUS , 6 (90%) required dialysis initially but 5/7 patients (80%) developed ESRD and were dependent on dialysis by the end of three months. it may be because of the reason that none could receive Eculizumab although all patients were plasmapharesis .in contrary to Huerta et al[15] who reported that 33% patients who could not receive eculizumab developed ESRD, our 80 % patients got ESRD. however French group has reported a high incidence of ESRD i.e. 62% o during the first month and 76% requiring RRT at the end of the follow-up[17].

Treatment modality also has significant impact on thrombotic microangiopathies. plasmapharesis should be starting immediately after suspecting TMA, not waiting for ADAMSTS 13 levels .early plasmapharesis improves outcome both hematological and renal in TTP while only hematological in HUS. Pulse steroid therapy may be given as an adjunct therapy with plasmapharesis in TTP, platelets transfusions should be avoided, but only in case of bleeding, blood transfusion when required. In case of postnatal TMA, eculizumabmust be given as early as possible to improve renal recovery[16]. Theeculizumab regimen includes four weekly 900-mg infusions followed by 1,200-mg infusions every fortnight. We could not use Eculizumab as treatment option in HUS as this medicine is not available in this part of the world, and our patients could not afford either.

# CONCLUSION

**Conclusion:** The spectrum of thrombotic microangiopathies (TMA) during pregnancy has very complex presentation and therefore very difficult to differentiate. Early identification and prompt treatment with plasma exchange, plasmapharesis and pulsed steroid therapy,Eculizumabcan lessen the risk of neonatal and maternal mortality and improve the outcome of both of them.

**Recommendation:** The study highlights the spectrum of TMA in pregnancy related acute renal injury and its outcome. Therefore, we recommend that institutions, especially in Pakistan, should adopt a policy for early identification and quick treatment of TMA in pregnancy in order to decrease the risk of both mother and infant mortality and morbidity.

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**Author's Contribution:**

| | |
|---|---|
| Concept & Design of Study: | Fazal Mohammad |
| Drafting: | Fozia Mohammad Bakhsh |
| Data Analysis: | Syed Mohkam |
| Revisiting Critically: | Fazal Mohammad, Fozia Mohammad Bakhsh |
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**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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