Haemostatic Dysfunction in Pregnancy Related Renal Disease

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Introduction: Acute renal failure in pregnancy is a challenging clinical condition and coagulation disturbance add to distressing condition of patient. The present study was carried to determine status of haemostasis in these patients. In this study 40 pregnant females who presented with acute renal failure were taken.

Study Design: It was a descriptive and case-series study.

Material and Methods: Forty pregnant females were included in the study. The demographic information Name, Age, Sex and address was noted. The history of present illness was obtained and they were examined for positive signs. Routine laboratory investigations CBC (Haemoglobin, TLC, DLC and platelet count) were carried out on sysmex KX21 and verified by peripheral smear examination. Serum urea and creatinine levels were obtained to establish ARF and see the degree of renal insult. Prothrombin time, Activated partial thromboplastin time and Fibrinogen levels were carried out to establish coagulopathy. These tests were performed by the standard manual method which is also the gold standard.

Results: In our study gastroenteritis (22%) and Ante partum haemorrhage (15%) were among the leading causes of pregnancy related renal failure. Prothrombin time was significantly raised in 42%, Activated Partial Thromboplastine Time in 45% and raised fibrinogen in 20% of cases.

Discussion: Pregnancy related acute renal failure is a disappearing entity in west but in our set up it is still a significant cause of antenatal morbidity. Many studies especially in the developing countries matched our results.

Conclusion: Disturbed haemostasis in pregnancy related acute renal failure is a significant condition and patients should be closely monitored to prevent morbidity and mortality.

Key Words: Coagulation, Pregnancy, Acute Renal Failure, Prothrombin time.

Introduction

Physiologic changes occurring in pregnancy involve nearly every organ system, and the kidneys are no exception. Acute renal failure during pregnancy is one of the most challenging clinical problems. In recent year the incidence of acute renal failure has decreased in developed countries but still continues to be common in developing countries. Acute renal failure (ARF) is defined as an abrupt or rapid loss of renal function resulting in retention of nitrogenous (urea and creatinine) and non-nitrogenous waste products. This can be with or without a decrement in urine output.[1]

Coagulopathy in acute renal failure in general and particularly associated with pregnancy is ill defined and not very clear. However, several studies have reported haemostatic abnormalities in ARF, both in terms of bleeding and coagulation disturbances. The pathogenesis of haemostasis in acute renal failure is multifactorial, and are a consequence of uremia, renal artery damage, and Von Willibrand factor with factor VIII and beta-thromboglobin activation along with this abnormal platelet function and count. It may lead to prolonged bleeding time and change in prothrombin time, activated partial thromboplastin time, thrombin time and fibrinogen levels. In acute renal failure of any etiology, the mortality rate associated with haemorrhagic propensity ranges from 3-to15%.[2]

Pregnancy is a hypercoagulable state and in this state many a times obstetrical complications are causative factors for acute renal failure in 15% to10% of patients[3]. Thrombophilia in pregnancy has also been linked to many aspects . Severe pregnancy complications such as severe preeclampsia, intrauterine growth retardation , abruptio placentae and stillbirth are all associated with thrombophilia. Interestingly pregnancy itself can cause acute renal failure and renal disease can present for the first time during pregnancy.[4] Acute renal failure in pregnancy may be due to various causes, including haemolysis, septicemia, and hypovolaemia e.g. pre-eclampsia, antepartum haemorrhage, intrapartum or postpartum haemorrhage, DIC, abortion.

Objectives and Aims

- To study the frequency of haemostatic disturbances in pregnancy related acute renal failure.
- To observe coagulation profile in different etiologies of pregnancy related acute renal failure.

Material and Methods

Study Design: It was a descriptive and case-series study.

Setting: The study was conducted at the pathology department King Edward Medical University and the cases were

collected from all the four medical wards, obstetrics and gynecological and nephrology units affiliated with Mayo Hospital Lahore.

Duration of Study: One year.

Subjects: Forty pregnant females who presented with acute renal failure were included in the study.

Methods: A thorough and methodical clinical history was taken. It was supported by relevant investigations. Patient's consent was taken. The demographic information Name, Age, Sex and address was noted. Routine laboratory investigations CBC (Haemoglobin, Total Leukocyte Count, Differential Leukocyte Count and platelet count) were carried out on sysmex KX_{21} and verified by peripheral smear examination. t-test and chi square were applied to all the results

Serum urea and creatinine levels were obtained to establish ARF and see the degree of renal insult.

Following tests were carried out to establish coagulopathy:

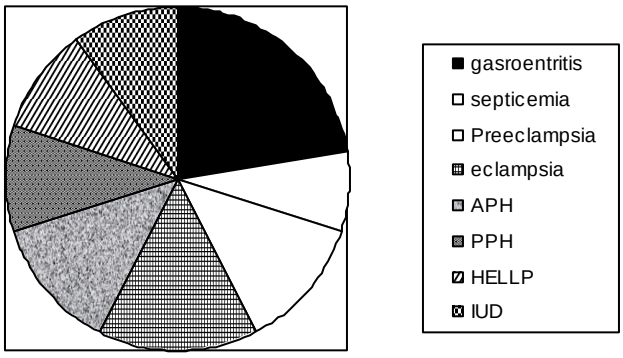
i) **Platelet count:** Platelet count was measured by automated counter sysmex KX-21 and checked manually.
ii) **Prothrombin time:** It measured the clotting time of plasma in the presence thromboplastin. It was carried out in citrated plasma at the temperature of 37 degree Celsius.
iii) **Activated partial thromboplastin time:** It measured the clotting time of plasma after activation of contact factors but without added thromboplastin. It was also carried out in citrated plasma at the temperature of 37 degree Celsius.
iv) **Fibrinogen levels:** Fibrinogen levels were determined when different dilutions of the patients plasma were clotted by a strong thrombin solution.

Results and Observations

A total of 40 adult patients were included in the study .The mean age of patients was 33.54 ± 10.51 with range of 20-45 years. The presenting clinical features in patients were pallor in 18 (45%), hemorrhage 10 (25%) fever in 23 (57%), anuria in 22 (55%), oligouria in 18 (45%), petechae in 22 (55%), edema feet in 15 (37%) and diarrhea in 10 (25%) patients.

Table 1: Causes of Pregnancy related Renal Failure.

Diseases Associated with ARF	Number of Patients
Gastroenteritis	09 (22%)
APH	06 (15%)
Eclampsia	05 (12.5%)
Preeclampsia	05 (12.5%)
PPH	04 (10%)
HELLP	04 (10%)
IUD	04 (10%)
Septicaemia	03 (7.5%)
Total	40



Key: APH (ante partum hemorrhage), IUD (intra uterine death), PPH (post partum hemorrhage).

Acute renal failure in these patients was attributed to different causes (table 1). Gastroentritis surprisingly was the leading cause (22%) followed by APH (15%).

In these patients plasma prothrombin time mean value was 16.57 ± 5.29 second with range of 11-26 seconds. In controls the means value was 13.58 ± 0.57 second. The mean value of prothrombin time in patients was 3.5 second longer than the controls which is statistically highly significant (P value < 0.0001).

Plasma activated partial thromboplastin time mean value was 39.05 ± 9.95 second with range of 25-110 seconds. In controls the value was 24.94 ± 1.31 sec. This mean value of the patients is 15 seconds greater than controls. This prolongation is statistically highly significant. (P value < 0.0001).

Fibrinogen levels can be measured in venous blood. In this study plasma fibrinogen levels showed a wide range of 1.10-3.66g/I with the mean value of 2.38 ± 1.30 g/I. Normal levels are about 1.5-3.0 g/L. Fibrinogen levels were raised in 8 out of 40 patients. In this study the platelet count varies from 4000-455,000/mm.[3] The mean platelet count in the patients was 212,500 ± 63000/mm^3 which falls in the normal range of 150,000 – 4000,000/mm.[3]

Coagulation parameters and fibrinogen levels of different diseases are shown in table 2. Prothrombin time was raised in 42% of cases while APTT was raised in 45% cases. Fibrinogen on other hand was raised in 20% cases.

Discussion

Pregnancy related acute renal failure (PR-ARF) is a disappearing entity in west and the most important reasons for this favorable evolution seem to be an improved medical care and more effective measures of careful prevention, mainly regarding tempestive delivery.[5]

Coagulation profile is useful for assessing the etiology of ARF as well as establishing the level of injury/insult to the body and its various systems. Prothrombin time or PT is such an important indicator that it has been included in prognostic scoring system.[6] In our study prothrombin time was disturbed in 42% of the cases finding similar to these have been reported by Lins RL et al.[7]

Table 2: *Coagulation Parameters in Pregnancy Associated Renal Failure.*

DISEASES ASSOCIATED WITH ARF	NUMBER OF PATIENTS	RAISED PT	RAISED APTT	RAISED FIBRINGEN LEVEL
Gastrentritis	09	04 (44%)	04 (44%)	01 (11%)
Septicaemia	03	02 (66%)	01 (33%)	01 (33%)
Eclampsia	5	03 (60%)	04 (80%)	01 (20%)
APH	06	01 (16%)	02 (33%)	02 (33%)
Preeclampsia	05	01 (20%)	01 (20%)	01 (20%)
PPH	04	02 (50%)	02 (50%)	01 (25%)
HELLP	04	02 (50%)	02 (50%)	01 (25%)
IUD	4	02 (50%)	02 (50%)	0
Total	40	17 (42%)	18 (45%)	08 (20%)

The activated partial thromboplastin time (APTT) is a measure of the integrity of the intrinsic and common pathways of the coagulation cascade. In our study plasma activated partial thromboplastin time mean value was 39.05 ± 9.95 second with range of 25-110 seconds. 45% of cases with pregnancy related ARF showed prolonged APTT which correlates with studies by Maribito S etal.[8]

Fibrinogen, is synthesised by the liver. Recent research has shown that fibrin plays a key role in the inflammatory response. It is also an acute phase reactant. It was increased in 20% of our cases which is a finding supported by many other studies and explained by the fact that pregnancy is an hypercoagulable state.[9]

Gastroentritis is the commonest and important cause of acute renal failure in tropical countries. Failure to correct hypovolemia in gastroenteritis results in acute tubular necrosis and renal failure. In our study 44% cases which presented with acute renal failure associated with had raised PT and APTT while only 11% had raised fibrinogen .In Nepal and India various studies reported gastroenteritis as a cause of acute renal failure in 22-44.5% of the cases.[10]

George G. Ganopolsky and Francis J. Castellino explains acute renal failure and coagulopathy in septicemia. The inflammatory state is closely related to coagulation through several elements as endothelial protein C receptor, thrombomodulin , and protease-activated receptors, tissue factor, F VII, FXI, and FXII, protein C, tissue factor pathway inhibitor, and anti-thrombin-III. Both of the above workers found that there is disturbed coagulopathy in ARF Their results showed a similar value of coagulation disturbance as our study which showed disturbance in 66% of cases of septicemia.[11]

Sanders CL, Lucas MJ. state that common complications of pregnancy such as hypertension and hypovolemia can be associated with acute renal injury or its aggravation. Tendency to thrombosis, has been linked to many aspects of pregnancy such as severe preeclampsia, intrauterine growth retardation, abruptio placentae and stillbirth. In our study 60-80% patients of eclampsia showed raised PT and APTT and raised fibrinogen approximately 20% of cases. Close to above results have been seen in studies by Sanders CL, Lucas MJ.[12]

Severe peripartum hemorrhage contributes to maternal morbidity and mortality and is one of the most frequent emergencies in obstetrics, occurring at a prevalence of 0.5-5.0%. Coagulation disorders can cause antepartum hemorrhage or vice versa ARF in antepartum hemorrhage can disturb coagulation parameters. In our studies 16-33% of cases had raised PT and APTT. Fibrinogen was raised in 16% cases. Similarly in post partum hemorrhage 50% of cases with acute renal failure had disturbed PT and APTT. Similar observations have been made by others.[13]

Pregnancy-induced hypertension, preeclampsia and HELLP syndrome are related and overlap in their presentations. Morbidity and mortality rates associated with HELLP have been reported to be as high as 25 percent. From 1 to 25 percent of affected women develop serious complications such as DIC, placental abruption, adult respiratory distress syndrome, hepatic and renal failure, pulmonary edema and many others.[14] The case reports by Chris et al and McBrein show results paralleling our study with PT and APTT raised in 50% while fibrinogen raised in 25% of cases only.[15]

Intruterine death may cause acute renal failure in pregnancy or vice versa acute renal failure may cause the such severe injury to fetus resulting in intrauterine death. Diseases such as eclampsia, pre-eclampsia, HELLP, HUS, DIC[16] and others can cause acute renal failure and coagulation disturbances in pregnancies and along with it abnormalities in fetal growth resulting in IUD.[17] Among the 4 cases we included with acute renal failure only 25% of cases showed disturbed coagulation and bleeding profile. G Constantine and V Menon however do not agree with our study.[18]

Conclusion

In this study following conclusions were made:

- The etiology of pregnancy related acute renal failure (ARF) is variable.
- PT and APPT are the key test for determining coagulopathy in patients of pregnancy related acute renal failure irrespective to the cause of ARF.
- Fibrinogen level is not a reliable index because it is dependent on other factors as well. Sometimes it is reduced as in consumptive coagulopathy and in other conditions it is raised as it is an acute phase reactant as well.
- Haemostatic disturbances in pregnancy related acute renal failure have great significance as they can enhance the rate of morbidity and mortality in patients of acute renal failure.

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